

This transcript is the uncertified transcript of the California CDPH Human Stem Cell Research (HSCR) Advisory Committee meeting held on October 1, 2008. This transcript has not been reviewed for accuracy and has not been approved by the CDPH HSCR Advisory Committee.

STATE of CA
Moderator: Dr. Shabbir Ahmad
October 01, 2008
1:00 pm PST

Man: (Unintelligible).

Coordinator: Excuse me. This is the operator.

Just as a reminder, today's call is being recorded. If anyone has any objections, you may disconnect at this time.

Ma'am, you may begin.

Henry Greely: Thank you.

Now, that we have permission from the conference call recorder, I welcome you all at this meeting of The California Department of Public Health, Human Stem Cell Research Advisory Committee.

This is Hank Greely, your chair. We're meeting at Stanford University in the Medical Services Office Building, Medical Sciences Office Building, where those of us who are here physically are enjoying a very pleasant lunch

provided courtesy of the Stanford Center for Biomedical Ethics and Stanford Center for Law and the Biosciences. So our thanks to both those institutions.

Let's go around, first, to the physical room with introductions and then we'll go online. Just let us know who you are and whether you're a member or member of the public. I'm Hank Greely a member of the committee and chair.

David Magnus: David Magnus, Stanford, a member of the committee.

Margaret McLean: Margaret McLean from Santa Clara University and a member of the committee.

Otoniel Martinez-Maza: Oto Martinez-Maza, excuse me, from UCLA School of Medicine, also a member of the committee.

Henry Greely: And staff?

Amber Christiansen: I'm Amber Christiansen with the Department of Public Health.

Patricia Rodriguez: Patricia Rodriguez, Department of Public Health.

Shabbir Ahmad: Shabbir Ahmad staffing the committee from Department of Public Health.

Heidi Mergenthaler: Heidi Mergenthaler, Department of Public Health.

Bertram Lubin: I'm Bert Lubin. I co-chair with Hank. I'm from Children's Hospital of Oakland.

Radhika Rao: And Radhika Rao from Hastings, member of the committee.

Geoff Lomax: Geoff Lomax, CIRM.

Henry Greely: So I think, Geoff is our only public observer here physically present.

Woman: (Okay).

Henry Greely: Now, seeing no one else who needs to be announced in the room, well we have Paula Bailey from the Stanford Center of Biomedical Ethics here as well.

David Magnus: We really have to thank for the lunch.

((Crosstalk))

Henry Greely: True, realistically.

So let's go to the phone, members first, please announce your presence.

Elizabeth Blackburn: Elizabeth Blackburn from UCSF.

Bernard Lo: Bernard Lo, UCSF.

Samuel Cheshier: And Samuel Cheshier, Stanford.

Gregory Stock: Gregory Stock from UCLA.

Henry Greely: Any other members? Members of the public on the phone?

(Lori Cavanaugh):(Lori Cavanaugh): from UCSF.

Jesse Reynolds: Jesse Reynolds from the Center for Genetics and Society.

Henry Greely: Anyone else?

Great. Welcome all. Between physical presence and telephonic presence, we have 10 of the 13 committee members here. We've heard from Dr. Weissman and Dr. Dorff that they won't be able to participate.

We had thought that Rusty Gage would be here via conference call. I hope he'll be able to call in, and we'll incorporate him when he comes.

Let me turn things over right now to Dr. Ahmad to see if he has anything to add as introductory matter.

Shabbir Ahmad: Thank you very much for your voluntary time again for the department and for this (unintelligible) advisory committee meeting for human stem cell research program for California Department of Public Health.

And I also echo Hank and the committee members for thanking Stanford to host this meeting and also providing the lunch to the participants over here.

My short update finally the state has the budget as all of you know the maternal, child, and adolescent health program, fared very very good, we have some cuts but overall compared to some other programs we were spared, there were some blue pencil vetoes certain programs within Department of Public Health were terminated, fully terminated. We received some cuts for some of our programs.

And now there is a lot of work at the department to revise or amend those contracts where there are, there are hundreds in MCAH.

The report I want to give which the committee might be interested in is the – report from institutions from IRBs and SCROs regarding the human stem cell research projects, we received almost 252 project reports on Form 1, which was basically for any kind of human stem cell research which is not fully funded by CIRM, which is partially funded by CIRM or funded from other sources other than CIRM. So overall, there were 250 reports - 252 reports.

We are now developing a report and reviewing for the legislators that the mandate for the department and when that report would be ready would be shared with the committee (unintelligible).

There are a couple of projects, which were reported on Form 2 and our intention is because they are less than five we may not develop a report for public because of the confidentiality issues. That still - it's not a final decision yet - but I think that's probably going to happen.

Henry Greely: Dr. Ahmad, would you remind us what Form 2 reporting...

Shabbir Ahmad: Sorry. Yeah, Part 2 is anywhere where there is procurement of the human egg for research purposes.

Man: (Thank you).

Henry Greely: And by a couple, was it actually literally two?

Shabbir Ahmad: That is...

((Crosstalk))

Shabbir Ahmad: ...we will be - we received two reports, yes.

((Crosstalk))

Shabbir Ahmad: The other update that the department would provide the revised 2008 National Academy of Science Guidelines to the book to the committee so don't purchase yours, we have already ordered. They are still in print and we will provide that.

And one question I have to the committee that would you like to receive some stem cell updates in the research, with the companies, what's going on, the staff normally goes through what's in the news, and would the committee like to see those updates?

Woman: (Yeah, I would).

Shabbir Ahmad: Okay, I see a "Yes" nod over here that...

Henry Greely: So let me ask this before nodding one way or the other, roughly what sort of volume are you talking about and send them electronically...

((Crosstalk))

Shabbir Ahmad: (That is good).

((Crosstalk))

Shabbir Ahmad: That electronically, that would be (unintelligible) - a number of emails, but we can tag them in a way (unintelligible) if you want to go to those. This is like (unintelligible) from Department of Public Health or something like that, by

that way, you can just put that in the folder and when you have time, you can go through those...

Henry Greely: Roughly, how many a week...?

Shabbir Ahmad: I receive from Heidi and Amber almost one, two every day, yeah, yeah. So I would say there'd be around 50 emails from us in a month, yes.

Man: Yeah, okay.

Henry Greely: Let's just take a quick straw vote show of hands. How many people would like to get forwarded those emails?

Bertram Lubin: Can we ask a modification of that that may be to combine them and send one or two emails a month instead of every other day.

Henry Greely: Maybe once a week.

((Crosstalk))

Bertram Lubin: Once a week.

Man: Yes, we get that.

((Crosstalk))

Bertram Lubin: People get stem cell reports. I mean we get a lot of them already.

Man: Right.

Bertram Lubin: And we anticipate this is going to be (unintelligible) but it would be nice. And I wouldn't mind getting one, but I wouldn't want to get another email every day or every other day.

Henry Greely: Would that add greatly to your administrative burden to package it as once a week?

Shabbir Ahmad: We - no, that should be okay. We - it would be fine with that once a week, we can package them in one email and then - and we'll tag them you'll clearly know that there's an update from stem cell research and that's your decision...

((Crosstalk))

Man: Okay.

Henry Greely: I see a lot of sort of approving nods...

((Crosstalk))

Henry Greely: ...around the table. Anybody on the phone, any of the members on the phone who want to say anything about getting these email updates on stem cell research from the Department?

Sounds like a good thing to do...

((Crosstalk))

Shabbir Ahmad: ...(great). Thank you.

Henry Greely: Thank you for offering that.

Shabbir Ahmad: Right.

I appreciate that. Thank you very much.

The other thing is we are updating the committee roster there are any changes in the phone number, email address, or anything that we will be sending an email to the committee, please update your contact information.

That's all I have, Hank.

Henry Greely: Okay great.

Shabbir Ahmad: Thank you very much, Hank.

Henry Greely: You know, I probably should have done this before asking Dr. Ahmad for report, but we really should approve the meeting minutes from last time.

Man: Right.

Henry Greely: Does anyone that we have received the minutes, I think, both electronically and physically in our package? Is there any have corrections, changes, or comments? Any member who have corrections, (unintelligible) comments on minutes?

Is there a motion to approve?

Man: (Unintelligible).

Henry Greely: That's a motion. Second I see, all is in favor of approving the minutes of our last meeting say "Aye."

Women: Aye.

Men: Aye.

Man: Aye.

Henry Greely: All those opposed say, "Nay."

Are there any abstentions?

Minutes are approved.

Let me - we've now had an additional member of the public, I think...

Woman: Yeah.

Henry Greely: ...arrive physically in our meeting room, so would you please let everybody know who you are including the seven or so people on the line?

(Leslie Spalding): Hi. I'm (Leslie Spalding). I'm here representing Shannon Smith Crowley for the American Society for Reproductive Medicine.

Henry Greely: Okay, welcome.

And has anybody else online on the phone (unintelligible) who was not here when we started the meeting?

Hearing none, I'll assume there are none.

Okay, I've got actually an early comment that is relevant I think to the committee, although not exactly committee activity, the Senate and the Assembly passed SB1565, during the last legislative session, a bill sponsored by Senator Kuehl and Senator Runner that would have affected stem cell research in a variety of ways. The Governor just earlier this week, vetoed 1565, which was in line with the recommendation from CIRM.

Bert Lubin and I also wrote a letter to the Governor recommending his veto of the bill. I can't tell you that (I think) we turned the tide on it. But at least we didn't mess it up.

((Crosstalk))

Henry Greely: That letter which I've got copies of and am distributing here in which I propose should probably go on to Web site at some point was, you know, clearing noted as being coming from Bert and me in our personal capacities and noted that we were the co-chairs for this committee, but said we were not speaking for the committee.

Some of you may wonder why we didn't try to speak for the committee and in this is really a combination of two factors, one, logistically I think we've heard about the efforts to veto this - I first heard about them about two weeks, you know, logistically trying to get the committees together and to approve the language seemed very difficult.

And also frankly, it wasn't clear to me that making a recommendation on - whether or not making a recommendation on vetoing legislation was an

appropriate thing for the committee, as a state committee, to do. It's not clear to me that's an inappropriate thing.

But between that and the logistical position, logistical concern, pretty much more straightforward (unintelligible) from Bert and myself, and Bert was happy to agree, and so we crafted this letter.

Those of you who are getting - who are over the phone, it will go out by email to the members and will be posted on the Web site so (unintelligible) non-members (unintelligible). And there's nothing all that's dramatically exciting in it, I think. But it will explain the reasons why Bert and I at least thought the governor should veto the bill, which were similar to - although not identical with in emphasis the reasons that CIRM proposed (unintelligible) bill.

We've had another person who entered the room. Sir, could you identify yourself for...?

Allan Robins: Sure. Allan Robins from Novocell.

Henry Greely: From - a good.

((Crosstalk))

Henry Greely: Thank you very much for coming.

((Crosstalk))

Henry Greely: And did somebody else come on the phone? There was a funny noise on the phone.

((Crosstalk))

Greg Stock: Yeah, it was - I was having a bad connection and redialed in. This is Greg Stock, from UCLA.

Henry Greely: Great. So it's Greg (unintelligible) and Greg Sub 2 is now on the line, Greg the second.

Okay. So now, we're - I believe we're at agenda item three, unless there is any - unless anybody else wants to make any comments or any announcements relevant to the committee's work?

Anything from around the room, any of the members on the phone want to say anything?

All right, well before we go to agenda item three, we've got three, four, five and six and mind you, this is going to be an interesting meeting and maybe not the same as many of our past meetings.

((Crosstalk))

Henry Greely: I'm not sure one way or the other whether we'll end up actually voting on anything this meeting as opposed to just listening and discussing and trying to understand some things better.

It may well turn out that we've got some motions to vote on. It may well turn out that we don't. I just don't know how that's likely to fly.

I do think it's possible that our meeting won't go all the way till 5 o'clock.
And I hope no one will be too heartbroken if we manage to end a little early. I
know at least my co-chair...

Bertram Lubin: And also Geoff...

((Crosstalk))

Henry Greely: There are a couple of people around the table who would be not heartbroken if
we ended at 4:00, but if we need to go past 4:00, we'll go past 4:00 and say
good-bye to them (unintelligible) wishes.

So we've got three agenda items approve, what's listed as approval of
revisions to the guidelines with respect to specific informed consent
requirements for somatic cells and CDPH technical amendments to the
guidelines.

That discussion of revising the guidelines mainly with respect to the induced
pluripotent stem cells but also to some other CIRM revisions to their standards
and with amendments to the NAS guide - and in light of the - amendment to
the NAS guidelines.

And listed as Item 6 is a discussion of ethical and scientific problems with
consent form, for the NIH approved embryonic stem cell lines.

The flagged item stems from the article that Rob Streiffer of University of
Wisconsin published focusing on the NIH approved cell lines and the consent
forms for them.

Unless there is a strong objection, I'd like to rearrange the order of our agenda, if I can legally do that.

Man: Dr. (Moyer) just smiled.

((Crosstalk))

Shabbir Ahmad: The...Allan has some schedule, Allan can you stay until four or five or...?

Henry Greely: No, we're actually Shabbir - I would like to rearrange it so that he can - so we can go to that as topic.

((Crosstalk))

Shabbir Ahmad: Okay, okay. So you know, that's fine. Yes, that's fine (unintelligible).

Henry Greely: Largely out of courtesy to Allan, I'm afraid....(unintelligible).

Allan Robins: Robins.

Henry Greely: Allan Robins who is here from Novocell the successor in interest to BresaGen one of the two companies specifically mentioned, whose stem cells were specifically mentioned in the Streiffer article.

Anybody on the phone have any objection to taking agenda item six next?

Man: No.

Woman: (Fine).

Henry Greely: Hearing none, let's go to agenda item six, a little background on...

((Crosstalk))

Henry Greely: Rob Streiffer's article which you've all seen and looked at the consent form, which he actually had to get from a Freedom of Information Act request to NIH, and they were not very forthcoming in terms of all volunteering them.

Fourth, stem cell lines that were NIH approved from six different sources, Rob's article found concerns about all of them, I think, it's fair to say but particular concern about the stem cell line created by two companies, Cellartis and BresaGen.

This has prompted a fair amount of discussion around the country in terms of what the appropriate response to that is. There's a statement from CIRM that I will ask Geoff Lomax, didn't know I was going to do that Geoff, to say a word or two about in terms of the treatment of these lines.

And it seemed like something that would be appropriate for our committee to discuss. Having said that, it's not clear to me whether our committee should or even can try to amend the guidelines with respect to this or set out some other statements with advisory reports, with something - intending to have more than advisory report. I don't know what, if anything, will come out of today's discussion of this.

But it's an interesting and I think important issue, one in which not all the fact - one of the traditional facts that have been trickling out since the Streiffer article.

And I think it would be useful certainly for us and perhaps for SCROs and other interested parties around the state and the country that they add some discussion to this issue.

Geoff, would you say a word about CIRM to this that CIRM statement in your reading in the folder (unintelligible) members by the DPH...

Man: (All right).

Henry Greely: (Unintelligible) Call you DHS.

((Crosstalk))

Geoff Lomax: Sure, thanks for the opportunity to present to you all.

We had received a number of inquiries about the status of the lines identified in the article particularly, the BresaGen line and - well, the two lines in question.

And I think what had happened from our perspective is that the conversation had sort of carried on, (professionally) I think there were some sense in the research community that in fact we were going to act on these lines. And so really the statement from us was to clarify that what - we had no intention at this time to modify our regulation.

So we've pegged our regulations to the National Academy's list so - and that was a policy decision. It was a policy decision, recommendation that came from our standards working group, endorsed by our governing board, the ICOC.

So for us that's the policy decision that has been made. We have not been asked to revisit that by the board and it has not been taken up by the working group. So at this time, we really wanted to clarify that our (unintelligible) policy was and that it remained pegged to the NIH (unless) should the NIH act on this that would immediately impact whatever lines are available to our grantees, but just again to clarify our policy decision have remained - our policy remained based on sort of the NIH position.

Henry Greely: So this maybe a question that didn't come up in the CIRM deliberation. But is it appropriate - the way I understand the CIRM policy, it says our regulations still say this - that being this way fits our regulation in terms of being appropriately derived - acceptably derived of - or useable stem cell lines.

Is this - it's not my understanding that it's - as Stem Cell Research Oversight Committees in California have to allow these lines (unintelligible) is that your understanding?

Geoff Lomax: That's absolutely, in fact that question has come up a number of times and we've always advised folks who would pose the questions that the Oversight Committee certainly have - it's within their sort of authority to indicate that certain lines should not be used and that's within their - certainly in the context of research which they would - they're responsible for approving, they could simply not approve the research based on some fundamental objection.

And the language in the regulation does give some latitude there to say they are to evaluate on sort of scientific and ethical basis. And I think that's the language that gives the latitude to - an oversight committee to have some, you know, to use discretion there.

I think the other thing to keep in mind is we did in the latest round of revisions there is, if you noticed, there is a slight decoupling where we have the concept of an authorized authority for stem cell lines and that's where we talk about - we talk about authorized authorities and then go through and give a series a lists, if you will, of authorities such as the United Kingdom HFEA, the NIH, et cetera. And then we have the concept of derived under these conditions.

And part of the rationale behind that decoupling was the recognition that there was an inherent tension sometimes between those lists and the conditions under which stem cell lines have been derived and the letter of our definition of what constitutes acceptably derived and to sort of in a sense either alleviate some of that tension we've sort of - there's kind of a branch, if you will, in the regulations recognizing that these things should not be equated entirely as equal, but there - per policy purposes, there are some differentiation that, you know, needs to be thought of.

So that comes across in our latest revision.

Henry Greely: And it's also from my review of the NAS amendment as far as I can tell, the NAS amendments don't really speak to this issue. Is that fair? My review of this is fairly short, but as far as I can tell - in part I think because this issue really become visible (unintelligible) well into their drafting stage.

I don't know whether they would have addressed it even if it come up earlier but the article first came to I think a lot of people's attention in late June and the NAS already had a draft distributed for review at that time of its amendments.

David Magnus: I just want to get question for clarification for something in the future. With this new sort of bifurcated approach between sort of the descriptions of what

sort of counts as acceptably derived versus what's acceptable by virtue of being part of an authority, if one of those accepted authorities pays for embryos, is that going to be okay by virtue of the fact that it falls under the authority going forward or would that require (unintelligible) an adjustment to the regulations?

Henry Greely: Payment for embryos is being otherwise...

Man: Yup.

Henry Greely: ...banned in the CIRM regulation.

Geoff Lomax: That's right. I mean...

Man: (That should)...

Geoff Lomax: ...that's upon - I mean, let me just say at the forefront, the initial intent really was to - so the recognition that a set of historic materials was very difficult to reconcile against the moving forward standard.

So the listing really helped I think in at least a policy way to create a clean demarcation between we know they are materials that came into existence prior to 2006 when these regulations took effect that are generally utilized in research and should continue to be used in that regard.

Now, again, to get, that raises, you know, a fundamental, you know, problem there, and it is conceivable that in certain jurisdictions issues of payment or compensation may create a tension between the jurisdictional policy and the standard for if you were to do that derivation as a CIRM grantee.

At the moment, we have - we are not aware of any example where we are confronting that. However, as that - if that situation were to arise, I think that would be a discussion where we simply have to revisit. This is a, you know, again, a point where there's always a bit of friction between, you know, a standard that's trying to accomplish something, you know, within the regulatory context.

But things don't kind of always line up exactly right. Now I just see that as where we, again, come back to the process to resolve it, and I would hate to sort of tell you here today what that answer is going to be knowing that I'm going to need to defer it to the process to resolve it.

David Magnus: Okay, so it wouldn't be just, there would be discussion about how to resolve that as opposed to just (unintelligible) regulation (unintelligible) what do we have here if regulation say this, and that's (unintelligible) I was thinking of the UK thing but we need to have things (unintelligible) the definition would be sort of approvable by virtue of...

((Crosstalk))

Geoff Lomax: That's right. I would be surprised if we were not to have that conversation. I think the problem is we can't predict the future and we're trying to sort of balance a rational research program with the reality of the materials that are available to support that program and this is where we ended up.

Henry Greely: And we can always predict the future, we just can't be sure we're right.

((Crosstalk))

Henry Greely: Usually you can be sure that we're wrong.

Well okay to just remind everybody listening, the particular issue that the Streiffer article noted with special force were the cell lines from BresaGen and the cell lines from Cellartis.

The consents which you received from NIH with respect to those have been distributed in the packets to members and are I think posted to the Web site, the Cellartis consent that we received seems to be a consent for culturing embryos for a few additional days and then destroying them and at least the consent he received doesn't do anything (unintelligible) cell lines and that was the concern he had expressed about the Cellartis cell lines.

The BresaGen consent he received from NIH was of concern because it appeared to be basically a clinical consent for IVF treatment with one sentence talking about potential users (unintelligible) from some of the materials but not the sort of consent that we are accustomed to seeing for human subject research.

To be fair it's not clear that at that point this would have been considered even subjects research under the common rule or that BresaGen or the in-vitro fertilization laboratory that performed these procedures would have been governed by the common rule the Federal Regulation that establishes the whole IRB system, but that consent did not go through the IRB, did not go through an IRB as far as Streiffer could tell. I think that still possibly right.

We have (unintelligible) the Streiffer article came out in June, there's been a lot of discussion of it, some additional facts have been accumulating over that time.

At some point, I think (second to the last) David Magnus would talk about that a little bit because he's just back from a stem cell meeting in Wisconsin (unintelligible) discussed in some length.

But before I do that, I think, you know, pending any questions or comments from other members of the committee, I think I'd like to ask Dr. Robins to say a few words. The committee invited Novacell, which is the successor in interest of BresaGen to be present at the committee meeting and give us their views on this issue. Not paying for his time and expenses, so we're very grateful that he was willing to appear and talk about this.

I believe that we made a similar offer to Cellartis, but I have not heard what happened with that. Amber do you know anything about that or Heidi?

Woman: (Unintelligible).

Henry Greely: In one way or the other the Cellartis did not - is not here.

David Magnus: It won't matter.

Henry Greely: Yeah. But we did make the offer sometime to Cellartis to come and talk. Question mark at the end of that, no?

Woman: Yes (unintelligible).

Henry Greely: Okay. So we offered BresaGen and BresaGen accepted and we are grateful. Any members either here or on the phone have any comments before we go to Dr. Robins?

Dr. Robins, the floor is yours (again), thank you very much for being willing to come.

Allan Robins: It's okay. My pleasure.

And what I thought I would do is walk you through sort of chronologically what happened at that time and I would - with the company the chief scientific officer and partially in charge of this program. So I have a fairly good understanding. Anybody would like to ask questions as we go along, please feel free.

Henry Greely: Can people on the phone hear him?

Woman: Yes...

((Crosstalk))

Henry Greely: Why don't you move closer to - well, actually we've got that microphone (unintelligible).

Allan Robins: Is it better?

Henry Greely: Okay.

Allan Robins: (Unintelligible).

Man: (Unintelligible) if you would.

Man: Sure.

((Crosstalk))

Allan Robins: So I thought I'd start up by just saying a little bit about BresaGen. BresaGen Inc. is a company that was set up in October of 2000. It's a Delaware corporation and a wholly owned subsidiary of BresaGen Limited. As you can probably tell from my accent, it's an Australian company. It's an Australian company that was listed on the Australian Stock Exchange and a publicly traded company listed in 1998. And that company had two franchises, one being proteon pharmaceuticals manufacturing and development and the other one being stem cell franchise.

And we made a decision at the board level sometime during 2000 to acquire a small company in the US that was headquartered in Athens, Georgia, and to set up a wholly owned subsidiary, and myself as chief scientific officer. So at the (unintelligible) meeting came to the US to run this facility.

So we really set it up to exploit human ES cell opportunity. So we had licensed some intellectual property in Australia. We already had a license from Wisconsin, from WARF, we were the first initial group next to Geron to have a commercial license from WARF. And they supplied us with their cell lines, but very early on the transfer and the growth of these cells was so much an art form that after about nine months, we decided that we should isolate our own cell lines because we'd been unable to get their lines to grow that they were transferring to us.

In late 2000 we met with an IVF Clinic in Atlanta, and we agreed that we would draft up an agreement to which would be the basis on isolation of the ES cells.

They also convinced us that it would be a good idea to use fresh embryos that deemed by the embryologist to be unfit for transfer or freezing as a source material to derive these cell lines.

And so, because they said, you know, these embryos occur every week, they use a certain amount of them for research purposes and, you know, (unintelligible) discarded.

And so, we drew up an agreement, the consent form and the agreement were overseen by our corporate lawyer and by our chief medical officer (Chris Shaftner). He was also the chief medical officer of his company, (Systemic) here in (unintelligible) had considerable experience with these sorts of agreements.

So in the consent form I sent to Shabbir so I assume that you all have a copy of it.

Henry Greely: Yes.

Allan Robins: We believe as far as we could tell from the draft guidelines that that consent form followed those draft guidelines pretty closely except for the fact that the draft guidelines were drawn up for the use of frozen embryos.

And so, in the draft guidelines, there was supposed to be some temporal distance between consent for IVF process and consent to donate embryos to derive stem cells.

Here we had a situation where embryos were being fertilized and five days later decisions were being made by an embryologist about whether to transfer, to freeze or to discard and use for research.

So, you know, within that process, this differed from the guidelines, but we think the rest of the consent pretty much falls within the guidelines that existed at the time and of course, this consent - is there a question?

Man: (Well)...

((Crosstalk))

Allan Robins: Okay. So this consent was supposed to go along with the IVF consent, which to our knowledge the IVF consent had been through an IRB. And I thought it was Western, but now I think it's (Northside IRB) that approved that.

Henry Greely: Just make sure that everybody is clear the documents of consent that you guys drew up is this one-page, two-sided...

Allan Robins: Yeah.

Henry Greely: ...(unintelligible) one piece of paper document and it exhibits one patient consent.

Allan Robins: Yes.

Henry Greely: (Unintelligible) handwriting in the upper right corner, BresaGen intended informed consent form, right?

Allan Robins: Right.

Henry Greely: Okay. Good.

Allan Robins: So we signed that agreement with the IVF clinic in early 2000, I can't share the agreement with you. I went back and looked at it. There are confidentiality clauses included in the agreement. Which don't allow me to share, but I can tell you that the agreement obligated the IVF clinic to obtain consent for ES cell derivation before they handed embryos over to us.

We commenced isolation in January of 2000, and we were immediately successful. So - and I can tell you we used space at the IVF clinic for the isolation because BresaGen itself rented premises from the University of Georgia and the University of Georgia were uncomfortable with us deriving ES cell lines on their premises. They were worried about their NIH funding, so they asked us, could we do it somewhere else.

The IVF clinic kindly donated us some space that may not be used for (week). We paid some rent for that and we paid for all our consumables and things of that nature, so we put a post-doc down in the IVF clinic and she was down there for two or three months.

Once we had isolated the cell lines we started work on characterization and our particular interest was in Parkinson's disease so we started differentiating the cells for dopaminergic neurons.

At this point in time, NIH was not on the same. We didn't know what President Bush was going to do in terms of the decision. But some time in June, NIH contacted me and they were trying to do some homework to find out basically how many ES cell lines existed around the world.

And they said, "they didn't know what the President was going to do, but one of the possibilities was that he was going to grant fathering in lines that already existed." And so, we said, fine, we told them. At the time, we had four

lines, we subsequently lost one so now and then we had three lines, BGO 1, BGO 2, BGO 3.

Sometime in July, so this is six months down the track after isolation, NIH said that, you know, this was most likely to be the President's position that he was going to grandfather in, we didn't know when he was going to make that decision, but they needed to know that the cell lines had been ethically derived and so they asked for the consent.

What gave them was the consent that Streiffer cites in his paper and we also showed them this consent form. I was uncomfortable at the time giving them the consent form because we had worked with this IVF clinic (unintelligible), you know, that had been gracious enough to let us use their premises.

The only thing they got out of this was I think, one, maybe it was two of their people were authors on the paper when we published it, but they got nothing else out of it.

But which when NIH asked for the consent that it became apparent that the IVF clinic had not done what it had said it was going to do and had these consents signed.

They - I mean, we asked them why? Their reason was that at the time of this IVF procedure, they did not want to put their patients under extra stress and they thought this would cause them extra stress- more paperwork to sign. They told us that they had globally consented the patient and I had a letter from them that actually says they verbally consented the patients, but that letter has some inaccuracies in it. So I would not for one swear to the veracity of this statement, so I wanted to (unintelligible) people.

So we weren't told about this, obviously until six months after the fact, after we'd derived the cell lines and even though the IVF clinic was contractually obligated to obtain the written consents, they didn't and being pragmatists we kind of moved on, we explained the situation to NIH. They decided that the consents were okay, some see that as political expediency, but there are other ES cell lines derived at the time, which were derived from embryos and not by us but by third parties derived from embryos created for the purpose of making ES cell lines, and they did not put those ES cell lines on the President's list.

So they didn't put on every ES cell line that existed at that point in time. And as I said just in closing, I have a letter from the IVF clinic from one of the directors of the clinic, a 2004 letter saying that the patients were appropriately consented, but I haven't shared that with you because I don't think it's reliable because there are other things in there I know that's inaccurate.

Henry Greely: Thank you, Dr. Robins. Are there (unintelligible) said another person joined our meeting. Ma'am could you identify yourself for the members (unintelligible)?

Justine Durrell: Sure. Justin Durrell.

Henry Greely: And are you... (unintelligible)?

((Crosstalk))

Justine Durrell: I'm an attorney out of San Francisco. And I came to see what was going on.

Henry Greely: Welcome.

Justine Durrell: And I couldn't find the place for half an hour, but here I am finally.

Henry Greely: Then probably couldn't find a parking place (unintelligible).

((Crosstalk))

Henry Greely: We try to be hospitable bunch here at Stanford but the university seems to destroy parking places better than anything else. Which I understand is kind of the general characteristic of universities around the world.

Man: Yeah.

Henry Greely: So Dr. Robins, thank you. Questions for Dr. Robins from the table or from the phone?

David?

David Magnus: I want to - thanks again (unintelligible) for coming (unintelligible).

So just to be clear when they said that they - in the letter that they had given consent, obtained consent orally but not in writing, they told you that they had (unintelligible) orally gotten consent with the elements...

((Crosstalk))

Allan Robins: Right. They told us at the time, 2001, that they verbally consented the patients. The wording in the letter actually says that the patients were appropriately consented, but there are other things in that letter, which I know to be inaccurate, so (unintelligible) bringing down the track (unintelligible)

this was the guy who signed the contract and was the guy that we
(unintelligible) at the clinic (unintelligible).

Henry Greely: Presumably since we're using fresh embryos for the research, these patients would have been consented shortly before in or shortly before January 2001 when you derived the lines, right?

Allan Robins: At that time, yes.

Henry Greely: Within a couple of days probably of your...

((Crosstalk))

Allan Robins: (Unintelligible) yes, I mean, when they collect a fresh oocyte they do the IVF procedure and five days later the embryo was (unintelligible).

Man: (Yeah).

((Crosstalk))

Radhika Rao: So, I'm not sure that I understand, but there are two consent forms here and so is it Exhibit 1, the patient consent form or the material that was sent in our packets, patient consent for therapy, human IVF and embryo transfer Item 1?

Allan Robins: So the consent form that we talked about secondly, which I don't have in front of me, but that is the IVF clinic's own consent form.

Radhika Rao: Yes.

Allan Robins: And within that consent form, there is a (unintelligible) talking about using the embryos of insufficient quality (unintelligible).

Radhika Rao: Yes.

Allan Robins: So that is a consent form that the IVF clinic used, that has nothing to do (unintelligible) nothing to do (unintelligible). And this is the consent form they were using because they themselves were doing other research on those embryos trying to improve culture techniques and things of that nature.

Henry Greely: So that was the informed consent form that was signed...?

((Crosstalk))

Allan Robins: ...This is the consent form that was signed by the patients.

Radhika Rao: Was signed by the patients, okay.

Allan Robins: This consent form (unintelligible) to our agreement with the IVF clinic so this Exhibit 1, this is the consent form that we put together based on the guidelines that was supposed to be signed along with this consent form.

Radhika Rao: But it wasn't?

((Crosstalk))

Radhika Rao: Okay, now (I'm lost).

((Crosstalk))

Allan Robins: This is now the IVF clinic did not present this to the patients even though they were obligated to do so by the contract that they signed with us.

Henry Greely: So to be clear, it wasn't that the patient saw that and refused to sign it – it's that it was never presented to the patient...

Allan Robins: Never presented.

Henry Greely: ...in spite of the fact that per your agreement...

((Crosstalk))

David Magnus: Here is (unintelligible) they claimed that they did orally communicate with us and (unintelligible), but we're not sure...

((Crosstalk))

Radhika Rao: Okay. I get it now.

((Crosstalk))

Allan Robins: That's what they claimed.

But, you know, we were kind of hostile at the time because we had thought we put something in place and you would have thought if they weren't going to...

((Crosstalk))

Allan Robins: ...in writing (unintelligible) discuss it with us (unintelligible).

Henry Greely: (Unintelligible) well understand how you must have felt when you found that out.

Did you - BresaGen give any consideration to trying to locate and re-consent the donors of the embryos that, at least the ones successfully used to make...

((Crosstalk))

Allan Robins: Yeah. So what they did very well was anonymize, and so we just got embryos. We gave numbers (unintelligible). So we would have, any IVF clinic, would have no clue as to who we should be consenting.

Henry Greely: (Although you'd have) (unintelligible) a time frame, you'd know that it was somebody who came in within a couple of days of a particular day?

Allan Robins: Right, but no, the thing is the isolation process is inefficient and so we used, I think, it's 25 or 30 embryos to isolate the three lines and so, whose embryo derived a line and whose embryo didn't derive the line...

((Crosstalk))

Allan Robins: ...(unintelligible) you just can't consent to everybody and say your embryo may have derived a line but it may not (unintelligible).

Henry Greely: (And sort) (unintelligible) may have been disconcerting I think for them but also if you've got 29 out of 30, you still would not be able to say with any certainty that you've got three.

Allan Robins: Yeah.

Henry Greely: Probably you actually could if you went to enough trouble - go through enough trouble to genotype the parents and the cell lines...

((Crosstalk))

Henry Greely: ...but that would take not a trivial amount of additional effort.

And the parents might - you know, the parents that the donors might - well, not be interested in that.

Allan Robins: But, you know, this - and we were isolating the cell lines we were trying (unintelligible) abide by guidelines that existed at the time. It was completely unanticipated at that point in time that these cell lines would end up on that around the US and the rest of the world being used by researchers, I mean, we didn't set up to distribute these cell lines, we wanted them for our own research and development.

Henry Greely: Now, this - I recognize you may not be able to answer this question because of proprietary - I may be seeking something (unintelligible) proprietary information. Can you tell us anything about how widely distributed and used these particular cell lines are?

Allan Robins: We did over - I think we did about 120 distributions ourselves and since then, we have given others - because, you know, in a company setting you're kind of treading water you're not doing anything while you're distributing cell lines.

So we empowered other groups that had NIH grants to set up centers to distribute locally. So there's a center in Seattle that distributes our cell lines up

there and now, the national stem cell bank (unintelligible), they've only just come online, so they have not distributed any of them.

Henry Greely: Do you have any information you can share with us about how many of the lines, how many copies of the lines have been distributed by those other entities?

Allan Robins: No. I don't have track of that.

Henry Greely: Okay.

Allan Robins: But I think apart from the WiCell lines and the ESI lines, the BresaGen lines are the most published (unintelligible) use that as the method of how widely used they are. I think we're pretty even with the ESI lines for certain application.

Henry Greely: As a member of the Stanford SCRO we've seen - I've seen and David another member - quite a few protocols come through. We haven't seen the BresaGen lines used much at Stanford, but Stanford is just one site.

Allan Robins: I think there are at least two researchers here who have the lines (unintelligible).

Henry Greely: And we've seen two protocols out of 40 protocols (unintelligible) 50 protocols something like that.

Dr. Lomax, do you have something to add on to that?

Geoff Lomax: Well to add to that, I mean, we've conducted a similar sweep of our data, which are somewhat limited because what we have are data where we record

the lines that researchers have proposed to use and we have subsequently learned that what goes into initial proposal doesn't correlate exactly with what comes out at the other end.

But we've seen ratios, even smaller ratios than they are sort of one or two and 40. We've seen very little indication that these lines are sort of substantial and I think - (unintelligible) what comes to mind is for the application indicated interest in the line but that doesn't necessarily mean they're being used.

So these are sort of lines that appear to have (unintelligible) much less interest than say something like an H9 or a line that's widely distributed (unintelligible).

Henry Greely: So in fairness, the (unintelligible) between the proposal and the reality runs in both directions, so some of the proposals that didn't mention BresaGen line might actually ended up using them.

Geoff Lomax: That's right and we're - and just for reference in the future, we're - intend to approve a tracking of this type of information for exactly this type of reason, so we're coming back to institutions with we're going to start looking at tracking the actual approvals of lines that are in use in research, so.

Henry Greely: I haven't forgotten everybody on the phone, but I'm going to hog one more question before (unintelligible) the phone or anybody else in the room wants to ask some, Exhibit 1 the consent form that you expected and contractually obligated the idea of coming to you. Had that gone through an IRB...?

Allan Robins: No, it has not.

Henry Greely: Had you given any thought to consideration as to whether it should go through an IRB?

Allan Robins: We did.

((Crosstalk))

Allan Robins: Yeah, we talked about that quite a bit, but we - I mean, again, it was expediency. That was going to take us three or four months. And we're a small biotech company bringing money in (unintelligible). We needed to get things done.

So the other point I wanted to make in terms of the BresaGen lines while it's certainly not as widely used as the Wisconsin lines, there are a number of people making genetically modified lines, Invitrogen being one of them and they already have two of those lines for sale.

So I think and we've had a number of deals with Invitrogen not only around the lines we developed a defined media (unintelligible) in one of two defined medias on the market (unintelligible), and they (unintelligible) a new effort into making genetically modified lines with the BresaGen cell lines, you know, I know that has nothing to do with moral and ethical considerations, but it's why I'm prepared to sort of come over here and talk to you and tell you and share things with you that we haven't necessarily shared before because at the end of the day, we wanted to be pragmatic and move on and not disadvantage the IVF clinic in any way, and they presumably made a decision, a spur of the moment decision which they thought was right and - but, you know, Invitrogen (unintelligible) genetically modified the BresaGen lines, and so.

Henry Greely: Let me give a chance to any of the members on the phone to ask questions of Dr. Robins.

Bernard Lo: Well this is Bernie Lo. Actually I have two questions if that's okay.

Henry Greely: Sure.

Bernard Lo: First, I want to thank Dr. Robins for coming and presenting us this information. Extremely useful to sort of have this information rather than just the document.

I have two questions. One has to do with the scientific value of the lines. It strikes me that clearly there are some things about the donation consent process that we all wish had been a little different. That can't be changed. So I guess one question is, are there things about this line that are particularly useful going forward starting with the original lines. I understand that Invitrogen and others have made genetically modified lines which may be useful to use.

But for researchers just starting out with the original BresaGen line sort of can I get a sense of the particular things about the line, is it robust to - does it grow robustly is it easy to take care off, things like that?

And the second question, this is a tough question because clearly it's sort of what if, but I understand and I appreciate the sort of the speed of which things were happening when you derived these lines.

But you have this arrangement with the IVF clinic to have them get a signed consent form and then they sent you presumably the frozen embryos, obviously, without a consent form.

Was there a consideration at the time of saying, well, thanks very much we've got the embryos, we're working on them but, you know, we'd really like to have those signed consent forms for documentation to protect ourselves as a company down the line, you know, to be able to document everything?

So could I ask those two questions, I'd appreciate it?

Allan Robins: Right, the first question about the utility of the lines – two of the lines make neuro cell type so neuroectoderm very efficiently, but I understand there are other lines that make neuroectoderm pretty efficiently too, but BGO1 and BGO2 make neuroectoderm very efficiently.

And, you know, that in my experience - that's about it.

((Crosstalk))

Allan Robins: In terms of the culture and things of that nature, I think with the development of defined media with understanding signaling pathways that drive proliferation and self renewal as opposed to differentiation that in our opinion 99% of the lines are very easy to grow now.

They behave very robustly in culture, so I think (unintelligible) there was information about this line being easier or that line being easier, had to do with the fact that culturing the cells was very artful at the time, and it had to do more with the skill of the handler.

But now that we've - a few years gone down the path, with single cell passage these things we grow them as large mono layers, we ourselves are growing over 10 to the 10 cells in a single batch, you know, very homogenous, very

undifferentiated (unintelligible) there are two defined medias out there in which the cells grow very robustly.

Bernard Lo: Uh-huh.

Allan Robins: So the second question just to go back on the point, these were not frozen embryos. These were fresh embryos...

((Crosstalk))

Bernard Lo: Exactly, that's right, uh-huh.

Allan Robins: ...and we were working - he had a post-doc within the confines of the IVF clinic and the work to derive those four cell lines all took place within three or four weeks. So we had immediate success and the cell lines were derived more or less immediately.

And so it's a reasonable question, shouldn't we have asked for the consent forms to be anonymized and given to us and certainly that was the intention at the end of the day but, you know, it happened so quickly, that the answer was no and basically in real time the embryologist was grading embryos. And embryos that weren't of sufficient quality if there are any there on the day our post-doc was ready to accept them and start the derivation process.

So when you freeze embryos, of course there's time to think about all those other things because you can start the derivation process at will but when they're fresh, you start the derivation process when they are available and sometimes they're within the middle of the night, so that's how it was.

((Crosstalk))

Henry Greely: So what made this a little different was your post-doc was actually in the clinic. It's not like these embryos got shipped from the clinic to BresaGen...

Allan Robins: No.

((Crosstalk))

Henry Greely: ...BresaGen office some place where they came in with the shipping forms somebody walked them over to her?

((Crosstalk))

Allan Robins: Right, you know, there were a lab away.

Man: Yeah.

Allan Robins: And so, you know, yes, we originally wanted to do that, but we talked to the University of Georgia where we were renting premises and they said, we did not (unintelligible)ES cell lines on our premises.

Henry Greely: Bernie, do you have any followups...?

((Crosstalk))

Bernard Lo: No. Thanks very much. That's helpful.

Henry Greely: Other questions, from members on the line (unintelligible)?

Man: No, thanks.

Henry Greely: Okay. Not hearing any, Dr. Robins, thank you very much for your presentation.

Allan Robins: Okay.

Henry Greely: You're certainly welcome to stay for the remainder of our session or however much of it or as little of it as you wish to.

Let me now open things up to the committee members for the discussion of this and, David, if I can, I'd like to like to start with you because it sounded to me from our communication that you actually learned something, a fair amount at this Wisconsin meeting that's relevant.

David Magnus: Well the Cellaritis lines (unintelligible) - that the consent form that the NIH have on file, which would clearly not have been adequate, were deemed not to be adequate by Cellaritis as well.

And so they re-consented all the people prior to derivation.

And so the updated consent forms, which are available on the Web site of, they may be (unintelligible) name of the journal, but they are available on the Web, but in any case they do meet the standards of the time and Rob has discussed that. And I think it may be on Rob's Web site, so he's now put up a posting saying that's the Cellartis cell lines in fact do meet the standards. It's (unintelligible).

Henry Greely: Just out of curiosity, do you know whether Cellartis gave the updated (unintelligible) consent to NIH and NIH just didn't give them to Rob or whether...

David Magnus: That is unknown. And by that I mean Rob does not know (unintelligible).

Henry Greely: Other comments on this issue?

Radhika Rao: Is the original Cellartis consent form the one that we have Item 2?

Henry Greely: Correct.

David Magnus: (Yeah).

Radhika Rao: Okay.

David Magnus: Yeah. So that was not the final consent.

Henry Greely: And I think it doesn't take a very deep examination of that consent to see it's deeply problematic as a consent for creation of human embryonic stem cell lines, because it never says anything about creating human embryonic stem cell...

Woman: Yeah.

Henry Greely: ...or any other very broad use. So, David, it's your conclusion based on what you've heard and you actually saw the updated Cellartis consent?

David Magnus: Yes, I just can't remember what Web site (unintelligible).

Henry Greely: So you think then that it's your view that as a result of those consents maybe which maybe meet the standards at least of the day (unintelligible) that don't meet the standards of the CIRM regulation as of now or our guidelines as of

now, but they meet the basic fundamental informed consent standards as of the time they were derived. So you think they don't present any ethical concern at this point?

David Magnus: Correct. And that is by, and Rob Streiffer agrees with that too (unintelligible).

Henry Greely: So on the BresaGen lines, Dr. Robins presentation was very candid and I appreciate it and I'm very sympathetic to BresaGen's situation here.

The fact remains that you didn't get this, that there aren't signed consent forms from the donors of this material that would seem to me the standards that even at that time would have been applied and that BresaGen itself wanted to see applied to those.

BresaGen seems to have tried its best or at least tried hard, made reasonable efforts to get (unintelligible) consent, did not go to make unreasonable efforts, but pushed extraordinarily hard for it, but made reasonable efforts to do it, but should that affect the ethical status of these lines now seven-plus years almost to eight years after they were derived. I think is the interesting question and then a subsidiary question there is to what extent is the - should this committee be interested in, or should anybody be interested in that? So I'll put those two questions on the table and open it for discussion on that, David.

David Magnus: So one piece of information that's new for me that I think was helpful is the possibility, though far from certainty, that in fact there was adequate consent at the time through verbal (unintelligible) really no requirement, you know, looking at the guidelines our requirements for consent that ASRM had in 1999, sorry, 1997 and the NIH embryo research panel guidelines for 1994 that - both of those would have been in play. But I'm not sure that those would have required (unintelligible).

I respect the fact that the easy way out for BresaGen would be to say, you've got this letter saying that they were done, you've got an agreement in advance so they said that they did it orally, you've got that they were going to do orally, they said they did it adequately, should actually got out of the documentation from that point of view and I respect the fact that you left it open that you're not really confident that it's necessarily true and that you've been very honest and I'm nervous about punishing you for being extraordinarily honest.

Allan Robins: I'm not saying it's untrue, I'm just saying that part of the letter is incorrect.

David Magnus: I understand and appreciate that. But at any rate, so one question is whether or not there was in fact adequate consent and it seems to me that's it's now somewhat uncertain. They might or might not have had adequate consent even if it wasn't adequate (unintelligible).

There's also no question that it wasn't optimal consent. I can tell you that there was a lot of - at the Wisconsin meeting of the SCROs. We really went through the arguments in some detail, favor and against using some of the lines that didn't meet the standards at the time for having consent.

Now, I'll say that, you know, it's complicated. There are some convincing arguments obviously Rob's got a very coherent set of arguments I've got these things, we're working on mapping these out and we're hoping to publish something that gives some guidance.

But I - we ended up (unintelligible) being myself and Norm Foss, Alta Charo, and Rob Streiffer and a few other SCRO members. I can tell you one thing that I would recommended that - as a possible way of thinking about it, taking

advantage of some of the other guidelines that we saw by NAS and by CIRM which it seems to me that the prudential argument, just my argument, which is why I feel comfortable sharing it, which is that if there's some question about the ethics of the line, where's there's a legitimate question on whether it should be used (unintelligible) potential interest to it that there needs to be a scientific - a good scientific reason for using a line that has that kind of functional (unintelligible).

So if I was thinking about guidelines, at a minimum for guidance that I would give to SCRO's in terms of guidance it would be analogous to what we do currently for the use of creation of embryos or the destruction of embryos that SCRO's should require investigators to give some justification for why they need to use a line for which the consent was somewhat questionable.

And if there's no justification for that, then prudence dictates that they'd be better off using, all things being equal, a line that does not have those questions raised about it. But there is a good reason for using the lines like for example that it's been genetically modified to meet with (unintelligible) useful in a way that other things are not or if it turns out they are better than other lines for certain types of research.

Perhaps you've been using this for the last three years that you're familiar with it.

Man: Correct.

David Magnus: So there's some reason that you can give for why you want to do it that's a sufficient rationale that that would be a legitimate way to move forward.

Henry Greely: That's an interesting argument. It seems to me that it also applies perhaps a little less for all of the pre-2005 or 2006 CIRM regulation lines. All of which were done with consents that are less good than we would like today but that were adequate that one could say you've got a choice between the 2003 line with non-optimal consent and a 2007 line with great consent and scientifically you're equipoised it would be a better idea to use, the ethically more secure one.

David Magnus: I think that's right. I think the fact that the earlier lines were better characterized was why they typically wound up used so they should be able to articulate that as a rationale (unintelligible).

Gregory Stock: And are there - two questions, Greg Stock, are there any ways of going back and trying to improve the consent online and what do you see as the - I mean, you've mentioned that the situation in equal (unintelligible) perhaps once you go with the better consent, ones with preferable consent but what are the, you know, the dangers of proceeding with the line that in fact has some sort of a questionable consent associated with it, maybe it's familiarity, maybe it's price, maybe there could be all sorts of things that are, you know, rather subtle and maybe would not rise to a level that a SCRO would be interested in.

So those are two questions basically it depends how you weigh those external sort of evaluation of the reasons and the second is, is there a possibility of going back. I mean, what are the dangers associated with just leaving them in place?

Henry Greely: Well I think in terms of just going back from what Dr. Robins said it sounds like it would be difficult not necessarily impossible, you might if the IVF clinic has maintained decent records figure out who the 30 couples were, who came in in the relevant time frame or maybe the 50 couples who came in the

relevant time frame during which the 30 embryos you used were created, go seek their permission to do at least some minimal genotyping of those - of at least one of those two potential parents and compare that to the genotyping of the cell lines I think that's conceivable...

((Crosstalk))

David Magnus: (Unintelligible) It's been enough years that the possibility you're going to track down all those families (unintelligible).

((Crosstalk))

Woman: Yeah.

Henry Greely: You could pretty much guarantee that you won't track that...

Gregory Stock: Because they were basically - I didn't hear that part, they were anonymized from a cluster of some 30 to 50 couples, is that what happened?

Henry Greely: We don't actually - I'm not sure that we know how many couples, BresaGen used 25 to 30 embryos to make this - the embryos could have been used by BresaGen within a couple of days of their creation.

Gregory Stock: I see, okay.

Henry Greely: In the time window during which the BresaGen was doing the work that led to these lines, if the clinic kept records of who their clients were or patients were during that period, you might be able to identify that universe from which those lines those embryos would have come but probably not on one to one

basis and going from there to finding those people getting their consent, tying it down genetically, it's not impossible but it...

Gregory Stock: It doesn't sound like it. Yeah.

Henry Greely: Not easy.

Gregory Stock: Not very feasible.

Allan Robins: It's certainly not something the company is going to do. I mean, it's not...

Henry Greely: Yeah.

Allan Robins: ...commercially viable and we mostly are working with other lines that we have derived anyway.

Gregory Stock: Uh-huh.

Henry Greely: I don't know whether that came through loudly enough since Dr. Robins has moved.

Gregory Stock: Yes, I heard that.

Henry Greely: Yeah, and it's a point I should have made myself, and an obvious point, but for the company to go back and do this extraordinary effort....

Gregory Stock: Well of what value are they to the company on a commercial level? I mean, the company - it clearly has dealt with some broader associated with - issues associated with them. It could dispose of them if it wished to, what is the commercial value to the company?

Allan Robins: It's very little at the moment. I mean the cells are being distributed by the national stem cell bank and we get something out of that when they distribute a cell line, but I think it's 25% of \$5000, whatever that is, \$1250, what is it...

Gregory Stock: I see, okay.

Allan Robins: And also we have deals with Invitrogen where Invitrogen are making genetically modified lines but, you know, one has been available for - well for over a year, so it's the one that I know about income on and the income is less than \$10,000. So in a company that spends a million dollars a month, it's not...

Gregory Stock: Right.

Allan Robins: You know, I'm more trying to - coming forward now telling the story trying to protect downside for Invitrogen who has put a lot of work into this and I feel somewhat morally obligated to try to at least tell the story so that people can draw their opinions based on facts.

Henry Greely: Other comments from members at the table or who are on the phone, comments or questions? Bert?

((Crosstalk))

Bertram Lubin: Well I wanted to bring up, it's not specifically related to this but in a recent announcement from CIRM about opportunities to do research with other programs throughout the world in partnership where money comes - let's say Stanford has as a program and Melbourne has a program, the money won't go to Melbourne but materials might be shared.

We might want to be thinking about when that happens how were those materials obtained and is that something we should be thinking about before we get into looking at these kinds of applications because they're actively looking in places where (unintelligible) might further the goals of the stem cell research. I mean, this is not the same thing, but it actually has some similarities.

Allan Robins: It's very relevant. I mean, we are going to apply for a grant with a group from Monash which (unintelligible) cell lines, which way I don't know, but certainly materials will go one way or the other.

Henry Greely: Well I think in terms of the guidelines from Department of Public Health, those guidelines apply to research - certainly apply to research in California that's not exempt because it's purely CIRM funded.

Bertram Lubin: Right.

Henry Greely: It's always a tricky issue but I suspect it would not apply to research done by Californians outside of California...

((Crosstalk))

Bertram Lubin: No, I was actually thinking the lines would be coming, let's say from Monash to Stanford (unintelligible)...

((Crosstalk))

Henry Greely: But if it's done in California, I think they do have to meet...

Bertram Lubin: The criteria?

Henry Greely: ...to meet the criteria in the guidelines to be acceptably derived and I would think although I'm looking now at Dr. Lomax, I would think that if it was done with CIRM funding, they're going to have to be acceptably derived no matter where they're from or where the research is actually being done if CIRM funds are being used (unintelligible) understanding.

Geoff Lomax: Yes, that's correct.

Henry Greely: And it's a long way to say it, though right?

Geoff Lomax: But I think it's (unintelligible) clearly spelled out in grants administration policy that says anyone receiving CIRM funded researchers must comply with all and including these guidelines.

Man: Okay.

Geoff Lomax: Yes.

((Crosstalk))

Henry Greely: Radhika?

Radhika Rao: No, I think somebody joined us.

Henry Greely: Is there somebody new on the phone or - somebody said...?

((Crosstalk))

Radhika Rao: Somebody said hello.

((Crosstalk))

Shannon Smith-Crowley : This is Shannon Smith-Crowley from ASRM, and I'm in my car so I have it muted so it takes me a second to change over, but I'm just listening.

Henry Greely: Okay. We welcome you. I'm afraid I've forgotten her name, but you have an assistant here (unintelligible)...

((Crosstalk))

Henry Greely: You've been represented even if you haven't been online.

Shannon Smith-Crowley: Okay. Thanks.

Henry Greely: Other comments from committee members?

Dr. McLean?

Margaret McLean: I just want to follow up on what David said. I'm inclined to think where we've had instances where we're not certain how robust the informed consent was or if it even was "adequate" that there should be a good argument made on the part of the group that wants to use that particular line as to why that line must be used as compared to another one for which we do know that we have appropriate consent.

Ands so, you know, some type of principle that says, you know, use sorts of lines where the informed consent processes is of question, you know, only if

this research cannot be done on another cell line and it's a sufficient, you know, help to, you know, (unintelligible) science along.

Henry Greely: Yeah. One of the things that makes our current situation I think particularly tricky or conflicted and David had mentioned this to me before the meeting, but I now understand it much better, since the only cell line that currently seems to be in some question or significant question is the BresaGen line and yet it seems from Dr. Robins' presentation that BresaGen really tried to do the right thing.

((Crosstalk))

Henry Greely: I'm sorry, the three BresaGen lines...

((Crosstalk))

Allan Robins: Yeah.

Henry Greely: But with respect to all three of them and the fourth that is now defunct.

It looks like BresaGen tried to do the right thing, and so it's a very sympathetic party here and one hates to take action or to recommend action that might disadvantage somebody who actually tried to do it well even though through factors that seem to be certainly at the very most very little of their responsibility and perhaps not their responsibility at all. It didn't turn out that way.

Allan Robins: Well we could have asked for the consents...

((Crosstalk))

Henry Greely: Yeah, you could have...

Allan Robins: ...the chap on the phone made that point before.

((Crosstalk))

Henry Greely: But, you know...

Allan Robins: Hindsight is great. You can think of lots of things you could have done.

Henry Greely: The retrospective scope is the world's best instrument.

David?

((Crosstalk))

David Magnus: Given that the truth is for commercial perspective the value of these lines are in fact so limited that the (unintelligible) were to actually going to be useful and that of course if somebody could actually make a case work. And I don't think it's commercially going to have that big an impact on BresaGen/Novocell, and I would think that for Invitrogen for their work to be of value there - it better be the case that they're going to be able to make that anyone planning on using those genetically modified lines, that they actually have some value over and above other things or they're not going to get used anyway.

So I'm not sure that placing the burden on them is a terribly great punishment or a great burden and it actually helps, I think, at least to some extent address the potential or the uncertain ethical shortcomings of the line and reflecting its

uncertain nature and the uncertain nature of, I mean, I won't go into detail unless somebody requests it, but if you go into detail about all of the different arguments and counter arguments for why that Rob's (unintelligible) or Norm's (unintelligible) and how you can sort it out.

You know, it's very complicated and I think there are some subtleties in terms of judgment there. I think this captures it, shows the wealth of concern and also has the value of paralleling exactly how we already treat the derivation of cell lines, how we already treat the use of embryonic material. You have to give justification there, there aren't alternative methods. So they get parallel things that we already have in place.

So I think that judgment Greg had mentioned earlier how are SCRO's going to decide that something rises to the level of that's something SCRO's are used to dealing with and then we have to deal with already for these other areas and there may be some variations on how that judgment gets made from SCRO to SCRO but that's okay. That's how IRB's work, that's how SCRO's work.

Allan Robins: David, how do you deal with progenitors that are derived with ES cells? We had two agreements in place there haven't been commercial activity at this point in time where we were deriving neural progenitor cells which are useful to the research community in general from those BresaGen lines and we'll be supplying them to commercial entities for distribution.

((Crosstalk)).

Allan Robins: You know, there are neural progenitors derived from human ES cells already for sale by Millipore, which I think they are derived from the Wisconsin lines, but I'm not entirely sure about that.

So well would that...

David Magnus: I would think the same thing. It has to (unintelligible) because I think those (unintelligible) covered materials that are derived (unintelligible), so it's still - it has to be acceptably derived.

So as far as they fall under the regulations that they'd have to be acceptably derived, the investigators would have to give an argument or the justification for why those lines are useful and better to use than other lines.

Henry Greely: Well let me turn our attention to a somewhat different procedural side of this. It's been a really interesting discussion. What should or can this committee do or say. I don't - from what I've heard it's not clear to me that this is something that rises to the level of wanting to amend the guidelines, but is it possible that this committee could have a motion, a resolution, a statement expressing its view, the view of the advisory committee not necessarily the view of the Department of Public Health to SCROs saying that, you know, first we commend to your attention the transcripts of this meeting or the audio capture of this meeting because we think it has some factual information that hasn't been broadly available before, and second that we think that SCROs even if something is grandfathered because of its NIH or UK or other status SCROs still have an obligation to the extent that ethical issues are raised about those lines to think about those ethical issues.

And that all things being equal, a SCRO should encourage or discourage depending on how you want to put the weight, researchers to use lines - yeah, to only use lines that have less pristine provenance if there's some good reason to do it, some good presumably scientific reason but potentially other good reasons as well.

That's sort of my thinking out loud about what might be appropriate, so it's really two different things there. One is the process that this committee make a statement that would be available to SCROs as advice to the SCROs.

And secondly, in terms of what the content of that statement would be we say and we think you've got a responsibility to think about these things. They're tricky (unintelligible) all the facts out there, all things being equal the better consents, the less (unintelligible) should probably need some better - some good reason to use those lines. Reactions to that from anybody around the table or on the phone and, you know, I've been saying members but members of the public, yeah, might as well - we might as well open this up to comments from members of the public as well both on the underlying questions of BresaGen and on this activity, but I'd first like to hear from members of the committee in terms of how the committee might act. Certainly, before we take any vote if we do take a vote that there will be an opportunity for public comment.

Dr. Rao? Professor Rao?

((Crosstalk))

Radhika Rao: Yes. I think that's a good idea that there will be that kind of advice. If it's within our purview, if it's our function and I'd like the good sort of scientific reason or maybe a good research reason, the only thing I was a little bit worried about and I can't imagine that this would ever be true is, you know, a purely financial reason.

I mean, the idea that somehow there are lines that don't have the proper consent and they would be cheaper and that you could use them and that those

sort of be - this idea that, you know, other - because other lines are more expensive.

Now, I can't imagine that that's actually true and that there's any mapping of that kind, but I think that Greg Stock raised the suggestion that maybe researchers might choose certain lines because they are cheaper and a justification that said, well, I want to use this line even though it may be of, you know, less pure provenance because of that seems to me to be a little bit troubling.

Henry Greely: You know, it would allow CIRM's limited funding to go farther.

Radhika Rao: Right. So I guess there's a good economic reason for it.

Henry Greely: Right. And you could say we'll allow further research to be done...

Radhika Rao: No, I'm not worried about that because I can't imagine that there is any correlation between price...

((Crosstalk))

David Magnus: I don't think we should make a carve out for that just for the following reasons. I don't - I can't imagine that ever arising in practice.

Radhika Rao: Yes.

David Magnus: And if it ever did, what if there was a particular genetic aspect of one of the BresaGen lines or a questionable line (unintelligible) a line that's just absolutely, one that's questionable, one we're not sure about consent.

Radhika Rao: Right.

Man: Right? So (unintelligible) question about (unintelligible) and it's got a promoter gene that makes it valuable and there's only one other promoter cell line and are asking \$50,000 to use this or something because they know, somebody's trying to take advantage of the knowledge about the situation and that means in practice none of the grant funded people can actually do the research because it's priced out.

To me, that would be a good reason for using the other line. So I think the SCRO has to use judgment about what they consider a good reason, that's what SCROs are for. So they be required to give a good reason and then the SCRO decides what counts as a good reason.

Henry Greely: Dr. Robins.

Allan Robins: At least for the NIH lines, they're all the same price from the national stem cell bank, it's \$500 per line, but I do think unless you guys have foresight that I don't that it's not necessarily true, the government policy is going to change things next year so you still have the two (unintelligible) lines, 21 which are NIH approved line and direct maybe another 300 or so around the world, maybe more that are non-NIH approved, and I don't think it's necessarily certain that that's going to change.

Henry Greely: I will certainly not claim perfect foresight or I would have retired long ago, however, I'd be willing to make a bet with you about that proposition.

Bernard Lo: Hank? This is Bernie, can I get my hand up there to get in line to say something?

Henry Greely: Yeah, you're in line. You're number one.

Bernard Lo: Okay. I'm wanting to sort of follow up on what I think is a very useful approach that David sketched out and I think it's Margaret and you and Radhika also sort of carry forth.

And sort of to me a balancing between concerns about the provenance of some of the NIH lines or other lines versus the scientific value of allowing those lines to use, and I guess I'm wanting to try to make that balancing a bit more nuanced or sophisticated. Maybe this is more - this probably is more appropriate for this paper I take it that David and the others he mentioned are working on.

Man: Yeah.

Bernard Lo: I'm concerned about sort of how we're framing this and I guess there are two questions that I think those of you who are law policy folks who are used to sort of setting the (unintelligible) gradations of balance can help us with. First it strikes me that the default really should be not to use a line who's provenance has been questioned and the more questions raised, the stronger the presumption not to use it.

So it strikes me that here, we're not just talking about sort of things that clearly met the standards of the day but are inadequate by 2009 standards, but really real concerns that Dr. Robins, who was kind enough to share with us about what do we really know -- so what went on and their claims that oral consent was obtained and yet not just in this circumstance but, you know, most of the circumstances were very low, too. As a matter of policy, they sort of just take someone's word that they sort of got the consent the way it was supposed to be done.

So this comment really is – more kind of, what’s the strength of the reason that would override the presumption? I know you can - just see if you can frame it in different ways: a plausible reason, a good reason, a convincing reason, a compelling reason. And I think I’m sort of thinking through the – when someone says okay, we’ve invested in creating a line through genetic modification or deriving it to a certain narrow lineage, a neural progenitor cell, there’s a value to that, which seems pretty clear - some other way.

So I’m not so sure about someone saying, well, you know, I’ve kind of worked with this in my lab, I know how to do it, you know, we’re all set up to do it, let’s just go ahead. I’d sort of like to get a better sense, maybe from a scientist there, if you have someone who’s been working with one line and now you’ve said - well, you can continue the experiment you’ve started or something, but, you know, the next time you kind of start a new set of experiments, it’d really be better to switch to a different line. I take it easier to grow, but, obviously, you’re going to take some time to get adjusted to it.

How much is the convenience of the researcher and the time lost to the competitor going to factor into this as opposed to there’s something special about this line that would really set me back a lot as opposed to just a little inconvenience.

Henry Greely: Good question. Anybody want to take that on? Dr. Robins?

Allan Robins: So, if one does one’s housekeeping properly, when you receive a vial of frozen cells from now the National Stem Cell Bank or whether it was from BresaGen or WiCell or whoever, the first thing one does is expand that and make a master cell bank from it - and then from that master cell bank, you do

all the sort of necessary characterization to show that that cell is what you think it is and particularly that it's karyotypically normal.

And then what - one would normally take one vial from the master cell bank and expand that to make a working cell bank. Now I'm not saying this is what everybody does, but this is certainly what we do in our company, and it's certainly a very good practice to do that because it'd make sure you have that cell line forever and forever.

So you're talking about maybe 8 to 12 months' work and quite a lot of money to do that characterization. So if one has set up and taken care of house properly and set up banks of cells, you would be very loathe to get one vial of the new cell line and so you would have to do that all over again.

Henry Greely: Other thoughts? Comments? (David)?

David Magnus: Just to followup on what Bernie said about trying to have something a little more nuanced...

The key, I think, between - so the key to be able to make I think this calculation depends, partly, on the evaluation of the quality of the nature of the questions that are raised about the line in question. So the weaker the concerns, the less justification I think you need to be able to overcome...

Man: Uh-huh.

David Magnus: ...those by using that.

Woman: Uh-huh.

David Magnus: In this particular case, in addition to the question about whether there was (unintelligible) verbal consent, I think there are other issues that are at stake to decide whether or not the kinds of objections that were raised by Rob are sufficient to show you should keep a line.

So, granted that was not adequate, I think that's enough to show there's at least a question.

Henry Greely: Granted that the consent may not have been adequate.

David Magnus: Well, let's - if we suppose even for the sake of argument that we knew that that consent was not adequate even at, by the standards of the time, that would not be sufficient to show that a line should not be used. There are other arguments, counterarguments that have been made to try and argue for why that's not enough to show that the argument shouldn't be made.

I've gotten permission from Norm to share this argument so I can say sort of an outline of it. But if - essentially, you can, you know, from his point of view, if you think about the ethical concerns that people reasonably have about embryonic stem cell research that they would raise, it really comes down to two primary things. One is that embryos may be destroyed in the creation of the research. And the second is that they may be used to create chimeras that have human characteristics that many people find morally objectionable or that raise some threats to human dignity.

Now the former, even as inadequate as the consent was, it is pretty clear that embryos are going to be destroyed because they're going to be either discarded or used for research. So that one was met.

And the second one is met by the fact that we have SCROs that require that research that's going to be problematic (unintelligible) human traits will not take place.

So any institution that has a SCRO to oversee the research meets the primary ethical concern that people really care about. If that's true, then - that was not adequate even by the standards of the time, it's not clear that that's enough to show that using the lines (unintelligible) would be morally problematic itself.

Now I'm not saying that's a knockdown argument. It's one of like many. But I think there's a lot that needs to be gone through to really think about the nature of the objections and how questionable it is, and we have to do a balancing between how problematic it is versus the value of the research and make that determination, and that's really what this - what I think the SCROs ought to be doing.

Henry Greely: I have to say I find Norm's argument, not all that persuasive on the first point is the idea that a clinical consent would have provided strong evidence that these parties would not have been troubled by the creation of embryonic stem cell lines because I think destruction of the embryo in the normal course of clinical practice might well be different, of course, on people than its destruction in the course of making an embryonic stem cell line. But I'm sure Norm and I could argue about that...

((Crosstalk))

Henry Greely: Till the dogs came home.

David Magnus: I don't know if there's any evidence that that's true.

Henry Greely: But I don't know there's any evidence that it's false either, which actually brings me back to what I wanted to say, I thought that Bernie's point is a real good one and appeals and we really should have gotten you in law school, Bernie.

The point about burdens of proof, presumptions, and questions of standards of proof, is it clear and convincing, preponderance to the evidence beyond reasonable - all that is great law school stuff.

I wonder whether that's something for us to talk about and make suggestions to SCROs about, or whether that's something that is within the discretion of the individual SCROs, how they decide to approach the - how they decide to weigh the ethical issues and a positive response that...

((Crosstalk))

Henry Greely: ...throw it out there as a - as one possible process-related way to deal with that very important issue of weighting and presumptions.

Radhika?

Radhika Rao: Could I ask Geoff Lomax whether CIRM, I mean, I saw - I read the CIRM statement, but has CIRM thought about this balancing question and about researchers who want to use these lines and those being more questionable versus less questionable and whether they should provide some justification, any justification? Or, if it's approved, is it simply okay?

Geoff Lomax: The lines that aren't approved -- in other words, lines that aren't identified on - on the list (unintelligible), basically the regulations -- and for lines - and specifically for lines that (unintelligible) prior to November 2006, which is the

date the regulations took effect, CIRM has initiated a petition process that gathered - that seeks to gather information that's more or less consistent with the level of information you all are talking about in this conversation. And then that - there is a procedure through which that application is evaluated. And ultimately, the result of that evaluation, either a recommendation to approve the line or a recommendation to not approve the line, is taken to the ICOC for their vote.

Henry Greely: Dr. Ahmad, let me ask you the process question that I raised earlier as our liaison with the Department. Do you think it would be appropriate for this committee to make statements about this topic, as the committee statement, not the Department statement for - to provide some advice which they may or may not choose to take to the SCROs around the State?

Shabbir Ahmad: That is possible. I think the information, the second part of your earlier comment so that this information should be (unintelligible) to the SCRO committee on this process. I think the committee can decide whether it is - and wise that should be posted on the department and that it's the advice from the committee. It is something between the advice and the guidelines that can be - that developed out of this committee and posted on the Website.

And I was consulting Pat on that. This committee has the policy to either advise or to develop the guidelines, which can go into the guidelines or it is just posted on the Website.

Henry Greely: Any other committee members have a strong view about how we should go forward, or suggestion about how we should go forward?

David Magnus: I propose that we draft some guidance language that seeks to account some of the things that we've been talking about, that we circulate it, and that we see -

and then we look into whether or not we should either create a guideline around it or post it on the Web. The advantage of getting formal guideline is to get a period of public comments. We'll have some advantages in terms of public buy-ins that we're on the right track. But otherwise - so there are (unintelligible) that we start by drafting something.

Henry Greely: Can I - go ahead.

Shabbir Ahmad: We may have to - even if it is advice from the Committee, we would put forward for public comments...

Man: Okay.

((Crosstalk))

David Magnus: ...then that's great.

Henry Greely: But, of course, to the extent the Committee's advice, just having it out there as the Committee's initial advice would possibly provide some help to the SCROs even before it has gone - fully gone through the public notification process, recognizing that the advice might get modified as a result of the process.

David Magnus: Right.

Henry Greely: So David, can I take what you've just said as a motion...

David Magnus: Yes.

Henry Greely: ...that we work to develop a statement – to then be circulated -- and the exact status of that statement should also be determined at a subsequent meeting along with our findings, our conclusions over the exact wording of the statement?

David Magnus: Yes.

Henry Greely: Is there a second to that motion?

Woman: I second.

Henry Greely: Okay. Is there a discussion from Committee members? And then I'll ask for discussion from the public, because we do want to hear the public before we take any votes on something like this.

Committee member discussion of the motion?

Any folks on the phone? I don't want to....

Woman: (Unintelligible).

Henry Greely: I don't want anyone to be out of sight out of mind.

((Crosstalk))

Henry Greely: Okay. Members of the Committee here?

Members of the public either here or on the phone?

I think then - it looks like it's time for a vote on this issue. All in favor of the motion that we work to develop a statement to be agreed upon or not at a subsequent meeting to be a guideline or advice or something in between, also to be decided at a subsequent meeting.

Please signify by saying aye.

Man: Aye.

Woman: Aye.

Man: Aye.

Man: Aye.

Woman: Aye.

Henry Greely: Any opposed? Make funny noises on the telephone line.

Any opposed? Say no.

Any abstentions?

Man: (Unintelligible)...

((Crosstalk))

Henry Greely: Oops, sorry.

((Crosstalk on phone from outside parties))

Henry Greely: Okay. The motion that - with that bizarre interlude, the motion carries. It's currently 2:55...

((Continued telephonic disruptions from outside parties))

Henry Greely: ...for us to take a break. And, Amber, maybe you can reboot our telephone and get...

((BREAK))

((Crosstalk))

Henry Greely: Let's reconvene?

((Crosstalk))

Man: Yeah.

Henry Greely: Are the people on the phone - our members on the phone, are you still there?

Woman: Yes.

Man: Yes.

Woman: Yes.

Henry Greely: Okay. Excellent.

Man: Yeah. Hi.

Henry Greely: I haven't heard any more commentary from somebody else's conversation in the middle of this. So I think we're probably okay on that at this point.

((Crosstalk))

Man: Okay.

((Crosstalk))

Henry Greely: Yeah.

And the (unintelligible) in my own life that I don't need to hear about screw-ups done by somebody else.

((Crosstalk))

Henry Greely: So back to the agenda, my co-chair Dr. Lubin needs to leave before too much longer as our guest, our public participant, Geoff Lomax. And I think that actually, I'd like to, again, barring objections from people, shift the agenda around.

I will say one thing about Agenda Item Number 3 which was the revisions to the guidelines, with respect to specific informed consent of requirement of somatic cells used in iPSC research. We have our (unintelligible) late July meeting where we agreed those to make those changes.

I have drafted some proposed changes but I've done it so recently and they have been not circulated to you so that I think it would not be appropriate for

us to try to vote on them here on such short notice. But I will hand them out physically to those here. For those of you who aren't here, we'll get them to you after meeting so people can take a look at them.

But it's really just my attempt to technically write amendments to our guidelines that would track what we decided on July 28 to try to track the amendment CIRM regulations with respect to cell line - covered cell lines derived from somatic cells. So this is the issue of - for somatic cells that were collected not for the purposes of stem cell derivation.

Stem cell lines derived from such somatic cells, this amendment would allow the - those to be used with sort of general informed consent and not with specific informed consent required for you to (unintelligible), et cetera.

That's what we voted on last July. This is just language to try to implement that, but I only - I mean that even I haven't really read over it, we're all just handing it out and coming back to it.

David?

David Magnus: So I have - I think I want throw a discussion and a potential for a different approach to this issue that would be very different than this kind of amendment.

Henry Greely: But as I understand it, your approach would be a broader approach with respect to iPSCs in general, correct?

David Magnus: Correct.

Henry Greely: So that actually is the agenda item which I want to move.

David Magnus: Though, it would have relevance to this as well.

Henry Greely: I understand.

David Magnus: Okay.

Henry Greely: So Agenda Item 3, the specific wording of the iPSC somatic cell acceptably derived stuff. I handed that out. Those of you on the phone will get it; those of you who aren't members will see it on the Website. And let's put that aside for now.

Agenda Item 4 is a DPH technical amendment, suggested technical amendments to the guidelines. Let me suggest that we move that to the end of the meeting and possibly even to another meeting.

Shabbir Ahmad: That's fine.

Henry Greely: Dr. Ahmad?

Shabbir Ahmad: That should be fine. Amber you want to say what it is?

Henry Greely: Yeah. What's it about, Amber?

Amber Christiansen: Sure. It's just a correction to - on the very last page, Section 11, letter C and D, we have each SCRO committee that is reviewed covered research shall report, et cetera.

So it's just replacing what's covered and putting in human embryonic stem cell research.

Henry Greely: Okay, which conforms to what we're asking for reporting on?

That sounds like it will be non-controversial and in fact, maybe we'll come back to that quickly at the end of this meeting. Do we have that in the package you sent out, the proposed amendment?

Amber Christiansen: No. We planned to combine it with...

Henry Greely: Got it.

Amber Christiansen: ...other changes...

Henry Greely: It's my fault.

((Crosstalk))

Henry Greely: So let's get to Agenda Item Number 5. I think it's Number 5, discussion for revising the guidelines for human stem cell research. That actually sounds a lot more definite and ambitious than I had in mind for this meeting. I'm not sure that we'll actually have specific proposals for revisions at this meeting, though we might (unintelligible) ideas along those lines.

But I thought at the very least, it would be good for us as a committee at the very least to discuss what we thought the implications of the development of the iPSC technology might have for our guidelines. Should they be kept - should we give advice with respect to induced pluripotent stem cells?

If we should, should it be in the form of the guidelines? This gets into some very deep and tricky questions about what the legal status of the guidelines

actually is and to what extent statutory authorization for the guidelines would apply to iPSCs beyond embryonic cells and to what extent it would be necessary to if the guidelines were read - as advisory guidelines rather than required?

I don't know that we need to plumb those depths today, but I thought it would be useful for us to have a discussion about whether and to what extent we think the iPSCs - what we think this committee might want to say or how it might think about the incorporation of iPSC technology into the guidelines and structure we have.

I think David earlier made a nice - made the point nicely that fundamentally, there seem to be really two pressing issues that led to the development of SCROs and ESCROs. The primary one I think frankly was the embryo issue, the embryo and oocyte issue with this moral, religious, ethical and political significance. Without that, I don't think - my guess is we wouldn't have SCROs or ESCROs.

But another issue of some great interest and importance stems from the transplantation of these cells into a non-human animal and the potential for human/non-human chimeras which has raised some concern.

iPSCs, at least if they are not used as a source for safe somatic cell nuclear transfer, don't raise the first question. They're created and derived without the use of embryo, oocytes, sperm, et cetera.

They do certainly potentially, more than potentially, they will raise the second question because just like human embryonic stem cell lines, at the very least, there'll be transplantation into animals to confirm that they're pluripotent.

And probably transplantation into animals for reasons beyond that with the potential at least of chimera - of issues around chimeras to come up.

We have listed here also the amendments to the NAS guidelines on hESC research. But the NAS amendments were distributed deal with several issues. But I think it's fair to say that one of the biggest things they take on is how iPSCs should fit in to their structure.

And their conclusion is not very much. Most part those issues should be dealt with - by IRBs and by...

((Crosstalk))

Henry Greely: ..IACUC which is - whatever IACUC is.

Bertram Lubin: Animal.

Henry Greely: Institutional Animal Care and Use Committee. It's the second time this week that I've forgotten that acronym.

So having said that as introduction, let me open the floor and see who wants to talk about iPSCs which respect our charge?

((Crosstalk))

Henry Greely: Let me say one more thing. I can never relinquish the floor easily.

It is the case that CIRM does cover iPSCs. And the CIRM statutes Proposition 71 requires it to regulate at least to some extent, all stem cell research funded by CIRM, whether that's dealing with adult stem cells, embryonic stem cells,

germ-line stem cells or presumably induced pluripotent stem cells. And there seemed to be defined as covered cell lines under the CIRM regulation.

But again, to those of you on the phone, I'm staring at Dr. Lomax.

Geoff Lomax: Yeah. I think that - I mean, the specific - the operational aspect of the regulations are the research intended to derive a covered stem cell line. So I think there's reasonable consensus that full reprogramming is the intent there is to bring the cell back to a state that it would fall under the definition of a covered stem cell line.

Henry Greely: Yeah.

So comments. Dr. Magnus?

David Magnus: So I have a proposal. So just as by way of background, I believe we should spend on the whole - not the concern as part of our charge and the scope with iPSC that we should primarily be concerned on this committee with less, I think with what SB1260 charges us to do which is deal primarily with embryonic stem cell research.

Moreover, I have some doubts about how easy it's going to be to implement some of the guidelines or federal regulations for CIRM for the state. I think there's a big - first of all, there's a big difference between saying you have to do certain things in order to get the money that we're going to give you and saying you can't do something in the State of California. (Unintelligible).

And then finally more substantively, I'm nervous about basing something on it and you have (motion of) attention. We talked about this earlier today. But if somebody is collecting tissue and using it for a variety of purposes and then

they come across an article, a bunch of articles they read about iPSC research and realized oh, you know what, probably somebody is going to use these line for this, assuming they might do.

Does that mean they now have to turn in a request for revision to the IRB and to the SCRO because they have now the intent, and so they now have to meet the change informed consent requirements? I just - I'm very nervous about how slippery this notion of intention is on the part of the investigators who are doing research I think in practice.

And so, for that reason, I propose the following changes. So I would propose that we change the guidelines in the definition section of Section 2 where we defined covered stem cell line. Right now the language says covered stem cell line means a culture-derived human pluripotent stem cell population that is capable of sustained propagation in culture, self-renewal to produce daughter cells with equivalent developmental potential. This section includes both embryonic and non-embryonic human stem cell lines regardless of origin and it defines pluripotent.

So I propose the following amendment to that that we should say covered cell line means a culture-derived human pluripotent stem cell population derived from a totipotent cell that is capable of sustained propagation in culture, and self-renewal to produce daughter cells with equivalent developmental potential. It's really limited to potentially embryonic stem cell research or equivalent so we don't have to, like say totipotent so we don't have to get in a debate about whether or not SCNTs produce embryos or do you have a (unintelligible) that produces (unintelligible) really the embryo.

And I would Amend Number C, covered cells means covered stem cell lines or cells differentiated from cells that are from covered stem cell lines to have,

add gametes differentiated from any human pluripotent cell lines regardless of the source will be considered covered cells.

And I would move that sentence about defining pluripotent from e I would move that up to c.

I think if we do this, that will restrict the scope of what we're concerned with, to cover the things that I think are most concerned and then we'd eliminate iPSC from (unintelligible).

I would, however, then add that I think we should do this and add the following as a guideline that the language in the consent form, the required consent language that CIRM has developed as are mirrored in our guidelines should be listed as a model for good consent for IRBs. And that second that we recommend that SCROs be utilized as a resource for sites that review for iPSC research and the like. But that we essentially leave it up to the institution to decide whether they want...

Henry Greely: I guess I have two concerns about that. I don't know that they make me disagree with the recommendation. But they are things that - I think SCRO review is - where SCRO review plays a useful role - would play useful role with iPSC. And one is the chimera issue. Your resolution, your approach as far as I can tell, is the chimera issue nowhere?

David Magnus: Correct.

Henry Greely: Except maybe at the IACUC, but it's not really an IACUC kind of issue.

David Magnus: Right.

Henry Greely: Or at least it hasn't been spun out that way.

And the other one which I haven't mentioned but now reoccurred to me is the human trials' issue. At least in the human trials issue you will have IRBs. Does SCRO have a role in human trials?

I think in part because of the embryonic source of the hESCs which is (unintelligible) SCRO jurisdiction, but in part because we're nervous about putting pluripotent cells in humans.

((Crosstalk))

Henry Greely: ...consequences should be.

David Magnus: Well I understand, if I recall under our regulations, I don't think we use covered cell lines for our clinical trials that we actually use embryonic.

Henry Greely: Well, I mean whether they're in here or not currently, that is a potential concern about even the use of iPSCs where arguably, the expertise of the SCRO and its knowledge about pluripotent cells could be useful as an addition as a supplement or an adjunct to IRB review or FDA IND review.

David Magnus: It seems a good reason to me for why we should recommend that IRBs and IACUCs utilize SCROs for scientific and ethical review.

Henry Greely: Yeah but we have no power to make them do that.

David Magnus: I would think that's a better way - in vitro research. It makes no sense to me why we would (unintelligible) of these issues oversight in those areas that

makes no sense to me. And it's not even clear (unintelligible). It's not clear that it's really...

Henry Greely: Any other comments on this?

Bertram Lubin: There is a lot of animal work that's been done on human cells going in the animals for years...

David Magnus: Exactly.

Bertram Lubin: ...before this even got started.

David Magnus: Exactly.

Bertram Lubin: Tumors and cancers and brain tumors and, et cetera, et cetera, they're not as - they're not historically doing it from these cells. I actually very much agree with what you think. There is a review process for that. And actually, the animal review is tougher than the human review.

David Magnus: Right.

Bertram Lubin: So it's not a trivial review.

Henry Greely: Except the animal review is looking at the welfare of the animal. And this issue really - you could spend - I mean presumably (unintelligible) situation where you've got a mouse with full human consciousness might arguably it would be cruel to the mouse. That would be issue for the IACUC.

But - and I feel sort of odd making this argument because I'd say I'm impressed but I'm not all that impressed with the concerns about human/non-

human chimeras. But there are respectable people, reasonable people who are quite concerned of this and some unreasonable people, too. But there are reasonable people who aren't quite concerned about it, and right now I'm not sure that shows up at the IACUC. The IACUC worries about the welfare of the animal; it doesn't worry about what makes (unintelligible) chimera might say about - what consequences that might have for concepts of human dignity.

And Bert, you're absolutely right, we've been doing this for probably more than a century - certainly for decades, a point I'm making these arguments. However, one can say when you're putting say even breast cancer cells into a mouse, you have a decent idea of what's going to happen with them. If you were to put completely undifferentiated human embryonic stem cells into a skid mouse, you're not sure where they're going to go and what they're going to be particularly the earlier stage of the mouse's development, the greater their potential integration into the ultimate mouse.

Now, I think fantasies about the mouse standing up on its hind legs and saying, "Hi, I'm Mickey," are fantasies. But that kind of concern or some weaker variance of that concern is out there and out there not just from people who haven't thought about it very much.

David Magnus: That is out there independent of the pluripotent cells and cell issues because you've placed the human neurons in a mouse, it's been done for long before SCROs were set up.

Henry Greely: Yeah.

David Magnus: Then - there are issues associated...

((Crosstalk))

Henry Greely: But of course it's the neural progenitor cells which have additional special coverage because of the importance of - because this is such a crucial issue or such a controversial issue with respect to the potential nervous system.

I mean, you're right, it's predated pluripotent cells. I think pluripotent cells...

((Crosstalk))

David Magnus:because of the way CIRM was written, the regulations there which we mirrored, there's a carve-out for neural progenitor stem cells which should be left in place (unintelligible). There would still be a SCRO review of placing neural progenitor cells. Which I think are the ethically tricky issues. I'm not convinced there is anything tricky other than putting neural progenitors...

((Crosstalk))

Henry Greely: But what if you were putting an undifferentiated iPSC into the brain of an early fetal mouse? I think that raise the concerns that you and I may not have but other people have about the human/non-human chimera.

David Magnus: It sounds like a good reason for an approved IACUC to take advantage of what expertise they've got, you know, from SCRO or whatever experience they got and already approved research with (unintelligible).

Henry Greely: David and I can argue with each other almost anytime, although, in fact we - in fact despite that we work a mile from each other. We tend to see each other more often away from Stanford than at Stanford. Life is too busy.

Radhika?

Radhika Rao: Okay.

So to be clear on what David is proposing, are you proposing then that the induced pluripotent stem cells wouldn't be covered by these guidelines, they would be basically excluded and they would be reviewed under IRB's different kind of approval, but all of these requirements wouldn't apply?

Henry Greely: Well we would suggest that IRBs and IACUCs should review...

((Crosstalk))

Radhika Rao: Should review them.

Henry Greely: We have no power.

Radhika Rao: We would have no power. Okay.

((Crosstalk))

Radhika Rao: So I want to raise...

((Crosstalk))

Henry Greely: ...no power to make sure IRBs and IACUCs did review them.

Radhika Rao: Well, I want to raise one additional concern that I think our guidelines raise which is, you know, you say Norman Foss suggests that the real concern here is one; destruction of embryos; and two, human animal chimeras. But I think our guidelines also express concern about commodification of the human

body because of the prohibitions on sale. And it's not just for gametes and embryos, but also it seems as if for other tissues.

So it seems to me that you could have concerns about commodification. That don't raise issues of human animal chimera, don't raise issues of embryo destruction but might apply here. And if, because then we would be saying that you can buy and sell human tissue for - yes, you can, I know. But currently you can't under our guidelines. This is a concrete.

((Crosstalk))

David Magnus: (Unintelligible) advice to non-iPSC research and combined cells (unintelligible).

Radhika Rao: Yes.

((Crosstalk))

David Magnus: But the mere fact that I'm going to make something pluripotent, it suddenly changes...

Radhika Rao: Suddenly changes.

((Crosstalk))

David Magnus: There's nothing special about pluripotent research in that regard than commodification that requires that we have to have a special regulation in this area. We don't require it for other kinds of tissue and cell research. We've been doing it for a long time. Why should the mere fact - why is pluripotency morally relevant for that tissue?

((Crosstalk))

Henry Greely: (Unintelligible) totipotency morally relevant?

David Magnus: Yeah. Because that's what people really care about, something that concerns...

((Crosstalk))

Radhika Rao: I don't think - yeah.

((Crosstalk))

Radhika Rao: I don't think either totipotency or pluripotency is necessarily morally relevant. I think what we are doing here is carving out different regimes and saying that when something becomes - when there's sort of heightened public eye on it, we are fearful about commodification in that context. And so, you know, I guess the question becomes which world should this, you know, be placed.

((Crosstalk))

David Magnus: Public doesn't care about induced pluripotent stem cell research in the way they care about embryonic stem cell research. They care about totipotency because that's embryos or embryo-like things (unintelligible) that's the problem we're trying to (unintelligible) debate, right? That's what the people care about that's one of the main issues. That's why we have SCROs, why we have this committee. They don't care about - the public does not care about iPSC they care about embryonic research.

Henry Greely: And the chimera issue?

David Magnus: That's a trickier one, but I recommended they do it and again, that's an issue that arises independent of issues on pluripotency. I'm just not convinced by pluripotency. I mean, to me, I mean I went back to why we first created the broader language of pluripotent cell line. I thought when we had discussion on it, the reason was we were concerned primarily about embryo-like. Well we should have done and talked about totipotency from the beginning, that we were worried about were embryo-like things that would skirt the regulation by not being clearly embryonic research stem cell.

So I think that's why we have...

((Crosstalk))

Henry Greely: See, that's not my recollection at least in my motives, whether I ever truly know my motives at that time when...

((Crosstalk))

Henry Greely: ...properly is two big question marks.

But I think the pluripotency is significant with respect to the chimera issue. It's not the only way in which you get troubling chimeras, but it is a potentially more troubling kind of transplant than most of the other human tissues that would be transplanted. And I think it's a concern in the human subject and the clinical trial's context. And although, I haven't thought about it, I think Radhika is right that there is a concern in the commodification and commercialization area.

Again, it's not necessarily that much difference from the concern about selling kidneys or selling skin or selling hair which we allow.

David Magnus: Or cells. We commercialize cells all the time.

Henry Greely: Right. But that doesn't necessarily mean it's not a relevant issue just because you can point to where places where we don't regulate it or don't provide guidance on it doesn't mean, therefore, we should never provide guidance on it. We could even say, you know, historically, (unintelligible) so that these things are exempt. We wish that we were starting over; they weren't exempt. We recognize there's nothing we can do about them now. Here's the new thing that we have an opportunity to do something about, so we should.

Having said all that, I'm still not sure where I come down ultimately in your position, on your motion, but I do think the counter-interests are greater than you've acknowledged or the (unintelligible).

Bertram Lubin: Can you describe the scenario if we didn't validate it and SCRO were required? So, where do you start? Do you start with the (mass), do you start with the IRB, do you start with SCRO before you go to the (mass) and the IRB? There are three committees you go through.

Henry Greely: But we do that now all the time with the human embryonic stem cell research. They got to get IRB...

((Crosstalk))

Bertram Lubin: ...IRB.

Henry Greely: Anytime it gets transplanted in animals, you've got to go to the IACUC.

Bertram Lubin: So it's the same thing.

Henry Greely: That's the same thing. And it's a pain, but our system deals with it reasonably well, our system at Stanford seems to be able to deal with that three-fold or four-fold because sometimes you get bio-safety committees involved too, right?

It's a hassle, but it's one that it's...

David Magnus: I think - I can't think that that's the way that we should recommend that they should do something like that. But I think trying - but again, the primary advantage of the approach that I'm suggesting in having a separate carve-out is that it avoids getting to the informed consent issue. Because I think that's - I'm fine to say this from the language that as recommended that IRB should think about using but try and craft the language that, you know, everybody has to conform to everything that this regulation say for the consent. Anytime they're thinking that they might use this for this or intend to use it for this, I think is the wrong way to go.

Henry Greely: Yeah.

David Magnus: And these types of advantages are the way in avoiding that problem.

Henry Greely: True, you avoid any sort of (line-drawing) problem by eliminating any sort of line. Sometimes that's the right thing to do, but another alternative is to try and craft a clearer or a clear line. And my understanding from our discussion last July on the phone was that CIRM's position with respect to the somatic cells and to be clear on whether we could do it or not, I'll come back to that if it's is part of your CIRM grant you are planning to collect somatic cells for

the purposes of making a derived cell line - covered cell line, then you got to go through the (formal consent).

If instead you're getting CIRM money to play around with iPSCs or even make iPSCs and you're buying somatic cells from ATCC or some other sequence, some other source, they collected them without the purpose of contributing to your iPSC or covered cell line research, then you just have to make sure they had (stem) normal consent.

Geoff Lomax: So whether the real intent of those amendments was the acknowledgment that the historic archive of somatic cells for which researchers have an interest in iPS experimentation could not satisfy the detailed consent requirements. They had sub-standard consent if you will.

So what it was saying was that if the cell conforms to the federal standard for anonymity, they're okay to use for iPS. So it was trying to address a roadblock in the system where researchers under the previous regulation were not able to use sort of historically-characterized somatic cells to do iPS work which was the basis for a lot of the original iPS work. So they couldn't replicate the original research.

But I would point out and, I think David, you made an important point upfront, just to reiterate it I think and just to amplify this, I need to - you know, in the context of a CIRM proposal, you know, why I - I don't think there's a sentiment that we would change the regulation. It's very - in a sense, it's very narrow. It's a funded grant, there's a very limited context and I think the point you're making which does - I mean, so unfortunately, Allan left.

It'd be very - be interesting to hear from somebody who's doing ongoing research that doesn't have this that discrete sort of proposal component but it's

more than a move, that's where I think your - that's why I think it's different in why the scope of your - the policies you're dealing with is qualitatively different and unique. And I think that's an - it's an important way to recognize. I don't have any words of wisdom there, but there is that qualitative difference in terms of the scope of what we regulate.

Henry Greely: That's certainly true, but as a SCRO number for now -- three years? I don't know how long our SCRO has been around. And a lot of the protocols that we see come in with CIRM funding and non-CIRM funding, the researcher gets approval for his research or her research plan and has funding from a variety of different sources. If there's any CIRM funding in that, we have to follow your regulations.

Furthermore, any institution in California getting CIRM funding has to have a SCRO that has to apply - that has to deal with iPSCs at least some of the time when it comes in with CIRM. So it's not like our committee could eliminate the need for SCROs in California to deal with iPSCs, not unless CIRM makes a change there.

So to some extent, you know, there are - the simplification that might seem plausible here is smaller than it initially appears.

David Magnus: I actually thought (unintelligible) they already have a CIRM sort of protocol in place, it means more likely that the people are going to go ahead in utilizing the SCRO in appropriate ways probably could handle the chimera issues and do that appropriately, but not having this formally as part of regulation might ease things up a little bit.

I'll give you one other concern I've got about the informed consent thing and this does apply to the CIRM regulations as well, with embryonic stem cell

research where you're procuring embryos even from disease sources using PGD, you can (mass) and you might have both PGD embryos as well as (unintelligible) to the embryos.

But (unintelligible) going on, where are using cells from (unintelligible) certain diseases and setting them. So you're never going to put those in humans because it would be extremely dangerous. And you might know that at time and, yet, it's going to be required that as an element of consent you actually tell them that you may, you know, that material that we - the cell will be (unintelligible) maybe 20 years, blah-blah-blah, and may be put in humans, and that you may know if you do a particular research line that that will never happen.

And then - and now, because you knew that and you put that in your consent form to reassure people don't worry, your cells aren't going to be used to hurt people, you might have somebody do it that would violate the consent standards for CIRM.

Geoff Lomax: But they wouldn't - just to clarify that we did include the phrase where applicable. And I think maybe that's insufficient if there is a legal argument. And that we actually tried to indicate at the front-end of the consent that if certain things were not applicable to this particular protocol, there's not a strict thou shall read everyone everything on this list. There - I hope there's room for discretion there. And if your counsel was indicated that that isn't the case, I'd be very interested in taking that back to the working group.

David Magnus: That is how we've been mostly looking at it here. We have to meet all the standards...

Henry Greely: It certainly may be easiest - the safest thing is to just include everything in there. But that is interesting.

David Magnus: That is...

Geoff Lomax: There is that language in there which wasn't in that National Academies Guidelines, by the way. So you'll notice wherever we have those deviations from the National Academies' language, it's probably there for a reason.

Man: I would just say that - with David here, with your hypothetical, even that's not necessarily true, let's say we came up with an iPSC cell line from an iPSC, for Huntington's disease, you differentiated the cells into neurons to study the progress of Huntington's disease, but you also differentiated the dementia, I don't know, fibroblasts, and for some reason and here I just have to sort of wave my hand and says who - to say who knows why you might end up putting those fibroblasts that have a defective Huntington in genes into human in the confidence that you're putting them in the big toe, they're not going to get integrated, they're not going to revert to neurons, get into the brain and cause Huntington's disease.

David Magnus: Can you apply that and that somebody doing (research) from my side of it, they don't want to do that as possibly...

Henry Greely: Yeah.

David Magnus: (Unintelligible) part of the stem process. And at least the way we've been interpreting it, that would be...

((Crosstalk))

Henry Greely: Although we saw from Dr. Robins, you know, how much do you know who ultimately is going to use your cell line for what; we're going to figure that.

I want to really press the people on the phone, members on the phone. I think this is a really important issue and if any of you have thoughts on it, I'm going to come back and press the people in the room again as well.

Thank you Dr. Lomax, who's now leaving, for your participation.

Geoff Lomax: Thank you.

Henry Greely: We always appreciate your help and insight.

Geoff Lomax: And I'll try to join you in a few minutes.

Henry Greely: Okay.

So those of you on the phone, anybody have any thoughts on what we should do with respect to iPSC? I think this is a big deal.

Bernard Lo: Well, this is Bernie. I had a hard time trying to follow all of the discussion but one point I'm not sure came out is that is the real role for SCROs to handle issues in depth. I mean if you think about the discussion that we had earlier about accepting lines that had questions about provenance and weighing kind of the scientific value, which I take is only a sort of microcosm of what happened at David's conference.

I think we should move side of the fact that neither IRBs or/nor IACUC is going to be able to do that both because of their charge, their composition and their time constraints.

I mean IACUC is just overwhelmed with, really, the details of animal welfare. And they really have said they're not in a position to handle the flip side of what the implications are for the humans who donated the cells that are going into the animals.

So I think that although we might design a system, ideally, that would sort of be more integrated and sort of not - sort of push issues from iPS cell lines into having to look more closely at consent and other things than they need to, I think it's also unrealistic to think that either IACUCs or even IRBs are going to look at some of the issues SCROs handle in more depth.

Henry Greely: And I'll just add to Bernie's comment there that in addition to the time constraints, at least at some institutions it's possible that the bureaucracies behind IRBs and IACUCs actively discourage the discussion - policy discussion, ethical discussions, et cetera, in favor of quick predictable cookie-cutter results, or so I've heard.

Margaret?

Margaret McLean: Just following up on that line a little bit, one of the things that has kind of stuck with me when the first two reports came out about the derivation of iPSCs, the response - the kind of commentary that came, you know, both from the Wisconsin group and from the Japanese group was, you know, this is great science and it solved the ethical dilemmas around the stem cells.

Man: Yeah.

Margaret McLean: And so the way I kind of think about this is that we'd - I don't think we want to take that shortcut and say, well, we're not going to, you know, we

think that these can be handled like any other cells, et cetera, and we really have now gotten to the point where there are no more kind of ethical concerns around deriving stem cells - since we're no longer using embryos. As if those were the only, you know, that kind of embryonic state was the only thing that was ethically troubling.

So, you know, I don't know what that says about who should or how should, but I think that we do need to resist, you know, that temptation that I think, you know, Thomson certainly fell into in saying, "Well, and now we've kind of solved the ethical issues." You know, it took me ten years but I, you know, but I've got it and now we've got - and of course, there are currently the incredible safety concerns about the process using a viral vector that's necessary in order to create these cells in the first place.

Henry Greely: And at least one oncogene I think in both of the methods that are...

((Crosstalk))

Margaret McLean: I think it's two oncogenes but it's - I mean, there's an oncogenic piece, at least. And so, you know, so there will be and there is now a lot of research around how to induce these sorts of cells without using viral vectors. And they're running into the same kind of problems that they've run into for 20 some odd years with gene transfer therapy research.

So this isn't this kind of clean and clear ethically as I think, you know, it was promoted to be, and I just want to be certain that we keep that in front of us.

David Magnus: Well, I'm not going to say there isn't ethical issues. It's whether they're new...

Margaret McLean: That's right.

David Magnus: Because sure, all the things you just (unintelligible) about, safety are really going to be important; that's why we have IRBs, right? That's why when we do human (unintelligible) research, there's a requirement for having adequate scientific review for anything that's going to be done, right?

So, yeah, that's good. Those are ethical issues. We've got to address them because there's lots of other kinds of research that are accountable for that and we're accountable of, which is what to me is the issue what makes pluripotency different. So when Thomson is saying we've solved the ethical issues, it's not that we've solved all ethical issues; there's still going to be these other problems it's that the things that gave rise to SB1260 and gave rise to the NAS report and gave rise to concerns were mostly around issues around embryos. And all those types of issues, they're real important in our regulations – and what SCROs should (unintelligible).

Henry Greely: Well, and that's at least one of the statutory provisions says it is the policy of the State of California that research involving embryonic, adult or...

Man: And fetal.

Henry Greely: ...- and fetal stem cells, now it doesn't say iPSC...

David Magnus: Right.

Henry Greely: ...which didn't exist and weren't even dreamt of at that time. I don't know whether they would have said that or not, but that section at least clearly goes beyond just the destruction of embryo.

David Magnus: There's not a section that says it's a policy of this regulation and then all the regulation or the rest of the statute concerns embryonic stem cell research. There's not another mention of adult or fetal in the rest of the statute

Henry Greely: But as a result of that statute which is a section, it may or may not - as what the legal meaning of something that says it is the policy of the State of California is, I find as a lawyer challenging those regulations.

David Magnus: But we have committees. We have IRBs, we have...

((Crosstalk))

Henry Greely: You know, Stanford SCRO is cognizant of hematopoietic research because of that section.

((Crosstalk))

David Magnus: Other SCROs do not...

((Crosstalk))

Henry Greely: Bert, you need to leave fairly soon.

Bertram Lubin: Yeah. I think they're really important discussions. So I'm just curious how you're going to try to take this today. Are you...

Henry Greely: I don't think we're going to have a resolution.

David Magnus: Well I want to see if I might - is what I think (unintelligible) sympathetic to my approach or not...

Henry Greely: Okay. So we can just draw straws over that. But my guess is from what I'm hearing that you're not going to get approval by acclamation. Those...

Man: No, no.

((Crosstalk))

David Magnus: I (unintelligible) what I'm mostly hearing is Bert's support of this and nobody else.

((Crosstalk))

Radhika Rao: No. No. No. No. I don't think...

((Crosstalk))

Bertram Lubin: And when you say supportive, I'm thinking about listening to the rest of these discussions.

Henry Greely: Because I'm not sure that that ultimately...

Bertram Lubin: We all want to do the right thing.

Radhika Rao: Yeah.

Henry Greely: But I do think that it's going to help you...

((Crosstalk))

Bertram Lubin: ...discussion.

Henry Greely: ...little more discussion.

Man: Yeah.

Henry Greely: I think we should have another discussion on it.

Bertram Lubin: So I would like to throw out even an additional thing. And I'm not sort of being a horn for something that we do. But we've been working with cells that we derived from a placenta that are pluripotent...

(Unintelligible). I mean they are not - they don't - that's a whole other tissue that's discarded that theoretically doesn't have those, but has other issues.

((Crosstalk))

Man: ...fetal cells...

Bertram Lubin: That's what I was thinking as you said the word "fetal" they are fetal cells.

((Crosstalk))

Bertram Lubin: Actually, they are.

David magnu: (Unintelligible) fetal, right?

Bertram Lubin: Yes.

So should we - I'm not saying that we should write something now, but the field is going to change. We've seen that with this. Somebody may come up with something. And I mean I know people -- we probably all do -- that are working on making iPS without viral vectors.

Man: Right. Right

Bertram Lubin: And so the issue of the viral vectors and the oncogene, five years from now or even shorter may not be an issue. So we're not going to - we're going to have to be ready to address things as they change because they're going to change.

Henry Greely: You know, it's my sense and, David, unless you strongly disagree and I suspect you won't, I don't want to put your motion up for a vote today. But I don't want to say that we'll never come back to it. I've actually liked this. If we have another meeting, which I hope we will, it's kind of like we survive the budget crunch somehow, okay.

Then I'd like this to be on the agendas for a continuation because I think there's more for us all to think about. And then it would help if you send us to, you know, send your language to the department which will then circulate it to all up - all of us.

Again, I want to go back to the people on the phone now, Elizabeth, Sam, Greg, I heard from Bernie. If you're still on there, do any of you have anything you want to throw in about what we should be thinking about with respect to iPSCs?

Elizabeth Blackburn: Well, I know Bernie did discuss this in the context of our campus discussion, right, in SCRO. Certainly, it's - as you said, the ethical issues are all of those really which are covered by all these other sorts of considerations,

you know, with the possible exception of some of the potential, you know, near pluripotency that you might get in certain animal (unintelligible) experiment. But otherwise, it does seem to me that not - I'm not so sure of this group.

Henry Greely: So it sounds like you're at least sympathetic with or perhaps aligned with David and Bert's calling it a position is too strong, but they're tendency?.

Bertram Lubin: Opening...

Woman: Okay. So...

((Crosstalk))

Henry Greely: Greg or Sam, is there anything to add?

Oto?

Otoniel Martinez-Maza:: I'm supportive of your views and I think, in fact, that some of the potential concerns regarding oncogenecity can be handled, say, by IRB. And I think that that even issues regarding chimeric animals could be handled by ARC since they were appropriately trained and prepared to deal with those things. So, I...

Henry Greely: I don't disagree with that. I just don't know that we can assume that they will be dealt with by IACUC or ARC, you know, APLAC or...

Bernard Lo: Well one other way to go about this is to put that as an ideal. I mean, you're really talking about integrated review that combines issues for IRBs that are expert in, issues that SCROs are expert in, issues that IACUC are expert in.

Now maybe what we should do is trying to define what all needs to be covered and leave it up to the individual institution to develop the organizational framework to do it efficiently and effectively.

Henry Greely: That's an interesting thought, Bernie. I still think we should have made you a lawyer. So give the institutions the obligation...

((Crosstalk))

Henry Greely: ...to make sure that the appropriate review to these iPSCs...

((Crosstalk))

Henry Greely: ...with respects to animals and human subjects, et cetera, has gone on, does not specify where...

Bernard Lo: Right. I think you want to give flexibility for people to figure out how to do it in a way that works best with their institution. It's really - you know, what we tried to do at CIRM was to create goal-oriented regulations rather than process-oriented regulations. And sort of say here's what you need to do; we'll give you the flexibility to try and figure out how to get there.

Henry Greely: An interesting idea and one I think we should explore at our next meeting when I think we should continue this discussion. Maybe in anticipation of the next meeting, people with views on this could write them up, send them into the department which can then - distribute them to members and presumably also remember this if you're writing something up, post it on the Website so the public will also have some idea what's going on.

And so, we could come into the next meeting with sort of a head start based on this discussion and on further thought that people might have on this issue of the appropriate treatment of iPSCs.

Bertram Lubin: Can I ask (unintelligible) are SCROs listed in the state? Do you know all the SCROs?

Henry Greely: Yeah, (unintelligible) all the SCROs are?

Bertram Lubin: So then we can access - send it out to the individuals we're working at, get some feedback from...

((Crosstalk))

Shabbir Ahmad: You know, we don't have the complete list but we have a lot.

Man: Yeah.

Henry Greely: So do you have, say, for example, email addresses...

Bertram Lubin: Yeah, that's probably good thing.

Henry Greely: ...contacts of the 252 reporting sites? That certainly would be a very large chunk.

Bertram Lubin: We probably won't get many responses.

((Crosstalk))

David Magnus: Also would you be interested in knowing how SCROs around the country think? That actually came up at the Wisconsin meeting. And there is actually a listserv of SCROs...

Man: (Unintelligible).

((Crosstalk))

David Magnus: ... and I'll tell you what worries me about (unintelligible), figured very prominently (unintelligible) in California. And so the vast majority of SCROs around the country are not – they call themselves ESCROs and they're not going to cover iPSC.

Henry Greely: Right. And this part of the - that is the external quirk...

((Crosstalk))

Henry Greely: ...of CIRM.

Man: Right.

Henry Greely: We do have to have - we - our SCROs do currently, at least under the CIRM regs, have to have some oversight of this thing because of the CIRM position which puts us in a somewhat difficult...

Yeah. One thing for the (unintelligible), they're not - which it might be intriguing to try to put together a workshop or a conference on this issue not funded by the department but funded by outside sources but have the committee members invited to that and have a committee meeting after such a

workshop. That's a very speculative sort of thing, it involves a lot of work - somebody doing a lot of work in finding money.

Bertram Lubin: CIRM is interested in funding...

((Crosstalk))

Bertram Lubin: I mean, that's what they were saying...

Henry Greely: Geoff, have you called in yet?

Man: No.

((Crosstalk))

Bertram Lubin: But Geoff did say, you know, no one is applying for these workshops. They have some funds for workshops.

Woman: Uh-huh.

Henry Greely: Interesting.

Geoff Lomax: Yup.

((Crosstalk))

Geoff Lomax: Well, I am here. And, you know, we are considering some type of, you know, conference grant mechanism. We've got lot of ideas around oversight and I don't know - I think we'd have to evaluate this particular issue amongst another - a number of issues that have been brought to our attention, but it

doesn't mean that a workshop couldn't incorporate a number of issues. So it's certainly something we're working on. At the moment, we don't have our conference grant mechanism nailed down, but I think by early next year, my hope is that that mechanism may be available.

Henry Greely: Maybe too late for us but...

Man: Yeah.

Geoff Lomax: That's sort of the timeframe, I think, we're working on at the moment given what's already in the queue.

Henry Greely: Okay. Well then frankly, having said that, you know, given the realities of everybody's schedule and the calendar year, we're not going to have another meeting of this committee in 2008. And by the time we get one scheduled, the earliest possible throws us is into Thanksgiving and the winter holidays and everything else. So realistically we'd be looking at January-February 2009 for our next meeting if all went well.

Bertram Lubin: I'd be happy to have that one too if you want to...

Shabbir Ahmad: We will have next meeting in Southern California.

Radhika Rao: No, it doesn't make sense?

((Crosstalk))

David Magnus: We failed to make quorum...

((Crosstalk))

David Magnus: ...when we had it in Southern California.

((Crosstalk))

Henry Greely: But I - but, you know...

Woman: Too many...

Henry Greely: ...the Department needs us to do it and have a meeting in Southern California then we can certainly talk about.

Shabbir Ahmad: We can talk about...

((Crosstalk))

Radhika Rao: It's a lot cheaper for you.

Man: Over here.

Woman: Yeah. Yeah.

((Crosstalk))

Henry Greely: Two-thirds of the citizens of the State of California lives South of Santa Barbara. So I can understand why the state might have a desire to let the massive public presence to the meeting...

Woman: Yeah.

Henry Greely: ...be reflective in the entirety of the state.

((Crosstalk))

Henry Greely: We thank you for the public presence.

Do we have anything else to say at this point about iPSCs? I think this has been a productive and interesting discussion. My proposal is we kick it over to the next meeting with the understanding that this is a big deal. This is something we should give a lot of talk to. There are good arguments in every direction and there may be some alternatives such as the one Bernie suggested that might be innovative ways to achieve some of our goals without causing unnecessary bureaucracy, mission creep, et cetera.

Radhika Rao: I have one more kind of empirical type question...

Henry Greely: Yeah.

Radhika Rao: ...which is related to, you know, David's proposal. Do we know that there are - are there a lot of institutions doing research that have IRBs but don't have SCROs that would be interested in doing stem cell research in doing induced-pluripotent stem cell research that would be sort of helped by a carve-out, you know?

Because, I mean - because Hank's suggestion is well, given CIRM restrictions that many of the institutions that are doing stem cell research already have a SCRO and are doing it. But it seems to me the benefit of a carve-out, if you want to have a carve-out, is to not - to allow institutions not to have to create a SCRO simply because they want to do this kind of research when they don't want to do the other kind of research and they don't already have them.

Henry Greely: So, they'd have to be doing iPSC research without CIRM funded.

Radhika Rao: Yes.

David Magnus: And it's not only that...

Radhika Rao: Because if there are such institutions, then it seems to me you have a stronger argument for this.

If, on the other hand, there's no efficiency gained to be achieved and we have all of these concerns, I mean, David says they're not really very different, but if we're not getting efficiency gains, why not include, you know, induced pluripotent stem cell. On the other hand, if there are institution private non-university maybe, institutions that would be in interested in this kind...

Henry Greely: Biotech companies?

Radhika Rao: Yeah. Like the Redlands.

((Crosstalk))

Henry Greely: ...small colleges. I mean, I could imagine places like Redlands College.

Radhika Rao: Yeah, that have an IRB but don't have...

((Crosstalk))

Bertram Lubin: ...(unintelligible) bridge funding thing is new training thing which was for non-universities to set up stem cell training thing is going to be in the places that we're just talking about.

Man: Right.

Bertram Lubin: And they don't have SCROs right now, I can assure you.

Henry Greely: Santa Clara might be good.

((Crosstalk))

Henry Greely: ...embryonic work.

Margaret McLean: Yes, as long as they're not embryonic work.

Man: (Unintelligible).

Woman: Yeah.

((Crosstalk))

David Magnus: Also in Wisconsin, we talked about SCROs and that what they're supposed to be doing? The vision that I think, that we have of SCROs and how they can (unintelligible) like that, the kind of SCROs that we have in Stanford, in UCSF, UCLA, (unintelligible) where there are dozens, dozens of people, researchers working in these areas so you can have a very (unintelligible) researchers who have the expertise to serve on it, and the training particular protocol coming in, not to be on that protocol.

But the reality is for the vast majority of places that are doing embryonic stem cell research even if on paper they have a SCRO, they do not have anybody with particular expertise because we've got one stem cell researcher at their institution, that person is going to be on the protocol, so they can't be the reviewer. And that means their SCROs actually don't have any more expertise doing the reviews than the IRBs have. And that's the reality to the vast majority of SCROs around the country and even in California.

Man: Right.

Henry Greely: Although not necessarily for the vast majority of research because I suspect places like UCLA, UCSF, UCSD, Stanford...

David Magnus: Do the majority of...

((Crosstalk))

Henry Greely: ...is the vast majority of research...

((Crosstalk))

Henry Greely: Pat?

((Crosstalk))

Patricia Rodriguez: I just wanted to know a little bit (unintelligible)...

Man: Yeah.

Patricia Rodriguez: Yeah, and that is that I think that the ideas that came out today clearly indicate that maybe - because the statutes the way that they're in now, unfortunately, (unintelligible) a lot of us in developing. And even though there is language, it's often (unintelligible).

The authority (unintelligible) that are established aren't as limited to embryonic (unintelligible). So I think you may be wanting to do a pushback especially since even the SCROs are not even required beyond what (unintelligible) at this time.

So you may get some pushback there and there may be some authority issues. Ad I think that really needs to be a lot of legislation (unintelligible) authority.

And another, just a cautionary comment I would make is that when (unintelligible) guidelines for example on (unintelligible), they're supposed to follow the rules of administrative procedure act which requires the guidelines (unintelligible). And that's - they're pretty strict in that they seem that whoever is being required follows (unintelligible) clearly understand what they need to do. So when you're talking about something like a balancing test (unintelligible) because you need to tell them exactly what it is they need to do so that they have some sort of ability to make decisions...

((Crosstalk))

Patricia Rodriguez: So the guidelines need to be very clear.

Henry Greely: So, presumably the guidelines that we have already - that you have already adopted did go through that (OAL) review and that meet that standard. So if...

Patricia Rodriguez: Well, I will say the guidelines that CIRM did were approved by the Office of Administrative Law. Ours mimic CIRM (unintelligible).

Henry Greely: So ours didn't go through an independent (OAL) review?

((Crosstalk))

Henry Greely: Well, this is all interesting. I think we've got a nice setup for a good discussion at our next meeting. Let me propose that we call this agenda item over for today.

It's couple of minutes after 4. I think, from having heard from Amber what the proposed technical change in the guidelines is that that's something we can probably deal with the committee in the next 90 seconds or so. So let me propose that we move to that agenda item and then...

((Crosstalk))

Henry Greely: Amber, would you again tell us what it is that the - how the Department would like to make a change in these guidelines?

Amber Christiansen: Sure. So it's Section 11, Recordkeeping and Reporting section, Page 18. Letter C it says each SCRO committee that has reviewed covered research shall report to the Department and it continues on.

So there are two instances of covered research in Letter C and we'd like to change that to human embryonic stem cell because of the (unintelligible) requirements for us to report on.

Henry Greely: So the form only requires reporting on it. And well a little bit of Part 2 form is oocytes. But that's different from this. That's not part of this guideline, right?

Amber Christiansen: Right.

Henry Greely: Okay.

Well, although (unintelligible) which is at the bottom of C it's a separate item in...

Amber Christiansen: Uh-huh.

Henry Greely: That sounds appropriate to me. Does anybody, is there any discussion on it?

David?

((Crosstalk))

Man: ...we go change...

Man: Okay.

((Crosstalk))

Henry Greely: Motion in second. Is there any discussion, including discussion on the phone line? Is there any discussion from the public members of the public present either in the room or on the phone line?

Hearing none, I think the question is ripe. All those in favor, signify by saying aye.

Woman: Aye.

Man: Aye.

Woman: Aye.

Henry Greely: All opposed say nay?

I also voted aye by the way.

I heard at least Elizabeth aye there. Is that right?

Elizabeth Blackburn: Yes. I aye, (Chris).

Man: Aye.

Man: Okay.

((Crosstalk))

Henry Greely: Oh good.

So we've got more than seven. We've got at least eight yes votes which means we have at least a quorum. The motion passes unanimously.

We've had a productive three hours or so. We've reached that section of the agenda, the dreaded section called New Business - only dreaded if somebody opens their mouth. Do we have any new business?

Hearing none, I'm sure we would gladly entertain a motion to adjourn. Is there such a motion?

Second?

All in favor, please signify by leaving.

I propose the meeting is adjourned. Thank you all very much including the public participants for your time and attention. Good meeting, I think and we'll see you next time.

END