BEFORE THE

INDEPENDENT CITIZENS' OVERSIGHT COMMITTEE
TO THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
ORGANIZED PURSUANT TO THE
CALIFORNIA STEM CELL RESEARCH AND CURES ACT

INFORMATIONAL MEETING

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I N D E X

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Informational Meeting of the Independent Citizens Oversight Committee
To the California Institute for Regenerative Medicine
Organized Pursuant to the
California Stem Cell Research and Cures Act

CHAIRMAN KLEIN: If we can try and convene this. We have the pleasure of Alta Charo making a presentation to us tonight, but it's going to be a late evening. A number of the Board members have come from some distance already, a number of the public members have come from a significant distance, and if we can get started, it would be very helpful.

Before we begin the formal session, are there -- we would remind you that during the question-and-answer period, we will have three-minute guideline on questions. And before we begin the actual presentation, as we call this public meeting to order, are there any initial questions from the public before we start the presentation? Seeing none, I would like to introduce Alta Charo.

And it is our great privilege to have her here from Wisconsin. Hopefully this is a little warmer than Wisconsin.

MS. CHARO: About 62 degrees warmer.

CHAIRMAN KLEIN: Alta Charo is a professor of

law and bioethics at the University of Wisconsin at Madison. And she is on the faculty of the law school and the medical school's department of medical history and bioethics. She's associate dean there at the law school, including, I believe, properly, dean for admissions, among her other duties.

MS. CHARO: No. Sorry. Can't help out your kids. I can hire your spouses.

CHAIRMAN KLEIN: She offers courses on health law, bioethics and biotechnology law, food and drug law, medical ethics, reproductive rights, torts, and legislative drafting, a very broad and impressive spectrum of expertise. In addition, she has served on the University of Wisconsin's Hospital Clinics Ethics Committee, the University's Institutional Review Board for the Protection of Human Subjects in Medical Research, and the University's Bioethics Advisory Committee.

Professor Charo serves on the expert advisory boards on several organizations in stem cell research, including the Juvenile Diabetes Research Foundation, Wi-Cell, which is connected to the University of Wisconsin Foundation, and the Wisconsin Stem Cell Research Program. In 1994 Professor Charo served on the NIH Human Embryo Research Panel, and from 1996 to

2001, she was a member of President Clinton's National Bioethics Advisory Commission.

Since 2001 she has been a member of National Academy of Sciences Board on Life Sciences and serves as liaison to or a member of several National Academy of Sciences IOM committees working in the area of research ethics, public health ethics, and stem cell policy.

More recently, I called Bruce Alberts, the President of the National Academies, and asked if he could send the best and brightest minds to California for a workshop on bioethics and stem cell research. Alta Charo is one of the real stars of the National Academy he chose to come and make a presentation.

So with that, I present to you one of the most imminent individuals in this country and perhaps in the world on stem cell research, Alta Charo.

(Applause.)

MS. CHARO: I hadn't realized that Klein was an Irish name because that was a lot of blarney, but I thank you for it. It was lovely.

I can't help but notice that there has been some concern about issues surrounding conflict of interest. And so although we've had way too much introduction, I do want to take just a moment to spell

out for you rather rapidly the organizations I'm associated with. And if anybody has any questions about the nature of the association or whether it poses a conflict, this will give you enough information to start asking those questions.

As Bob mentioned, I am a member of the National Academies' Board on Life Sciences, and in that capacity, I'm the liaison from the Board to the committee that is, in fact, right now drafting voluntary national guidelines for stem cell research. I'm also, as he mentioned, a member of the JDRF's Ethics Board. And JDRF, you should know, is a grantor in this field. I was a member of the Ethics and Science Advisory Group called Cures Now, which was part of the political activity surrounding federal bills in the area of cloning and stem cells a couple years back.

I was and am a member of the University of Wisconsin's Campuswide Bioethics Advisory Committee, which, among other things, reviews specific stem cell research protocols that might pose some questions about things like public safety or ethics. And in that capacity helped to write the UW's internal UW stem cell policy. A member, as he said, of the University of Wisconsin Stem Cell Research Program. That's our campus program. And also a member of the Advisory

Board for Wi-Cell, which is a separate private entity with a connection to the UW's -- actually to the Wisconsin Alumni Research Foundation.

I will tell you that in none of these capacities have I ever earned a penny. I will say that in some of those capacities, I did earn frequent flier miles. Frankly, those are worth something. I'm also a member of the Howard Hughes Medical Institute's Bioethics Advisory Board. That Board looks at a variety of things, including stem cell research policy for HHMI investigators. I do get paid by HHMI, but it's a flat annual fee and has nothing to do with the topics or what we do.

If anybody has any questions in the future, if there are any reporters that would like to investigate that, I hope that gives you enough of a clue. No. It's typical in a science meeting to spell out anything that might constitute a conflict of interest.

What I'd like to do today is to outline some categories of things that might need to be addressed in the context of setting standards, and then briefly introduce each one of the topics separately, and then offer an opportunity for conversation in the room, and then stop the conversation, move on to the next topic

rather than holding everything for the end. This way people don't lose track of their questions, and we can build on the conversations.

Here are the topics I'd like to bring to your attention tonight. And these are not exactly the topics that are spelled out in Prop 71. Those topics are going to be the focus of my conversation tomorrow with the ICOC where I really want to focus in on the things that are mandated by Prop 71. This is a somewhat larger list of the issues that I, from my experience dealing with all these organizations and their guidelines setting efforts, these are the kinds of issues that come up and require some thought.

First, whether or not to establish additional committees above and beyond the ones that exist. And we'll talk first about the range of those committees and where there are gaps. Second, special rules about the procurement of the biological materials needed for the derivation of new lines, and any special rules governing the derivation of new lines. Fourth, whether or not to participate, and if so how, in a banking and distribution process for the cell lines. Then any special limitations that ought or ought not to be placed on the actual laboratory work that is done with the cell lines once they already exist. And finally, a

small, but not inconsiderable, issue in this field of collaborations, which is transnational collaborations.

So moving on to the question first of the general scope. This may seem obvious, but there are different kinds of issues that are raised in this area. I probably should have organized it as procurement derivation and banking. In the area of procurement, you have a choice about whether or not you want to set standards that govern how you get sperm, eggs, somatic cells, and embryos from people. There are already existing rules out there from the federal government that cover much of that material, and it's a choice about whether or not you want to address it.

With regard to derivation, it's about whether or not you wish to ask for special justifications for the derivation of new lines when existing lines could arguably be used to accomplish the same kind of research goals. And then with regard to banking, do you want to set standards for how to bank or standards for what kinds of banks will be allowed to provide cell lines to your CIRM investigators because one of the issues is going to be how much you're going to insist upon knowing the providence of each line, how far any concerns about the providence, how it was obtained, how it was derived, the conditions and justifications, how

far will you go back into the past to look at that before allowing somebody to use a line.

And the more that you want to look back to the absolute origin of the line, the more important it is that there be some process for keeping information about its original terms of derivation constantly connected to that line indefinitely into the future so that every institution, every grantor can decide whether or not this line is one that we will fund people to work with.

It's complicated to manage it just as a logistical thing, and that's why stem cell banks are often suggested as a possibility.

In addition, when it comes to the procurement and derivation issues, clearly the most common source is going to be surplus embryos from IVF clinics. I think that's the paradigm case that people have in mind. Couples that are relinquishing embryos, having decided that they cannot use them for themselves, and having decided that they don't want to or are unable to donate them to other couples. Here are some examples of other ways that you might use biological materials to generate embryonic stem cell lines that require you to decide are you going to write standards for this. I'm not saying are you going to fund this, but do you

want to write standards for this or do you want to just put that aside for the moment?

Embryos can be made deliberately just for research purposes, certainly a more controversial kind of source of embryos. And in the past this has actually caused even people like President Clinton to see a distinction between the use of surplus embryos that were otherwise doomed to destruction and the use of embryos that are made solely for research purposes. President Clinton's policy was not to make it illegal to do this, but he did say that he would not fund research that required deliberately making embryos for research. You can do that with IVF. You don't have to do that with something fancy like the next thing, somatic cell nuclear transfer.

SCNT is the usual way people imagine this situation arising; that is, I want to study a particular disease. Susan Bryant there now has BRCA 1, according to my example, and we want to study BRCA 1, so we're going to use cloning technologies, SCNT, to generate an embryo that has the BRCA 1 mutation so we can study it in vitro. That's the paradigm we think of for making embryos, but it can also be made through IVF.

Parthenogenesis is not yet something that's

really on the map in a big way, but it is certainly already in the scientific literature, and for some people has been identified as a potential avenue toward evading some of the ethical controversy surrounding the use of ordinary embryos because of the possibility that parthenotes, embryos created by parthenogenesis or activated eggs -- I'm not even sure what the language ought to be here -- that activated eggs or parthenotes would be able to develop for long enough to throw off embryonic stem cells, but not develop long enough to be viable under any circumstances for a viable pregnancy to term.

Rudy Jaenisch at MIT would probably be a very good source of information on something like this because a lot of the concern about parthenogenesis focuses on problems with imprinting. Androgenesis probably should be up there as well. That's a little bit more out there, but there actually is at least one paper talking about the ways in which you can combine two sperm in order to create an embryo-like body.

Rudy would probably say that SCNT also creates something like a parthenote; that is, something that is not viable, but here it's about kind of ways in which people are using the terminology. Certainly in mammals we have seen a very reduced level of viability;

that is, the rate of normal birth is low, but not nonexistent. And so for people who use the word "viable" to mean at least the potential of one ever out of whatever denominator coming to term as equals viable, cloning would generate what they call viable embryos. Rudy would say they're not because he uses the word differently. But with parthenogenesis and androgenesis, I think the jury is still truly out as to the viability of the resulting entities. And if they can throw off embryonic stem cells, that might be another source, again, having to ask do you want your standards to anticipate this? Do you want to just put it aside and say we'll worry about it for another day?

Obviously stem cell research has been going on for years, particularly with the mouse. That's where most of the literature has been. Do you want to have your standards in any way cover things having to do with research using stem cells derived from nonhuman animals? I ask this because as we get down later to questions about research uses of existing lines, one of the things we're going to see is testing the lines. Testing in vivo differentiation is going to require in many cases human/nonhuman combinations. We've already seen animal/animal combinations using two different species to test exactly the same kind of thing, looking

at how an undifferentiated or partially differentiated embryonic stem cell will function once it is transplanted into a different animal. And you will use different animals because you want to be able to clearly differentiate the tissue you transplanted from the existing tissue of the existing organism.

And so to some extent the issues around the unnaturalness of combining two different kinds of animals or the concerns about safety issues are really quite similar when it comes to nonhuman/nonhuman combinations. And, again, your choice whether or not you want your standards to address this, whether or not you want the standards for that kind of research to be similar to the standards used for the human/nonhuman combinations.

Research using human adult stem cells, certainly the procurement issues are somewhat different, although some of the review committees will be the same. Procuring adult stem cells requires interaction with a human being, retrieval of biological material, as we'll see in a couple more slides. As you get to the point where you are talking about research subjects, there are existing protections. They'll cover this. So there are some procurement issues in common.

And second, again, when it comes to research uses of the cell lines, if those who are advocating aggressive research in the area of adult stem cell research, so that we always know exactly where adult versus embryonic versus embryonic germ is the superior option, we are probably going to have to do the same kind of research experiments with the adult stem cells; for example, creation of chimeras, human/nonhuman combinations, to test the actual plasticity, the actual patterns of differentiation in vivo. And therefore, again, do you want to have your standards cover these things.

And then finally, research using fetal stem cells or embryonic germ cells. Embryonic stem cells being what John Gerhardt had used at Hopkins. He derived them from the gonads, fetal gonads, from fetal cadavers. And in this case there actually are specific federal regulations because there are federal rules that govern the use of fetal tissue in research. Mostly those are rules that cover things like no money exchanging for obtaining the fetal tissue and also prohibitions on what they call directed donation. That is, a prohibition on me saying you can take the fetal tissue from my fetal cadaver, whether it's my aborted or miscarried fetus, you can take the tissue, but only

if you give it to my friend Bob or my father. They have prohibitions on directed donations specifically to avoid any possible inducement, not only to the donation of fetal tissue, but more somewhat remotely an inducement to have an abortion in order to generate a fetal cadaver from which tissue can be retrieved.

So I just note for your interest and for your despair that there are many other areas of embryonic stem cell research that have commonalities. And when you write standards for the paradigm case about surplus embryos from IVF clinics or the somatic cell nuclear transfer embryos, you are also offering yourself the opportunity to look for commonalities and insist upon them, or to just say too much to try to chew at the outset and we'll work on that next.

Let me stop with the scope question. Like I said, I'd like to do one topic and then open it up for conversation, and then move on to the question of oversight committees. So I'm going to take my cue from somebody here from CIRM in terms of how long we should lead the conversation.

CHAIRMAN KLEIN: I think if we can take questions just first from the members and then from the public, but we will try and pace ourselves as we go. If we get any section of comments that seems a bit

long, we'll try and defer some of the remaining questions to the end and try and pick them up there.

Any questions from the members on this issue?

DR. SAMUELSON: Joan Samuelson. And it's a question of scope. If you are going to drill down and become more specific than -- maybe this isn't appropriate -- then the question is what sort of standard should we follow in setting the standards? This is the one amazing person, brilliant person, like you, do we always need a committee of wise people from various perspectives? How do we lay our own ethical foundation? This may not be appropriate now.

CHAIRMAN KLEIN: Joan, in answering that question, maybe she can also address what the National Academies is doing to pull together its model standards and the basic timetable for those standards as a benchmark.

MS. CHARO: Sure. Let me start first with the narrower answer to your question, which is that you've got some California law on this point. As I understand it, whatever you adopt as a starting point, because in some degree all standards are based on ethical analyses that fundamentally are arbitrary because if you keep drilling down, you are going to get to certain assumptions or certain approaches in

philosophy that really cannot be proven. You ultimately just make a choice among them.

But as a political matter, as I understand it, your first set of standards are going to be interim standards that will be subjected to a fairly lengthy public comment process. That will necessarily, as just a pragmatic matter, mean that whatever standards you arrive at at the end are going to reflect some effort to make them politically viable within California. So that's the narrow answer to your question. It's kind of the escape answer.

The National Academies is hoping to help you in this effort. National Academies are currently working, as I mentioned in passing with the conflict of interest statement, they're working to develop national voluntary guidelines because the National Academies' process requires absolute confidentiality. Until the report is publicly released, I'm not at liberty to say what those guidelines will be.

But I am here to talk to you about what my experience in that committee and in other settings has taught me about the topics that need to be covered. And there are going to be, as we get a little further down, some very specific questions that you need to answer. And you can answer yes or you could answer no.

National Academies will have one set of answers; you could have the same or different and then subject it to the public review process.

And the National Academies is hoping to have this report made public in April. What date in April I don't know exactly, but I can tell you that the work has reached a frenzied pace. Nobody in Washington is unaware of what is happening three time zones away. So there is every hope that the standards produced there, which are themselves the result of a process that took advantage of expertise from different ethical and political points of view. There was a public workshop with people such as Leon Kass and Bill Herlbud from here at Stanford who are certainly strong skeptics of many of the policies that have been advocated by, for example, this Board, but also by strong supporters.

The Committee itself is made up of people who are very knowledgeable, but don't actually have a dog in the fight. There are no researchers on the Committee that will be getting grants from this kind of thing. But the research community is going to be, I believe, because I don't know who the reviewers are going to be, the research committee is going to be asked to help in the review process so that whatever guidelines we're proposing as a draft can be processed

by people who actually have to live by them and we'll get some feedback from that community, but they don't have control over the final product.

And then the report will go out with the names of all the people who were associated with it, so everybody's political and economic interests will be pretty obvious.

DR. PRIETO: How far have other entities that are involved in stem cell research gotten in developing and putting out a set of standards and guidelines for this research?

MS. CHARO: The ones I'm most familiar with that have gone the furthest are my own University of Wisconsin and the JDRF. That's not to say others haven't done it. Actually I understand that the American Association of Cancer Research -- is that the right name -- AACR, is just coming out with a draft on nuclear transplantation, right. I know I was reviewing the draft about a month ago, and I just got an E-mail this evening with a little attachment I haven't opened. So I think that might be the final.

In the case of the University of Wisconsin, it happened because Jamie Thompson was there. He was publishing. We knew that we were going to be in the eye of the storm. And one of your now Californians,

Ginger Hinshaw, who is the provost at US Davis, was then the dean of our graduate school, and it was her idea to create a committee. That committee actually does have published incredibly abbreviated little statements, abbreviated quite deliberately because there was no interest in reproducing these kind of mammoth government reports.

The bottom line was a statement of guidelines having to do with the acceptability of the research, the acceptability of deriving new lines including by nuclear transfer when it was needed for scientific purposes and existing lines weren't going to be adequate for the purpose. Specific identification of things that posed problems that ought to bring a stem cell researcher back to the Committee for a specific discussion, focus there being on anything that involves transfer to a uterus, human or animal, because of concerns about live births that would be births with birth defects that would cause suffering either for a human or an animal.

Second area of concern that was identified had to do with human/nonhuman combinations, the creation of so-called chimeras, in which you're going to be seeing, for example, human cells differentiating in an animal, wanting to make sure that we understood

the pattern of differentiation and the effect it might have on the animal.

Obviously if you begin to think about that, you tend to have a little more concern about human cells differentiating into a neurological system than you would, for example, human cells differentiating into an animal pancreas because of the degree of both kind of public alarm and scientific uncertainty about exactly what level of sophistication in the evolutionary order the mammal has to be and what degree of combination of human and nonhuman cells it would take to actually affect the architecture as well as the kind of gross cellular content of a brain to the point where you can actually begin to worry about what are currently very difficult questions in science and philosophy about the nature of consciousness.

And so, for example, you might worry -- you might ask questions, as we did, about whether you're doing it with human and chicken versus human and primate, whether you are doing it human cell into pancreas or human cell into brain. One of the things we found in that standard setting process was that you couldn't anticipate every situation adequately and spell it out in legislative language.

We found that we needed to go for a

process-oriented standard. Gross categories of things that raised concerns that needed individualized discussion so that you really understood the experiment and you really understood the state of the science at the time the experiment was being done. Rather than try to anticipate every situation and kind of legislate the rule, we wound up with categories. If you look at our little abbreviated standards, you will see categories that are clearly okay. You don't have to come to our committee and other categories where we want you to come to us, and then some categories where we said it's absolutely not acceptable to do this at all on the UW. This is just for the UW Campus. That's what our rules cover. For example, doing essentially a genetic alteration of a human embryo by the insertion of other human embryonic stem cells, creating a human chimera, and then bringing it to term. Absolutely unacceptable.

So that was our approach. The Juvenile Diabetes Research Foundation, they had kind of evolution, and it's really been an evolution. It's been a kind of iterative process in which gross standards about things like the need for consent underlying the original derivation of lines as a precondition for letting their funded researchers use a

line. That was a kind of categorical standard. And it led on a case-by-case basis to these very detailed discussions. A researcher wants to use this line, and we need evidence about its derivation and the consent process. How many IRB reviews, and does it have to be reviewed by every institution or is one IRB enough, and then everybody can defer to that IRB, I mean real nuts and bolts stuff that only really works out as you try to apply the standard and you begin to see where there ambiguities that you hadn't anticipated.

Then in other cases they were taking a more kind of blanket approach just to keep life simple. So originally if you look at the earlier published iterations of JDRF's guidelines, they weren't going to fund things that had to do with lines that came from nuclear transfer origins. They were not going to fund any work that involved chimeras. And then over time, the question is, as people present proposals, do you want to rethink those in light of where the science is and in light of what's needed and in light of the protections that we can now begin to imagine putting into place.

In some ways it answers your question too about how do you set standards. Not so much about whether you're going to become a utilitarian or a

contienne, but do you try to set black and white rules forever, or do you try to create a system that's as much about process as it is about the substantive rules?

CHAIRMAN KLEIN: Alta, one of the beauties is you know so much about the subject, that we can drill down to tremendous depth; but given the length of the items you need to cover, what I would suggest is that between the Board members, if we can get the questions on the table here, since you are going to be a consultant to the Institute, you could augment your presentation here with further response, at least if we can get more questions on the table and give us the view from above, as well as questions from the public, I think that we'll get through a greater portion of the agenda. But it is beautiful to see the depth of your knowledge in the field. Any additional questions from the Board?

MR. SHESTACK: Jon Shestack. It's not really a question for you, but it's a question for all of us, which is I think some of the things we may need to know is the state of availability. For instance, there is an assumption perhaps in the public that we will be working -- that primarily researchers will be working with surplus embryos from IVF clinics. But I, for one,

am not informed about whether or not, in fact, there is sufficient supply of those just in somebody's chiro preserve that we could have, or, in fact, will there be down the line real pressure to produce embryos.

And it's an important thing ultimately for us to have a sense of what is available in the country and, I guess, maybe particularly in California, and then are those, for instance, those embryos, were they actually consented for research purposes or not. How many of those were consented. I just would love to understand something about the depth of the research that's currently available, and that will help us know how much we have to push or stretch to go down the line on scope.

CHAIRMAN KLEIN: Okay.

DR. BRYANT: I just had a comment about that. I think that in addition to knowing the scope, there's also other reasons that you might not want to limit yourself to just surplus IVF embryos. For instance, in Wilmot, England, they just got a license to make cell lines based on ALS embryos. If you want to study a particular disease, you might want to have embryos that you can make cell lines from.

MR. SHESTACK: Absolutely. It's just for the Board and the public to get a full picture because

those questions will come up, and there may be an assumption that there is an inexhaustible supply of this other thing and there isn't. And then there are opportunities that you can only get through other methods, and we have to be aware of them.

MS. WILSON: Just a quick question. It may be, because it will be less controversial, but where would you put cord blood stem cells on there?

MS. CHARO: Under adult. I think of cord blood as a source for adult blood stem cells.

DR. POMEROY: One of the questions that I think this raises is how we're going to coordinate the Grants Group Working with the Standards Group because the scope of what we need to define in terms of standards will be dictated by what types of grants we're going to be funding. For example, are we funding animal models, I think, animal stem cells? That's a question that we haven't really grappled with yet. Are we doing cord blood? Are we doing adult? And that will dictate which standards we need. So there's going to have to be some coordination there I hadn't really thought of before this.

CHAIRMAN KLEIN: In terms of what you reference from the National Academies, how much of this list is intended to be addressed? Is that public

knowledge?

MS. CHARO: It's not public knowledge. That sounds so annoying.

DR. POMEROY: When will we know?

MS. CHARO: I think April.

CHAIRMAN KLEIN: The question, Jon, was how much of this scope is addressed in National Academies' study.

MR. SHESTACK: It's not public information?

MS. CHARO: It is not. Now, if you look at the charge, which is public, on the NAS website, it speaks specifically to stem cells made from human embryos and from somatic cell nuclear transfer, and does not in its charge talk about things like adult stem cells or animal stem cells. But I can't tell you where it actually went, but the charge is public.

CHAIRMAN KLEIN: Doctor.

DR. PRIETO: I would just really like to echo a little bit what Jonathan said, that I think many of us could use a little bit more background information on what the actual availability and potential of different types of stem cell lines is for the type of research we're anticipating.

CHAIRMAN KLEIN: I think that as a follow-on to these presentations, and because of the interface,

there's the intention to have a scientific presentation that really goes into these issues of limitations. For example, Dr. Doug Melton from Harvard has proposed providing a library nationally that is developed with disease-specific lines developed for each disease with somatic cell nuclear transfer with redundancy, two institutions covering each line, so that you don't get every institution trying to create the lines from scratch and have a uniformity in the lines.

So I think it's intent to follow with Dr. Melton and others doing a presentation that addresses those fundamental scientific issues that interface with the standards.

DR. POMEROY: I think there are also issues that we're going to have to deal with about ethnic and racial diversity to make sure that we really have representative lines available as well.

CHAIRMAN KLEIN: Absolutely. In that regard, I think this is a very healthy conversation. And if we can follow Jon Shestack's and chronicle our list of scientific areas of interest, it will be helpful to make sure that when we bring those presentations forward, we have any research done that we can access in the relatively near future.

MR. SHESTACK: I'd love to move on. I just

wanted to say that it will be a critical thing that the Standards Group will want to know that and have a sense of it.

CHAIRMAN KLEIN: Okay. Could we quickly go to the public and see if at this juncture are there any public questions? No public questions at this juncture.

MS. CHARO: I'm going to be very brief on this one because I know that is not actually in Prop 71, so let's think about this more as a kind of thought experiment about how one goes about this.

By way of background, I want to emphasize something that came out in the NAS meeting that was held in December. There are a large number of existing committees at every institution that already have oversight responsibilities with or another aspects of this research. The question is do you want to add another committee to the layer for the purpose of coordination, filling in any gaps that you perceive as being unacceptable, and for providing other functions, such as education and ongoing review of your standards?

So the examples, and you can go back to the transcript from the December meeting for more detail, the examples of the ongoing oversight include IRB and HIPPA Privacy Board oversight of much, but not all, of

the procurement process. It oversees, in the case of IRB's, procurement of eggs and sperm and somatic cells. In the case of procurement of embryos, if there is some kind of identifying link between the donors and the embryos and the resulting cell lines, it will trigger a whole host of human subjects protections overseen by the IRB and privacy protections through HIPPA.

There are, therefore, opportunities to have embryos donated in a coded or anonymous fashion where consent is required because obviously you need consent before you can take something that people have that is owned, in quotes, because the state law is not really clear, but no question these couples have the dispositional authority. So you can't do without consent, but you can under some circumstances be out from under IRB review of that procurement process.

Question: Do you want to fill in that gap with more review by the IRB, by some other committee, etc.?

Laboratory research with existing lines may well require review from an institutional biosafety committee if it involves recombinant DNA research with the lines. And that will be quite common, genetic manipulation of the lines. And when you begin to combine the human embryonic stem cells with whole

animals, then you might need to get review from your institutional animal care and use committee.

Here are some examples of things that an additional oversight committee could do for you. Maintaining registries so you know who's doing what where, ensuring that all the other reviews I've listed are actually being done, adding extra layers of review, if you want them. I'm not saying you should have them. I'm just saying this is the kind of question that's arisen. Do you want people to have to provide a special justification before they can derive a new line? Should the justifications vary depending upon the degree of controversy surrounding that derivation method? Obviously using cloning technology, more controversial than others.

And if that's so, to whom are they justifying it? And finally, one of the things that came out in the 1994 Embryo Research Panel Report, when it looked like NIH was going to have a window for embryo research funding, we talked about the need to make sure that the federal government only funded research that was really necessary and could actually generate scientific benefit, which seemed to suggest that you limit the recipients to people who have some certain set of qualifications to make sure that you're not wasting

your material or using embryos in an inappropriate and frivolous fashion.

If you begin to think about having this extra oversight to either fill in gaps or coordinate existing reviews, then the questions become do you want the individual institutions, the Stanford, the UCSF, the UCSD, the UC Merced institutions each individually doing this, or do you want to centralize it? Have it be something that's a function of the granting process. Basic question.

Do you want to allow any or all of the standards that you're allowed to waive? You can't waive federal standards; but if you've got your own standards, do you want to have circumstances where they can be waived? For example, somebody is going to follow somebody else's standards, and you've certified those other people's standards as adequate. I don't know who certifies it, and I don't know what the criteria are. That's up to you.

Do you want to have somebody that is going to be charged with periodic review of your standards because obviously the science changes, the thinking changes, our understanding of the risks and benefits change. And then something I'm sure you're all terribly familiar with, once you decide you're going to

have a committee, then you've got to worry about how you're going to set it up, who's going to be on it, and what they have to tell everybody publicly about themselves before they can serve.

So this is something that may be a little further down the line. It may be something that you can consider only after you've decided what your substantive standards are and you can see better what process is going to be needed to implement them. And so maybe for the sake of time, I'll move to the next one about substantive standards.

CHAIRMAN KLEIN: I would call members of the public's attention to the fact that the Standards Committee, which is the advisory committee to the Board, is, in fact, charged with most of these functions, including periodic review and revision of standards and recommendations to the Board as well as the monitoring functions that have been described. Now, there may be functions that are outside of what this committee should appropriately do. There may be a special task force or committees that are necessary, but most of the functions designed here, to extent they're centralized, are charged in the Initiative with the Standards Committee.

To the extent that local committees perform

these functions at review institutions, such as institutional review boards at local institutions, they're outside of the function performed by the Standards Committee.

MS. CHARO: I'm glad that you said that because I didn't appreciate the degree to which the Standards Committee was going to perform these functions already. It will be an interesting question how they interact with the institutions. And if the institutions want to have in any way their own oversight committee, then you're going to have yet another kind of set of interactions that have to be somehow managed in terms of who has authority at the end.

MR. SHESTACK: Are you saying that -- Alta Charo said there's certain basic things that any institutional review board deals with as a matter of course and there are certain standards? They may vary from institution from institution, but nine-tenths of the, you know, the grants may be going to institutions that have IRB. Are you saying that even so, the Standards Committee is charged with that level of standards, for instance, anonymization and privacy issues and HIPPA issues? And if not, then what about grants given by this group to industry where there

isn't necessarily the same kind of HIPPA and IRB requirements?

MS. CHARO: If I may, Bob, just to clarify what might be a mistaken assumption that people generally have, the IRB role in this whole area is substantial, but it's limited. Not only do the IRB's not necessarily have any oversight over certain forms of procurement having to do with anonymized embryos; but once you're beyond procurement, unless you're dealing with a line that identifies the donors in an easy way, which is rare, most lines are coded and they meet the Federal Rules for what's considered to be sufficiently obscured. At that point the IRB's drop out of the picture. The lab work itself is not an IRB kind of -- reviewing the lab work itself is not an IRB kind of function.

That's why I mentioned these others, the IBC's and the IACUC's and stuff. This is what some people perceive as a gap in regulation. Other people see it as a reflection of ordinary American policy in which laboratory research except for these exceptional things having to do with animals or radiation or genetic engineering is not regulated because it was never regulated. It was never perceived as a need of it.

So that's where your Standards Committee, as a condition of giving out money, or in an institution, a local institution creating some extra body like the one we have at the University of Wisconsin, can decide that it wants to step in and substantively regulate a field that has never been regulated in America, which is basic lab research. So this is a very big question. And for the research community it's really important because many researchers will be shocked to think that they are now going to have to have any conversation with anybody because they never did genetic engineering with their stuff, they never did radiation, they never did animal work, they never dealt with humans. Why am I talking to a committee?

CHAIRMAN KLEIN: In the reference to your question, Jon, the proposed schedule that's under discussion, not been decided, has suggested that the grants to private companies be deferred to a later date than those to the research institutions. That is one of the reasons because it's expected that there will be additional standards work that is necessary in dealing with private companies, that, whereas, there are other internal regulations that may be more complete in place at research institutions, universities, for example.

But Dr. Pomeroy.

DR. POMEROY: I'm interested that we haven't talked about intellectual property or the possibility of charging, you know, for the products that come out of this work. Is that not within the scope of the Standards Committee?

MS. CHARO: It's up to the Standards Committee what's within the scope of the Standards Committee. It's not within the scope of my expertise. I know enough to be able to be a good dinner conversationalist on the topic of intellectual property, but I wouldn't presume to be a consultant or advisor on that.

DR. POMEROY: Maybe I could ask Mr. Klein to answer that question in his opinion.

CHAIRMAN KLEIN: The Board needs to make a decision of whether that's going to be handled through the Board or through the Standards Committee. And that's not an issue that the Board has yet dealt with, although the Board has delegated two members to the Science and Technology Intellectual Property Task Force established by Assembly Concurrent Resolution 252 to come back to the Board with intellectual property proposals.

The Board is moving through a process where intellectual property is one of the critical items, but

has not been delegated yet in terms of the responsibility for those decisions and the direction.

DR. POMEROY: I guess another way to ask the question is is there additional ethical oversight that's required if the purpose of the experiment is to directly result in a product that will be sold versus if it's basic science? Is that ethically different? I turn that one back to our speaker.

MS. CHARO: It depends upon some of the starting discussions that animate your standards. Take as an example a standard that says we will not -- we, CIRM, will not fund the derivation of a new line unless you provide an adequate justification for why the existing lines are insufficient and, and, you prove to us that the new line will be used in ways that further the public interest by doing X.

Somebody here talked about needing to get -- maybe it was you, Dr. Pomeroy -- about needing to get genetic diversity. If you build into your standards something about the kind of end use of the research, that gives you an opening to the discussion about whether or not there are going to be payments, whether or not there's going to be any person or company that has any kind of control by virtue of intellectual property rights that might interfere with what you

would like the line to be used for, etc. But it kind of depends on where you start whether or not that becomes relevant at the end.

CHAIRMAN KLEIN: Well, I think that we can proceed.

MS. CHARO: You know, in the course of this conversation, we've actually anticipated some of the things, thank God, because we've only got an hour left. So the first one, I think, I've already mentioned; that is, should IRB review be required for all procurements, even the ones that are currently not subject to IRB review under federal regulation? And the comment about industry is relevant here too. It's true that many industrial settings won't necessarily have their own IRB. And because they were doing privately funded research without any of the other usual triggers for federal regs, they were able to do research without going to IRB's. You are, of course, free to always add IRB review requirements. And if they don't have a local IRB, there is a long-standing tradition, even within the federally regulated system, of being able to use somebody else's IRB or an independent IRB. So there are ways to do that if you choose to make IRB review a requirement.

Now, going to your question again about the

availability of embryos. Even beyond the shear number of embryos that are frozen, the number of those embryos for which the relevant parties are known and can still be identified in terms of their phone number and address and asked do you want to give consent, etc., putting aside just that, the American Society for Reproductive Medicine has sponsored some surveys about the number of frozen embryos. And I think it's Dr. Hoffman that had a survey about attitudes toward donation and such.

There is a small percentage, about 8 to 10 percent, I believe, of those embryos that were made using donated gametes. That is, you have a couple making an embryo, either the male or female can't use their own gametes, and so you get donor gametes. Most commonly it is anonymous. Now, in many cases it's anonymous to the recipients, but the records exist as to who that donor was. In other cases, it would be really, really hard to track down who the anonymous donor was. And especially for the older embryos because the practice many years ago had been to actually make those records so muddied, that nobody could ever backtrack because of the thought that that was actually better for the child. The thinking has changed over the years, but nonetheless it's present.

One of the things that has come up in other settings, and indeed Bernie Lo from UCSF has written eloquently on this topic, is whether or not consent should be required, not only from the couple that made the embryo, but also from any gamete donor, which would mean that in cases where you couldn't identify those gamete donors, it would make the embryo ineligible for use for deriving a new line, thus reducing the population of available embryos somewhat further.

Like I said, about 8 to 10 percent, I believe, of the embryos that are made in the United States use donated gametes. So this is one of those kind of yes/no, just pick an answer and stick with it kind of questions for your Standards Committee. And it's going about a kind of balancing act of the kind of notion of entitlement on the part of the donors who originally gave gametes for reproductive purposes at a time nobody imagined that it was likely that the embryos would wind up being used for research.

How important do you think that original understanding was? How offensive to do you think it would be to these people to know that it's possible their materials had been used? Since nobody knows if it's their own embryos, it's every person who's ever been a sperm donor or an egg donor that's been left

wondering whatever happened down the line to my materials versus the effect on the availability of embryos. So check a box yes/no to answer that question.

Now, on reimbursement, again, kind of getting down to really hard tack questions, right, Prop 71 was extremely clear that you are not supposed to pay people for their biological materials, whether it's your somatic cells or your eggs or your sperm or your embryos. But reimbursement is typically offered even in totally noncommercial settings. Europe and Canada have long prohibited payments for embryos and prohibited payments for things like sperm donation. In those countries it really is donation as opposed to sperm vending, which is what we really have in the United States.

I come from UW. We had a guy named Sandy Shapiro. I got to tell you this. Sandy Shapiro ran the IVF lab, and all around the med school, he had these little signs going I'm looking for a few good men.

Even in these completely noncommercial settings, reimbursement is permitted, but the reimbursement itself turns out to be a kind of contested word and contested definition. For example,

does it mean just actual out-of-pocket expenses, taxi fare? If it does, and as I've learned when Amy sent me the State limits on meals, does it mean somebody defines what is a reasonable out-of-pocket expense, right, or is it your actual out-of-pocket expense, whatever you happen to spend? So if it's going to be reasonable, reasonable according to whom? Who's in charge of deciding it? As soon as you decide you're going to limit the out of pocket, you've got to decide who's going to be decision maker.

It's very important, by the way, and I say this as an aside, but very, very important to never write your standards in the passive tense. If you do that, you lose track of when, in fact, in that standard is buried the problem of who has to do it.

Regulations shall be issued on this topic is going to get you in trouble because it means you never had to think about so-and-so will issue regulations. And then you got to decide who the so-and-so is. So active tense is really important.

Now, the other thing about reimbursement is opportunity clauses. Sometimes people have to take time off from work or they'll have to give up some other opportunity. And if you're going to reimburse them for an opportunity cost, they had to give up four

hours of their vacation time or their sick time at work, then question again about reasonable, but also the reality is the opportunity cost for somebody who is paid a high hourly wage is going to be greater than for somebody who is paid a low hourly wage. So do you then give the person who works at KFC a very small reimbursement for opportunity costs equal to four hours of minimum wage work and somebody who happens to have a higher paying job in union settings will get a higher reimbursement cost? Again, just something you've got to think about before you set your standards for what constitutes reimbursement.

MR. SHESTACK: The California law prohibits paying an egg donor in any circumstance.

MS. CHARO: I understood Prop 71 wrote it right in there.

CHAIRMAN KLEIN: It does. It only permits actual out-of-pocket reimbursement and does not include opportunity cost in that definition.

MS. CHARO: That simplifies that.

MR. SHESTACK: This is an important point because there are many people out in the community who have a sense that this bonanza in stem cell research will lead to poor women being induced to go through IVF, for which there is, someone said, no true informed

consent, we don't know that the ultimate result of this process is safe in order to provide multiple eggs or even one egg. And this is a concern I encounter in the community all the time, and I'm not able to just say, oh, well, that couldn't possibly be because it's against the law to pay for an egg in California.

CHAIRMAN KLEIN: Very specifically, it does not permit reimbursement of lost time at work or opportunity costs, so there's no compensation. It only deals with third-party costs, cost of the doctor, cost for the hospital.

MR. SHESTACK: No researcher that -- if any researcher who we were funding was obtaining eggs through payment, they would be in violation of the law.

CHAIRMAN KLEIN: That's correct.

MS. CHARO: This --

MR. SHESTACK: Simple answer to that question.

MS. CHARO: -- gets back again, though, to -- maybe I'm anticipating, but it's timely -- it gets then to the question about how far back you want to track. So fine, you're not going to pay egg donors in California for CIRM-funded derivations. Fine. That's pretty clear.

Now you've got another researcher who comes

to you and says I want to collaborate with so-and-so who works in Massachusetts. And we're going to work together, and he's going to ship me some of his lines. I want money to work with the lines. I'm not going to derive anything. I just want to work with the lines. Does your funding hinge on whether or not the Massachusetts lines were derived in a fashion that did not involve any opportunity cost reimbursements? In other words, how close do the original derivation rules for outside of California, outside of CIRM-funded lines, have to be to your CIRM rules before you'll let somebody work with them on CIRM money?

You know, this is something where you could insist on absolute identity. You could go for what would be considered substantially equivalence. That's a phrase that pops up in federal law pretty often. I can tell you substantial equivalence is a term that then invites all sorts of iterations of understanding, but it's used precisely for that reason because you can't seem to write it out.

MR. SHESTACK: Or just set a cut-off date, which is what the President did. No stem cell lines derived after a certain period of time.

MS. CHARO: You could certainly use a cut-off date. You could use anything you wanted as a

limitation. Of course, you'd want to be able to spell out the rationale for the particular limit. My point simply is this. You have to decide not only what your own standards are going to be, but whether your standards are just for the things you're actually funding, or they're also standards for everybody who gets to basically collaborate with you or anybody who's worked -- your researchers get to rely upon or buy into.

Another common guideline that you will see popping up in the international setting, this, for example, is very close to the Israeli guideline, has to do with the distancing between the physicians at the fertility clinic and the investigators who want to derive the new lines. How much, if any, separation must there be? In some cases you're going to have investigators who are also working at the fertility clinics. In other cases, and probably more commonly, the fertility clinics are clinical only, and the investigator is at the hospital. But since many institutions have a research and clinical unit within the same, for example, medical school, how many degrees of separation do you want to have and why because most of these guidelines come out of some effort to make sure that there are no inducements to, not only

donating embryos, but no inducements to creating more embryos than were needed for clinical need. In other words, an effort to make sure clinical care is never distorted by the possibility of research down the road. That's a kind of recurring theme in the guidelines that you see in Canada, in Israel, and elsewhere.

And when it comes to procurement and derivation, of course, informed consent seems to be what people kind of focus on. These things that I'm listing are things that occur either in existing guidelines in the United States or elsewhere in the world. If you want to look at other countries as examples, by the way, for fairly detailed ones, I would suggest Israel, Canada, the United Kingdom, Singapore. They haven't actually finalized them, but they've got fairly detailed recommendations. Australia, which has two pieces of fairly detailed legislation.

MR. SHESTACK: Is UK all Europe?

MS. CHARO: United Kingdom is just England, Scotland, and Wales. Belgium, I believe, substantively follows pretty much the same guidelines as the UK.

CHAIRMAN KLEIN: United Kingdom, I think, is closer to our situation in fact pattern than Australia would be because in Australia there are limitations on the range of their research.

MS. CHARO: Australia now has legislation prohibiting cloning research. So they are more limited there than in the UK.

CHAIRMAN KLEIN: So UK's regulations might be broader and cover more of the scope of our research.

MS. CHARO: Right. Ditto for Canada. Canada also is not funding any research that involves deliberate creation of embryos. So that's going to knock out deliberate creation through IVF or through SCNT. But when it comes to the informed consent process, particularly with existing embryos, the doomed embryos that are going to be discarded, here all these countries are potentially instructive in their list. Here are the items that tend to come up in the list.

And the question for you is simply in your standard-setting process, are you going to insist on any or all of these? And are you going to insist that it always be the same at every institution?

So information about possible clinical uses down the line, restrictions on the directed donation. Remember, that came up with the fetal tissue research. Keep in mind on directed donation, obviously when you get into SCNT for autologous transplantation -- that's still very futuristic -- you really need to be allowed to direct the donation back to yourself. But in other

contexts, perhaps you want to have a comment on that. Issues surrounding information that people need to have about how identities are managed and how information is going to be kept confidential, how much of that do you need to tell people before you'll consider their consent to be informed?

This is a particularly interesting one, and I actually commend to your attention, if you really get into this one, a report from the Clinton Bioethics Commission called "Research With Human Biological Materials."

MR. SHESTACK: From what commission?

MS. CHARO: Clinton -- it's the National Bioethics Advisory Commission that I served under President Clinton. And we wrote an entire report about research with biological materials. If you have, as you probably will, some coded information that links the donors to the cell lines, and you're going to probably have it because in the future, if you want to use those cell lines to develop transplantable tissue, the FDA is going to require that you be able to talk to them about the donors, about the donor's medical and genetic backgrounds, and be able to confirm the safety of those lines for the development of transplantable tissue.

In those cases, that traceable link means that a researcher working with a cell line might have an adventitious finding, might discover something in that cell line that has to do with a genetic or epigenetic phenomenon that is at least potentially of clinical significance to the original donors. It might be a clue to them that they are at risk of having a child who's affected with something, or it might be a clue that they themselves might be affected with something.

This question of recontact turns out to be very touchy. You can have people donate and agree that they will never be recontacted under any circumstances no matter what is found, and that is the clean and simple way to do it. I know that there are companies, for example, in Massachusetts, now that are working in the pharmacogenomics area that are taking that tack because it's the only way they felt they could manage it. So they just put up a firewall. We will never tell you even if we could save your life. And you need to know that and agree to it before you donate. So taking a kind of pure autonomy point of view, they say people agree to it, that's the rule.

MR. SHESTACK: And you're donating blood, though, simple blood donation.

MS. CHARO: Usually it's blood or it's residue tissue, residual tissue after surgery, things like that. Others say, well, maybe we can create a kind of recontact system. So we will set up criteria for how important does it have to be, how certain are we that it has clinical significance? To whom do we have to prove it? To whom do we give it to transmit it in turn to these people? Right. It's very complicated to do this, but you can, and others will recommend that people be given a whole series of check-off options. I don't want to be told if there's nothing you can do to cure me, but I do want to be told if there's a preventive intervention. It can get quite elaborate.

If you decide there will be no recontact at all, no matter what the coding is, you don't have to worry about this. But if you decide that you want to really think it through and maybe go for a more elaborate arrangement, then I commend that report to you because it kind of lays it out a little bit and helps you begin the thinking process.

Again, on informed consent, debates about whether or not people should be informed about the full range of research uses for the downstream products, the embryonic stem cells, and the resulting tissue. Particularly because some of the research techniques

may be ones that to scientists seem rather ordinary, but to the lay public seem quite extraordinary and might have an emotional component for them. Well, it was okay, but I don't want my materials or I don't want my embryos used for something that involves genetic engineering or chimeras. Again, a question about how much you want to tell people before you think that they're adequately informed. How detailed does it have to be?

Keep in mind whether or not you want to limit yourself because it could be that this list, which says genetic manipulation, mixing of human and nonhuman, is insufficient, and that four years from now, there's going to be another experiment that somebody realizes they need to do. Are you going to now consider those lines ineligible because the original consenting process didn't mention it, or is it going to be more of a kind of could include such things as, but is not limited to? Again, just trying to think through the details of what's going to be in your consent process.

CHAIRMAN KLEIN: Would it be an overstatement to say that since human embryonic stem cell research is part of the charge to the National Academies, that informed consent is an important topic that one might expect to be covered?

MS. CHARO: I can't believe -- I can't say what the National Academies is going to do, but I can tell you that every single national guideline that I've seen at the UK, in Canada, in Israel, and Belgium, they all talk about the elements of informed consent. That's where this list is coming from.

MR. SHESTACK: Doesn't mean they're going to write an informed consent form for us.

MS. CHARO: No. But it also does mean, though, that there are consent forms that exist that can be used as a starting point in which you can actually go through a set of guidelines, and you can check off is it reflected in this form, and use that as the beginning of your template, and then amend it accordingly. I believe I actually gave Amy a copy of the consent form we used at the University of Wisconsin. I'm not even sure if it answers all these questions. Frankly, I haven't looked at it that recently. I'm sure it answers a lot of them, but probably doesn't answer all of them.

CHAIRMAN KLEIN: And we do have the opportunity to use existing models, if the Board were to choose so, that actually have worked and have been vetted institutionally and tested and tried by actual use, and then during our nine-month public hearing

process enhancing those processes and those systems.

But if we could stop for a moment, at this moment to see if there's any public questions on this block of information. Well, there's a tremendous amount of information you're giving, and we're going to have a transcript for everyone. Hopefully that's a great benefit.

MS. CHARO: I can talk faster if you like.

Next, restrictions on receiving financial benefits. This often comes up. In some cases, you know, people aren't -- researchers are forbidden to offer people some share of the financial rewards, should they come, keeping in mind that the vast majority of research yields no intellectual property of any value at all. But most guidelines will address whether or not you have to say it. Some guidelines, by the way, Bob, are going to be very directed. They're going to say you shall tell people about the future uses. You shall tell people about contact or you may, but others will simply say the guideline says each institution has to decide what it's going to do and then write a form accordingly. So long as people are informed of that institution's rules, that's sufficient.

That's kind of a basic strategic or tactical

decision you have to make, which is how much you want to give local bodies the power to make their own decisions versus taking a directed approach on some of these questions. And that's also about how fundamentally important you think they are.

But actually I guess I knew where I was going without knowing where I was going, which is are you going to use standard forms or allow local variation. Keep in mind that the more local variation that there is, on the one hand, the more opportunity you get for all those local institutions to serve as your test sites. But at the same time, the more possible confusion and paperwork nightmare you are creating when it comes to documenting the precise details about the derivation processes and the informed consent in the event that collaborators need, by their own institution's rules, to make sure they only collaborate with people and use lines that met their own institution's standards. That is, standardization is great for interchangeability of cell lines and collaborative opportunities with a minimum of individualized investigation about the lines. Local variation is great for creating a kind of social laboratory for how to do this stuff right. Tactical decision that has to be made.

And here's one that actually does not seem to come up in discussion very often, but I predict it would, so I put it on my list, and it's conscience clauses because we've seem them come up in the context of abortion. I just came out of working on one having to do with pharmacist recusals in Wisconsin. What do you do if you've got facility clinic personnel who simply do not want to be part of this? There are people who are very comfortable using assisted reproduction to make children, but not at all comfortable using the products of assisted reproduction in the research setting. So what is going to be your conscience clause policy, and to whom exactly does it apply? And how do you make sure that whatever policy you choose, it does not in any way put patient safety at risk in the context of their clinical care?

MR. SHESTACK: Why is that our issue and not the issue of the fertility clinic?

MS. CHARO: Could be just the issue -- I'm not telling you what you have to do. I'm just telling you what things you might want to think about whether you want to do.

8:19, move on to derivation. At this point now we're kind of summing up some things that come up having to do with oversight committees and informed

consent. Basically, once your investigators get money from you, right, I understand that they're going to have to go through periodic audits and such, but are they going to have to be reporting to anybody, including your Standards Committee, your Grant Committees, anybody, about their compliance with all the various requirements, for example, IRB's, IBC's, IACUC's, HIPPA privacy boards, or are you just going to trust that they're complying with these things because, of course, there are already independent disciplinary mechanisms. You fail to go to your IRB and somebody figures it out, you can be disciplined by your institution, etc., etc.

Do you want to take on the task of making sure, coordinating the compliance, or do you want to just leave it the way it is now, which is really it's up to individuals and their individual risk for failures.

As I mentioned before, when it comes to the derivations, informed consent is one thing, but having gotten the embryos with full informed consent, do you plan to put any limitations on their right to now derive new lines, for example, substantive limitations like how important the work is before you will let them use your money. And as I think I mentioned earlier,

the question of whether or not those rationales will change depending upon the nature of the underlying embryo.

Stem cell banking is, I think, absolutely going to be the next wave of discussion in the scientific community because it's really getting rather difficult to keep track of all the lines and all the details about the lines. It's not just these ethical issues in which you want to somehow have each line identified with all details about its derivation process, but it's also the more technical issues about characterizations and how many passes and how many passages and such.

Standards for characterization so that there is both a scientific and ethical reason, rationale for having some kind of banking, whether it's physical or virtual banking.

California, because you have a very substantial funding opportunity here for a large number of investigators, is in a better position than most institutions to think about whether or not to really take the lead in a banking effort. Its advantages are the ability to exercise greater degree of control over the implementation of your standards. The disadvantage is that it's got major hassle factor in terms of

setting it up. Truly a nontrivial exercise, but, of course, there are things like the AETB that do this kind of thing. There are many ways to go about it, and I wouldn't suggest that I'm the expert on it, but it's certainly an issue.

If you go down this road, then some of these ethical issues are going to require that you also figure out how you're going to now confirm for the bank things like the providence of the cell lines and also tracking across multiple deliveries. Often you deliver a line to investigator A in Northern California, but investigator A then delivers that line to investigator B in central California, who in turn gives it to investigator C in southern. So lines get out of your physical control and begin to move independently across the network of researchers. Again, you need tracking mechanisms if you are going to make this effective.

MR. SHESTACK: If they make them cheap, they just get them all from you.

MS. CHARO: You could do that too. You could make a condition of receiving CIRM funding that you get the cell line directly --

CHAIRMAN KLEIN: Jon, if you could repeat that.

MR. SHESTACK: I just said if you make them

inexpensive, they get them from you. There are gene banks and tissue banks. There is always the question of giving to -- one researcher giving to his colleague or colleagues; but if you make access easy enough and inexpensive enough, you can maintain. There is always the question of quality control because you give bad data if you bad -- if you have contamination, but there are ways to protect against that.

MS. CHARO: That's exactly right; but, of course, all of that would suggest that a stem cell bank would be very helpful because it's very hard to make it cheap and easy if you don't have a bank.

MR. SHESTACK: But then if there's a stem cell bank in California, does that run into patent issues with your institution, for instance?

MS. CHARO: I will let you talk to my institution about that because I'm not a patent law expert. I really don't. I'm not just being coy here. I'm really not a patent law expert.

Let me get now -- I'm watching the time, let me get to something that in some ways already came up, but I really think is part of what the public concern has been about beyond the issue of consent or fears about exploitation and such. I think a lot of the fear has been what is this research going to actually

consist of. And I kind of went through some of this at the beginning, so let me just highlight briefly some of the really key things.

Questions about human and nonhuman primate combinations really take on a very different appearance than the human/nonhuman, nonprimate mammals because primate and human are so close, the concerns about zoonosis, as well as the concerns about kind of notions of sentience and the origins of conscience all take on heightened importance, coupled with, I think, the animal rights, animal welfare communities' concern tending to increase with the intellectual sophistication of the animals. Not to say that they're not concerned about rats and mice, but I think you'll naturally see the degrees of concern increase as they perceive the animals having a more complex emotional life.

So very important to decide exactly what, if any, limits you are planning to place on your funded researchers with regard to very specific kinds of experiments. And if you place those limits on them, exactly how you write the limits. As I was saying, is it going to be iterative? Are you going to try to anticipate? And who makes the decision? Is it decisive? Is it an approval process, or is it just a

conversation process? And where does it take place, at the local institution or centrally with CIRM?

And that's also why I put up the breeding issue; that is, if you have animals, let's say you've got a sheep that has had stem cells introduced in order to see whether or not they differentiate properly into the pancreas. You will do that with a sheep fetus, for example. In many cases you will sacrifice the sheep fetus prior to birth in order to look at the differentiation patterns. But what if you decide, for whatever reason, that the experiment requires bringing the sheep to term? This may be the case where you need to see patterns of differentiation postnatally. Then you've got to ask about breeding issues, which will depend upon where you've inserted the material and how early you've inserted the material.

If you insert material at the blastocyst stage, you've got the possibility of making changes in the gonads, and breeding then becomes a question. If you do it later in developmental stages, then the differentiation will be more confined, let's say, to the pancreas only, and breeding is less of a question even though there you are going to want to be very sure about the migration patterns of the material. But if the gonads are fully formed, chances are there's no way

to actually affect the germ cells. Again, this is again about limitations. Deciding what kind of limitations, if any, you want takes a lot of collaboration, I think, between the ethics crowd and the science crowd.

You really can't think these things through without understanding why in the world somebody would need to do this research. And without understanding what in the world this research might yield in terms of concrete results in the appearance and function of the blastocyst, the fetus, or the live-born animal. So this is one that requires a great deal of collaboration across disciplinary lines.

And I just say as a piece of advice I think it would be foolish to have the ethicists just kind of wave their hands and come up with rules without really sitting down with the scientists and spending a lot of time with them. It also happens to be, I think, a flash point in terms of alarm value.

Chimeras create tremendous alarm. The announcement by Advanced Cell Technology that they had used a cow egg and a human somatic cell to generate, I think it was, an eight celled zygote or embryo, that generated this unbelievable splash of publicity. Even President Clinton sent down a letter to our Commission

almost immediately saying what is this? I don't want to be doing this. Tell me that the federal government is never going to be doing this.

And it was amazing because people immediately began flashing on things like cows with human faces or humans with udders. I mean the cartoonists went crazy, and it was a little bit like a reprise of the whole Dolly thing where people completely misunderstood Dolly and thought that you were Xeroxing people so that a 47-year-old who's cloned would have a 47-year-old clone standing there next day.

So the alarm value and the misunderstanding value is very high in this research. And there's also aspects of the research that are genuinely problematic, like I said, in terms of the degree of interpenetration of the cells and also always, always when you are dealing with chimeras, the concerns about zoonosis. It's an area that on the one hand, you're tempted to poo-poo the public concerns as based on misunderstanding, and at the same time, you've got to keep in mind that there are real concerns to be dealt with.

And, again, to just emphasize, there are different variables, and it's not just two. It's going to be a kind of multidimensional grid that you'll be

creating, I suspect, having to do with the particular kinds of animals that are being put into combination, the particular stages of development, and the particular stages of sacrifice, and the particular possibilities for breeding. So figuring out what the key factors in the review are going to be, if there is going to be a limitation, often requires sitting down and creating that grid and then seeing in that grid if there are things that are clearly never going to be permitted with your money, things that seem unproblematic as soon as you understand what they're about, and things that are okay so long as you take certain precautions, and things that you can't make up your mind until you hear it in detail.

CHAIRMAN KLEIN: In this regard, I might remind the members of the Board and the public that these areas of research can be segmented. That is, one of the items for discussion is that we not originally entertain proposals in the initial rounds for clinical trials, for example. It is possible as well to decide that in the initial rounds we not engage proposals for primates and higher animal form trials until we have more time for standards. So we're able to take research up to a certain level, develop standards for that, and take more time for other standards to be

developed, if that's the Board's decision.

MS. CHARO: Actually this brings up a really good point, which is that you only need standards for the things you are going to fund. Seriously. You don't have to regulate the universe if you're only planning to inhabit the earth. And so long as you have a correlation between what you're planning to fund and the standards that will apply to that, you can move in this kind piecemeal fashion without any difficulty at all. Right.

This was the last slide, so maybe I should just do it fast, and then we'll open it up for the rest of the time for conversation. It's only that the international collaborations, that there are special rules about international collaborations that you are going to want to keep in mind. Among them the European Data Privacy Directive will have an effect on the ability of your European collaborators to send medical information along with their lines to the United States unless you can prove that our privacy protections are adequate. And by the way, IRB and HIPPA rules are not considered to be in and of themselves adequate to meet the European directive.

Second, in many cases countries, Australia is an example, have rules that prohibit the importation of

cell lines that do not meet their own ethical standards so that your cell lines that were derived from NT embryos, you know, SCNT embryos or such, will not be eligible for exportation to Australia. Similarly, you have the choice of saying no importation of lines that don't meet standards for you, so everybody can have their embryo and embryonic stem cell trade wars in terms of the import/export rules.

Basically, when you get down to this level of detail, you're going to want to sit down and talk with your researchers about the kind of people they want to be working with, where they tend to be, and then take a closer look at those individual national guidelines and see where there might be potential for conflict, and try to work out some kind of system in which you understand where it's an irresolvable conflict, where a memorandum of understanding is necessary, where you might even be willing to adapt your own rules. And for your own researchers, will they be ever exempted from following procedures here for nonfederally mandated reviews so long as they're following procedures there; that is, can they buy in, can they opt into somebody else's system if they're collaborating with them in Israel, for example, or in Sweden, and get waived out of any special review requirements you have here, or

are you going to want everybody to go through all the reviews of all the respective countries so that all your I's and T's and everything is dotted.

Again, it's a kind of procedural question. And it's worth thinking about because when you get to these kinds of things, there may be very different concepts about the process by which you place substantive limits and have process for review over the particular research protocols.

So if you are funding somebody at UC Irvine who wants to do an experiment that here would have required long conversation and permission from somebody, but follows the rules in England where, provided that they've got a license, it's all done, they might be, therefore, able to use your money to do research that nobody else in California can do because they can't opt into the UK Human Fertilization Embryology Authority Licensing System. So this kind of interchangeability kind of loops back into the substantive rules.

That's my last slide to torment you with.

CHAIRMAN KLEIN: I believe Dr. Wright had a question.

DR. WRIGHT: I did. Bob, actually I think it's a question for you too. What you said about the

bioethicists and scientists getting together and having prolonged dialogue around these issues, remind me. I know that there are bioethicists on the Standards, but is there another forum where that same sort of discussion is going to take place or does it come from Standards to the larger group?

CHAIRMAN KLEIN: It comes from Standards to the Board. There are four bioethicists required, a minimum of four, required to be on the Standards Committee, specifically. And so they would hopefully promote and focus on those issues. In addition, they have in the bioethics issues raised by the National Academy and other institutional groups providing benchmark standards that we would look at, that we also have benefit of having the consulting expertise of Alta Charo in dealing with focus information directly to the Board as an outside consultant in the ethics area.

Dr. Oswald Steward.

DR. STEWARD: I don't want to put words in your mouth, but I think you said that the decision at the University of Wisconsin was to do this in a process-based, I think was the term you used, rather than dotting every I, crossing every T.

MS. CHARO: Yeah. It was mixed. Categories followed by process.

DR. STEWARD: So in retrospect, how does that work? In other words, have there been any major bumps in the road that would have said that this process really was a mistake?

MS. CHARO: Not that. Indeed, the process was helpful because it was in the process that we then discovered some experiments that needed new guidelines. We had somebody come and propose something to us that we had never thought of and so realized that we needed to begin to amend the guidelines. That's a huge advantage and allows you this very nice iterative evolutionary process.

I think that -- I'm probably speaking out of school. I think that to make it work requires a mechanism to get people to come to you. Now, in the case of CIRM, you may have that mechanism at hand, right. You won't cut the check until they come to you, and that tends to motivate people pretty well. We didn't have that power.

If you think about it, even in the more established like IRB review, IRB review requires that people recognize that they are doing human subjects research and voluntarily present themselves to be regulated. Think about what we were asking people to do. And the only thing that keeps them coming is that

if they publish papers and anybody notices that they did human subjects research without mentioning in their footnote the IRB review No. XYZ, maybe they'll get nailed.

Again, with our bioethics commission, we had suggested that journal editors try to add to this by requiring it. In the case of UW, the question is how effectively have we gotten all the right people to come to us? I don't know how to answer that. It's like how do I know what's out there if I don't know what's out there? In reality, because I'm on so many of these advisory committees, I have a pretty good sense of what's going on on campus, and I have not heard or seen anything happening that would have required coming back.

It's mostly this chimera-type stuff that we really wanted people coming back to us for on individualized consultations. And the UW research, if you look at our papers, has tended to be really basic science stuff. They're working on culture media and they're working on characterizations and karyotyping and all sorts of real basic science stuff that doesn't raise any of these issues.

DR. STEWARD: If I could just follow up on that question. Maybe the major difference is that, in

fact, at UW you're trying to regulate what goes on at the institution. I guess the question would be is the carrot here coming for funding? Is it sufficient to regulate what gets carried on with the funds that the CIRM provides, or are we trying to, in fact, set the standards for research regardless of where that funding comes from? Does that play in?

MS. CHARO: The fact is -- now I'm going to speak as a lawyer as much as an ethicist. The federal government has traditionally used funding as its means for regulating. They don't regulate human subjects research directly. It's regulated as a condition of receipt of federal funding or the condition on the approval of a FDA product. The one we're most familiar with is if you get your money from HHS, you've got to follow 45 CFR part 46, subpart A, B, C, and D. And if you don't want to do that, don't take our money. That is the spending power of the Constitution, and it allows Congress to get around all sorts of jurisdictional limits in terms of what it's allowed to regulate because, like your parents always said, if you're going to live in my house, you're going to live my way.

You have that power by your funding mechanism. The effect that the federal government had

when it did that was to occupy the field fairly broadly. They created a kind of professional norm. It wasn't enforceable necessarily, but professions work by reference to customary standards of professional practice. And if you have enough funding and you're pervasive enough, then even the nonfederally funded, in the Federal example, will often fall in line.

Recombinant DNA research, the Recombinant DNA Advisory Committee technically only had authority over NIH-funded research. And yet without question it became the extant national standard for genetic engineering and gene therapy work regardless of the source of funding. You had a few rebellious scientists along the way, but fairly few.

So if CIRM becomes a really major player in the funding arena, $300 million per year certainly would seem to put you in that class, and coupled with that, if you happened to decide that your standards that you impose upon your funded researchers are going to be functionally exported, that is, your researchers cannot collaborate with somebody whose lines or behaviors do not comport with your own standards, you will now combine kind of persuasive power by shear numbers with this kind of exportation of standards.

That, by the way, is taken out of the federal

play book. We export our human subjects research ethics standards to foreign countries even in places where they're not particularly well-suited by making compliance with U.S. regulations a condition of doing the research in that country with an American collaborator.

So we do research in Honduras where it may or may not make sense to have exactly the same kind of paperwork requirements, but, boy, you're going to do a collaboration with a Honduran researcher, unless you get special waivers and exemptions, you're going to have to do it our way with all of our paperwork. People are going to be asked to sign their forms in a country where signing your name often was -- often put at risk of being killed by the death squads, but that's how we do it. So you can export your standards by virtue of your rules about collaboration.

CHAIRMAN KLEIN: Dr. Pomeroy.

DR. POMEROY: So everything we've been talking about this evening is about self-policing, self-regulation. What should the role of other groups be in providing oversight? And obviously one of the groups that's expressed particular interest is the State legislature. What are your feelings about that?

MS. CHARO: It's not an ethical issue, is it?

It's more of a political issue.

DR. POMEROY: True, but you must still have some thoughts.

MS. CHARO: Wow. Let me think about that and come back to you. Seriously. Don't let me get out of here without trying to answer it, but let me think before I try to answer it.

CHAIRMAN KLEIN: There's a couple points of information that may be helpful to everyone. The National Academy has a particular interest in the framework we're talking about of getting their standards out in this time frame of April on the hope that we adopt them in California as a national standard because of the dominant player. It's hoped that then other states adopt them, and it becomes a uniform set of standards in the country, which would be tremendously helpful to research if there's consistent standards being carried out throughout.

The other point informationally is that there's a Senate Bill 322 that we've been cooperating with. They have yet to fully name their committee. The intent of that bill was to propose standards in California. The Initiative specifically sets out a separate standards process with the issue on the table being to create stability in standards because of the

Putnier (phonetic) experience where a tremendous number of people put in huge amount of effort, and the very day their standards were proposed, the Presidential letter withdrew those standards because of pressure dealing with NIH funding, that really the change in Congress in the fall of 1994 would have -- it led to a situation where there was substantial pressure not to allow this stem cell research to go forward if they wanted NIH funding to proceed on track. So those standards got withdrawn.

The desire is to create a stable system of standards. And the Institute specifically is not subject to changes of standards that may evolve with changes in governors. I think there's a general question here is what is the value of stable standards that do not change with every political cycle every two years or every four years as applicable?

MS. CHARO: For which I think the answer is probably well known to every scientist, which is that you can't invest in the start-up without having some confidence that you'll be allowed to finish the work. And we certainly, because of the experiences in the 25 years, we have a huge pipeline problem. We simply do not have a cohort of undergraduates, graduate students, post-docs, and assistant professors who are all coming

up through the ranks doing this kind of research. There is no pipeline out there. It is only now in the last year or two beginning to develop. And the lack of stable rules and stable funding only further hinders efforts to create a pipeline where none exists. We are 25 years behind the rest of the world because of the absence of funding by the federal government. The stable standards are extremely important.

That said, legislatures and laws are like water. They will find every crack. And so if there is anything that is not precluded under what is seemingly an ironclad written proposition, there's every chance that legislatures will want to get in the act. And their motivations will not necessarily be evil. There's a different set of concerns at the legislative level about the needs of the polity, about the needs for a civil society, about the needs for people to feel confidence in their government or comfortable that things aren't going too far, and they'll often write rules that don't necessarily reflect their judgment about what is morally correct or morally incorrect, but it will be their judgment about what is going to keep people happy enough and quiet enough to move on to the next issue. It's called compromising.

And a funding institution has the choice to

do that or not. You can become principled and pure, or you can become some combination of principled and pragmatic. That's your choice. I think legislatures, by their nature, have to have a component of pragmatism.

CHAIRMAN KLEIN: Are there public questions at this point? I think --

MS. BURKE: I just wanted to make a comment about the pipeline, which is that there's no bioethics sort of pipeline of people who are prepared to step into the gaps that stem cell research funded at a $300 million per year effort is going to create. And that we'd like to ask the Committee to think about the fact that they could look at certain things that they're responsible for and the ethical guidelines, sort of like NIH is responsible for, the committee is sort of a mini NIH for stem cell research, but that each institution is going to require a core of bioethic support for stem cell research in every institution that's funded throughout the State. And that one of the things that the Committee could think about is what level of oversight has to be centralized and what level of oversight needs to be in each local area where there are these one-on-one discussions between researchers and ethicists about what they want to do and why they

want to do it. My name is Sara Burke.

CHAIRMAN KLEIN: The public should know you're not required to provide your name, but it's helpful in terms of follow-up. If you do provide it, if we know your area of interest, we can direct additional information to you as it becomes available.

DR. SAMUELSON: I have a question about that comment. Is that the norm, that in a field that has ethical issues routinely, that bioethicists do pop up or are developed who end up being engaged in that?

MS. CHARO: We are like weeds. We will pop up everywhere. You know, there's -- far be it from me not accept the suggestion that this should be a full employment bill for bioethicists in the best climate and geography in the world.

I think there's a lot of merit in what you are saying, but I think you also underestimate the number of people in the field who have at least taken a crack at the global stuff, if not at some of the nitty-gritty that we've gotten to here and there in this discussion. Because there actually have been 25 years worth of reports, conferences, political agitation, journal articles about embryo research, for which many, but not all, but many of these issues arise.

So I think there are probably more people out there that can be tapped than might be obvious at first glance. But you're absolutely right, that when you get down beyond the generalities, there hasn't been much opportunity to struggle with a lot of these things.

As far as whether or not bioethics has ever been kind of incorporated into something, well, it is not routine. Nanotechnology is beginning to pop up everywhere, and it doesn't necessarily pop up always in conjunction with a nanotechnology ethicist. Although I can tell you the ethics community has noticed that this may be the next big thing.

But there is one example, the human genome project. The human genome project came in for a lot of criticism about big science, big budget, unclear payoffs. Some of that criticism is still out there, and we're still waiting for the full range of big payoffs.

One of the strongest critics was Jeremy Rifkin, who is the Foundation on Economic Trends. I happen to believe that Jeremy was not solely responsible for what I'm about to describe to you, but he thinks he was. And that is that the human genome project had written into it a kind of ethics set-aside in which a certain percentage, I think it was 3

percent, of the funding for the human genome project had to go to ethical, legal, and social implications of the human genome project. Some of that money was well spent, and there's a much larger cohort of people who are very savvy now about genomics and genetic screening and about intellectual property and all sorts of things having to do with genomes and genetics in the ethics community. Absolutely built expertise.

Some of it wasted. There were a lot of conferences that basically had the same old people talking about the same old things. Some of the research was really good. There was empirical research that was funded that actually got at social attitudes and at personal experiences that were very informative.

I don't think anybody in the clinical community had appreciated exactly how little people want to actually know about their genetics under many circumstances. So the assumption that more information is always better turned out to be unfounded in some circumstances. But some of the empirical research was really just quite foolish and got funded because the study section committees really liked empirical research because they could really see if the methodology made sense and it didn't really matter if the question did; whereas, all the airy-fairy

philosophy was harder to evaluate.

It can be done, a set-aside to provide a venue, a forum to develop expertise, to do public education and outreach. It just is not necessarily a guarantor of any particular valuable outcome.

CHAIRMAN KLEIN: Thank you. I think we have another member from the public.

DR. BARGLOW: I'm Raymond Barglow from Stem Cell Action Network. I think you mentioned -- you mentioned legislators. They have particular interest and they're very valid interests. For one thing, affordability of the cures that are produced, that they should be available to people, even people of low income, for instance.

Then another concern which is oftentimes expressed is that given this very large investment, the taxpayers want a return. And from the patient point of view in particular, the way that return is going to happen, it's going to come by curing illnesses, and that's going to save just tremendous amounts of money because these illnesses are chronic illnesses that are so destructive. If we can start to cure some of them, we'll really lower our health costs.

I think that there is a fear, however, and I think patient advocates experience this, that the

State, in trying to seek revenues through, say, licensing and IP arrangements, there is some possibility that this might get in the way of actually the kind of freedom, the kind of collaboration that this science requires in order to go forward. So I think that there's a possible tension there, and I hope that we'll all be aware of that tension, and try to deal with it in a sensible way.

CHAIRMAN KLEIN: Thank you very much. Any additional public comment? Any additional Board comment?

Well, I'd like to point out that this was a tremendous effort with incredible amount of information, all achieved within the scheduled time period, which is near miraculous. So but thank you very much, and I think we should give a round of applause.

(Applause.)

CHAIRMAN KLEIN: And the Board should be aware that if you have questions that we can organize, that in addition to the presentation tomorrow for the Board, Alta Charo has a consulting relationship with the Institute where we can continue to refer questions to her and convince her to come out to a climate that is 62 degrees warmer than her current situs.

MS. CHARO: And in the summer 25 degrees cooler.

CHAIRMAN KLEIN: Longer term benefits. Thank you all. Thank the public. And this session will be deemed closed.

(The meeting was then concluded at 08:55 P.M.)