STATE OF CALIFORNIA
Moderator: Shabbir Ahmad
June 8, 2006
2:00 pm CT

Coordinator: Excuse me, this is the conference coordinator. I just need to inform everyone that the conference call is being recorded. If you have any objection, you may disconnect. Thank you.

Please begin your conference.

Henry Greely: Hi. This is Hank Greely, Chair of the committee with the long name that I can never completely remember.

Is anyone on the teleconference able to hear me?

Man: Yes.

Woman: Yes.

Woman: Yes.

Henry Greely: Excellent.

((Crosstalk))

Henry Greely: For a while there while you guys were chattering, we were hearing you but you weren't hearing us. So…

Woman: Oh, great.

Man: Okay.

Man: Yeah.

Woman: We didn't use any names…

((Crosstalk))

Henry Greely: Anything you've said, can and will be used against you.

Well, I'd like to welcome everyone here to Stanford Medical School in reality or virtually to the second meeting of the California Department of Health Services Human Stem Cell Research Advisory Committee.

We have a fairly full agenda today, but I hope we can have a useful and productive meeting. I think we certainly will.

With me is Deputy Chair, Vice-Chair is Bert Lubin from the Children's Hospital Oakland Research Institute.

And what we'll do is have a roll call, first, of the committee members who are here in the room and then any committee members who are on by teleconference and rather than actually call a roll let me just ask committee members to identify themselves, give us your name and where you're from and I'll start.

I'm Hank Greely from Stanford Law School.

Bertram Lubin: Bert Lubin, Children's Hospital Oakland Research Institute.

Radhika Rao: Radhika Rao, Hastings Law School.

David Magnus: David Magnus, Stanford Center for Biomedical Ethics.

Bernard Lo: Bernard Lo, University of California, San Francisco School of Medicine.

Margaret McLean: Margaret McLean, Santa Clara University.

Gregory Stock: Gregory Stock, UCLA, School of Medicine.

Henry Greely: (Sam)?

Samuel Cheshier: Samuel Cheshier, Department of Neurosurgery, Stanford School of Medicine.

Henry Greely: Okay. And I think that's all the committee members who are present in the room. Do we have any committee members on the phone?

Elliot Dorff: Yes. Elliot Dorff from the University of Judaism.

Henry Greely: Glad you're with us, Elliot.

Elliot Dorff: Thank you.

Henry Greely: We also have present several representatives from the Department of Health Services. Why don't you introduce yourselves?

Cindy Chambers: Cindy Chambers.

Shabbir Ahmad: Shabbir Ahmad.

Heidi Mergenthaler: Heidi Mergenthaler.

Patricia Rodriguez: Patricia Rodriguez.

Henry Greely: Okay.

Why don't we also then have the people who are guests, the members of the public, first, in the room and then on the telephone, tell us who you are and you may have to speak - why don't you step up a little closer to one of the microphones so people on the phone can hear you. And let's start, Angie, with you and just go around the table.

((Crosstalk))

Angie Boyd: Angie Boyd, Stanford Center for Biomedical Ethics.

Henry Greely: Step up to the mike (unintelligible). It just came unplugged, Bernie, or it is unplugged.

Man: I'll be (unintelligible).

Jenny McCormick: Hi. (Jenny McCormick), Stanford Center for Biomedical Ethics.

Kirk Kleinschmidt: Kirk Kleinschmidt, California Institute for Regenerative Medicine.

Geoffrey Lomax: Geoff Lomax from California Institute for Regenerative Medicine.

Mildred Cho: Mildred Cho, Stanford Center for Biomedical Ethics.

Elizabeth Langdon-Gray: Elizabeth Langdon-Gray from the University of California, Office of the President.

Heather Richman: Heather Richman, Stanford, Government Relations.

Emily Galpern: Emily Galpern, Center for Genetics and Society.

Henry Greely: Anybody else?

And we have, at least, one invited guest here who will be speaking later.

Jane Lebkowski: Jane Lebkowski from Geron.

Henry Greely: Okay. And our other invited guest is not here yet?

David Magnus: He's going to be here at 1:30.

Henry Greely: Okay. So that's everybody - all members, guests in the room.

Those of you on the telephone, could you identify yourself, please.

Susan Fogel: Hi. This is Susan Fogel with the Pro-Choice Alliance for Responsible Research.

Nicole Vazquez: Hi. Nicole Vazquez with the Senate Health Committee in Senator Deborah Ortiz's office.

Terri Thorfinnson: Terri Thorfinnson, Chief, Office of Women's Health.

Shannon Smith-Crowley: Shannon Smith-Crowley, American College of Obstetricians and Gynecologists, and American Society for Reproductive Medicine.

Susann Steinberg: Dr. Susann Steinberg, Maternal, Child, Adolescent Health, Department of Health Services.

Henry Greely: Anybody else?

Okay. Well welcome to everyone.

We will start on the agenda with the meeting minutes from our first meeting on February 24, 2006, those minutes have been distributed members of the committee.

Are there any corrections, changes, additions, deletions from - to those minutes?

Elliot Dorff: Good compliments to the minutes taker.

Bertram Lubin: Second that, compliment.

Henry Greely: Great.

Gregory Stock: I would like to say that as well.

((Crosstalk))

Gregory Stock: Are the minutes meant to reflect the comments that are made during the discussion. Because it seems that they only reflect the relatively formal comments, would it be useful to have that included in the minutes at any away?

Henry Greely: Our minute taker/takers like to speak to that?

Shabbir Ahmad: There is a transcript for the whole meeting. You want go into more details. It's word by word, and it is posted on that Department of Health Services web page.

So, this is more like - yes, in fact, (unintelligible).

Man: Its length to the minutes. I mean you can access it from the web…

Shabbir Ahmad: Right.

Henry Greely: So, we have the minutes which are more a record of the actions taken by the committee, but in addition an entire transcript available to the public through the Web site, right?

Shabbir Ahmad: That's right.

Man: Great.

Henry Greely: Okay. So with that understanding, are there any other comments about the minutes? The chair would welcome a motion to approve the minutes.

Man: Move.

Man: Move.

Henry Greely: Second?

((Crosstalk))

Man: Second.

Henry Greely: All in favor say "aye."

Man: Aye.

Man: Aye.

Man: Aye.

Henry Greely: Opposed? Abstentions?

The minutes have been approved.

We're now adding an item to the agenda - administrative matters. Dr. Ahmad has several administrative matters he needs to handle with the committee.

So, Dr. Ahmad.

Shabbir Ahmad: Welcome to the second advisory committee meeting on behalf of the Department of Health Services.

Some of you who claimed for their travel, they have not reimbursed yet, and the reason for that is, this is a statutory board or committee. And the requirement from the secretary of state is that there should be an oath of office.

And we have included in your package a form, which is the oath of office and, (you know), to make - it easier for you Sandy Littlefield over here she's notarized, so whenever you have a chance, you can sign in her presence and she would notarize it, and that the way we would be able pay to the advisory committee. Just as a step we have to administratively take first. The…

Henry Greely: So those of you who thought 110 day delay between being paid was normal government business, it's not that…

Shabbir Ahmad: Sorry for that. We apologize for that. Yeah.

Also, we - some of the members, we do not have the conflict of interest forms signed in our record. So in your folders that if you have the form, that means you have to sign it today and give it to Cindy or me during the break or after the meeting.

So those were the two (unintelligible), which I want to discuss here.

Henry Greely: And, Shabbir, do we have a plan for Dr. Dorff and the other members of the committee who are not…

Shabbir Ahmad: They would be…

((Crosstalk))

Shabbir Ahmad: …through the mail, yes.

((Crosstalk))

Henry Greely: Okay. Any questions for Dr. Ahmad?

Bertram Lubin: So I'd like to ask the question about the conflict. And maybe I just mentioned it to Hank before, that sometimes you start out without (some of the) relationship and then develop a relationship with industry later on if you didn't have at the beginning.

But I think we have to be aware that if something like that happens, you can notify and when it happens. And it affects me personally and I wanted to disclose it now just to be sure the committee felt comfortable with my role.

Within the last few days, we've signed a relationship with ViaCell, which is a cord blood banking company based in Cambridge, Mass., to continue the cord blood services that we offer to families across the United States.

So it's not embryonic stem cells. I don't think it's a conflict, but if the committee felt otherwise... I'd be willing do whatever the committee decided.

Henry Greely: And (the way, in these case) is Children's Hospital of Oakland Research Institute.

Bertram Lubin: That is correct. Right.

Man: Right.

((Crosstalk))

Shabbir Ahmad: I think we can only (update the) (unintelligible), yeah, that's…

((Crosstalk))

Bertram Lubin: So I guess my personal question was, how do we handle - somebody raised that, are you going to handle that or you want the committee to handle it?

Shabbir Ahmad: (Yeah). I think if there's any change in the conflict of interest (rather if there or not), you can inform us that this is a change and we can update the form.

Bertram Lubin: So I guess my question was, is it a conflict? What I'm presenting - has anyone…

((Crosstalk))

Bertram Lubin: Any - personally and then maybe for an example.

Henry Greely: I'm not sure who actually has the power to make that decision.

Man: Right.

Henry Greely: From my perspective as chair of the committee, since the agreement deals only with cord blood and this committee deals only, by definition, at least to this point with human embryonic stem cells - human embryonic stem cells and human embryonic stem cell research, I don't see any substantial conflicts there.

Although, I think any other members of the committee - (their views on this).

Gregory Stock: Well, it just means - the conflict of interest doesn't mean that if you have a conflict of interest, then you have to lose yourself in some way. You just put down anything that might be considered a conflict of interest answer whether you feel that would interfere with your ability to act impartially, and that's it.

Bertram Lubin: So that's the way I interpreted it, but I wanted to be sure that others felt the same way.

Henry Greely: So, Dr. Lubin, do you think this would interfere…

Bertram Lubin: No.

Henry Greely: …with your ability to act impartially?

Bertram Lubin: I think that could be fine with that (unintelligible).

Henry Greely: Okay. Any other comments from the committee on the conflict of interest? Questions.

I do think - I'm glad Bert raised this because I do think it's - I hope our work won't go on indefinitely, but as things go on we develop new attachment to new obligations.

We should keep in mind that if there is anything that might be a conflict of interest, we should let the Department of Health Services know.

Man: Thank you.

Henry Greely: Okay?

So any other administrative matters, Dr. Ahmad?

Shabbir Ahmad: (That's it), thank you.

Henry Greely: All right. Well then, let's turn to the more substantive matters on the agenda.

Though really, I think, three major things for the committee to do today: One is to discuss SB 1260, both to discuss whether we think the committee should have a position on it, and if so what that position should be. Although I'm not sure that temporally those two questions will be separated quite so neatly as I've just described them.

The second is discussion of the subcommittee reports in terms of what subsequently we believe the guidelines of those proposed by this committee should include and how, if at all, they should vary from the regulations of the California Institute for Regenerative Medicine, which I will hereafter call CIRM.

And then the third substantive issue is discussion of our future work plan and progress toward our final recommended guidelines, which I hope would be relatively short.

As part of the - I hope our discussion will be short. And I hope our progress won't take that long, both of those.

Now as part of the discussion, the subcommittee reports we will have two short presentations dealing with the clinical trial research standards subcommittee, one from Bryan Myers from Stanford University and one from Jane Lebkowski from Geron Corporation.

So, let's start with SB 1260. The committee has received a copy of the current version now passed by the State Senate of SB 1260, and we've had a little bit of discussion via email of at least to request via email for people to think about the issues they've got.

I actually am afraid that the procedural issue about whether we should take a position and the substantive issue about what position we should take are probably so intertwined that we can't usefully separate them. I mean if we - if whether we should take a position may depend in part on whether we've got positions we think we should take.

So rather than try to do a separation of those two issues that I think would be somewhat artificial, I will open the floor in a second to general discussion of SB 1260 in the committee.

The - and the second is, I just want to remind everyone that what SB 1260 does in general, it continues many of the provisions of SB 362, which was passed in 2003, which would sunset on January 1, 2007.

The requirement that human embryonic stem cell research be approved by IRBs, some of the details of that requirements, the requirements of the Department of Health Services create guidelines to help IRBs, all of those are contained in SB 362 - 322 -- I'm sorry – SB 322 and would expire next January 1 unless they're continued.

In addition to continuing those - many of those provisions, so I would note that it does not continue the requirements the department appoint this committee or run and operate this committee that submitted from its continuation of the SB 322.

In addition to the continuation of SB 322, I'd say the main aspect - the main other issues covered by 1260 are a variety of new regulations dealing with oocyte procurement largely in California, but also imposing the same standards on the use in California of oocytes that were procured elsewhere.

I think that's a fair, albeit, short summary of the legislation. Before we open the floor to discussion in general, I would like to welcome another committee member. I'd note that Dr. Weissman has appeared.

Hello, Irv.

Irving Weissman: Thank you very much.

Henry Greely: But it's (Montana) barbecue, (so then).

So having said that, the floor is open for discussion of SB 1260, both what we think about it and what we think if we should do anything about it as a committee.

Elliot Dorff: Well, hi, this is Elliot.

You gave an account of why you think that the new legislation does not have a committee such as ours as part of it. And just, namely, so it's not to shackle the department any more than necessary but, you know, but it

is - I mean that's a very - that's a kind reading of it. Is that an accurate reading of it?

Woman: Well…

((Crosstalk))

Henry Greely: I don't know.

Nicole Vasquez: Hi. May I speak? This is Nicole Vasquez, (unintelligible) for Senator Ortiz.

Henry Greely: Sure, go ahead.

Nicole Vasquez: Hi. Thank you.

This is, by way of explanation, the decision was made to not resurrect the committee, given that we understood the timeline for the committee's work would be that it would be able to complete its work, it's charge by the end of the calendar year, so that was one reason.

In addition and a more compelling reason is that the bill needed to have as little cost as possible. And we were informed that the department would be able to tag a rather large cost to the bill that would make it really not viable in the Senate Appropriations Committee. We were going to next after the policy committee, but we took that amendment.

Therefore, we decided to allow the committee to sunset on its natural course, but that was not made with any kind of judgment about the committees, anything about - I just would really urge you to not take any kind of opinion about the committee and its composition or its results, anything like that was really the cost and the schedule that you're naturally following allows you to complete your work by the end of the calendar year.

Man: Okay, thank you.

Henry Greely: You said no offense and I supposed I should say no offense taken.

Nicole Vasquez: Thank you.

Henry Greely: But is it then the case that the new statute would not become effective until January 1 if it's passed, is that your understanding?

Nicole Vasquez: Yes, that's the date that it would be enacted, will be January 1. So the guidelines that would be needed to be issue by the department, the responsibility for that would continue given that section and the remaining sections about oversight on IRB, those would continue into the future indefinitely. In our bill we don't have a sunset on those and under the previous bills, of course, under 322.

Although we assumed that the department would issue guidelines as a result of your committee's work. There's no assurance of that given that that section would have also gone away at the end of this year…

Henry Greely: Correct.

Nicole Vasquez: …on January 1. So, that's why we retained those, and that does have actually have a cost to it, that the Senate Appropriations Committee estimated at - I forget the amount actually. I think it's in the tune to the $200,000- $300,000 range. So there is already a cost to the remaining activities that are required as a result of – us removing those sunsets.

Henry Greely: Just out of curiosity, do you know the number for what the Appropriations Committee estimated the cost to the committee would be?

Nicole Vasquez: I don't have that in front of me, but I know it was higher than - I think it was higher than half a million, I'm not sure. But we were told it was substantial - enough for us to know that it will be problematic for us to get it through – not only the Appropriations Committee, but to get the kind of support from your public (insight of the IO) that we would like on this bill, and this bill does enjoy bipartisian support at this point, it would not if we were to have an additional cost in the bill.

Henry Greely: Well, that's an intriguing mystery. I think my fellow committee members and I are stared in each other wondering how we cost, you know, half a million dollars.

Man: (Now I wonder on) who's got it.

((Crosstalk))

Henry Greely: Not the Chair…

((Crosstalk))

Nicole Vasquez: Well, I think the department can inform you of what their estimates are, and they're represented at the table today, so…

Henry Greely: I…

Nicole Vasquez: (unintelligible).

Henry Greely: I understand and it's…

Nicole Vasquez: …(unintelligible).

Henry Greely: …relatively moot anyway. It's an issue of what your motivations - what the senator's motivation were in drafting the bill, which is now drafted and passed to the Senate.

Since I've got you on the line, do you have any understanding about the status of the bill in the assembly, whether it's been set for committee hearing, and so on?

Nicole Vasquez: It has not yet. It was in front of the Assembly Rules Committee today where it was referred. I believe, to Assembly Health Committee, I don't have confirmation of that yet, and they may be meeting this afternoon. So we'll know at the end of the day where it was referred to, and then at that point, when we'll set it in conjunction with the Assembly Health Committee.

I'm assuming it only goes to that one policy committee and then it probably gets set for - I would probably ask for their June 28 hearing, but I need to consult with the other stakeholders who we work with on the bill to see about the dates that we'd all prepare given everybody's schedule. But it could be either on the 20th of June or on the 27th of June.

Henry Greely: Okay. Thank you. Those are useful.

Comments from - other comments from the committee about SB 1260?

Radhika Rao: Could will clarify that SB 1260 is not intended to apply to fertility procedures. It's solely to apply - it's meant only to apply with oocytes that are retrieved for the purposes of stem cell research. Is that correct?

Shannon Smith-Crowley: This is Shannon Smith-Crowley representing the IVF physicians. And I made sure that it - and everybody actually been very great about making sure that this bill specifically applies to research only.

Henry Greely: Well, okay, although there is language and it's talking about the donation of oocytes for the creation of treatments. And if I were an IVF clinic I might be concerned about whether they qualify it as treatments for infertility. But I assume you guys have done your homework and that you feel confident. That's your issue not ours.

Other comments from the committee?

David Magnus: We talked in our subcommittee a little about couple of different concerns. So one concern that we have is that the scope of the - which coincides is actually…

Susan Fogel: Excuse me, this is Susan Fogel. Could you please identify yourself for the benefit of us on the phone?

David Magnus: This is David Magnus from…

Susan Fogel: Thank you.

David Magnus: … Stanford Center for Biomedical Ethics.

So our concern was that there are some ways in which the bill is too narrow and in particular, in contrast to the CIRM regulations, there are some - there are other cell lines that it seems to - the sorts of guidelines that we would be promulgating or the department will be promulgating would be relevant to, but that the way (unintelligible) would be silent on that.

And in particular, basically, the - what the language of "covered cell lines" from CIRM would be included, including potential neural stem cell that would be used in animal research, which the NAS guidelines allude to, and also generally, pluripotent cells, rather than strictly embryonic cells. So those ought to all be included as what the guidelines should cover, so that was one concern.

Other concerns, I guess, I understand the motivation for leaving out the committee, but the second concern is that as the science develops - it's likely that there are going to be a need for changes in the guidelines and not having some kind of committee with external authority and validation from the scientific and ethical community, I think would put the department in a tough spot in terms of being able to promulgate any kind of guidelines that would have absolute authority behind them for what might be required. Those are really the couple of the concerns.

Henry Greely: There is, of course - this is Hank Greely, again, the Chair.

There is, of course - the broader issue of having SB 1260 continue the regulatory structure, first, put in place by 322 in an era before there were the National Academy of Sciences guidelines and before the CIRM was created by Prop. 71.

So what this does, it's done a new creation, but it perpetuates or continues two having two different regulatory schemes: one that applies to CIRM, one that applies to all research in California with human embryonic stem cells, that's not funded by CIRM. And the regulatory scheme, the statutory scheme, at least, applying to this committee area, non-CIRM funded research, is substantially different from the NAS guidelines, which we expect are those that are going to be implemented throughout the United States and maybe in a variety of other places as well.

So to be precise, the idea that the focus on IRB approval even for research that would not otherwise require it because it would not involve human subjects for purposes of the Federal regulation and the lack of any mention of the ESCRO or SCRO concept is at least troubling.

Now presumably, my guess is and it's only a guess of course at this point, my guess is this committee's recommended guidelines, which I suspect and as far as the department would adopt will include the ESCRO kind of concept and the NAS guidelines. But it is at least odd that there's a continuation of what was an understandable statutory scheme from 2003 after the regulatory world has changed in the United

States in general and in California, specifically. And that inconsistency - though I don't know that it is deadly is at least a little troubling to me.

Dr. Lo.

Bernard Lo: This is Bernard Lo. I would like to follow up on Hank's comments.

I think it is not just a matter of having different regulatory schemes, although I think consistency in this case would be useful. But more to the point, there were sound reasons the NAS report and (unintelligible) may, of course, (setting) of growth stem cell research oversight committee distinct from IRB has to do with the expertise of IRBs, their composition, their charge. And many of the more troubling ethical issues regarding embryonic stem cell research really don't square very well with either the composition or charge of IRBs.

So I think as one thinks about what would be an optimal regulatory scheme (unintelligible) IRB what's optimal may change. I think there were sound reasons for the NAS, (unintelligible) to review report to recommend this, the SCRO concept and certainly (unintelligible) and standards. At CIRM, we found those arguments persuasive and our guidelines will have a SCRO oversight committee.

So I think it's more than just sort of a name or sort of a box on an organizational chart. I think there were good reasons to alter the IRB concept for this different kind of research, and I think it would not serve to protect the subject of research for (unintelligible) concerns not to take advantage of that line of thinking.

Man: (Right).

Henry Greely: Sort of along the lines of just offering at this stage, my personal advice with respect to 1260, there's a funny little provision and it said, I think must not have been fully intended that prohibits any employee or relative of an employee of any "research organization" from taking part in the research by which, implicitly it seems to mean oocyte donation - it doesn't define where the relative is, it doesn't define what a research organization is.

I would suggest that at least 10% of the State of California is probably a relative of by blood or marriage, somebody whose employed by the University California system, which would be a research organization doing this kind of research, and I understand the goal to try to avoid abuses and exploitation of employees along the lines of what's been alleged and apparently did happen in South Korea, but I think the drafting of that is quite overbroad.

I'm also a little troubled by the expansion of what I thought was a good idea in the CIRM regulations. The compensation for ovarian hyperstimulation in oocyte donors to - in 1260, the compensations (there

onward) that the coverage for health costs, for health expenses to make sure that their medical problems are covered.

The expansion of that from ovarian hyperstimulation syndrome, which is a well-understood time limited technique problem to any adverse consequences raises concerns about just how broadly that might be, how many years that might lapse, et cetera. May turn out to be a good idea, but I think it requires some careful thought about whether you really want to expand it that far.

Dr. Lo?

Bernard Lo: If I can just offer, I think, a point of clarification. The CIRM regulations talk about cost and no charge to the oocyte donor for direct and proximate complications. So it's actually a little broader than ovarian hyperstimulation, but (our advise was for both direct and proximal) in terms of needing to be in that clause to try (unintelligible) that happened, you know, immediately.

Now after the oocyte retrieval procedure we did not contemplate that to include, for example, allegations of ovarian cancer or infertility happening many many years after they have (unintelligible) potential (clauses) impacts on the outcome might be hard to judge.

Henry Greely: That's very useful, and I should also note that SB 1260 does have a little more limitation than I just gave. In Section 125341 Act, which is the relevant section, it says that it ensure, if the IRB in this case doing the review, that the subject has access to and coverage for medical care for any adverse consequence that is a direct result of the procedure, that does get the direct language in. But it doesn't get the proximal language then in terms of the possibility of allegations of long-term damage 10, 20, 30, 40 years in the future or the subsequent generations as we saw with the DES issue. That's a significant difference.

Again, I'm not sure ultimately whether that means it's a bad idea. But I think it requires some significant thought, and I know the CIRM working group did put significant thought into the language and the limitations of its provision.

Other comments from the committee?

Dr. Weissman.

Irving Weissman: I just want to add (to David). I didn't quite hear when you said (but), one word, neuronal stem cell. So, in what part of 1260 which you think would be - should it be in?

David Magnus: Well, I think that's (unintelligible) so what would be subject to potentially the guidelines (that could be develop), should be neural progenitor stem cells.

(unintelligible) screen primarily including stem cell lines and into them, we have any kind of ESCRO type requirement that seemed like a sort of thing that ought to get reviewed.

It does get reviewed by if it's CIRM funded, but it won't - if it's reviewed by the state because the way in which the language of both 322 and this new legislation is worded, it only applies to embryonic stem cells.

Man: So would you include other tissues in cell line or tissues cell line?

David Magnus: No, I would use…

((Crosstalk))

David Magnus: I would use the same language - definition (to cover) biologics that CIRM uses, (so) the three sets would be embryonic stem cell…

((Crosstalk))

David Magnus: pluripotent stem cells and neurogenic stem cell and that would be it.

((Crosstalk))

Man: And not (unintelligible).

Man: (unintelligible).

Henry Greely: You know, I think there are a - there have been a number of interesting comments made. My guess is this committee at this meeting is not really in a position to be able to agree on specific concerns that we all have with this legislation, but it does have - the significant number of us have some concerns about this legislation.

I wonder if the appropriate way for us to proceed might not be for the committee, and this is a question for which I'm not sure of the answer. It's not a question. It might not be for the committee to have a resolution or otherwise to express that it has some concerns about this legislation and hopes the legislature of the assembly now and possibly in some circumstances the Senate will give some deeper consideration to some of the issues that we have raised.

Any thoughts about that? Does that strike any sparks with any committee members?

I see at least a couple of heads sort of nod.

Greg, Dr. Stock.

((Crosstalk))

Man: …to me.

Gregory Stock: Greg Stock doctor, UCLA, School Medicine.

It seems to me that the only reasonable thing to do is there in fact is general agreement if there are concerns about the existing bill, then we should at least voice our concerns or else having discussion would seem to be rather relevant to - (unintelligible) (discussion).

Henry Greely: So not everyone- not everyone has spoken, and if there are those on the committee who have no - who don't share these concerns or have no concerns about the bill, perfectly appropriate for you to express that.

Bertram Lubin: Well, can I ask clarification? This is Bert Lubin from Children's Hospital in Oakland.

So the plan to monitor the IRBs or all stem cell research in the State that this committee was formed on, and we're supposed to have that done in two months and then this committee no longer exists once this is passed. Did I hear that correctly? (You said)…

Henry Greely: As I understand what we heard, they expect us - our recommendations will be done by the end of the calendar year.

Bertram Lubin: This year?

Henry Greely: Two-thousand-and-six.

Radhika Rao: December 31, exactly, that's correct.

Henry Greely: Now, actually I expect and hope and we'll talk about this later that we'll be done even more sooner than that.

Bertram Lubin: Okay.

Henry Greely: In terms of our current charge, it is possible that - and I think I actually share - I believe it was Dr. Magnus' concern that a committee like ours, whether it's ours or not, god knows I don't need the money I'm getting payment for being the chair.

Man: Five hundred thousand.

((Crosstalk))

Henry Greely: The 500,000 minus half a million, right, that I'm getting as chair, but it doesn't have to be this committee or this people, but I think a committee like this does have a useful continuing role to serve as the state deals with stem cell research.

But I do think, I hope, I expect, I intend that this committee's immediate work of proposing guidelines to the DHS under its - under - as it was charged in 322 will be completed before the end of this calendar year. No guarantees, but that's sure what I'm going to shoot for.

Other questions or comments? Is there a motion? Right now there's no motion on this floor.

Man: (what are we motioning for?).

Woman: Yeah.

Henry Greely: (Well)…

((Crosstalk))

Henry Greely: The motion is whatever motion somebody makes.

Elliot Dorff: Hey, this is Elliot Dorff.

I'd like to move that we share our concerns with the ones that have just been voiced with Senator Ortiz, and so that at least she and the others involved in drafting this can know of them.

Henry Greely: Could I make a friendly amendment, Elliot?

Elliot Dorff: Sure.

Henry Greely: Rather than directly to one particular senator, there were two co-sponsors, but I think more generally, that we'd share that the committee has concerns and what some of the committee members' specific concerns were…

Elliot Dorff: Right.

Henry Greely: …with the legislature - with the legislators and their staffs.

Elliot Dorff: Sounds great to me. Good.

Henry Greely: Is there a second?

Margaret McLean: Second.

Man: Second.

Henry Greely: Motions to move in second, and any discussion of the motion?

Nicole Vasquez: May I ask a question?

Henry Greely: Who are you?

Nicole Vasquez: Nicole Vasquez with Senator Ortiz's office.

Henry Greely: Yes, indeed.

Nicole Vasquez: Given that the bill will be heard in the Assembly Health Committee in just a few weeks and has been in print for some time now, if substantial concerns are raised, they need to be - and I just ask you in terms of it a favor and time frame, we need to resolve them within the next few weeks, which means that we need to hear about them, specifically, in writing what you suggest as possible changes, they have to go through an entire process with our stakeholder group and with - a discussion with - the Senate Committees have reviewed the bill already as well as the joint authors.

So there is a substantial amount of work that would need to be done in order to make changes into this bill at this point, so I'm just wanting to put that out there as a procedural issue that at this point, it is a difficult task for us to make any kind of substantial changes to the bill, so just be aware of our placement at this time.

Henry Greely: Thank you.

I understand, and I expect that within a couple of minutes we will have at least committee approval for statement of our concerns, and we can get you a written version and perhaps even a transcript of this section of the meeting as quickly as possible.

Dr. Ahmad, do you have a guess about if we ask for transcription of this particular section, how quickly we could get that?

Shabbir Ahmad: Within a week - we can have - I think, three to four days (unintelligible).

Henry Greely: So we'll certainly pass on to the legislature these views as specifically as we can as soon as possible.

Dr. Lo?

Bernard Lo: You know, I appreciate the need with respect (unintelligible) to transmit our ideas as quickly as possible for Senator Ortiz' staff and the other legislators in a timely fashion.

I was going to suggest that perhaps that to the chair, (Hank) Greely's point of a small subcommittee group (appointment) not - rather than just (send her) the - just the (broad minutes) to actually try and put something, you know, (unintelligible) something (together) more (than just) minutes and the discussion.

Henry Greely: I think that's possible, although what I believe would be appropriate when we've got agreement on - I think we will have agreement on - we haven't taken a vote yet, but my hunch, as a political animal, is that we'll have agreement that the committee has concerns and hopes the legislature

will take a hard look at it, the Chair or some - or a subcommittee appointed by the Chair could draft something saying, specific members may - expressed the following concerns, but I don't think we're in a position where the committee as a whole endorsing the specific concerns people adopted. Is that acceptable?

Elliot Dorff: Yeah.

Henry Greely: Okay.

Nicole Vasquez: Mr. Chair, this is Nicole Vasquez, again.

There is a question about what's the consequence of accepting changes would be traditionally when the department does ask for amendment. It could be with technical (unintelligible) or with the support division if amendments are adopted.

So we would want clarity on what the department's position is in tandem with the consideration of the committee's suggestion.

Henry Greely: Well, we certainly can't speak to the department.

((Crosstalk))

Henry Greely: We don't pretend to speak for the department. The department is fully capable and able of speaking for itself.

I don't know whether Dr. Ahmad is currently charged with the ability to speak for the department on this. But our committee would say what we say and you folks in Sacramento who know better your own procedures will make of what you will. The department is not me.

Shabbir Ahmad: Nicole - this Shabbir. Whatever comes from the committee that is not the representation of the department in any way that is the committee's feeling on the bill. So I just want to clarify that, (yes).

Nicole Vasquez: That's helpful. Thank you.

Henry Greely: Dr. Stock?

Gregory Stock: Yeah. I would like to suggest that perhaps Dr. Lo - we seem to talk significantly and many of the concerns were voiced initially by him, we actually put together for the end of the day within a - just a listing of those particular concerns, and the committee could actually vote on it as to whether it agreed with that or not because to me, the idea of having the transcript reflect some conversation about some general concerns the committee had, it seems to me it's creating overhead. Certainly we can do that with the short period of time, it's really not a useful comment for the political processes going on to look at (rises) to the level that we actually as a group feel that it's worth making that comment and we

should do so and otherwise, perhaps it's not worthy moving forward (with it).

Margaret McLean: Margaret McLean, Santa Clara University.

And I agree with Dr. Stock. I think that to - just say we have something to say and try and tease it out of this transcript is not going to put the weight and the energy behind the comments that I think the committee would - or at least members of the committee would like to have behind.

Henry Greely: Well, to some extent, well, I understand - I'd understood what Dr. Lo suggested as speaking to what both Dr. McLean and Dr. Stock had suggested that we have a document created fairly quickly that puts in language more precise and more clear than the transcript would what concerns were expressed by members of the committee.

I am personally reluctant to have the members of the committee who are at this meeting without necessarily having studied each of the issues closely have a vote and express their opinion on whether they individually think this - each particular concern is powerful or not powerful as opposed to saying members of the committee had the following specific concerns.

That's my own view, and it certainly can be overruled by the committee.

Gregory Stock: It feels to me that if it is in fact that is the tone of the comment that they will possibly look at. They will certainly not be given very much weight because we expressed a lot of things, and it's just because they're coming from somebody who happens to be sitting at the committee table, it's not particularly compelling, when in fact most of us have thought about these issues that we can indicate whether we think these are issues of concern.

I don't know - personally, I would feel comfortable with making that indication on my part. And if the committee as a whole doesn't feel like adopting those, then that would be a good statement, too. It would at least give direction to the degree to which we think these are reasonable concerns.

Henry Greely: And Dr. Lo then Dr. Magnus.

Bernard Lo: Well I have my computer open now to follow up on Greg's suggestion and why don't I try and draft some them things, and we can just go around a little bit later if we can - if we agree, I think it would be wise to say we agree on this issue and if we don't, then I agree with Greg, just the fact that one person said it won't (unintelligible).

Woman: Yeah.

Henry Greely: Dr. Magnus?

David Magnus: I just agree with that too, I think it's good. I mean in order to have an impact on what's going to happen, it's not enough to just say we have a general concern, then I think we should (unintelligible) but, you know, let it happen. So we've got something very specific that we do have an agreement about and that's what we should do.

Henry Greely: Okay. We have a motion on the floor. Maybe what we should do is table it for now. Return to this issue later in the meeting that the list Dr. Lo will compile and then go through specific recommendations one at a time and see. Is that an acceptable course of conduct for everyone?

((Crosstalk))

Gregory Stock: I move that we actually direct Dr. Lo to prepare that list and then we will just (vote).

Henry Greely: No, I think we could probably do that without a motion, (right)?

Gregory Stock: Okay.

Henry Greely: I trust Bernie.

Bernard Lo: (unintelligible).

Henry Greely: Okay. Well, in that case, I think we hold in advance for the time being our further discussion of 1260 and move on to the next agenda item, which is the working group progress report and committee discussion. To remind everyone, at our last meeting, we decided to break into a couple of different working groups that most, but not all members of the committee, participated in; one looking at issues with respect to clinical trials, one looking at the broadly described other issues.

David Magnus chaired the first working group. I chaired the second. We both, I think, approached it with the - from a starting point as we expressed in the February meeting, the CIRM proposed regulations and ways in which we thought this committee's proposed guidelines should differ from those with the understanding that there are some real advantages to uniformity within the states, and that if - with all other things being equal if possible, it would be nice to have guidelines with respect to CIRM-funded research and non-CIRM-funded research that were the same.

So, I think we'll proceed first to a discussion of the clinical trial working groups' discussions and conclusions. And as part of that discussion, we'll have two presentations. But let me start by turning things over to Dr. Magnus to present the comments and conclusions of the clinical trial working group.

David Magnus: (Okay), thanks. We had a number of issues that we had some agreement upon within our subgroup and some of the recommendations have been sent to you. There were are also some issues that we thought

we needed more input on before we'd be able to reach any conclusions, that's one of the reasons why we wanted to invite a couple of speakers, for example, whether or not to acquire data safety monitoring boards for all such clinical trials. And if so, whether or not having any requirements about where the reporting lines go, and just in general, give us a little more background as we're proceeding.

We had a few things that seemed obvious that we thought needed to be done such as the fact that any recipients of either embryonic stem cells or materials derived from embryonic stem cell, the recipient of such materials deserve to know where those things came from and how they were produced.

To date the – recommendations, requirements and guidelines from CIRM and from the National Academy of Sciences have really dealt with the oocyte procurement issue, embryo derivations of stem cells, but the clinical trials issues have not been addressed. So that's exactly what we're here to deal with.

I'll go through our recommendations after we hear from our speakers, but I thought it would be helpful if we could start with our two speakers (and sort of) give us some backgrounds into what we're talking about.

And if there's no objection, Bryan do you mind if we have Jane go first. Okay?

And so our first speaker is Dr. Lebkowski from Geron.

Jane Lebkowski: Okay.

Shabbir Ahmad: Maybe we can - if you can come to the mike, please.

Woman: Microphone…

((Crosstalk))

Henry Greely: And are you going to be using PowerPoint?

Jane Lebkowski: No, not, (unintelligible).

Henry Greely: Great.

Is - Bryan Myers, are you going to be using (PowerPoint)?

((Crosstalk))

Bryan Myers: No, I (did not know I was) speaking (today).

((Crosstalk))

Man: (Well, then) I have to (unintelligible).

Henry Greely: Okay. And actually, (can) somebody turn this PowerPoint off?

Man: Right.

Woman: (unintelligible).

Henry Greely: Because I don't think we're going to be using this, and it's (shining in my eyes).

Jane Lebkowski: Okay. I'll call this (unintelligible).

Man: Thanks.

Man: Are you through with your (unintelligible).

David Magnus: (Yeah), but I'm not.

Man: Yeah.

Henry Greely: They haven't made me an offer (unintelligible).

Jane Lebkowski: (I'm sorry).

What I thought I would do is just give you very short - Okay.

Give you a very short update on who and what Geron is and a little bit about…

Okay. Well…

((Crosstalk))

Man: One second, please.

Man: Okay.

Man: There you go.

Henry Greely: (Your) chair and vice chair now are…

Jane Lebkowski: That's right.

Henry Greely: …not blinded.

Jane Lebkowski: And what we're doing in terms of trying to develop human embryonic stem cell technology and take it forward into clinical trial. Again, the two-minute update on what Geron is, Geron a company, a small company in Menlo Park, California, about 90 different employees right now. Most of

which are in California, some of which are in - at the Roslin Institute also in Scotland and became very involved to our interest in telomerase, actually became very involved in looking at embryonic stem cells because of their thoughts of expressing telomerase. And subsequently, self-funded three different laboratories to derive embryonic stem cells of which one of them was Jamie Thomson, who was the first person to successfully derive embryonic stem cells.

Since 1999, we have been really internally and together through our collaborators -- academic collaborators -- looking at trying to develop the technology base that it would take in order to make therapies based on embryonic stem cells a reality.

So we've spent a lot of time learning and just characterizing the undifferentiated cells themselves. A few specific lines that have come from the University of Wisconsin, we spent a lot of time right now learning how to grow those cells and how to get them off of feeder cells that you probably know about in terms of which they were originally derived and how to grow them in defined conditions and how to characterize those cells.

We've spent a lot of time learning how to differentiate those cells into many cell types and then subsequently look at how can we characterize those populations, both in vitro and in vivo in animal models.

And subsequently have then started and initiated various safety studies that how can we characterize this cell and to study them in as best as we can to top the animal model where this - that represent the types of diseases that we would be testing these in and how can we assess their safety in terms of any particular toxicity issues, tumorgenicity issues, anything else that you might want to conceive of.

So we are - have been focusing our attention really on three different projects in spinal cord injury, which is our lead project right now. One, where we're looking at differentiating cardiomyocytes from embryonic stem cells for the treatment of heart failure and thirdly, islet cells for diabetes.

As I said, our most advanced project right now is in spinal cord injury where we have some proof of concept data already through one of our collaborators at UC, Irvine, that shows that by differentiating these cells into oligodendroglial progenitor cells and transplanting those into spinal - to rats that have spinal cord injuries that we can see some improvement in locomotor behavior of these animals that have contusion injury.

And right now, we are very actively pursuing our - (it's actually) involved executing our safety studies that involved, again, looking at how are we going to deliver these cells, and how can we safely deliver these cells.

The - what are any potential toxicities associated with these cells including the tumorgenicity of these differentiated cells. Do they form

tumors? We're doing some very long and elaborate studies right now to show - to determine whether these cells have, in fact, (to) potential.

To date, we have no data suggesting that they do, but we are - those studies need to continue up for a long period of time. We want to know where the cells go. And again, any potential side - noxious side effects, induction of pain, anything that might be associated with the transplantation of those cells.

We've also now been working with a clinical advisory group that represents many different multiple physicians, (psychiatrist), ethicists and the lay public to actually look at designing the clinical trials for this particular program.

So, one of the questions that was asked here is, you know, what are - when do you think that clinical trials could get started in California. You know, I'm a little bit hesitant to say because I don't know what the data is going to hold. I tend to be data driven.

But assuming that all of the data is good, we could be looking at going into the clinic with our particular program in spinal cord injury somewhere in the 14 to 16-month time frame.

Okay?

We're - and so, that's basically kind of where we are with that program in cardiomyocytes and in diabetes applications probably a little bit longer.

There was a question here about, are there any ethical issues or challenges that we should be thinking about or that we are missing. Well, I haven't been privy to all the discussions that have gone on here, but there are numerous ethical issues and challenges; and be happy to address any particular questions that you might have or anything that, you know, I can be as helpful with. Most of the - many of the issues that we're dealing with are not only related to embryonic stem cells in particular but also due to - in particular the particular patient population that we're dealing with. And dealing with the kinds of transplant procedures that will be required regardless of whether it's embryonic stem cell, a neural stem cell or any other type of the application.

One of the questions here was an issue about requiring subjects to receive embryonic stem cells or product from embryonic stem cell, should they be informed of the source material that is being placed in them, for instance, from destroyed embryos.

From our perspective, I think that's an absolute. I think that, you know, or from our intended informed consent, the disclosure of that, you know, would be - is expected, okay?

So I don't see an issue with that. I think it's actually an important thing that patients be informed of where these embryonic stem cells, you

know, came from and if they did come from, in the case from what we're looking at is embryos that were discarded and were consented for these applications.

There is another question here with – do we require - will there be an issue requiring that a DSMB - requiring a DSMB for any such clinical trials and possibly having the DSMB reporting directly to the academic institution. The question having a DSMB involved in these trials, I think is not an issue. It's something that, again, we are likely and fully intend in terms of our clinical trials to have involved.

We're still looking at the composition of that particular DSMB but having a DSMB involved is - I don't see a major issue for that, possibly, having the DSMBs reporting to the academic institution.

The question that I would turn around and say for what purpose is it to disclose the information that the DSMB would have and report that directly to the academic institutions? There could be some potential conflicts here because in many cases, the DSMB trial especially if you're looking at a blinded trial, the blinding could be an issue and that the academic institutions or the groups that are actually running the trials are not supposed to be exposed to the unblinded results.

So that again, depending on what you want your DSMB to do and what its charge is, there could be some direct complications in reporting that to the primary investigators. However, there is an obligation on the sponsor's part to disclose any safety issues to the investigators and to the IRBs of the investigators.

So, again, the question would be clarification, what is the purpose of having in fact the DSMB report directly to the academic institution?

Again, another question that was asked was given the unproven nature of the embryonic stem cell therapies, we want - might want to emphasize no benefit is expected to accrue the patients in early clinical trials. I think, yes, that's likely to - especially in the very early stages of the clinical trials, that is likely to occur.

I might rephrase it to say that that is unknown as opposed to you won't have any benefits. It's in many cases the answer is unknown depending on what dose ranges you are and what kinds of clinical trials - the design of your clinical trials, you could conceive of seeing some efficacy in an early clinical trial, probably not the initial cohorts, but maybe later on.

So I'm not sure of the exact wording. I agree in principle, and I think we all agree in principle to emphasize the fact that, you know, not to hype this technology especially in the early clinical trials, but I think maybe the exact wording should be considered.

It said, given the above, should there be any restrictions to the choice of study population? The - yeah, I think that the choice of subject population

is really something that is very important and very important to the work done very closely with the physicians involved and the local IRBs that are going to be looking at the particular study population because - I mean I think it - there's a huge - could be a huge variability depending on what clinical population you're looking at and what indications you're looking at.

And then the last question was analogous to restrictions on germ line transfer. Would we consider restricting placement of embryonic stem cells into embryos with the intent of producing an infant child or (clinical trial)? And I think that's an absolute. I mean, as far as - I think that that is requiring that and recommending that is if - I think that there's no major issue with that at all.

So those are kind of my comments from the questions that were provided to me and just a little bit of history of where kind of, where we're at.

Henry Greely: Questions, Dr. Weissman.

Irving Weissman: So, we're now trying to brave a whole new big issue. I think it's important for any group that devises the language around some kind of research that we try to be as accurate medically and scientifically as we can.

Jane Lebkowski: Exactly.

Irving Weissman: And I'll just remind you that the definition of embryo and therefore…

Jane Lebkowski: Uh-huh.

Irving Weissman: … the informing that you are destroying an embryo is controversial.

Jane Lebkowski: Uh-huh.

Irving Weissman: I don't mean to make it a personal controversy. I have no axe to grind, I promise you. But when I looked up in (Doorman's) Medical Dictionary, I'll give you the exact edition (if you like).

In animals -- here's the definition of embryo -- those derivatives of the fertilized ovum that eventually become the offspring during their period of most rapid development, that is after the long axis appears until all major structures are represented. In man, the developing organism is an embryo from about two weeks after fertilization to the end of the seventh or eighth week. And the (one) definition which, of course, became law in England overseeing in vitro fertilization what was permissible to do, was based on this definition.

Now, of course, if you Google it, you'll get a thousand…

Jane Lebkowski: Yeah.

Irving Weissman: …definitions according to whatever the person wants or thinks. But I think it's wrong for us to take a language that is so emotional and so political and make the wrong medical definition.

Jane Lebkowski: Uh-huh.

Irving Weissman: That is to say to inform parents that we would - or patients that we're going to treat them with something that destroys an embryo. I, you know, if you wanted put all the different definitions around it, that's fine, but I think it's wrong medically for us to say that's an embryo.

Henry Greely: Dr. Magnus.

David Magnus: Well, so the concern that we have just mirrors the same issue that arose in the oocyte procurement process or the use of excess IVF embryos is that because there are people who are - who do believe that these are embryos and opposed to this kind of issue…

((Crosstalk))

Man: (unintelligible).

David Magnus: (unintelligible), I don't care as much about the semantics the point is, there are people who are opposed to this kind of research, and they have a right to know if…

((Crosstalk))

Irving Weissman: Absolutely.

Jane Lebkowski: Oh, absolutely.

Irving Weissman: Absolutely.

((Crosstalk))

Irving Weissman: That's not the question.

Woman: Yeah.

Irving Weissman: The question is, we are a medical advisory board and a scientific advisory board and legal and ethical advisory board, so we ought to at least inform the public, in our advisory role that the word "embryo" doesn't always apply to this, conceptus.

David Magnus: But not to say that if we're very good medically and have the rigid language medically, that none of the participants who are medically trained will understand. That would not serve the purpose and the goal…

((Crosstalk))

Woman: Yeah.

Henry Greely: Dr. Weissman, what term would you propose for a…

((Crosstalk))

Henry Greely: …product of fertilization up till two weeks?

Irving Weissman: Conceptus or pre-implantation conceptus?

Radhika Rao: What about pre-embryo? I sometimes see that….

Irving Weissman: That was debated in the English parliament, and they didn't actually come up with that. They came up with this definition.

(So what I want to say)…

Henry Greely: What's the English…

((Crosstalk))

Irving Weissman: …not to say that we're trying to fool anybody…

Jane Lebkowski: Right.

Irving Weissman: …or say anything to anybody that would change their mind if I (demand), I think we could just describe it in the most intimate detail in plain English and let them know what it is exactly because as we did here, I think that the issue is, are we going to be, as an advisory body appointed by the state, promulgating a word that may not be correctly describing the entity.

Jane Lebkowski: Uh-huh.

Henry Greely: Dr. Stock.

Gregory Stock: You know, I would actually - I think this is a very important point because these terms are emotionally related.

Jane Lebkowski: Uh-huh.

Gregory Stock: And so in an effort to not be critiqued at any way, there's a tendency to adopt the most extreme (unintelligible)…

((Crosstalk))

Jane Lebkowski: (Exactly).

Gregory Stock: …that in many, many cases, and I think that you could get around that by easily by making a description that is; one, that would be the common

medical usage or at least indicate you can say a pre-embryo or conceptus, some people feel that this is tantamount to being an embryo and there's a great deal of controversy about that. So you could acknowledge the controversy without accepting the language.

Jane Lebkowski: Uh-huh.

Gregory Stock: It's the same thing to say, for example, that you have to inform the person that no personal benefit is going to…

Jane Lebkowski: Right.

Gregory Stock: …(arrive) out of the experiment.

To me, that's rather extreme because many people who are doing that, who are engaged, they know full well or (certainly) if there is form that it's very extremely unlikely that they're going to get any benefits, but…

Jane Lebkowski: Uh-huh.

Gregory Stock: ...maybe they are going to contribute knowledge that will eventually lead to, you know, longer term sort of view that will lead you to personal treatment to them or to others that they have involvement with.

((Crosstalk))

Gregory Stock: So, just by acknowledging that possibility is not somehow playing on that person's emotion. And I think we've always tended to go a little bit too far. You can see it particularly with the idea that no woman is supposed to be paid for a procedure of this sort at which places great burdens on the ability to actually get eggs for research purposes.

Henry Greely: Well, I think this is a useful discussion, but let's put it in the context of where we are in the committee process. Our goal for today is to get substantive agreement on the guidelines that will then be drafted over the course of the summer for (when) folks approval by the committee sometime in the fall.

I'd take Dr. Weissman's comment as an admonition to the drafters to be very careful about the medical correctness of the language they use, and I think that's a completely appropriate comment or - and I'm glad you made it. But I'd like us to keep our focus on what's substantive and in which substantive ways do we think this committee should go beyond or differ from the regulations proposed by CIRM.

Other questions for Dr. Lebkowski?

Bertram Lubin: So I had a question. Bert Lubin from Children's in Oakland.

So the review of the protocol before it goes into a clinical trial…

Jane Lebkowski: Uh-huh.

Bertram Lubin: …is not by the IRB and an institution (unintelligible) because what's Bernie had commented on earlier of the IRB isn't really a committee that could review the science that's going to be discussed. There needs to be another body either ESCRO or scientific advisory committee that would look specifically at it. And the IRB has to be involved, but that's not the committee that looks at the science part.

Did I miss that in your presentation?

Jane Lebkowski: In my presentation at this point in time, the institutions that are looking at this will be having their IRBs look at the protocol. Most of the institutions that we have been talking to in terms of executing these clinical protocols do not have an ESCRO committee involved in their own institution.

Man: Are those in California…

((Crosstalk))

Jane Lebkowski: Worldwide.

Man: Some are in California?

Jane Lebkowski: One is.

Man: Interesting.

Henry Greely: Other questions? Dr. Lo.

Bernard Lo: That sounds like very, very useful. Thank you.

Can I ask you a question about, obviously Geron is at the forefront of this research, I was wondering are there other sponsors that are likely to be bringing research to clinical trials in California or California-based companies within the same time period…

Henry Greely: With embryonic stem cells…

((Crosstalk))

Bernard Lo: (unintelligible).

Jane Lebkowski: You know, it's very hard for me to know - I mean of - the other organizations that are out there working on embryonic stem cells, I think we are likely to be the first. Although, you know, I don't know what's going on specifically in various institutions of our company. So I'm not aware of anybody who is contemplating clinical trials at this point.

Henry Greely: To your knowledge, the – has an IND been granted by the FDA to anyone for…

Jane Lebkowski: For embryonic stem cell?

Henry Greely: …embryonic stem cell research?

Jane Lebkowski: No, they have not.

Henry Greely: And you haven't (received one) yet?

Jane Lebkowski: No.

Henry Greely: Doctor - Professor Rao?

Radhika Rao: Radhika Rao, Hastings College of Law.

Jane Lebkowski: Yeah.

Radhika Rao: Thank you all (for your) presentation.

I was curious about the source of the embryonic stem cell. You said that they were derived from embryos (unintelligible).

Jane Lebkowski: And these are the original embryonic stem cell lines that were derived by Jamie Thomson that we are looking to – take into the clinic.

Actually, the one - first one we're looking at is the H1 cell line.

Henry Greely: And these are federally registered…

((Crosstalk))

Jane Lebkowski: They are federally - they are - yes.

Henry Greely: Dr. McLean.

Margaret McLean: Margaret McLean, Santa Clara University.

Again, thank you for your presentation.

My question has to do with the fact of the safety of those cells…

Jane Lebkowski: Uh-huh.

Margaret McLean: …in terms of having been on mouse feeder cells at one time.

Jane Lebkowski: Uh-huh, uh-huh.

Margaret McLean: That has been, you know, a concern constantly about…

Jane Lebkowski: Uh-huh, uh-huh.

Margaret McLean: …using…

Jane Lebkowski: Uh-huh.

Margaret McLean: …early derived stem cell lines, so if you could speak to that.

Jane Lebkowski: Yeah. I mean there has been - these lines have been screened out for a variety of different retroviruses, mouse pathogens through map testing. There has been - and we see no evidence that they are producing, for instance, that - or infected with mouse ecotropic, amphotrophic or (the entropic) retroviruses. They do not come out positive. At least our banks of these do not - are not positive for any other mouse pathogen.

There has been a concern about certain (asialic) acid residues that might be expressed on the surface of these cells as a result to exposure to mouse components, whether they be mouse feeder cells or whether they come from animal derived materials.

One of the things - we've done extensive work on our own laboratory, which has been independently confirmed by other groups that show that once you stop growing these cells on mouse feeder cells even in the case of conditioned media.

But if you stop growing, you know, mouse feeder cells and are growing on either on human feeder cells or as we do without any feeder cells, what you find is that the expression of these animal (asialic) residue agents completely goes away to the point where we screen now to see whether the products that we get from, for instance, these oligodendroglial progenitor cells that are derived from our embryonic stem cells are not (lyzed) or killed by antibodies -- human antibodies, human (unintelligible).

Woman: Okay.

Jane Lebkowski: So, the issue with - for instance, that the embryonic stem cell lines are irrevocably contaminated by mouse materials because of the exposure, for instance, to these (asialic) residues, the material is way over blown.

Henry Greely: Dr. Lo.

Bernard Lo: Can I follow up with another question? Another concern has been raised about some of the earlier lines having to do with…

((Crosstalk))

Bernard Lo: …genomic alteration.

Jane Lebkowski: Uh-huh.

Bernard Lo: …detected through…

Jane Lebkowski: Uh-huh.

Bernard Lo: …late pathogens and…

Jane Lebkowski: Uh-huh.

Bernard Lo: …The Hopkins group, party, describes the…

Jane Lebkowski: Uh-huh.

Bernard Lo: …the genomic sequencing…

Jane Lebkowski: Uh-huh.

Bernard Lo: …of various kinds of abnormalities that are all (unintelligible).

Jane Lebkowski: Uh-huh.

Bernard Lo: I know that Thomson has published in the (unintelligible) he looks at karyotyping…

Jane Lebkowski: Uh-huh.

Bernard Lo: …at both the H1 and H9 models …

Jane Lebkowski: Uh-huh.

Bernard Lo: …after they were grown in media…

Jane Lebkowski: Uh-huh, uh-huh.

Bernard Lo: Have you looked at or have finally looked at a genomic sequencing (of these models) and do they have the kinds of abnormalities that (unintelligible)?

Jane Lebkowski: Yeah.

Bernard Lo: And would those be a problem (unintelligible)?

Jane Lebkowski: This is different - it's a great question. It's absolutely a very complicated question.

We do screen for karyotyping - by karyotyping. We looked at (g-banding) for all of our cells. Is it the most sensitive way of looking at them? The answer is no, okay?

But we do - in fact, we've looked at cell lines for many, many, many now, tens and tens of hundreds of pathogens. And we think we look by (g-banding) to see if there are chromosomal abnormalities.

When we do see a chromosomal abnormality, what we do is we discard the line and go back to our master cell bank in order to get another (unintelligible).

We, right now, know that our master cell bank is in fact going - is karyotypically normal as far as everything has been looked at by (g-banding).

That being said, if you look at every cell in that embryonic stem - in that master cell bank, I am sure you will find eventually some chromosomal abnormality, okay, whether you look at it by genomic sequencing, whether you look at it by any kind of fine, finer analysis.

That's not necessarily just a issue with embryonic stem cells. That is a issue with any cell-based therapy that you would be looking at.

Eventually, you're going to find the cells that have a karyotypic abnormality. Karyotypic abnormalities occur naturally in nature, in vivo and in the body.

What we're trying to do is the approach that we are taking right now is - in our safety studies, is to look at (pathaging) the embryonic stem cells to a fairly late (pathage), let them accumulate as much as they possibly can, okay, and then you go on and make our product, then do the safety testing.

Do we see tumors arrive then, do we see any abnormalities associated with those cells that could have accumulated as much as possible, and that's our kind of approach, because I can't answer the question - I don't think any scientist could answer the question.

You know, what happens to that (rare cell) - I mean we could - theoretically, we would have sequenced every cell that we implant into a person to look for an abnormality in it. We can't answer those kinds of questions.

But we can answer the question, what happens if we take it to a defined population, take it up to 70 populations, pathogens, if you want, define it. And say, okay, here it is. I'm going to let them accumulate up to (pathogen 70), okay? I'm going to make my product and test it in safety model - extensive safety models.

And what I'm going to say then is under those circumstances when I give something to my patient, okay, when we're making clinical product, we're not going to take it beyond effective 70 or whatever that is, whatever that magic number.

Henry Greely: But to the extent - Dr. Lo's question was, are you doing genotyping to test these cells, the answer is no?

Jane Lebkowski: No. Right now, we're not.

Henry Greely: Thank you.

Other questions?

Man: Thank you very much.

Henry Greely: Well, yeah. On behalf of the committee, we thank you very much for your presentation for…

((Crosstalk))

Henry Greely: …making the long trip from Menlo Park.

Jane Lebkowski: Okay, thank you.

((Crosstalk))

Henry Greely: Dr. Lo?

Bernard Lo: (unintelligible) you mentioned the - your first kind of referral piece will certainly be a (multi-site) trials…

Jane Lebkowski: Likely, yes.

((Crosstalk))

Bernard Lo: …a multinations trial.

Jane Lebkowski: Yes. Well, not multination.

((Crosstalk))

Jane Lebkowski: Probably domestic, but we're getting inputs from around the world.

Bernard Lo: Let me - a question I have is how important is consistency of regulations across the different jurisdictions where you're doing clinical trials?

One state had regulatory procedures that were very different from the other sites. How would that affect your ability to carry out a timely and (rigorous test)?

Jane Lebkowski: The more disparity there is, the worse it is. I mean, it is - I mean, looking - if there is - I mean I would love to have some homogenous regulation.

If we have to look at, you know, tailoring things, especially in this particular indication where we're looking at, which is spinal cord injury. What we're looking at, we're probably going to have to have something like six to eight sites throughout the country in order to execute this trial.

If we have to look at, you know, different jurisdictions and different regulations and different jurisdictions, it makes that - all that much more difficult, especially in a population like spinal cord injury where it's not the most common indication (possibly). I mean it's not like heart failure or certain cancer applications, which are more prevalent.

You often need to have multiple sites in order to just to collect enough patient information in order to execute these trials. So, the harder it is to, you know, coordinate a multiple site trial, the more difficult it is.

David Magnus: Can I do a follow-up on that because it's interesting to me that given that fact, you mentioned that a lot of the sites you're using don't have ESCROs…

Jane Lebkowski: They've never even heard of it.

David Magnus: …or is part of the process, so you are not going to be following any of the NAS guidelines.

((Crosstalk))

Jane Lebkowski: That's not entirely clear yet, okay? But what I'm telling you is that when I go out there to talk to the clinical trial sites, they have no idea what an ESCRO committee is.

David Magnus: Uh-huh.

Jane Lebkowski: Okay?

So it's - in fact, myself bringing them the guidelines. They're talking that, so they're not prepared to deal with this in most institutions at all.

Henry Greely: And these are located in the United States?

Jane Lebkowski: United States.

Bertram Lubin: That's actually is quite remarkable because I would imagine there at centers -well, I don't know whether they're rehab centers or private centers. But I also think that there'll be a lot of people that would be interested in participating in a study that potentially could correct a major spinal cord injury.

Jane Lebkowski: Uh-huh.

Bertram Lubin: I suspect there could be a lot of - from the public standpoint, a lot of people who are wanting to participate.

Jane Lebkowski: In the trial?

Bertram Lubin: In the trial to correct the spinal cord injury…

((Crosstalk))

Jane Lebkowski: Well - yeah, again, it's…

Bertram Lubin: …with the potential that you could not be paralyzed?

Jane Lebkowski: Certainly. I mean, you know, again, depending on - you know, input that I've gotten - for one thing our trial's likely to be an acute spinal cord injury, not the chronic. Okay.

Bertram Lubin: Even then.

Jane Lebkowski: Exactly.

Bertram Lubin: (unintelligible).

Jane Lebkowski: Certainly potential, or I guess - and what I'm reporting right now is that in the centers that we have gone to which are some of the major centers of spinal cord injury, they are not aware of…

Man: (unintelligible)?

Jane Lebkowski: …of what an ESCRO committee is.

Bernard Lo: (But) the difference - I mean, (people) who treat the patients with spinal cord injury (treat them) are not the same people who do the basic science.

Bertram Lubin: Well, I understand that…

Woman: Yeah.

Bertram Lubin: …but don't they talk to each other? (I'm saying), you know, I would assume many are in medical centers.

Jane Lebkowski: They are but they're not…

((Crosstalk))

Bertram Lubin: It's not like all of a sudden this just happened.

Jane Lebkowski: Yeah.

Henry Greely: Very interesting. Dr. Lo?

Bernard Lo: Again, let me - I really appreciate your (unintelligible) this issue of regulatory (unintelligible).

Jane Lebkowski: Uh-huh.

Bernard Lo: I mean it would seem to me that trying to set up a complicated multi-site trial is, do we have enough sites to get to your protective end, if one or two of those sites were in states that have more complex and different regulatory requirements, all other things being equal, I would assume that you would try and replace them with states that had the same types of (unintelligible), again all other things being equal, but…

Jane Lebkowski: The answer is, yes. Okay? But there are a lots of complications too, okay, because when you're setting up a clinical trial like, you know, what we're talking about, you have to go where the patients are, okay? And you have to go to where the referral sites for patients and where they have the infrastructure to execute such a trial.

It is a fairly complicated trial, okay?

If - you can keep weeding out organizations and you can - a simple trial sites because they don't have one or the other on the set of, you know, requirements and you'll wind up with nothing.

Bernard Lo: They have to be able to do the science (unintelligible).

Jane Lebkowski: They have to be able - yeah.

Bernard Lo: But if you had enough sites, you could…

((Crosstalk))

Jane Lebkowski: If you had enough sites - yeah.

Man: (Okay).

Henry Greely: Well, in the interest of finishing both our work and our meeting in this calendar year, I'll try again to thank you and move on to the next speaker. But thanks very much.

Jane Lebkowski: Thank you.

((Crosstalk))

Man: Thank you.

((Crosstalk))

David Magnus: So now, Dr. Myers, who's got good expertise with DSMBs. And I had a very interesting conversation with him about some of the challenges that

they faced on our GCRC with regard to this issue about DSMBs, and how they're set up and how they're structured, and who they report to, and given all the difficulties in the details of what those requirements would be, I was- the subcommittee had thought it would be a good idea to bring somebody with this kind of expertise talk to us a little bit about what's involved in that, so thank you very much for coming.

((Crosstalk))

Henry Greely: Before he starts, if I can ask you to make sure that you spell out your acronyms. So DSMB and GCRC?

David Magnus: DSMB is the Data and Safety Monitoring Board. GCRC is (unintelligible)…

((Crosstalk))

Man: General Clinical Research Center.

Henry Greely: Okay.

Bryan Myers: Well, by way of backbone…

((Crosstalk))

Henry Greely: …close to a microphone, so (unintelligible) to Dr. Lo and - between Dr. Lo and Dr. McLean, if you would.

And while you're doing that, let me say, my expectation is after we finished our discussion with Dr. Myers, we will take a brief break for the benefit of any bladders in the room, or humans (unintelligible) (catch it with) the microphone.

Bryan Myers: Okay. So by way of backbone, there are something like 80 clinical research centers across the country. There's now a new concept, which is called a translational research center, which is being developed.

And the very first of these centers will be funded this coming academic year, and they will eventually absorb all the clinical research centers in the country. The number will be lowered from about 80 to about 50 because they're going to be much more comprehensive.

The notion of translational research is exactly what we've been hearing about today taking something from the laboratory to the bedside, where you're starting with almost no body of knowledge and I think that's a fair description of the challenge that you're going to face with stem cell trials.

So just as a matter of general principles, this will probably have to be a multi-center effort. From my own knowledge of what's available out there, I would say that it must be based in the GCRC, the clinical research centers in the country.

They're all in major medical schools. They have nursing and professional teams that are specially trained to conduct experiments (particularly when they) involved, transplantations (infusions) whatever, they're equipped for it, they know how to deal with this.

And so you don't want to be starting any of these studies in an environment where this kind of knowledge isn't available. So that's on the purely institutional side.

Now the issue of data safety and monitoring as you come to a report, and I can only use two recent developments as likely analogies for what you'll be facing.

The one is gene therapy and the other is the use of monoclonal antibodies that is directed against certain disease processes. It's a whole new area of therapeutic pathology.

Again, when I started, no one knew what we were getting into. It's becoming more widely spread in its use. They were all usually multi-centers as well, and always performed in clinical research centers.

And the question of how to develop a data safety monitoring plan to protect your patients is the one that Dr. Magnus asked me specifically to (think about).

Well, I think again, although this is a slightly different form of therapeutic biology that the basic concept of a multi-center trial is valid, (and going to be) experimental data, (gathered in animals).

And when some notion of the toxicity and potential safety as well as efficacy is learned from those animal models, you go through the FDA's three phases: Phase 1, Phase 2 and Phase 3. And that the same stages will almost certainly apply to looking at therapeutic effects and side effects of stem cell transplantation.

The way that we have structured our oversight on patient safety through data safety monitoring plan is that when we - application when protocol is received, first by the IRB and (more or less) simultaneously with the CRC, at least within our institution. And I suspect that that's a model you'll find you're going to have to follow.

The CRC requires in addition to early oversight of the science, and we have a general advisory committee who spans all the major disciplines and so in a position to provide the expertise as to the adequacy of the science, of course, you don't want to be doing anything potentially dangerous because that first step hasn't been taken.

Then the CRC also deals with patient safety, the ethical considerations, and how the whole thing is presented to the patients through the consent form process.

Data safety monitoring in the multi-center setting is complicated because it requires the Data Safety Monitoring Board - in the case of pharmaceutical trials or gene therapy, for example, which typically composed of several people, at least one of whom is a statistician in order to see whether the study is properly powered and follow that as they go along, and others who would be experts either in the therapy itself or in the underlying disease.

We've always regarded as an almost (inviolate) principle that these boards have to be independent. In other words, Geron may want to appoint their own data safety monitoring or - and they will come to Stanford as one of the potential centers and telling that we want to have an independent data safety monitoring board.

If it's going to be a multi-center study that's quite complicated the board obviously has to meet in some geographic area, remote from where the centers are and has to review the progress of the trial. And they obviously have to be potentially able to unblind themselves in order to know whether a given adverse event is connected to the therapeutic agent itself.

And if the drug company has its own data safety monitoring board, we (and I may be speaking for Stanford now) tend to say, okay, but for Stanford, at least for the Stanford patients, everything is (unintelligible) trial, we're going to have our own independent monitors as well.

Every time the monitoring board meets or anytime any center encounters an adverse event, a report is made simultaneously to the FDA, to the IRB at each institution participating, and to the CRC at each institution.

And the CRC and the (unintelligible), which I'm (head of and why I'm here today) that is composed of an adult researcher - a researcher of adult humans, a researcher of children and a bioethicist plus some personnel from the CRC itself.

So that we could activate an inquiry to the data safety monitoring board and if necessary we'd stop the study if something bad enough was going on. So this is the process, (the extra) steps and realizing this is happening through CIRM and is outside of the NIH. You might be tempted to want to start your own process from scratch. I think that, you know, it's probably not wise (unintelligible).

And that this particular model is the one that we work best and most safely for this series of trials that I now understand maybe only one to two years away. Now is the time to start planning.

If there is more detailed issue is likely (unintelligible), I'll be happy to do it.

Henry Greely: Thank you very much.

Questions, Dr. Magnus?

David Magnus: So for the GCRC, can non-NIH sponsored clinical trials utilize GCRC…

Bryan Myers: Yes, yes indeed.

The CRC - although, it's funded by the NIH, has two categories of studies. One are so called (a) studies, which are investigator initiated NIH funded and others are (b) studies (unintelligible), you know, (unintelligible), which are usually multi-center trials or trial initiated by the pharmaceutical industry. They have to pay a fee to the CRC for using their service. But they represent a fairly large (unintelligible) to the CRC. And they remain under the supervisions of the IRB and the advisory council (unintelligible).

Man: Okay.

David Magnus: For the committee, this is not one of the recommendations that we had. But the idea that to make sure that there is adequate expertise in these very sensitive clinical trials at least initially offered, I think what you're really proposing we consider are requirements -- at least in California -- that all (clinical) - all initial clinical trials be conducted in institution - academic institutions that have GCRC (unintelligible). So, that's not something we have addressed to the subcommittee but it's something that the committee should (consider).

Henry Greely: Dr. Lubin.

Bertram Lubin: So I would vote against that. I'm actually the president of the GCRC Program Directors Association in United States. So, I may not be familiar with GCRC, but I do appreciate the comments you made. But there a lot of good places that do research that weren't able to get a GCRC and really do outstanding research.

And if you take a look at Stanford, I'm sure this is true because it's true in UCSF, and all the major centers, a small percentage of the clinical trials that are done actually in GCRC.

And we as directors are trying to get more in, but most people get enough money in their budget from NIH and don't want to bother with the GCRC. Now that doesn't mean there aren't disease safety monitoring boards because there absolutely are. And so any NIH-sponsored work, NIH has the board and the board can cancel the study if they think there's a violation or if there's a safety issue. So funding is dependent upon approval by the disease safety and monitoring board.

So there is a very complex infrastructure of which the GCRC is certainly a contributor. The future of GCRC is of concern to those of us who were in the GCRC area because the new CTSA or Clinical Translation Science Award, that Dr. Zerhouni's advocating, don't have enough money in the budget to really support them.

And in the budgets that were prepared, the clinical research center budgets were not protected. So other things were protected but not that. So there's going to be a diminution of clinical research center resources to support clinical research trials.

I only bring this up not to say that all of the things you commented on are correct in terms of the value of this monitoring, but it's a changing field right now, and the money to support the activity of the GCRC is very questionable. And there'd be a lot of places that don't have them, and it would be very few that eventually in the first several runs like in the next several years that will get CTSA awards.

UCSF is one and we're part of that and Stanford, maybe has applied. But there is not going to be more than, probably (four) the first go around in the United States.

So I think the disease safety monitoring is important. I think the clinical research centers are fantastic. But I think if we're just dependent upon those, we wouldn't be able to do multi-center clinical trials.

And if we look at all the clinical problems we're in, some of them were in GCRC, some of them were not. I don't know - at Stanford I would suspect that you could - you could determine that just by going to your IRB office. Get the list of all the protocols that went through IRB, find what percentage were in the GCRC. Unfortunately, you'll find a small number.

Bryan Myers: Yes, but - we have a clinical trials department here that has nothing to do with the CRC.

Bertram Lubin: That's right.

Bryan Myers: There's no gene therapy there. And they're very rarely antibody products.

Yeah, I'm taking this up. This is far more complex than trying some drug (unintelligible).

((Crosstalk))

Bertram Lubin: Oh, I agree…

((Crosstalk))

Bertram Lubin: I do completely agree with you. I'm just saying, I'm not sure of the clinical research center model would be in that places to do the studies that you might want to do.

And places that don't have clinical research centers that are funded by NCRR or National Clinical for Research Resources are not necessarily not outstanding centers. They just don't have that (brand).

Henry Greely: Other questions?

So I sense the eagerness for the break. But that doesn't detract from our gratitude to you for coming and waiting for so patiently and giving us useful information about the GCRC and the DSMB. So thank you very much.

Man: Thank you.

Man: Thank you.

Man: …very much.

Henry Greely: Let me suggest to the committee that we take a 10-minute break, reconvene, at least according to this wall clock, 10 minutes after 3.

Man: Sure.

Henry Greely: So the committee is in recess.

((Crosstalk))

Man: (Fred), you want take a look at…

((Crosstalk))

Man: Hello?

Hello?

Susan Fogel: Hello.

Elliot Dorff: Hello.

Susan Fogel: This is Susan Fogel. Who's this?

Elliot Dorff: This is Elliot Dorff.

Susan Fogel: Hi. I think we're waiting for them to come back from their break.

Elliot Dorff: Right. I think that's right. Okay.

((Crosstalk))

Henry Greely: Ladies and gentlemen…

((Crosstalk))

Henry Greely: …we are past five from the end of the break. So let me call you back into session.

Woman: Uh-oh.

((Crosstalk))

Henry Greely: Are people on the telephone still there?

Elliot Dorff: Yes. This is Elliot Dorff. I'm still here.

Henry Greely: Hi, Elliot.

((Crosstalk))

Henry Greely: Okay.

Susan Fogel: This is Susan Fogel with the Pro-Choice Alliance, I'm still here.

Henry Greely: Okay. (Great guys). This is really more a general question to make sure the phone was still working. So we don't need to do a whole roll call again.

But I'd like to welcome back those of you who were here in person and those of you who are here via the telephone. We are now still in Agenda Item 6A, Working Group Progress Reports and Committee Discussion with respect to the clinical trial research standards.

And I'm about to the turn the floor back over to Dr. Magnus. And I hope what you - what I'd like us to do in the next not more than half hour or so, see if we've got some substantive points on which we agree. Remembering that these are instructions to the drafters in this group as to what the specific language of the guidelines that they'll be drafting over the summer will deal with.

So with that understanding, David.

David Magnus: Okay. So allow me to start with one thing that we did not include in our recommendations, but it did come out of the testimony that we just had and wish I'd thought of it earlier.

In innovative surgery, there's a concept called field strength, which is a requirement that before you do something that's very innovative that there has to be an assessment of sort of the capacities of the - and expertise that's available locally (to really) undertake something that's truly innovative.

And whether that's from having a GCRC or some other measure maybe there ought to be someway of having the assessment of the local field strength before something as innovative, as a clinical trial using human embryonic stem cells ought take place is I think something that's worth thinking about what requirement that would be, I don't know. But I think that's an interesting idea that we have (unintelligible) we had not (though of).

Henry Greely: So when you say field strength, you're actually not just talking about the strength of the scientific or medical field overall, but its strength in that particular location?

David Magnus: Correct. So how, you know, do they have (unintelligible) in clinical scientific expertise, regulatory expertise, support system, (a place) I think (it is) concerning there would be a lot of institutions that have no ESCRO committees considering doing human embryonic stem cell clinical trial. I think that's extraordinarily disconcerting, and potentially problematic.

Henry Greely: Okay.

David Magnus: So let me turn to the other things. So the - and these sort of (unintelligible) things where it seemed like we had pretty good strong consensus about these issues and seem to be endorsed even by our representative from Geron. And it's some where the things are more open. So I'm just going to go through the recommendations that our subcommittee had or things that we had sort of (range).

Henry Greely: And I'm not sure that everybody got a copy. This is - for the committee members, this is the email that I sent out yesterday. And I've got copy that I've also copies for the guest here.

For those of you who are listening by telephone who are not committee members, Elliot Dorff, I'm sorry I don't have a copy for you. But it summarizes the points coming out of the subcommittee. And they'll all be discussed in the course of this meeting, so you'll hear (them).

David Magnus: So on the first, let me speak pretty straightforward with just reaffirming the need for adherence to all the regulatory requirements, government clinical trials. This made clear which is something with just the case, which is state laws, state regulations, (do not take) precedent over any relevant federal regulatory issues, so we just want to affirm that any clinical trials must adhere to relevant federal requirements in addition to any state or local requirement.

Second, we believe that the recipients of embryonic stem cells or tissue derived from them are - have to know the sources or, you know, (unintelligible) including a relevant fact that something, that some people object to, may have been created or destroyed to produce the intervention under investigation. And the exact language of it, I mean, (unintelligible) the historian of embryology has talked a lot about the history of how this term has been used and unfortunately the reality is, it's all over the map.

It's not scientific and medical uses of the term has been extraordinarily inconsistent to using it. Sometimes recording these things as embryos sometimes (unintelligible) not a consistent scientific or medical usage of these things.

But whatever language we want to be using we should be thinking hard about. What's important is that what matters is what I think that there are subcommittee endorses the idea that people that are going to be recipients of such tissue have are entitled to know what the source of them is. And in case they should have any moral objections to participating in such research.

Third, that concluding that when IRB determines when such a trial is ready to proceed should be based on a recommendation from an independent embryonic stem cell research oversight committee.

So that there needs to be something like a SCRO that it would have sufficient expertise to address this issue and who's membership should follow the guidelines set forth by the CIRM and National Academy of Sciences. And that that body therefore should be looking carefully at any proposed clinical trial and endorse them as part of the approval process.

So that that endorsement should then go to the IRB since our - this is the law in California outside the CIRM, outside Proposition 71 only specified IRB actions. This is essentially a way of saying IRB should then require the assistance of SCROs in order to be able to assess whether or not a clinical trial should go forward.

Irving Weissman: But they don't have to have a SCRO at their own institution they just have a SCRO that they can (unintelligible) on for advise.

David Magnus: Right, - whatever the guidelines are for the CIRM and the National Academy of Sciences require should be the same one that should be in place for non-CIRM-funded research as well.

For safety reasons, we thought we should tell IRBs that it might be appropriate to require testing of donors of biological materials before allowing clinical trials take place. I think that's likely that the FDA will require that in any case and by giving people a heads up that this is a requirement has the added advantage that when the researchers are in the process of doing earlier research recognizing that this may be a requirement down the line might be helpful for framing how they set up their research and whether there is going to be recontacting for example. And so knowing that this may become a requirement would be useful to some research.

Irving Weissman: Well, you should specify what you're testing for, right?

David Magnus: Well, I think right now, if we don't…

Man: (unintelligible)

((Crosstalk))

Irving Weissman: No, federal government (unintelligible).

David Magnus: So I think - so the group that is writing, this is going to have to be careful, I would suggest being (unintelligible)…

Irving Weissman: Pathogenic agent.

David Magnus: Correct.

((Crosstalk))

Irving Weissman: Pathogenic agent and potential pathogenic agents

David Magnus: Or potentially genetic materials, Bernie Lo who has an article they published in Stem Cells that went through a list of some of the conditions that they thought might be required for safety reasons to be tested, you might want appeal to the things that were (unintelligible).

Irving Weissman: And you want to know also if there's any disease inherent in the (condition itself).

For safety reasons because that's the same report.

David Magnus: Sure.

So again, it grew bigger that it's got (unintelligible) guidance particularly is that is for safety reasons for the material being put in. I think however it's worded that is how that should be in terms of further testing for safety purposes and for the recipient of such tissues.

Gregory Stock: Can - you're referring to genetic testing often which can't that be done on the tissue itself?

David Magnus: Potentially.

Bernard Lo: One issue is there are conditions where you make diagnosis upon the basis of family history (unintelligible)?

Man: But that's just in testing…

Bernard Lo: So that would be testing and screening (unintelligible).

((Crosstalk))

David Magnus: We included for the present time, no hESC's should be placed in human embryos with the intent to create an infant sort of analogous to human germ line gene transfer. I believe that that's prohibited by NAS guidelines as well.

Henry Greely: Yes.

David Magnus: So we endorse that.

The next one would be more- we wanted to have more (input on) while we have the speakers. But I think after hearing from the speakers, I think it's clearly reasonable that we will require a data safety monitoring board for any clinical trial with human embryonic stem cell research.

One question then is about the reporting lines and if those are going to be independent I think the point from our - from Dr. Lebkowski that we have to be careful about unblinding and undoing the value of the research when you have reporting directly to the institutions, you take into account.

But at the same time, I think Dr. Myers' concerns about the independence of that also should be taken into account and so we need to decide exactly what kind of recommendation that you want to put in place here for both maintaining as much as possible the values of the research and the blinding aspect of it, at the same time having some degree of independence so that could be I think of an interesting challenge.

For this first hESC clinical trial, we recognize that IRBs start with presumption that there is no prospect of direct benefits to participants in early phase 1 research. And then any informed consent in the regulatory requirement should reflect that finding.

Irving Weissman: (Can you explain that) to me?

David Magnus: Sure. I mean that was also addressed a little bit by Dr. Lebkowski. So given the - that this is such an – excuse me, difficult, uncertain area and in addition in the early, early stage of the research especially the adult population to be starting sub (unintelligible) in the early phases, we thought it was particularly important to this population that the fact there's not going (to be a) benefit for (unintelligible) both because of the risk of the therapies and misconception and other regulatory requirements that follow from this - from the issue of (possibly) direct benefits should really be (made) very clear to IRB.

Irving Weissman: I always thought that you didn't do clinical trials unless there was a prospect of benefiting the patient (unintelligible).

Woman: No.

David Magnus: No. The standard is usually in Phase 1 research you'd actually start on healthy subjects where there's no benefit. The only reason you do it on diseased groups is if the risk is so high that you can't do such clinical trials on healthy subjects that you start doing it on sick patients. But if it's not so dangerous, normally Phase 1 research you'd want ideally to have healthy subjects for whom there's no issue of benefit at all for your clinical trials in Phase 1 and Phase 2 research.

Woman: (unintelligible).

((Crosstalk))

David Magnus: (Phase 1) determining maximum probable dosage.

Irving Weissman: So the ones I've been involved in, they always had the potential for benefit. And of course the more intrusive the Phase 1 procedure the more that you look for it, potential benefit, even though you weren't going to do a randomized trial that would tell you that there was a benefit.

Henry Greely: Potential for benefit to those specific subjects?

Irving Weissman: Yes. The subjects.

David Magnus: Not in need for the earliest part of the Phase 1 would you start at doses that are far sub therapeutic. You certainly wouldn't want…

Irving Weissman: We always did include in the stuff we were doing that if the dose was too low and this and that there was a way that the patient could come back into the trial if the higher dose Phases were being invented.

That - and that was…

It was always and I don't (unintelligible) seemed strange to me. It was always that you were delivering a therapeutic agent that prevents disease and if everything worked out it could have been the patient. And then if you weren't doing one into a subject that didn't have the disease (unintelligible).

David Magnus: But that's a different requirement that you have to understood is this for disease that they suffer from (if you get that into) disease (unintelligible). The issue about whether they're going to benefit (unintelligible) based on the research.

Henry Greely: Let me suggest that we continue through the list, but we'll come back to this. I think this the particular…

((Crosstalk))

David Magnus: …and I agree with that. You are one of the one that we thought some of this category on the somewhat controversial that we should talk about.

Because of the high risk of any "first use" in humans trials, we also thought (unintelligible) the trial and it initially should focus on serious life threatening diseases, chronic diseases that have a dramatic negative affect on quality life of participants.

This is a sort of way getting at the so called enhancement issues. So rather than having the early trials on things that we've might be seen as…

Henry Greely: Baldness for example.

David Magnus: Which I consider to be a chronic, personally a chronic disease and has a dramatic negative effect on quality of life.

Henry Greely: I thought it was enhancing.

David Magnus: But the first trial should be for fairly serious conditions.

Man: It seems to me there's a contradiction between your previous point and this point.

David Magnus: No. I think there is a difference between again whether or not the subject themselves are going to benefit as a result of participation, especially in early phase research and what sort of areas that you focus on. (unintelligible) this issue.

You can, right even if it's true that the early Phase 1 subjects won't benefit doesn't mean that don't lose hope that you're going to head for the therapy that will benefit some other people or maybe some people in Phase 2 or Phase 3.

Man: We are going to come back and assess these things later.

Man: Yes. Okay.

David Magnus: And then the ninth one the committee should discuss whether participants in clinical trials should, or should not be paid for participation in the research. And so either we take a stance on this or we shouldn't that we do, we should have a stance of some sort. So our subcommittee took no stance on this issue.

And then we can also concluded that - or again this is something we should discuss- should IRBs recognize research subjects and research donors as distinct categories of research for us to consider. That's pretty much it.

Henry Greely: Okay.

So what I suggest we do is have a discussion of these points to see whether we think that definitely think to once the drafter of the guidelines to incorporate. There are definite things we don't want the drafters of the guidelines to incorporate.

To understand that the drafters of the guidelines some set of this group will come back to the full committee and probably in the fall and will have another opportunity to say yes or no or a third category. The things we have of we want the drafters draft both ways or to think seriously about, but we're not sure yet, whether we're (unintelligible) completely in favor of them or completely opposed to them.

In addition, to looking at these 10 or 11, I guess now, points that Dr. Magnus brought out, if anyone has other things that I think we should

include in our recommendations with respect to clinical trials that the working group didn't come up with, now is a good time to state them.

And last before I shut up and turn it over to the committee. Remember this is… there are more proposed changes here vis-à-vis the CIRM regulation than we'll see in the other part, because the (CIRM) regulations don't focus on clinical trials at this point.

I suspect we all believe that they will at some point as clinical trials CIRM funded clinical trials become closer or at least they may, but at this point they don't.

So there is more for us to say about clinical trials particularly since these guidelines presumably presuming that they don't sunset, that the whole authority doesn't sunset next January 1st would govern things like Geron's clinical trials if done in California of which we've already heard may happen as early as next year.

David Magnus: Thank you. Could I make suggestion that we first (unintelligible) up the ones we have quick agreement on (unintelligible).

Henry Greely: I think that sounds good and (David) why don't you propose which ones you think those are?

((Crosstalk))

Bernard Lo: Before we go to that, (unintelligible) this clinical trials carried out in the state or is it also part of the organizations in the state who are sponsoring clinical trials (unintelligible)?

Henry Greely: That is an interesting question.

Bertram Lubin: And which was brought up by Geron.

Woman: Yeah. Good question.

Irving Weissman: So (unintelligible) receive CIRM funding, they could do clinical trials outside the state? An entity could.

Henry Greely: Right and then they have to go through the CIRM regs and not our guidelines. They'd be exempt from our guidelines.

Woman: But it's Geron (unintellibile)...

Man: And that we dictate the mistake (unintelligible).

Henry Greely: We could if we, the legislature could if it wanted to dictate to California companies...

Woman: Yeah.

Henry Greely: What they can and can't do.

Man: Do we know what they're saying? Do we have any guidance on this?

Henry Greely: I'm looking at statutory language, why don't you go forward and discuss what you'd point out the things you think are non-controversial and I'll see if I can give you (unintelligible). Am I the only lawyer?

((Crosstalk))

Henry Greely: Radhika and I can both just take a look and see if we can provide any guidance on this.

David Magnus: So I think the fact that we should follow all federal regulations, entitled to know where their cells comes from, that there should be ESCRO oversight, that there should be that safety should be (unintelligible) by the IRBs

((Crosstalk))

Elliot Dorff: Can I mention something on point Number 2?

Man: What's the question about this 2?

Henry Greely: Hold on Elliot is that you?

Elliot Dorff: Yeah. Including the facts that embryos - well first of all, you know, (unintelligible) from before should change the language of embryos to (concepti).

((Crosstalk))

David Magnus: Be proposed. This sort of the areas being proposed that will then be, that people have to look at and draft. So the question is, the concept of being proposed here that people should be told what the source is because they may have moral objections….

((Crosstalk))

Elliot Dorff: But before we go any further with it we might as well be - if we are telling the legislator not to use word embryos then we shouldn't use the word embryos either.

When we are talking about the things that from which stem cells are going to be coming or at least part of the stem cells that are going to becoming, then I think we should say concepti.

And then the other issue is this as including the fact that concepti may have been created to produce the intervention, or is that being allowed?

Is that - my understanding was that it was only going to be embryos that had been frozen from IVF procedures that were going to be used. That sounds as if we're saying that it's allowable to create embryos or to create (concepti) for this purpose.

Henry Greely: That is not illegal in California.

Woman: Even (unintelligible).

David Magnus: Right. Correct. And in fact that I think there's assumptions that that will happen.

Henry Greely: And such - I think UCSF is already proceeding because received the approval or is in the process of receiving approval to do that very thing.

Elliot on your first point about the language, yes we all agree that we need to be very careful and use language properly and that will happen between this meeting and the next meeting where this precise language comes forward.

Elliot Dorff: Okay.

Irving Weissman: But I don't want to (unintelligible) by the language we send on to this poor committee even though they are here, right? I don't want to (unintelligible).

Man: Right.

Woman: Yeah. Yeah.

Irving Weissman: So I think I want you to use the most accurate (scientific language) and add a little star that says some people call it like this, some people call it that. But I want the language to be adequate.

David Magnus: And it should be sufficient that the average participant in the research should be able to understand.

Irving Weissman: Good, because when you actually talk to the average participants about drawing embryos, because I've done this many times, they draw a (fetus).

Man: Right.

((Crosstalk))

Irving Weissman: So you tell me about the language that's commonly used by the average participant.

Man: Right.

Irving Weissman: So I (unintelligible).

Henry Greely: Your point's well taken and I agree with Dr. Dorff's point and the drafters will be so instructed.

((Crosstalk))

David Magnus: First 5 and I think half of 6 that there should be a (DSMB) that - that what the two (DSMB) reports to (unintelligible).

Henry Greely: Okay. I'll take questions and comments on the first side and the first half of the second.

Man: Great.

Gregory Stock: Number one, is it necessary to reaffirm the need to make assurance to regulatory requirements that are federal? Why is that important…

David Magnus: Just to make sure that nobody gets confused about thinking that state regulations trump federal ones or supplant them, but it can't hurt to put them in there. I think this was Bernie's suggestion on our sub committee that we reaffirm this and I don't see any reason why we shouldn't.

Henry Greely: (unintelligible) is a well-recognized long precedented procedure in legal drafting.

Gregory Stock: In number two, are you saying that they should always be informed that embryos may have been - the embryos, or whatever you may want to call them, may have been created or destroyed or if that was the case…

((Crosstalk))

David Magnus: If that was the case…basically the source and whether for some people who might morally object to the - what - in light of those issues (and/or cells) they have the right to know where those came from.

Gregory Stock: So you were saying that any cell line should have a history associated with it?

David Magnus: Correct, certainly.

Gregory Stock: There - I'm not sure, it doesn't seem to be a problem obviously but it's not…

The use of actually the research oversight committee; is that always going to be needed. In other words, are they just waiting with such expertise? It's not necessary. Would it be possible, for instance, to direct them to consider whether they have the expertise to fully evaluate a proposal and to seek assistance or something of that sort? Do you need a blanket statement that anything that comes up…..

((Crosstalk))

David Magnus: …just for clinical trial. It seems to me that all clinical trials will require an ESCRO oversight.

Henry Greely: And do - I believe under - would under the CIRM regulation, and do under the National Academy Guidelines.

Gregory Stock: And then in Number 4, you're requiring the testing of donors, I think that the emphasis should be on screening and then putting that with reports that we have.

David Magnus: Testing and probably testing and/or screening.

Gregory Stock: And I think it should be - the screening is more important because the testing can probably…

((Crosstalk))

David Magnus: …it could be that it - and again, it's going to be a safety issue and I want - you know, we don't know what this issue could be. It could be there are some prions that they're interested in that for whatever reason it's going to be hard to detect in the embryos (unintelligible)…

Henry Greely: Just to clarify what that - what Number 4 is about, is that they are - we should make sure that the informed consent informs people that they may be tested or screened, right?

David Magnus: No. We thought the IRBs should be told (unintelligible) that things - that it might be appropriate for safer…

Henry Greely: ...for the IRBs to require…

David Magnus: …to be tested (unintelligible) because of the informed consent consideration now because if - you're right, right now if you're a researcher, (unintelligible) stem cell line, and you may say, "I'm going to deal with an (anonymity issue or confidentiality issues)"

And then later it turned out that that's some really nifty cell lines that I think actually would be useful in clinical trial; like don't have any way of recontacting them. I might not very well be able and they will not be able to do clinical trials with that material.

So the good news (heads up) they could think about that now; it's going to be an issue (unintelligible) FDA may very well not allow them to use such material. They don't have any mechanism (for recontacting).

Bertram Lubin: So what you're really saying it's inclusive - it includes screening or testing that seem appropriate at the time it would be useful (unintelligible) whatever that is.

David Magnus: Correct.

Man: Okay.

Man: Number 5?

Irving Weissman: So, is it clear now? I think it's pretty clear enough that if somebody puts a human (unintelligible). And then follows it to the blastocyst stage that that is not considered (unintelligible)…

Man: Correct. Okay.

Irving Weissman: (unintelligible).

Henry Greely: But the language should make it clear.

Irving Weissman: The language that we used was - for its purpose to be defined (blank, blank, blank), it's the placement in the uterus of the human blastocyst (unintelligible).

David Magnus: (unintelligible)…

((Crosstalk))

Irving Weissman: Because you don't want to have somebody have a very important experiment they think they need to do and realize they are prohibited by the language.

Henry Greely: Good point.

((Crosstalk))

Man: A draft is, I'm sure…

((Crosstalk))

Bernard Lo: (unintelligible) talk about the action and not the intention..

Man: Yeah.

Man: Okay. That's all of my comments literally.

Henry Greely: Any other comments on one through five plus the first half of six?

Gregory Stock: We're requiring the (DSMB) it's not clear to me as there should always be a (DSMB) and once again that's something that should be absolutely required where it should be recommended and that be considered. I have the tendency…

David Magnus: I'll take this for, from the time being, for these early trials I think it should require the (DSMB) when using this kind of trial.

Gregory Stock: When you say things like at least for this early trial. That my experience that there usually is not a reduction in the amount of overhead that's done.

So, you know, if you really feel that, then you should have something that should have a sunset on…

((Crosstalk))

Henry Greely: We hope they won't.

David Magnus: But - so I think that would be reasonable for somebody to put in quotes.

Bernard Lo: Right. And I mean, I guess - can some of you give example of a - and (health) clinical trial that is not required…

((Crosstalk))

Man: …bone marrow transplant…

((Crosstalk))

Henry Greely: Thirty years from now, when this is standard of care and routine…

((Crosstalk))

Henry Greely: …minor tweak. So it's been a trial of a minor tweak, at that point it might not be appropriate but presumably someone else would have modified these guidelines or they will have sunset by then.

So any other comments on 1 through 5-1/2?

((Crosstalk))

Bernard Lo: And one thing for me, these are all - can refer to independent data safety monitoring board not controlled by the sponsor –they report to the sponsor but they make their deliberations independently. I think a separate issue which I think 5.5 following through voice a relationship (unintelligible)…

I would encourage be consistent (unintelligible) for other clinical trials on both innovative intervention; cancer trial and gene transfer trials prove it; I don't think we should try and do something inconsistent with or terribly different (unintelligible)…

Man: Okay.

David Magnus: But there are also the realities that there are criticisms in the way (unintelligible) because of the nature of the reporting to sponsors, even though theoretically they are supposed to be reporting to the individual institutions (unintelligible) that you note there are cases where that has not happened (unintelligible).

Man: Right.

((Crosstalk))

Bernard Lo: …reports of clinical trials and other research and it can attribute - they don't have the denominator and it can't (unintelligible). We need to be careful and I think we - what we're trying to do is right and we need to make sure that we could set up something that does what we want and don't think it has undesirable consequences.

Henry Greely: So let me suggest that at least for the time being that we move 5.5 into a category of we want the drafters to examine it, deeply think about it, come back and to recommend to us which may or may not include this requirement depending on what they found out.

Bernard Lo: I think, you know, (unintelligible) because the series has (unintelligible) but you know, there is, you know, they're going to be continuing to have trends that are kind of worrisome which you're not sure if they're statistically meaningful…

Man: Right.

((Crosstalk))

Henry Greely: So what about Number 7? This is one that I think there is likely to be at least some questioning, if not controversy about.

The - let me see if I can state this clearly, the point here is that with - early phase research in the first (hESC) clinical trials recognizing the appropriate cautions people have applied to both those terms, IRBs should start with the presumption that there is no prospect to direct benefit to the participants in the early phase research.

And the informed consent and other regulatory requirements should reflect that finding.

I think part of the earlier discussion that went on was a little bit skewed people talking past each other a bit because my understanding is Phase I trials in some areas are always done on sick people, on people with the relevant disease, particularly as they are dangerous trials where it would be unethical and inappropriate to subject a healthy subject to it.

But in many other medical areas you do it on healthy young subjects like the 22-year-old male in Britain who had a terrible (illness due to monoclonal antibodies) a few months ago.

So there are two different models now whether in fact you would do ever think about doing an early stage (hESC) trial for anything other than sick people and a sick (case) strike me as very unlikely. But we're now dealing with sort of the other side of it where you're putting it into somebody who is, you know, ill with the disease that you expect this (hESC) derivatives - (hESC) to do something about.

Is there for the very first trial a prospect that the individual subject in that trial, not the field as a whole or people with the disease as a whole, will be personally benefited by that trial?

The term prospect to direct benefit comes from the part of the common rule dealing with children; does not, I think, appear in the part of the common (rule) dealing with adults. I'm recalling correctly.

Elliot Dorff: My recollection, I was on NHRPAC, National Human Resource Protection Advisory Commission and when we dealt with the common rule and changes to it, my recollection was that, if you're talking about Phase 1 trials by definition you're talking about something which would not - which is not expected to be of any benefit to the participants with the exception of compassionate use.

So as the compassionate use kind of things is like for example, an AIDS trial where you have somebody in advance stages of AIDS where you are in fact trying Phase 1 drug because there is nothing else to try. But otherwise if you're talking about a Phase 1 trial but almost by - I think it's really by definition you're talking about a drug or a procedure that has no prospect of direct benefits of the participants.

Henry Greely: Yes. Some of the oncology trials I think are probably a little differently than we will differently were they hope they've got some reason to hope that it might help somebody.

But it usually turns out but it doesn't. Great.

Gregory Stock: Great. I think that a more robust way of putting this would be that there should be (unintelligible) one should strive to be absolutely truthful about the benefits and risk the researcher would develop.

Because, I mean it's given but it seems to me to put this in place here is why this rather than any other trial?

David Magnus: Because we do such in other frontier research particularly in gene transfer research we've done such an abysmal job in the informed consent process for that.

And you could see even in our speaker from Geron I think the language that - although she read it principal that (unintelligible) as extremely unlikely if certainly for the first people in those trials that there were would be no benefit.

The language that is typically is done is what (unintelligible) exact word placement there is it's "unknown whether there is going to be a benefit".

So (unintelligible) this may or may not benefit you. As you look at this social scientists who've tape recorded informed consent sessions for gene transfer trials that's often followed by statements like "of course that true for any therapy that we don't know that". And so under those circumstances the fact that overwhelmingly we find that subjects were enrolled in trials that have very little to zero chance of offering a prospect of benefit to them that their expectation is that they will get benefit and they believe that's the intention of the research…

Gregory Stock: If I'm understanding it correctly, you're saying that to be honest about (unintelligible) benefits would break new grounds.

David Magnus: Correct.

In fact, if you look at the informed consent forms for gene transfer trials (unintelligible), you can see misleading language used in the consent forms themselves that will make it almost - which continues to reinforce the idea of (unintelligible) benefits. We see overwhelmingly things like, "we are going to put a gene into you that replaces what's missing" and you see these descriptions that make it sound like you're getting therapy that will help you, followed by a concept with exertion later on that this may or may not benefit you. Again anybody would be under a misapprehension about what the goal of the research ….

Henry Greely: I've got Dr. Lubin, Weissman, and Lo.

Bertram Lubin: I hear you. I'll pass to the other two.

Irving Weissman: Well I just like to before we address this, I'd like to make sure that we say, point ten, that for a research donor (a donor of materials) with the possible exception of sperm donors there's no possible benefit.

To the donor, right? Now, we move on. And say now for the patient you don't want to mislead them because, I see where you're coming, because it could be used to entice somebody into a trial you want to make sure you guard it. But you're not walking in like a stupid person who hasn't done tons of pre-clinical work that convinces you that it's important to do the trial and with this patient population. You see what I'm saying? I'm trying to get your intent but I bridle at the statement that I'm about to put you under a therapy of which I believe there is no possible benefit. I don't believe that. I wouldn't do that experiment. I wouldn't.

Henry Greely: Dr. Lo.

Bernard Lo: Well I think it is worth (unintelligible) there's a bunch of issues here. I think if you go back to, and you're right Hank I've checked the (unintelligible)…..

It serves two functions. One, is to alert the IRB to pay attention to the risk benefit ratio.

And not to misestimate the benefit that accrues to the individual subject when there is a (unintelligible).

The second is with the informed consent. I think it's important that we understand which is it we are dealing with. A lot of the discussion in literature, I agree, is about the problems with the consent process. Now the recombinant DNA advisory committee as a result of Nancy King and Gayle Henderson's work now has what I think is a pretty good Web site on how to explain (unintelligible) gene transfer trials and what has evolved is an excellent. What is the research aim?

The requirement now is the research aim is very clear (unintelligible). Is it safe to put this into human beings? We want to see if this gets to the target tissue which we hope it gets to. And not to (unintelligible) if it's effective or not.

I think there are ways of phrasing it that I think really go to what Greg was saying. You've got to be truthful; honest about what it is you are trying to do and what the person might say.

And that's a different slant that seems to me then say, you know, you should just assume there is no direct prospect (unintelligible).

Gregory Stock: Even the use of the term direct is very much when people really reacting. Often they're thinking about larger effect so to just focus on what's direct and not the indirect or the longer time frame consequences.

Bernard Lo: Right.

((Crosstalk))

David Magnus: (Unintelligible) languages because there is some benefit to being enrolled in research even if the intervention under investigation doesn't don't do anything. Just the fact that you're in a clinical trial it has some value to people.

Man: You get to see a doctor.

David Magnus: They're seeing a doctor they might not have otherwise…there's some value just for coming in.

That's I think one of the reasons why the regs use that language "direct benefit". So it's (the benefits of the) intervention as opposed to the benefits of being there. And some trials also combine an intervention under investigation with other interventions that would be standard care in case you wanted to distinguish between the action of the intervention under investigation and the benefits from the (unintelligible).

Gregory Stock: Plus it's about honesty because you're being very linear also. People when they feel they're contributing to progress in a field which there is no cure, they often have responses that are positive and feel that they want to be involved in that.

So that they try and say be so narrow, I think it's the bad way of putting it.

Henry Greely: Boy, to accuse a philosopher of being linear it's (unintelligible). Dr. McLean.

Margaret McLean: I'm wondering if we need an adjective there that would say, no direct or I'm not going to quibble about that medical benefit or health benefit or something along that way.

Because there are these kind of intangibles of, you know, we could be a benefit to me to know that I might be helping someone else and that just attitudinal thing is a benefit to me.

So I wonder if we ought to, you know, maybe find an adjective there. The second thing is that it seems to me that informed consent in this case is likely to be, you know, kind of a two step process. In other words, you know, there is the informed part and then the chance to be certain that that information is being processed in the way that we're often not certain that that information is being processed.

And then the kind of consent piece to that once assured that the language is understood and, you know, the risk benefits are understood. And so it may be a thicker description of informed consent than we often use.

Henry Greely: Bert?

Bertram Lubin: Hello David I appreciate your (unintelligible) because this is a major area the NIH has taken a look at how IRBs are functioning. I mean, we're talking about sort of providing guidelines for our IRB.

If your IRBs don't do what we've been talking about here, (unintelligible) good IRB. I mean, there's serious concern at all institutions that do research about what the IRB does and what they ask and these are generally not scientists sitting around. They're people there to protect the rights and to know that whoever says they'll sign up, understands what they're doing and what the potential outcomes could be.

And maybe I just have more faith in the IRB system because I think we have a good IRB, but maybe - I don't see how (unintelligible) regulate IRBs which I think we're talking about.

David Magnus: But if you look empirically at this - so if you think of gene transfer research as a comparable, cutting-edge research, that's a good analog to what we are talking about, there's a lot of empirical studies about how

that's done and the IRB's are clearly not doing a good job. Because if you look at informed consent forms that went through IRBs, they're full of misleading language. You look at all…. there are maybe 2 or 3 studies published in the past year or two about informed consent forms and how awful they are. And that does not even count how - what actually happened in the actual consent process verbally where there's not as much data, but what has been collected was terrible.

Henry Greely: Okay, let me make a suggestion. I think based on what we've heard, this sounds like something that is worth thinking about as we're having somebody try to draft something up on taking into account all that has been said today.

It may not be something that we end up in September or whenever. Actually, it's (unintelligible). But I think we should put it in the category of something the drafters should take a shot at; as informed by the discussions that we've had, and move to Number 8, which is the one about first use in human trials should focus on serious life-threatening diseases or chronic diseases, et cetera, et cetera.

(I'll comment), this would apparently be and say that the first few trials - so I don't know whether it means actually the Number 1 or early use trials should not go for relatively minor conditions because the unknown (unintelligible) first use are substantial. (unintelligible). Dr. Stock

Gregory Stock: I see, but just as in the previous one, where we're saying that actually there are very few direct benefits. Immediately you're trying to establish a technology for that very reason. What the target is for the technology, the ultimate target, the link to try and link it to a serious disease is basically trying to piggy back on that sense that – oh that's something really serious that were going after here and that's why we should be able to do this or that.

It seems to me this, the IRBs once again, we should have confidence in the IRBs and we should direct them, perhaps, to make serious considerations or give serious thoughts to the risks and rewards that are involved.

But, you know, if it's for something that's not at all serious and there's progress made in that, undoubtedly it would have significant consequences for other diseases that are far more serious. So I think that we should make that kind of prohibition.

Henry Greely: Dr. Lo.

Bernard Lo: There is a ongoing clinical trial with something called ("Condrogen") which is a (mesenchymal) stem cell, adult stem cell, for people undergoing meniscus repair. Now, I don't know if meniscus repairs count as chronic diseases that have dramatic negative effects on quality of life (unintelligible).

Woman: Uh-huh.

Bernard Lo: But, I know, we're saying that we really want them for, you know, AIDS cancer-type thing or it's a kind of quality of life (unintelligible).

Man: That's right.

((Crosstalk))

Irving Weissman: I would agree with (Bernie) because I think that whole groups of people and whole companies can decide to go for a target that's not a life-threatening disease. Yet, it would be life-enhancing, maybe very enhancing initiative (block), (unintelligible) all that sort stuff.

So I think that putting this in doesn't do what you really want it to. You want to protect people but you want to protect people who are healthy that's what you want. And it seems to me that you're blocking a whole line of research and therapy that doesn't need to be blocked.

David Magnus: To be honest or so, I don't have any particular views about this one. The issue was raised - I think was raised by Bernie about the (draft in the) enhancement issue. So I think, you know, I don't try to (leave) with the enhancement versus therapy with patients, so this is the way of getting it first pass at that concern that we raised in the…

((Crosstalk))

Henry Greely: Is there any voice in favor of Number 8?

You know, you don't have Number 8 in front of you. It says process because of high risk of any "first used in human" close for trials. Early (hESC) Clinical Trials should focus on serious life-threatening diseases or chronic diseases that have a dramatic negative effect on the quality of life of participants. I guess the test we all kind of understand this thought behind it but that doesn't seem to be any strong support for it (unintelligible) strong support, Elliot?

Elliot Dorff: Another way to do it is to just simply say that because of the high risk as any first used in human trials, early human embryonic stem cell research should take into account the risk benefits. It should be sure to think seriously about the risk-benefit ratio.

Man: Which again, you know, really goes back to this issue of IRB doing their job properly, right?

Elliot Dorff: Right, exactly. But, you know, probably we would be then saying is that, you know, with this kind of research into this some new and therefore so risky, that they should be or, you know, they should re double their efforts to make sure that they evaluate the risk-benefit ratio carefully.

Man: (Very good).

Man: I agree with this completely. I guess I'm kind of confused that the - one of the things we do. A lot of what we do such as - like (exploitation) in IRB, we do a better job of what we're supposed to be doing.

Woman: Uh-huh.

Man: That we think there's…

((Crosstalk))

Man: But, you know, what this - I'm sorry, go ahead.

Bernard Lo: …do a better job; but I think it would really (unintelligible) you don't think IRB handle this, and their implication could thrall (unintelligible).

You know, I'm trying to get a sense of what, where we are headed (unintelligible).

Bertram Lubin: …I think David - when his comment struck something to me that I thought wasn't something I appreciated in my remarks and that is the gene therapy, we're not doing a gene therapy trial. So this might be a different IRB that even thinks about.

Now the ESCRO supposedly looks at that. But nevertheless, maybe IRBs that deal with the embryonic stem cell requests should have some guidelines on what they should be thinking about in terms of those because not everybody will be doing these. Because a fair number at least initially, and maybe somehow in this state we could say, these are things the IRB should plan to think about if they go along. It's like we learned from the gene therapy or monoclonal antibody infusion some of the more esoteric and less common clinical trials.

Man: I have Dr. Weissman then Dr. Stock.

Irving Weissman: So the problem is starting to revise (unintelligible) in this trial which I favor.

Woman: Okay.

Irving Weissman: Is that it implies without any evidence that there is high risk in the first trial. And I can conceive of many ways that you take embryonic stem cells down to a differentiated cell line and separate them and show in animal trials ad infinitum that they don't turn into tumors and you use it for disc repair, or meniscus repair, or filling in a defect (unintelligible) didn't work so well.

You know, there are many ways which could not be life-threatening condition. And if you bring in the assumption that this is high risk, you're prejudging the (field). There's no way to know that it's high risk.

David Magnus: So it's like - I think I get this language from Bernie so…..

((Crosstalk))

David Magnus: ...but it doesn't say that, actually to be fair, it doesn't say that early hESC's are high risk. What it says is that in general, there's a high risk of any first use of human trial (unintelligible).

Henry Greely: Success has a thousand parents, failure is an orphan. I'm beginning to think that Number 8 is a failure. Greg.

((Crosstalk))

Gregory Stock: Okay, I agree that we should drop 8 but the second thing that I see, it seems inappropriate in the discussion. These really are sort of exhortations to institutional review boards, but at the same time we said the IRBs aren't competent, therefore, we want ESCROs to be dealing with it. But in fact ESCROs probably aren't competent either so we're going to come up with, you know, here's what they should be thinking about.

So what's the use of having ESCROs - requiring ESCROs? I mean at some level you have to say there's a regulatory group that's going to be able to make case-by-case decisions to be clear, understandable and accurate about communications of risks to patients and to make decisions about risks and benefits.

And - because you would be [wanting] to go for a low-hanging fruit, I mean, you'd want to be going for easy things often. So we have to leave it to them.

Bertram Lubin: But I thought the ESCROs were the science and the IRBs were protection of humans that participate in science?

David Magnus: It's actually variable for it. I mean, ESCROs are also dealing with the ethics (unintelligible).

Henry Greely: And IRB's have to assess science as well to do the risk-benefit analysis. Radhika.

Radhika Rao: Yeah, I don't understand what (unintelligible) the IRBs are incompetent or not doing the job, so much as that the current informed consent disclosures are subject to misinterpretation and that perhaps in order to protect against the possibility that patients or people with diseases were going through clinical trial would misinterpret the, you know, the clinical trial and hopes that they would be benefited. In order to correct for that, they sort of overcorrect a little bit by telling them "look, there is no prospect of direct medical benefit to you".

As opposed to simply saying, we don't know whether there will be any benefit and then having somebody go into clinical trial hoping what that means is that - well, that really might be a benefit to me.

Gregory Stock: So to me…

Radhika Rao: So, just to be clear.

Gregory Stock: …you're being generous because I think it's obfuscation. If you go to something that really has very, very, very little chance of there being a benefit and then you say, "We don't know whether there is benefit or not." You're trying to mislead the person.

Henry Greely: I believe that in terms of risk-benefit analysis, further discussion of this probably isn't justified which is not a comment on anybody's contribution.

((Crosstalk))

Henry Greely: So let's move to Number 9.

David Magnus: (unintelligible) one question about 8, which is - so, if we get 8, get rid of 8 which I'd be happy to, the question I just have is - so I just had in my notes that there was an issue about enhancement.

So now taking 8 off the table, that was my first shot at handling the enhancement issue. And I should say, being honest about it one of the reasons why it doesn't say enhancement is truthfully because I don't personally believe in a distinction between enhancement and therapy.

So if there are - a concerns that Bernie - or anybody else might have about enhancement uses of embryonic stem cell research, I think it will be important for that to be put on the table now and express whatever language it should be. That should be on the table now.

Henry Greely: Bernie?

Bernard Lo: Let me try and clarify. My concern is with the review process - that when you have an innovative clinical trial that uses a technology, methodology (unintelligible) whatever that is.

There's a great opportunity to misunderstand the science. You're not appreciating it, and not really critique the preclinical work and say "well the FDA approved it (so it's got to be pretty good)".

Man: Yes.

Bernard Lo: And so, I think the - there is - I do have a concern about the review process with innovative clinical trial which (some stem cell trials will be of that nature). I think it's fine to someone on - I think the example Irv gave is very apropos I mean, if in fact, it goes to say, "Look, this is what they've done, to really minimize the risk it's not a pluripotent cell it's not even multipotent cells at this point it becomes really (unintelligible)". Someone needs to review that. And I'm not sure the FDA can be relied on to do that because their deliberations at this stage are not public.

I don't think the IRB should do this. So my concern is - I mean, part of this – one way you can try and address that is just to look at what (unintelligible). The real concern is the process of doing this kind of review.

So - and I think that's something in which if we want to go there which I'm not sure we do (unintelligible) starts to think well - is the IRB process (unintelligible) the optimal way to do this? Is it the appropriate way to do this?

David Magnus: So you suggest that we have that - that we just with this kind of issue endorse ESCROs as the solution or do you (unintelligible).

Bernard Lo: Well, I think we need to sort of think through (unintelligible) we think is the problem that has to be the nature of the review process as opposed to some institutions don't have IRB that are as great as we'd like them to be. So - because, you know, the solutions are very different. The mechanism is pretty sound but it doesn't always play out (unintelligible) it's so flawed that because of the way they're set up, who's on them, in charge. Now the ESCRO concept way of saying that the very nature of IRBs doesn't deal with issues that are very germane to some of this research that needs to be (dealt with).

And so, we're going to put a whole new regulatory body. There is a rationale for that but I think it's important that we're trying to think through what's the nature of the problem, how serious this is before you start trying to (unintelligible), you know, at the risk of sort of overstating (unintelligible) what is it we're trying to accomplish, what are our concerns (unintelligible).

David Magnus: Since you've already recommended ESCROs for all of the clinical trial, (unintelligible) you're talking about here?

Bernard Lo: Well, and ESCROs don't necessarily have a biostatistician they don't have some (unintelligible).

Henry Greely: Okay, I think those are valid – they're useful points to be kicked over to whoever starts doing the draft and to think about because I don't think we're going to usefully follow them up right now. You know, we have other things on our plates like Number 9. Which says, believes the whole committee - the subcommittee working group believes the whole committee should discuss whether participants in clinical trials should or should not be paid for participation.

David, are you going to say anything?

About that?

David Magnus: Yeah…

((Crosstalk))

Henry Greely: That's what it says.

((Crosstalk))

Henry Greely: Comments?

Bertram Lubin: Have you (separated) donors from subjects?

Henry Greely: (This is) participants in clinical trials, so…

((Crosstalk))

Henry Greely: …so it should be subjects in clinical trials, okay.

Woman: Yeah.

Bertram Lubin: So IRBs do permit reimbursements for time off work or for other things that they do. They don't permit a thousand dollars to enter in the study; but they do - there is something that the IRBs will permit for families that bring kids in if you're doing kids studies or whatever.

So there are some guidelines for this. You weren't referring to that or were you referring to that?

David Magnus: Yeah, (I believe), I mean, we've got some language about payments for…

Bertram Lubin: Not supposed to be an inducement to be in it, it's supposed to enable you to be in it - without losing what you do…

David Magnus: Actually, that's not true that all clinical trials do not, that prohibit payments of subjects. There are - have actually paid such inducements and there are some ethicists, (such as) (unintelligible). NIH has argued that that's okay, that that's no problem to pay people $5,000 or $10,000. The Lily studies they took homeless people and paid them substantial amounts of money to be enrolled in drug trials.

Henry Greely: The monoclonal antibody study was such (unintelligible) healthy young men who were being paid about 1500 pounds to a thousand pounds, something like that. For two week participation in one trial. That happens.

Man: (Yes).

David Magnus: So there is (unintelligible) in the ethics community there's a split about whether that's a good thing or bad thing.

Man: You know, but here we're really talking about donors I believe because…

((Crosstalk))

David Magnus: …so should we allow, do we want to take a stand…

Man: Yeah.

David Magnus: On whether or not subjects should be paid (unintelligible).

((Crosstalk))

Henry Greely: But Bernie, just point of information, is there, to your recollection, is there anything in the CIRM regs that could speak to this?

Bernard Lo: No.

Henry Greely: And with respect to the common rule in general it just falls under the no undue inducement, justice issues, et cetera, for IRB consideration?

So - and then the NAS guidelines. I do not believe speak to this either do they?

Woman: No.

Henry Greely: Because I don't believe the NAS guidelines by and large, they could all do clinical trials.

Man: Correct.

David Magnus: So this is a clinical trials issue (unintelligible). It could happen in 12 to 14 months, this could arrive. I mean Geron could pay people a thousand bucks (unintelligible).

Gregory Stock: To me, it feels somewhat inappropriate to try and take a stand in this issue where we're trying to deal with novel research and trying to address an issue that really has a great body of discussion that's associated with it. And there is some - what would be the purpose of making such - try to enter into that fray. You just need, let's say, it seems to me makes this more complex. I don't think we should take a position on it.

Henry Greely: Other views?

Radihka Rao: Is this any different from other forms of clinical trial research getting at the same point (unintelligible) we said that, currently the regulations don't necessarily speak to this issue and it - or maybe as dangerous as the kinds of clinical trials we're talking about it. Should we have different recommendations?

David Magnus: So just to play devil's advocate on the issue of (paying) donors. They obviously were similar (unintelligible), differences of opinion in the ethics community (unintelligible) that. It was an argument that given the controversial nature of this area, it would be politically prudent to err on the side of caution and so, similar kind of argument could be made that

given controversy about payment that there could - we could make an argument that it would be prudent to be on the more cautious end of things (unintelligible).

Gregory Stock: So my feeling about that is that it is to try and take the - make political statements in this is prudent basically, and say "well people are going to attack this research, it's a new kind of research".

Therefore, we should try and lean over backwards and do absolutely everything we can to protect us from such criticisms, which actually will not protect you from such criticisms anyway. Those aren't the real points, so I think it's a mistake, that approach (unintelligible).

Henry Greely: Is there anyone here or Dr. Dorff via phone, who is in favor of us writing a guideline that would ban compensation?

((Crosstalk))

Henry Greely: That would attempt to regulate compensation of research subjects in clinical trials.

Irving Weissman: This is vital information. So the common rule says no undue (inducement).

David Magnus: No undue inducement which is vague (unintelligible). That's a hopeless concept and it's not clear that it applies to anything (unintelligible).

Henry Greely: But it's there. It's in the rules. I think.

Man: Okay.

Henry Greely: Certainly IRBs can say that they're applying prohibition on undue inducements.

David Magnus: (So exactly, what that means?)

Henry Greely: Right.

((Crosstalk))

David Magnus: …in practice people are often paid several thousand dollars to enroll in trials and as a way of motivating them, that's the reason why they do tha. - was (Zeke says and his argument is) if it is too risky for them to do then you shouldn't approve it in the first place. If it's not too risky to do the research, why not? Pay them, try and get to enroll.

Henry Greely: Let me ask my question again though. Because depending on the answer, we might be able to able to short circuit this conversation which at 4:21 might not be such a bad idea.

Is anybody in favor of us writing a guideline regulating compensation for participants in clinical trials?

I don't see any hands.

Number 9 is gone.

Woman: Uh-huh.

Gregory Stock: So is it worthwhile putting something that this research is not uniquely subject to specific prohibitions on compensation. It is not - does not warrant a unique - and, you know, to actually speak to the issue that you're talking about, not to say that people should be paid but to say that there should not be - this research should not be treated differently than other research basically.

Henry Greely: Perhaps, I think that's a good thing for drafters to consider.

Bertram Lubin: Also, another thing to consider, each IRB may have a different policy.

Man: Right.

Bertram Lubin: We wouldn't do our studies if we had to pay someone to enter into the study. Our IRB wouldn't let that go through. And maybe Stanford is the same way, I don't know (unintelligible).

Radhika Rao: I don't know. I see (unintelligible).

((Crosstalk))

Man: Well, that depends on where you are.

((Crosstalk))

Henry Greely: There are all sorts of different kinds of studies.

((Crosstalk))

Henry Greely: Payment is usually dealing with Phase I trials usually in healthy people. Not always, but usually in healthy people.

And then there's some reimbursement issues for sick people in subsequent trials.

Number 10, David, I think it doesn't really fit in the clinical trial side, can we move on?

David Magnus: Sure.

Henry Greely: Okay.

So we now move to issues in embryonic stem cell research other than clinical trials. The working group that examined this was Professors Dorff, Gage,Greely, Martinez-Masa, and Rao. Professor Stock was part of the working group; but I managed to schedule the conference call on the time when he couldn't participate in it. Nothing personal. Genuinely, nothing personal.

So we have fewer recommendations. But we do have a few. The first is somewhat controversial, maybe somewhat controversial and I think requires some explanation. And maybe one of those - I think it's going to fall into the category of where we let the drafters take a shot at it, and then see what we think about it.

It says, we believe that these guidelines should cover all (pluripotent) human stem cells whether "embryonic" or not. And that actually, was sparked in me by some work that I did with (Chris Scott) who's now in the room and (Kent Taylor) on the scope of the WARF patents, dealing with embryonic stem cells.

And some question about what we actually mean by embryonic stem cells, we've had enough debate about what we mean by embryo, but no one seems concerned about calling these embryonic stem cells.

((Crosstalk))

Henry Greely: If - for example, one were able to make stem cells from (a parthenote) would those be embryonic stem cells or not? If one were able to make stem cells from somatic cell nuclear transfer, would that be an embryonic stem cell or not? If one were able to dedifferentiate adult cells or intermediate cells, back to your basic completely pluripotent state, would that be embryonic or not?

Many of the risks involved would be the same presumably. The issue of whether or not you're destroying something, whatever it is which may or may not be human is different in some of those than in others and different in some peoples' mind than others.

But the idea behind this which I do think requires some careful drafting if we want to go forward with it at all. If it quacks like a duck, it's a duck and if it presents the same risks as an embryonic stem cell, if it has the same sort of pluripotency.

And note we're not talking about any kind of differentiated intermediate cells but a fully pluripotent cell, it is like what we understand human embryonic stem cells to be.

If it has those risks, these sorts of - these guidelines should apply. And that's basically what that short sentence is trying to capture.

Dr. Weissman?

Irving Weissman: So the hard part about it is of course, is the assumption that (unintelligible). So there's a claim out there for a long time from (unintelliglbe) that she has an adult bone marrow stroma line that is pluripotent. When she transplants it, and her claim is she doesn't get tumors…

….Now, the biggest danger of pluripotent "embryonic stem cells" is their tumorgenicity, right?

If you get rid of tumorgenicity what are you worried about? So, you might be more specific and say pluripotent stem cells that have tumorgenicity.

Henry Greely: Or that have risks similar to those of hESC?

Irving Weissman: Yeah, but then you're, assuming that we'll find out some more risks for hESCs.

Henry Greely: Which I think is…

Irving Weissman: Is okay.

Henry Greely: Not an unreasonable assumption.

Bernie?

Bernard Lo: Well, I think in addition of tumorgenicity is the risk of misdifferentiation sort of reaching target tissues that are not the intended target tissue and differentiating this (unintelligible) so I don't - I mean, that may be another concern (unintelligible).

Henry Greely: Dr. McLean.

Margaret McLean: Again I, you know, I'm vague on definitions and I think we have a little bit of, you know, kind of fuzzy definition here and it's only going to get worse as, you know, ethics is driving "novel ways" of deriving pluripotent stem cells.

And you know, and so there the proposal that maybe we can take a single cell out of a blastocyst and use that to develop embryonic stem cells and go ahead and use the blastocyst to create a pregnancy. Those kinds of novel approaches that have come predominantly out of the president's counsel on bioethics and some of which are actually being worked on in a laboratory really starts to push at our language a lot.

And so, you know, I just want to be certain that as we do this, we're really careful about language so that we, you know, incorporate some of these novel approaches under the regulatory guidelines. And don't, you know, wind up creating, you know, something that's so narrow that it actually is out of date before it sunsets on July 1, 2007.

So, you know, the language I think is maybe the kind of toughest piece of crafting these guidelines.

Henry Greely: So that's supporting number one?

Margaret McLean: Well, it's saying that Number 1, you know, it may be that we need to do a little thicker definition of what constitutes the pluripotent, you know, stem cell.

Henry Greely: Supporting the idea that we draft something - try to draft something along these lines.

Margaret McLean: Along these lines that allows for these some, you know, kind of "novel" ways of producing stem cells and doesn't exclude them from the regulatory guidelines.

Henry Greely: Okay. Radhika and then David.

Radhika Rao: I agree that you probably should - the guideline should cover all sorts of human stem cells. But the SB 322 specifically speaks of us developing guidelines for research involving the derivation or use of human embryonic stem cells which I suggest that, that's our charge.

But your information shows that the question of what is embryonic stem cells could be conducted, so it would required and because of all of these examples that you gave that could be conceivably interpreted to be embryonic stem cells presumably our charge encompasses (unintelligilbe).

Henry Greely: And (about) the definition.

Radhika Rao: Right. Uh-huh.

Henry Greely: And David?

David Magnus: Well, because of changes in the legislation or whether we can figure out a way of just finding through our charge which seems to me reinventing the wheel, it's not that great an idea, so I think that we should - two committees work this out…

((Crosstalk))

David Magnus: …we've got the definitions; I think we should just use whatever CIRM has.

And they - and for me, the definition of pluripotent line and then in their discussions of chimeras they talk about , uh… neuroprogenitor stem cells and that would just have to have…

((Crosstalk))

Henry Greely: CIRM.

You know, the CIRM guidelines which are in our packet in this marked up version and it's not entirely clear to me…

Woman: Page 2.

Henry Greely: …which color is - what the different colors mean? But on page 2, it defines covered stem cell line.

It covers - it defines it in 100020 C. Covered stem cell line means the culture derived human pluripotent stem cell population that is capable of one, sustained propagation in culture, and two, self renewal to produce daughter cells with equivalent developmental potential.

This definition includes both embryonic and non-embryonic human stem cell lines regardless of the tissue of origin. Pluripotent means, capable of differentiation into mesoderm, ectoderm, and endoderm.

Man: Uh-huh.

Henry Greely: But, you know, David that's useful, except for Radhika's point that our statutory mandated, limited to embryonic stem cells which is not true of CIRM. So CIRM could include things that were frankly not embryonic in its regulation.

Radhika Rao: We have to explain.

Henry Greely: We have to explain why we think some of these things are appropriately used for regulatory purposes as embryonic. And that's mainly to the same definition or similar definition that it requires a little more drafting.

Can I ask that we kick this to the drafters? And I have a feeling I know who may be a drafter on this one; to see if he, pronoun carefully in this case, then can come up with something that will make sense to us in September.

Okay, Number 2. We noticed that some parts of the CIRM regs are not relevant to these guidelines such as the limitation on what research could be funded by CIRM.

Although some of those funding limitations might be reasserted in our guidelines as direct prohibitions.

So again, turning to the CIRM regulations, they list in 100030 activities not eligible for CIRM funding. And they include six things in that category -- Human reproductive cloning, which is already banned by other statutes and by the state constitution;

The culture of - yeah, the culture in vitro of embryos, et cetera, "embryos" after the appearance of the primitive streak or 12 days. The introduction

of stem cells into a covered stem cell line - from a covered stem cell line into non-human primate embryos;

The introduction of any stem cells, whether human or nonhuman into human embryos;

The breeding of any animal into which stem cells from a covered stem cell line have been introduced.

Those are the first five and those are all, I believe, directly from the National Academy of Science's recommendations.

For CIRM purposes, it's fine for them to say, "We're not going to fund it." Because they're a funding agency; we're writing guidelines and we're not a funding agency. If we want to take into account those NAS guidelines, we would need to say we don't think these should be allowed.

Item F. I don't think has an NAS equivalent and I'm not sure - it looks like it was added subsequently, that is the transfer to a uterus - presumably human uterus, of a genetically modified human embryo.

((Crosstalk))

Bernard Lo: This came from public comments that raised concerns that CIRM funding - the development of genetically - genetic modifications that could be passed on to future generations.

Henry Greely: So it was a concern about genetic…

((Crosstalk))

Bernard Lo: …being used…

((Crosstalk))

Henry Greely: Right. I guess my view is we probably should write a prohibition, a guideline that prohibits A through E. All the same things that are prohibited in the NAS Guidelines. I'm less clear on F.

David Magnus: I have a caveat; one of those items, which is the one that corresponds to the clinical trial issue about, you know, how we should use the language of transfers to uterus rather than simply putting stem cells into an embryo, I think that's too broad. (unintelligible). Narrow language is better.

Henry Greely: Although, I don't know, I don't recall right now exactly what the NAS language is.

David Magnus: I think the NAS language is maybe more broad…

Henry Greely: We'll see if we can come up with a task that Irv can do.

((Crosstalk))

Henry Greely: As he had earlier pointed that out when I was handing around those documents, he said, we've finally come up with a task that I can successfully do.

Bernard Lo: One minor point…

Henry Greely: Yes.

Bernard Lo: …the 12-day prohibition because that was in Prop 71 (unintelligible) …

Henry Greely: Right.

Bernard Lo: ….14 days (unintelligible).

Henry Greely: Right.

But, most of the rest of the world goes with 14, or primitive streak, whichever is earlier. You know, I think if we were starting fresh, we might want to be 14 in compliance with the rest of the world but given that CIRM is already locked in statutorily to 12 there may not be - it may make sense for us to be uniform with CIRM particularly since as far as I know nobody knows how or has tried to keep the human embryos viable for more than about 5 or 6 days ex vivo. I don't know if anybody can do it for 12 days.

Final language of the NAS prohibition on introduction of any stem cells into human embryos. It's in that section - it's in the guideline that - okay.

((Crosstalk))

Man: …or in which any embryonic stem cells…

((Crosstalk))

Henry Greely: So it's not just for implantation.

David Magnus: So, because we had suggested that maybe we might want to make it more narrow and only not (unintelligible) transferred into the uterus.

Henry Greely: So this would be a proposal to make it narrower than both the CIRM guidelines and NAS guidelines.

((Crosstalk))

Henry Greely: Okay.

What about the genetically modified human embryos? Is that something we think we need to…

((Crosstalk))

Henry Greely: So, tell you what, on D, the introduction of any human stem cells, any stem cells human or nonhuman, into human embryos. Let's draft that both ways and see what we think in September because I think this probably requires some careful thought, both about what the uses might be and the advantages and disadvantages of differing from the CIRM guidelines and the NAS guidelines, particularly the NAS guidelines.

((Crosstalk))

Henry Greely: Intent is always difficult to divine; language is - the words are what they are. Figuring out what they mean is always harder. But differing - we can know whether we differ in language or not. That has some cause.

Item 3. This notes that the CIRM required membership of the SCROs, differed from the NAS requirements of membership of the ESCROs by adding a patient advocate and suggesting that we do the same to stay consistent with CIRM, you know, it seems quite clear that any institution is not going to have two ESCROs -- an ESCRO for us and a SCRO for CIRM. I think this should be non-controversial, right?

Woman: Yeah. Yeah. All right.

Henry Greely: Number 4. Notice that CIRM regulations broke new ground in requiring health coverage for certain side effects of the egg donation process. Our working group believes that our guidelines should be the same, again, to be consistent with CIRM and because it seemed like a good idea?

Radhika Rao: And particularly if you want to prohibit payment and compensation to egg donors it seems as if it would be even more in the interest of fairness to allow for coverage of (unintelligible)…

Henry Greely: Any controversy there?

The last one is one that I think will be controversial where some members of the working group had some strong feelings. And it's related to, but I think significantly different from the discussion we had earlier about clinical trial participants.

Our working group believes the full committee should discuss the issue whether women who donate eggs for research purposes should receive some relatively modest payment to reimburse them partially for their time, risk and discomfort.

The NAS guidelines ban anything other than reimbursement for direct expenses. The CIRM guidelines similarly, although I think they use a little

more definition about what expenses are reimbursable or not reimbursable.

Radhika Rao: And they don't include lost wages.

Henry Greely: Bernie?

Bernard Lo: They do include actual lost wages.

Radhika Rao: Oh, they do. Okay.

Henry Greely: The 12 - the language of 1260 if it passes in its current state would go, would prohibit lost wages and most anything else. So we would be - I think if we recommended reimbursement here, I think we'd be the only guideline group to have done that. But then it doesn't necessarily mean we shouldn't do it. Greg?

Gregory Stock: Yeah, I happened to be at the time when you were having the conference call. I was at the National Academy of Science meeting on enhancement (unintelligible). And met someone there who is actually involved in the process when that - we drafted that prohibition of payments.

And they said that they, someone up in Wisconsin they were saying that they actually - there was a lot of trouble getting people to donate because, you know, this is a very unusual thing and then you actually have a payment system in place for fertility treatment where you're paying $4000 or more for donors and so you have to (unintelligible) get somebody to (unintelligible), because you have to get them to forego the payment that is made outside of business and so in the - in the fertility area.

And so it seems to me that it might be actually useful for us to acknowledge the uniqueness of this situation and say that compensation should be allowed to the extent that it is thought to be necessary to get research materials, you know, something to that effect.

Elliot Dorff: It's Elliot Dorff.

Henry Greely: Go ahead, Elliot.

Elliot Dorff: But the article I think that you sent out by Radhika, I think her name is.

Henry Greely: Our colleague Radhika Rao, she's right here.

Elliot Dorff: Right. I thought it was really very persuasive.

((Crosstalk))

Elliot Dorff: It's - I mean, it really spells out the argument on why, you know, I mean, arguments beyond the ones that I had raised. I mean, I had raised the

issues of the market, namely that if women are being paid routinely more than $5000, you know, for the donations of eggs for IVF then there simply would be no eggs or very few anyway for stem cell research unless women are paid, you know, in the same sort of, you know, more or less the same amount of money.

So I mean even though it might be - I mean, I would say, even though it might be morally more pure to, you know, to have this kind of research without any payment; that research will simply not happen unless you allow for this payment.

But her arguments, I think, go beyond that. I mean, her point is that, you know, it is paternalistic to say the least to say to women that they may not use these parts of their body if they, you know, for money if that's what they choose to do. And it's - and it is a difference between a perception that - toward the end of the article she talked about the fact that, the difference in perception of the body as a person versus property but, you know, if - you know, I mean, it may not be the ideal world that we would want but if we really want stem cell research to happen it seems to me that both for the moral reasons that she provides and the market ones that I was talking about that we at least have to allow for it.

Henry Greely: Dr. Magnus.

David Magnus: I think whatever one would have thought before the NAS guidelines and CIRM came out about this issue it's a moot point.

At this point, I don't think we have any choice but to be consistent with all of the other guidelines and recommendations. And remember the National Academy of Science have both requested all funders and all journals, not to publish articles that don't conform to their guidelines.

So I think what would be helpful though is we've had questions an issue raised that's an empirical issue about whether or not this prohibition will in fact serve as a deterrent to research.

I think what we could endorse is that as, you know, attempt to procure oocyte goes forward when people turn - and say no, it will be interesting to find out why and we can accumulate evidence that in fact, prohibition on payment is having a substantial negative effect on the - on this research than I think we might be in position to be able to go forward, to go back to CIRM, to go back to the NAS and we raise that issue in a data driven way.

Henry Greely: Dr. Lo, then Dr. Stock.

Bernard Lo: Yeah, just as clarification, this sort of goes with the history of California and it's interesting. There was - there already - was in place a California law banning the (unintelligible) valuable consideration for oocyte (unintelligible). Prop 71 then to be consistent with that, included language banning payments of allowing (unintelligible).

So the guidelines (unintelligible) regulation system position then has to be consistent with Prop. 71 and we felt that we were locked in by (unintelligible). Now if you talk with people, again on the NAS panel, a lot of them will say, well - California is banning payment so it would be really hard to have any (unintelligible) sort of domino effect. I agree with David very strongly that if there's empirical data (unintelligible) in terms of the ability to actually carry out the research, then I think that's another type of argument for in the future (unintelligible). You'd have to have a revision of Prop 71 (unintelligible) make that extremely difficult.

((Crosstalk))

Henry Greely: Dr. Stock.

Gregory Stock: Yeah. I - maybe I'm missing something; but I don't think that it's required that we follow the National Academy of Science guidelines. And I mean - so (it seems to me that), David, you're sort of saying, well, it might be a good idea; but we should go along with what was basically a political decision on the part of the National Academy of Science. And it's been copied because the National Academy of Science, it seems to me that it's appropriate if we actually believe that that's an inappropriate policy to state that, I mean the guidelines, what we're doing it's not clear how much effect it could have anyway. But it seems to me that that would be a good statement to make.

David Magnus: I think it would be very difficult to have such an important difference between CIRM funded embryonic stem cell research and non-CIRM funded research.

I think that's a big enough issue that would make a practical huge problem but we should be going forward (unintelligible) if we have empirical evidence to show that it's problem, maybe we could - I mean, and I don't remember when (unintelligible) for the legislation (unintelligible) Prop. 71 but when that happen then we have some evidence - right now, (let's face we) could not do that.

Gregory Stock: So there are two arguments. One is the practical argument and you're saying get data. Possible to do that which is also - maybe it will happen, maybe it won't. We could make a suggestion; my guess is it probably wouldn't happen. Not soon.

The other is that that's actually a very bad guideline and that there are many grounds to argue that that's inappropriate. And if that's the case, I think it's very useful for us to make a statement. These individual researchers were not saying that they have to pay. Individual researchers are well aware of what they're doing. They know that they're in National Academy of Science; and if we're concerned about that, we could say explicitly that we disagree and in fact, and it will be up to individual researchers to decide what, you know, that there will be certain consequences to that, but we think it's a wrong decision.

Radhika Rao: Well, one more point is that SB 1260, which looks like it's going to go through, actually would prohibit payment. So it wouldn't really - I mean, we could go ahead, and recommend that compensation be allowed; but it looks like that's not where the state is headed. So it seems that we would be kind of banging our heads against the wall.

Second thing is when I wrote this piece, I didn't necessarily mean to suggest, although it sounds like it; that I think that compensation should be allowed. Just that the inconsistent treatment of these (two regimes) seems to be particularly problematic.

Now maybe what that means is that we shouldn't be, that we should be limiting compensation in the IVF context and not allowing huge payments in one situation and no payments in the other and maybe it also means that - particularly in terms of CIRM-funded research or, you know, because that other people are profiting that you're expecting altruism from the, you know, the donor but allow commercialization on the other end that perhaps altruism should be extended across the board a little more - and I guess that, you know, CIRM people are thinking about this in terms of the requirements (unintelligible).

So it doesn't necessarily mean that, I didn't necessarily mean to suggest that compensation is more legally (unintelligible).

Henry Greely: So let me try to sum up where we are.

Woman: Are you also interested in public comment on this issue?

Henry Greely: Well, we are interested in public comment. We have a period for public comment. Unfortunately it's at the end of the session which is scheduled for 10 minutes from now but probably will be somewhat longer than 10 minutes from now.

I would like to keep the public comment in their current place. Although I realize we did deviate from that sort of with the staff member from Senator Ortiz's office for what seemed like very good reasons at the time.

What we've got right now, I think is two people -- Professor Stock and Professor Dorff who are strongly in favor of us saying that some sort of us draft something that says some sort of reimbursement would be appropriate.

I've heard Professor Lo, Professor Magnus, I think Professor Rao saying that it would not be, that we should not take that position.

Does anybody else on the committee want to express a view at this point? I think that although for me it is not an easy issue, I come down with Magnus, Rao, and Lo, though I think there are good arguments from both sides. Anybody else?

Dr. Weissman?

Irving Weissman: I agree with you. It's not an easy issue for me. I think CIRM paved the way. And I just don't see us contradicting that. I do believe (unintelligible) I agree with Dr. Stock, this will come back at the end of the first year if there are no eggs.

Henry Greely: Anybody else? I don't (unintelligible) but does anybody else want to take position?

Margaret?

Margaret McLean: Yes. I'm going to agree with Dr. Weissman on this side of the room here in terms of just the practicality of, you know, staying in step with the other, you know, regulatory guidelines.

But I do think this is a question that really needs to be addressed and whether we address it or not is, you know, we may not address it ourselves but it certainly is something that I think that the state needs to think about in terms of regulatory, you know, the regulatory environment for both IVF and for, you know, stem cell research.

Henry Greely: So right now, the 10 of us who are here physically or telephonically; I count 6 opposed, 2 in favor, 2 yet to speak.

I think we should draft this on the expectation that we're going to say, going to be consistent with the CIRM regs. I also think the drafter should point out some of the deep concerns both ethical and practical in that.

And you know, as with all of these points at this point, these are preliminary instructions to the drafters which can be revisited. And I think given the narrowness of our - given the differences in views and how close many people are in their own views; I think this would be very appropriate for the - for Elliot and Greg and any others that have us revisit come September; but for now, I take it to be instructions to the drafters are conform to the CIRM guidelines.

Dr. Stock?

Gregory Stock: Yeah. I would first like some clarification. It's not clear to me what the implications are of differing from the guidelines that exist? So what are the negative consequences - are suggesting that compensation be allowed.

And even if we would do and attempted to do that, we have other comments about 1260 even suggesting it to go to our guideline.

What are the - what are the consequences to consider - that you're concerned about?

Henry Greely: So you want to answer David?

David Magnus: One concern that I would have about it (unintelligible) I'm trying to remember exactly which things would be a problem. But if you had (unintelligible) in which you derived a stem cell line in which you compensated the donors, and then you wanted to use that - those materials later for a clinical trial that would be CIRM funded, my understanding of that would - will that be eligible for CIRM funding? So it would not be eligible for CIRM funding.

Henry Greely: For those on the phone, Dr. Lo shook his head "no".

David Magnus: So that's the problem. If you follow our recommended guidelines and you might not know it now; but down the road you may not be able (unintelligible).

Gregory Stock: So, are you saying it's a little bit like the Harvard facility or somebody who goes and creates new stem cell lines. It might not be - it's a little bit like arguing that probably nobody should do that because those wouldn't be eligible for federal research or that shouldn't be allowed. Is there anything different from that?

David Magnus: Yeah.

This is a - I mean this is going to be a major effort for funding of stem cell research in the state and you're basically saying that they're not anybody who goes down the road that we're suggesting is not going to be eligible anywhere down the road and other researchers won't be able to use any of those (unintelligible) research material that doesn't follow with CIRM guidelines. That seems to me to make it a (unintelligible). It's tough being a domino third or fourth on the list, but we are and the dominoes (are falling) and there it is. And so and it seems to me that it would be better to endorse collection of data and then (revisit) this issue and the State Legislature will be in a position to decide whether they need to make a change.

((Crosstalk))

Gregory Stock: So - just one other thing. Is there anything else or is that basically the best, major consequence?

David Magnus: That's a big one.

Gregory Stock: Would that conceivably be addressed by saying if we actually believe that there was a - that an appropriate environment would be to allow funding but that that was a very real problem and therefore it was something should be seriously considered by researchers because this would be the consequence of actually making those payments. Would it accomplish both things? And then probably researchers would not, in fact made payments but it would be a statement we felt that it was an inappropriate restriction. Because there was some…

David Magnus: And also inform them that the National Academy (unintelligible) Science for one is taking that seriously, so that it may be that research that's produced from this may not be able to get published in journals…

Gregory Stock: Identify what the consequence are but also say….

David Magnus: …and politically, that the state legislature currently opposes this kind of approach. I mean, we could go on and on; but it just seems to me why go down that road? Why not instead think about collecting data that might inform, making a (unintelligible) change for everyone.

Henry Greely: Okay. I think the drafters probably are well-informed but this is one where not only do - I think it should be reopened in September but I think we probably should invite the minority position, the only - the only well identified minority position we have thus far to draft some alternative language if you come back to the committee with one next week, view it in Greg I'm looking at you as I said that. I think that really covers the instructions to the drafters part of this.

My expectation about where we go from here is that over the summer people on this committee who volunteered for it and you'll be getting an e-mail from me volunteering some of you, or asking you to volunteer.

We'll try to turn this - turn these instructions into drafted guidelines which we can then discuss at a meeting in the fall presumably, hopefully early in the fall. And also one hopes with the language having been distributed to the members well in advance both for approval of the language and for revisiting the - any of the issues which we think should be revisited and a couple of these particularly in the clinical trial's area were put in the situation, well let's see let's write it up and see what happens, see what people think about it.

So you'll be hearing from me and my role of chair about your availability to do so with that drafting, but that's how - I think we can probably usefully proceed. Any comments from that?

Okay. We've got one more thing I think to do before we have a public comment session and I apologize for the fact that it's 3 minutes to 5 but I would like to get public comments.

The other thing we have to do is, well, maybe we'll do the public comments and then come back to this but we have to return to the issue of the committee's position vis-a-vis 1260, SB 1260.

Doctors Lo and - with Dr. Lo, is some help from Dr. Stock, have drafted out a short document on that.

Bert, could I ask you to hand this around?

Bertram Lubin: Sure.

Henry Greely: Thanks.

So we're handing that around, it's only a page, you know, and a little squib. But while that goes around, let's see if there are members of the public who want to comment.

And because they've been so patient on the phone let me go with the phone people first. I see one hand here physically present but I know it's very frustrating to be on a conference call, I hate it myself, so I'm extraordinary impressed if any of you other than Professor Dorff are still on.

I'm impressed that Elliot is still on, if he is.

Elliot Dorff: I'm on. I'm here.

Henry Greely: Okay. Well, thank you. So are there any members of the public on via telephone and want to make a brief statement?

Susan Fogel: Actually yes. This is Susan Fogel from the Pro-Choice Alliance for Responsible Research.

Henry Greely: Yes.

Susan Fogel: The first comment is about the public comment. I mean I don't know if this committee is formally required to adhere to the California open meeting laws. But the spirit of that law is to include the public in discussion, and get the benefit of their expertise and perspective. And that law requires that there be public comment at each agenda item.

Have it - you know, waiting till the end, if I had something to say about something we discussed 2 hours ago, really not very helpful to anybody. So I would have a request that in the future, we follow the spirit of Bagley Keene whether or not you're obligated to, and have a place that public to provide inputs and comment as you move along. That's my first comment.

Henry Greely: Okay.

Susan Fogel: My second comment has to do with the issues of compensation for women who provide eggs. And we have taken a position against compensation for some of the reasons, you know, you have your own reasons those of you who've objected to it for consistency.

But the reality is that that the fertility industry is not very well-regulated. The drugs that are given to women are being used off-label. There's very little research (coming) in this context.

And if you were going to proceed and collect data and the kinds of data you also - should - also should be asking the state to collect is the number of women who are given these drugs for research. What are the

outcomes? What are the health outcomes? And so that you have not just how much money do we have to put on the table to entice women to do this, but we also have good data that suggest perhaps there are better ways of getting the raw materials that researchers need.

There is a big difference between fertility and embryonic stem cell research on not the least since you talked about at great length - what have to do with these, the risk benefit analysis. For facility purposes, there is a child who's a very direct benefit to someone as opposed to the fact that women are providing this raw material.

The second thing is that there are very real health risks. What we've got in Korea, where 20% of the women who participated in those, and providing eggs in that research, developed fairly serious side effects. Some of which – some of whom - actually had to be hospitalized. And we would like to see some incentives for developing much safer ways of providing eggs for research. And I think that should be on your agenda too.

And then the last item has to do with which communities are targeted for eggs for fertility as opposed to which communities may be targeted for eggs for research. The fertility context, it is the genetic material of the woman who is being asked to give these eggs for which (donor) parents, potential parents, are paying.

And that's where your astronomical numbers come from, because it takes that much money to get those women with that genetic material - generally college women with histories of college parents, to want to go through this procedure. And we're really concerned about the potential of targeting and exploiting low income women without giving them, as you all noted enough - the best informed consent - information, so they're really making informed decisions.

We expect women to make good decisions when they're put in a safe environment, and when they're given good information.

So we need a lot of data. We don't know, thousands of eggs, tens of thousands of eggs, potentially many, many more eggs than are used in the fertility context are going to be used as this new research, and new technologies are developed. And I think we have to make sure we're creating safety, and (respect and) dignity for women.

Henry Greely: Okay.

Thank you. Other comments on the phone?

Hearing none; public comments in the room? Yes, ma'am.

Emily Galpern: (unintelligible).

Henry Greely: Yes, please do. Well, why don't you come over here where we've got a microphone?

Emily Galpern: Thank you.

Hi. I'm Emily Galpern with the Center for Genetics & Society. And I have three points that I wanted to make. One is just in terms of the female… (Dr. Greely) that you would have passed out, that is gone around, around SB 1260, on the bottom of the page where it says the committee may want to consider the following issues about SB 1260, whether it should continue to require IRB approval of all human embryonic stem cell research even when there's no human subject research under federal law.

So, one of the things that SB 1260 does, is it defines the women who provide eggs for research as research subjects so that they are then accorded all the protections of human subjects that are currently in federal and state regulations already. And I know there's discussion around that (unintelligible) about whether a woman should be considered.

And they don't - I think everybody agrees that they don't fall under traditional categories of we know they're not patients but they aren't falling under traditional categories of research subjects themselves. How do we define them?

And at this point, what happens to SB 1260 is to ensure, because there are no protection for research donors, to make sure that women are covered under the California and federal regulations that already have specific protection in place to make sure that subject's health and safety and dignity is guaranteed or is promoted to the best (extent) as possible.

And second thing as an organization that really wants to ensure that any treatments or cures that are developed from or may be developed from stem cell research in the future be widely accessible; we would hope that a company like, what's it called, Genron?

Henry Greely: Geron.

Emily Galpern: Would that also - the committee would recommend that research during clinical - the clinical trial research is making sure that there's a diverse representation in the subjects who are in the subject pool.

So that for example, if you can - diabetes research, we all know that there's a much higher rate of diabetes among Latinos and African Americans but not all of the (subjects are) white or all men, et cetera. So that (unintelligible) on the women, people from different racial and ethnic backgrounds (unintelligible). They're important enough to be something that we need to recommend to research institutions, to companies that are trying to develop treatments and cures.

And lastly, I just wanted to echo Susan Fogel's comments about compensation in that, I think one thing that's really important that I didn't hear it today in the discussion on compensation (unintelligible) have on that. That's not just an inter-practicality within our National Academy guidelines and CIRM guidelines already prohibit compensation.

But that we want to be really looking at what are the issues related to women's health, and there's some disagreement. Mostly, because there's not enough health data about what - and particularly the long-term effects are of the oocyte retrieval processing, particularly the effects from multiple ovarian (stimulation), you know, stimulation to try to produce multiple eggs.

I think it's important that when we talk about this issue, we talk public health issues. We talk about develop (unintelligible) women's health and safety, and make sure that those are integral part of the system. Thank you.

Henry Greely: Thank you. I would just note that on the first point about the human subject protection, that wasn't in there to talk about the treatment of the egg donors who I think are covered by IRBs currently. That there are some arguments about whether they really fit logically into that. But it was intended to deal with the use of stem cells from de-identified sources.

And in vitro experiments where there wouldn't be under the current federal rules any sort of human subject involved. It's a little bit different take on it. I think I can honestly say that since I wrote it, that's what I had in mind. Dr. Weissman?

((Crosstalk))

Irving Weissman: …One of the points you raised is to make sure that, you know, a diverse population (unintelligible) trials, I know that as (unintelligible) that is a requirement. To have federal funding whether you had a research and the language is pretty clear with me - the argument. And the direction, by (unintelligible); so we may want to look at that for assessment.

Man: Yes.

Henry Greely: I think I saw a lot of nodding around the table as you (unintelligible) in this.

All right. Is there any public comments?

Okay.

Any other public comments?

Woman: (unintelligible)

Well, let me close the public comment section, and return to the one last duty. We have to decide what we want to say about 1260. Now, we have a document that has show changes made. It's originally drafted by Dr. Lo, edited by Dr. Stock; talking about three specific points -- the issues around the NAS guidelines recommendations.

I should note, for the record, that Dr. McLean has to leave. And thank you for staying so long, Margaret…

Margaret McLean: You're welcome.

Henry Greely: So the arguments about the positive virtues of the NAS regulatory approach.

The second one is the issue of the appropriate limitations on medical care for adverse consequences, of egg retrieval.

And the third one is the issue of protecting research subjects of restricting relatives and employees of research institutions from being subjects. And these were certainly three of the issues we discussed when we were talking about concerns about 1260.

What I guess I propose is that we have a motion that says we have a number of concerns about 1260, and we think the legislature should examine it carefully. The attached memos set out at some concerns that we generally share, but it does not exclude other concerns that we may well have. My colleague Mildred Cho from the Stanford Bioethics Center - Biomedical Ethics Center, pointed out at the break that one of the provisions of 1260 requires the collection of a lot of information about women who donate eggs, including race, ethnicity, zip code, age - I think, a variety of other things, which might - which - that are supposed to be made public.

And might - depending on how public they were made, and the individual woman's circumstances be identified. Now the statute says you shouldn't release identifying information.

But it's not clear how those two would come together. So that's just another example of some reasons why we think this needs to be - why - I think we should think - this bill needs to be examined again carefully.

So that the - the idea would be - our resolution experts says that we have some concerns. That three of the concerns are discussed in the memorandum provided, but that doesn't mean that we all agree with every point in that memorandum. Or that we don't have additional concerns as well.

Comments from the committee?

Discussion? Dr. Magnus.

David Magnus: Is there anything else is there anything in here about (unintelligible), pluripotent line beyond (unintelligible). Do you think we should do that (unintelligible) CIRM? I think it would be good if 1260 would parallel with CIRM.

Henry Greely: Dr. Lo?

Bernard Lo: Yeah. I guess I want to sort of clarify sort of what Hank would like us to do here. My own view is this; however we can make the statement the more impact it's likely to have. So I think to say that (unintelligible) we have a number of concerns some of them are the following (unintelligible).

I think we actually (unintelligible) see if we can agree as a committee for at least some of these examples that the committee believe (unintelligible)

((Crosstalk))

Henry Greely: Yeah. What I actually intended, and did not express well was that we generally agreed with - that these are concerns. We may not agree with every word in this particular memo because we haven't had an opportunity to read it at great depth. But we agree that there are - but we all agree that there are concerns about the fact that this would continue the non-NAS-related regulatory structure; that it would have the problem with employees, and their relatives, and that we're worried about the expansion of the side effects from oocyte donation in a way that may be too broad or too unclear.

So my intent is that we have a motion that expresses our general agreement with these three points; so without necessarily saying that we all agree with every word in the memo.

And further this, as individuals, or even if we have further time, maybe ultimately as a complete committee, we might have other concerns as well. This is not - and this listing is not intended to exclude additional concerns. Dr. Stock?

Gregory Stock: Yes. Just in the way it's written, it really is a very innocuous statement. It's says that we would like it to be in alignment with the National Academy of Science. And that they should give consideration to a summary of what divisions of the National Academy were and it doesn't really make strong recommendations but it brings up as (unintelligible) we kind of - speaks to the point that you're making (unintelligible).

Henry Greely: And I should also note that anything that we send forward would no longer be in show-changes mode. So, great.

So it will be cleaned up in that sense as well. So we're voting - as I understand it, there's a resolution on this motion on the floor has not

been seconded so technically we shouldn't be having this discussion. Was it? Okay.

Okay. So moved and seconded. This is discussion - we're expressing our concern as conveyed in this memo. With the caveats about, maybe other concerns and so on. And let's authorize the drafters to clean up any typos, missing words, and put it into a non-show-changes mode.

Bernard Lo: I can do that.

Henry Greely: Is there further discussions of that motion?

Susan Fogel: Would you be willing to take public comments briefly?

Henry Greely: Yeah. I think that's fair.

Susan Fogel: This is Susan…

Henry Greely: I'm sorry, who are you again?

Susan Fogel: This is Susan Fogel, I'm with the Pro-Choice Alliance for Responsible Research and we've been working with Senator Ortiz on this bill. And I would like to suggest that some of your comments would be much more effectively addressed on were you instead of just sending out this letter kind of willie nillie to the legislature, since none of these concerns have been communicated to the Senator; if you instead had a I realize you're not going to meet again, so had a two-step plan which was to appoint a small working group to approach the senator about your suggestions.

I mean, I just think some of them - there would not be any objections to them at all. A couple of them she might even find very useful. And then - so that would be step one -- to resolve what can be resolved just through discussion.

And step two then would be whatever letter you wanted to send to the legislature based on whatever remaining concerns you might have.

Henry Greely: Well, you know, I think that as individuals certainly; we're not going to have another committee meeting probably until September. But as individuals certainly I think any of us would be happy, I suspect, to talk with the Senator or her staff about our concerns about this, and might be able to clarify it.

Now I have no interest in this being a confrontational measure, I expect fully Senator Ortiz's goodwill in trying to do what's best for California and its people, as do we. So I agree with your sentiments that we should work to make this better. And I think as individuals, we're happy to do that. Beyond that I think it's difficult for us to, because of the nature of our committee, to do much more.

Man: We are going to send it out to members of the legislature.

Henry Greely: Including Senator Ortiz.

Man: Including Senator Ortiz.

Man: Yes.

Henry Greely: So is there any other comment from the committee on the pending motion?

Seeing none, I call the question. All those in favor of the motion, signify by saying, "Aye."

((Crosstalk))

Henry Greely: Elliot, was that an aye?

Elliot Dorff: Yes.

Henry Greely: Thank you.

All those oppose, "nay"? Abstention?

The motion passes unanimously.

The chair would do one more thing - two more things. One is to recognize Dr. Lo, who apparently wants to do one more thing.

Bernard Lo: You have typos, suggestions for making the language nicer, please (unintelligible)…

Henry Greely: Okay, good. I'd like to thank the committee for their patience, we've got overtime. I'd like to thank the public commenter, as well as the two speakers who came in our invitation, and as well as the employees of the State Department of Health Services who drove down from Sacramento and have been very diligent in preparation for this meeting and in the furtherance meeting, as well as Paula Bailey from the Stanford Center for Biomedical Ethics who provided most of the staff support.

The chair will now recognize a motion to adjourn. Is there a second?

Woman: I second that.

Henry Greely: All those in favor, signify by standing up and leaving. Thank you very much, ladies and gentlemen.

((Crosstalk))

END