keep in mind that there are certain criteria that you'd really want to worry about in terms of characteristics of cells.

Dr. Harlan, and then Dr.--

DR. HARLAN: Well, my only comment with regard to Dr. Lederman's question was: implicit in your scenario as you presented it was that here was no animal model to test the viability of these cells in. So I think what the FDA continually--my read of it is that they say, "Do all the testing that's reasonable to expect." If there is no way to test the hypothetical cell that you're talking about, then I think the FDA would be reasonable, if you identified the patient population appropriately.

DR. KURTZBERG: I was going to just comment on the tripan blue question.

I don't think tripan blue is enough of a measure to tell you that your cells will preserve function and viability later. If you see a lot of cell death that's important. But you can have cells that will not exclude tripan blue five minutes later, but who will still die, you know, several days later.

So if you have a functional assay like a

colony assay or something like that, that would be a better measure.

CHAIRMAN RAO: Dr. Borer.

DR. BORER: Yes, I would like to agree with what Dr. Simons said, that you do need--I think you need an in vivo assay. I don't think it's a heart prep, because there is a difference--an important physical difference, I think--or there may be--between the outcome, in terms of the adequacy of delivery and the state of what's delivered, if you place the delivery device within turbulent flowing blood and a beating heart, than in a preparation that's external to the body, that's not subjected to those same mechanical stresses--even if it were a beating heart on a Langendorf apparatus or something--or something analogous to that.

So I think you do need some in vivo experience. I don't want to say how much, what model, how much in people. Those are degrees of specificity that I don't think we can get to here. But I agree with the point that Dr. Simons made that you do need in vivo experience.

CHAIRMAN RAO: Phillip?

DR. NOGUCHI: Not to comment specifically

on these particular catheters, but I will point out, since our device colleague is not here right at the moment, that under the device law you have something like this--this happens to be a blackberry. But as a manufacturer makes it, they are not restricted to always manufacturing everything themselves. So, for example, they may have several suppliers for the steel that's being used, or several suppliers for any of the lubricants, or for the tubing.

And so, from a real practical point of view, while rare, we do have experience where substitutions that are made by the manufacturer on a reasonable basis, based on their specifications and qualifications, can sometimes lead to fairly distinctive changes in the same device--let alone a comparable device--that can have severe adverse reactions.

And, again, we won't be talking about specifics, but let's just say that on a rare occasion, the fact that a device is made through multiple suppliers can lead to the question, and the realization, that sometimes we find it hardest to, off the shelf, just say: "This catheter is equivalent to this catheter," or "This device is

equivalent to this device," because it's not always quite the same supplied material.

CHAIRMAN RAO: We've had all of these experiences with tissue-culture plastic, and the same manufacturer changing the manufacturing protocol, and then the cells wouldn't grow. So, I mean, I completely agree with you that that's an issue to worry about.

Dr. Neylan?

DR. NEYLAN: I would love to take the opportunity to segue your comments to, I think, a closely related but perhaps still sidebar issue. And that is that just as the conversations here have demonstrated the importance of the interaction between the device and the constituents being delivered, I think there's another analogy that can be made within VDA about the importance that this instance brings up--and others like the drug-eluting stints--about perhaps finding new ways of working so that the different divisions can work more synchronously--CBER, and the devices division--so that it doesn't fall into some more prolonged review process, or step-wise review process, but perhaps could be done in a more consultative fashion.

DR. NOGUCHI: Just to quickly respond, that's exactly why we had Dr. Jensen throughout all the preparation for this, and he's been involved in all the reviews of all the products.

So--that point is well taken ,and we strongly endorse it.

CHAIRMAN RAO: Here's another question for the cardiologists, related to device--and I think Dr. Borer alluded to this already--is: though we can be accurate, we're not a hundred percent perfect in terms of delivering things. And with cells, then, that means if you deliver it into the cavity, or you deliver it into the epicardium, or you do that, then there's going to be a whole different effect of what you've delivered.

And should there be, when one does some sort of study like this, some way of monitoring that so that, you know--you're assessing a device and the cell, and should one be looking at bio-distribution after this has been done to worry about it? Or hopefully those things are discovered, because you've already looked at cells.

DR. BORER: Yes, I'll take the first crack at that.

At some point I was going to make the

suggestion that we should do just that. You know, nobody knows how much difference it makes. Jeremy's point is, of course, very well taken. We don't absolutely know where these things are being delivered with the best of implements. You know, there's reasonable accuracy but not total accuracy.

But we also don't know where they should be delivered. We don't know whether there is a difference in outcome if you deliver to the mid-wall, or whether you deliver to the endocardium or the epicardium. We don't know whether one part of the ventricle is more important than another; we don't whether the border zone or the center of an infarct--of a scar is important. We don't know any of those things. And information needs to be obtained.

Now, does that mean that all the information has to be available by the time a product may be ready for clinical use? I think perhaps not. It depends on the outcome from clinical studies. But information that would allow one to know these things would be very important if, for nothing else, for improvement of a product--even if a product were approved.

And I think that, therefore--getting back

to the point we all made earlier--there must be a data collection protocol set up that will allow data to be used from all the studies that are done, to allow us to answer questions like that. And I do believe that bio-distribution is very important-- knowing about it--not only throughout the whole body, but throughout the heart, so that we can somehow retrospectively relate the outcome to the location of what's been delivered. So I think it's very important.

CHAIRMAN RAO: Go ahead Joanne.

DR. KURTZBERG: I agree with everything you said. But I don't know, right now, of any safe way to label human cell and see them--on whatever you want to look at them with.

I mean, you can do things with iron and fluorescent dyes in animals, but those things are not safe for the cells, and there is no material that allows us to track human cells yet. We need one. It would be terrific. But I don't think it's there yet.

CHAIRMAN RAO: So would you say, Joanne, that this is true for animal studies when you're looking at them, or in preclinical studies, that there should be a way, but we can't necessarily

expect that that be done?

DR. KURTZBERG: I mean, it's just not ready for prime time in humans.

DR. BORER: Yes, I think that's a critical point. I think studies should be done in animals. But, I don't know whether the methods I'm going to describe are appropriate for the purpose.

But radio-nucleide based molecular imaging is becoming a reality. And it may be possible to monitor the presence and location of cells with label that can be administered after the fact to localize cells with certain characteristics. I mean, there would need to be enabling research to allow this to happen, but the imaging techniques have developed to the point where I think this may be a viable issue.

I think it's an important issue, so some time should be spent at some point looking at the various methods that can be used to identify cell types within the myocardium. But it may be that newer techniques for imaging could be used.

CHAIRMAN RAO: Dr. Simons, and then--

DR. SIMONS: I would like to come back to the safety issues of the needle-based material delivery.

Essentially, with all the needle devices now, there will be some loss--there will be some loss of the material. And, you know, depending on what the material is and what the catheter is, that it could be up to 50 or 70 percent of the dose. And it could be lost either in the left ventricular chamber, or it can be lost then through the coronary--into the myocardial vasculature and will immediately get washed out. And that happens to cells, too.

So I think it's something to sort of consider, because depending on the cell type used, you would clearly have a number of cells injected essentially in the left ventricular cavity. Whether that's a risk, I think, needs to be assessed. And this would be assessed, and it should be assessed, I think, in an animal model.

CHAIRMAN RAO: Here are a couple more questions for the cardiologists.

We heard that when you infuse cells in a long vessel--whether it's venous or arterial--that there are some specific complications of putting cells in; one was this idea of micro-emboli, and the other one was that you have ventricular changes in the echocardiogram.

Is this something that's of sufficient concern from experience, or that's something that one can learning by doing the experiment in an animal model? Or it's something that should be required or, you know, considered of urgent criteria? In any of things, in general?

DR. TAYLOR: Can I directly speak to that?

We know for years of our preclinical studies with surgical delivery, that we lose a relatively large percentage of the cells after we deliver them. And we may very well lose those both epicardially and into the left ventricular cavity. So I don't think it's that different for catheters than it is for surgical deliver in terms of the loss of cells.

More recently we have begun to develop some radio-nucleide labeling that lets us start to follow the bio-distribution of these cells. And I think what we're finding is size matters. The larger the cell, the more likely it is to be in the lungs; the smaller the cell, the more likely it is to be in the spleen or the liver--and that's not particularly surprising.

So I think--there probably is a whole lot of data already out there from surgical delivery of

these cells, and also from the delivery of bone marrow cells for other situations, that would directly feed into this, and we don't have to re-create that wheel.

CHAIRMAN RAO: Specifically, though, related to catheter delivery, though, one can't assume that it's going to be the same--right?--in terms of distribution.

DR. TAYLOR: No, but we do know that we've lost--we lose a significant number surgically into the ventricle as well.

DR. EPSTEIN: I'd like to just recall Bob Lederman's comments yesterday: we know that we're going to lose cells into the general circulation. So you could take an animal model and just inject the cells into the left atrium. You don't need a catheter. I mean, you know that cells are going to be lost into the circulation. And then, by whatever technique you may have, you could track them. But then what?

So, you know that the cells will be in the brain, in the spleen. But are you going to follow those animals for a year or two to see if there's an oncogenic--I mean, you know, that that's going to happen, and then you have to ask yourself, "What

do you do with that information?"

And I would have real questions as to how important that information is. Because you know what the answer is going to be.

Your other question is a very important one, and that is: the intra-coronary injection of cells--and I've forgotten the name of the gentleman who presented yesterday, with the dogs, showing small areas--

CHAIRMAN RAO: Mule.

DR. EPSTEIN: Yes--and we did a study like that--Dr. Unger of the FDA many years ago--where we injected endothelial cells that were harvested from the carotid arteries of dogs. These were autologous cells. And these were dogs with an amyloid constrictor around the circumflex coronary artery. We genetically altered those cells and we thought that we were going--it was really a smart experiment, injecting the genetically altered cells into the LAD to enhance collateral development. And all we did was kill dogs.

Because if you think about the situation, the LAD--the circumflex is totally occluded, and the LAD is feeding the entire left ventricle, essentially. And these cells embolize. I mean

they're too big to go through the capillaries.

So you probably wouldn't see any hemodynamic perturbationsif you gave those cells to an animal with normal coronary arteries. But if you have a collateral dependent--if you inject them into a feeder vessel, then you'll see what, you know, you saw yesterday.

So the clinical studies that have been done to date--acute myocardial infarction, total occlusion of an artery, opening up the artery, and then several days later injecting cells--in that situation, I think you're okay, because you'll never be worse off than with the situation you were in five days before, with a totally occluded artery.

But now if you extend that and say, okay, let's take patients with chronic coronary disease, where you're injecting cells into a vessel that may feed collaterals to the rest of the heart--you know, I think you really need animal studies for that, for safety, but you have to model it very carefully.

And my prediction is that it would be very dangerous. So, you know, once again it depends on the clinical situation.

CHAIRMAN RAO: Go ahead, Dr. Lederman.

DR. LEDERMAN: I think that's a very good point. Alternatively, you could model this--since we have very sensitive biomarkers--of myonecrosis, both imaging-based or biochemical. And these can be testing in healthy animals.

And if we--as I say, again, there are fairly high-sensitive biomarkers. We could administer whatever cell prep we're interested in by intra-coronary infusion under different conditions, and if there is no myonecrosis, I think that's probably a satisfactory test.

Do other members of the committee agree, or do they disagree?

You gave us a much more difficult-to-achieve test.

VOICE: [Off mike] But those are the patients [inaudible].

DR. LEDERMAN: I'm not disagreeing. I'm wondering if others have other opinions. It's not self-evident to me that your system, which is much more harder to accomplish, has more predictive--necessarily have more predictive value.

And I just wonder what other opinions might be?

CHAIRMAN RAO: Dr. Harlan, did you have a comment to make? Okay.

Let me see if I have a sense here--and nobody mentioned anything about monitoring, in terms of looking at arrhythmias of any sort. Is that something that one would consider as an important thing to do? And would that be something one would consider as a routine thing to do when one is testing?

DR. RUSKIN: Actually, I had mentioned something in response to one of the questions that was raised. And I would think if you were to pursue any of this work in a canine model--hopefully a relevant infarct model--that chronic monitoring with implanted telemetric devices would be appropriate, as would electrophysiologic testing--invasive testing--and just routine clinical monitoring for the kinds of adverse events that Jeff Borer described.

And I think those would be important to do, based on concerns about creating what may be a highly arrhythmagenic substrate. I'm not convinced that we know that happens, because of the kinds of patients in whom these procedures have been done. But at least the potential for doing that certainly

seems to be there, and it would have to be pursued, I think, pretty aggressively--including monitoring.

CHAIRMAN RAO: So--go ahead, Dr. Simons.

DR. SIMONS: If I can just amplify this point, because the concern of an arrhythmic even has been raised with skeletal myoblasts.

To my knowledge, this has not been raised with different cell types. So, do people around the table feel that this kind of monitoring is required for all cell types, or just for skeletal myoblasts?

CHAIRMAN RAO: I think we're just looking at delivery through a catheter, either through venous--or putting it in, not like a long-term thing--one week later monitoring, or--I'm just wondering about whether it's important, when you do the procedure--just like you would with dye or something--

DR. SIMONS: Oh, if you're talking about acute settings, it's standard to monitor. I mean, that's a standard of practice.

CHAIRMAN RAO: It would be something one would consider really important, you said.

DR. RUSKIN: I'd just like to respond to Dr. Simons' question.

My own bias would be in the beginning to be rather conservative and cautious with regard to monitoring in any of these models; my answer being, to his question: yes, I would be inclined to, even with other cell types--only because I think the potential exists for creating a substrate that is very dangerous.

I'm not at all convinced that happens. But introducing cells that morph into myofibers of any sort, in a situation in which we don't know how they line up, how they communicate, what the intracellular substrate looks like, what their action potential characteristics are, what their ion channel properties are--is one of the ways that I would, if you asked me to invent an arrhythmagenic substrate, that's one of the things I would think--one of the ways I would think of doing it.

So I think that the bar ought to be pretty high early on for some form of careful vigilance. The problem is that the sensitivity of these models is going to be low. And I would take no reassurance from the fact that nothing adverse was observed.

But, on the other hand, if adverse

outcomes are observed, it raises a very important issue, in terms of how one proceeds.

CHAIRMAN RAO: Go head, Dr. Schneider.

DR. SCHNEIDER: I'd like to follow up on Dr. Ruskin's cautionary note, and ask him how best might the FDA, or should the FDA take into account the established safety as demonstrated in Phase I trials elsewhere? I think that the nightmare scenario is appropriate, if it hasn't been done or 60 or 100 patients already. But once its been done in 60 or 100 patients already, it seems to me that, without cutting corners, and without jeopardizing safety, the information has an applicability.

DR. RUSKIN: I think that's a very important point. And electrophysiologists have sledgehammer answer for all of that, and it's called an ICD.

And my own bias is that, yes, I think there is information that's quite reassuring already, and that given the nature of the patient population being studied, it would be relatively easy, I would think, to do your Phase I studies in patients who are already recipients of implantable defibrillators--because of the primary prophylaxis trials that have recently been completed and that

point out, I think, quite clearly that most of the patients we're talking about here are already ICD candidates.

So that's the ultimate protection. And I think given the data that's already available, it's quite reasonable to move ahead--with appropriate caution, and the protection of a defibrillator.

CHAIRMAN RAO: So this maybe gets back to what Dr. Lederman raised, then, that if that's the case, and that's how you're going to do your Phase I clinical trials, why is it necessary to worry about it in the animal model?

DR. RUSKIN: Because I think we can learn a great deal from animal models, and if we--my sense--and, again, I'm naive about this, but I get the sense that we don't know exactly what the right cell type is, how to deliver it, in what kind of media. There are all sorts of unanswered questions. Are the cells going to be genetically modified, and so on, and are there going to be ways of ensuring that they lay down appropriately and form connections?

These are all unanswered questions. And I think until they're answered, the more information you get from preclinical models, the smarter you'll

be.

CHAIRMAN RAO: Dr. Cannon, you had a point you want to make?

DR. CANNON: I was just thinking, listening to Steve's comments, I would take exception, Steve, to your lack of concern about cells--large cells, now, not the peripheral blood mononuclear cells, by the myoblasts, the larger cells--about whether they go to the brain or not, and will that matter,

I think it might matter--after looking at what happens in the coronary circulation of dogs when these cells are injected, if a similar phenomenon were to occur in the brain, I would be worried that the patient may be different cognitively after the procedure than before the procedure, even though there may be benefit to the pump function of the heart.

So I think it would be important to know, in an animal model, injecting cells into the left ventricle, the left atrium, if they do lodge in the brain, and for how long. And, if so, certainly that would raise concerns for cognitive monitoring in this kind of application.

CHAIRMAN RAO: Joanne?

DR. KURTZBERG: You know, if you had been

here for the neural stem-cell meeting, they would be so happy if you could put cells into the left ventricle and get them into the brain.

[Laughter.]

I mean, that's very hard to do unless you have some kind of connection you're not supposed to have.

So, I mean, realistically, that probably is the one thing you don't have to worry about. They'll go all over the place, but to go into the brain at the time you inject them into the blood is not a worry, I don't think. It's actually a challenge for the people who want to get cells into the brain.

CHAIRMAN RAO: But it's a general problem, right? Anything which is in artery circulation essentially--where they might be distributed might be something to worry about, right?

DR. TAYLOR: I actually wanted to address the point of whether--Dr, Ruskin's point about whether or not we need to deal with--when 60 or 100 patients have already been treated, whether or not we need to still demand preclinical information. And I guess what we have to get back to is whether or not the cells are identical.

If the cells are not identical--just because one group can grow appropriate endothelial progenitor cells for three days in a dish doesn't mean if somebody else tries it they're going to get the same cells. So I think the data have to be fairly convincing that you're working with the same cell population, or it's not appropriate to base that on previous data.

And just calling it the same thing doesn't mean it is the same thing. The markers have to be the same.

CHAIRMAN RAO: Do you have a comment? Go ahead, Dr. Lederman.

DR. LEDERMAN: I also want to comment on Dr. Ruskin's point.

Certainly, it's defensible to advocate a strategy--in fact, European investigators have already sometimes applied a strategy of prophylactic defibrillator implantation before testing cell therapies for various applications. But to mandate that I think is a bit extreme in a way that would hurt the field, and patients in that, our most sensitive, surrogate markers of myocardial performance would then be unavailable for our patients. And that means MRI endpoint

assessment.

So, unfortunately, that's a very high price. And I think to mandate it is--

CHAIRMAN RAO: Remember, the committee doesn't mandate, and the committee's only advisory, and it's not looking at any specific applications.

DR. LEDERMAN: But, unfortunately--this is not a compromise.

DR. RUSKIN: Yes, your point's very well taken, and Mike Sunn has made the same point with regard to how it compromises imaging.

I didn't mean to suggest that anybody even think about mandating a population in whom this is done, or mandating the use of a prophylactic ICD. What I was suggesting was that there's a very large patient population that already exists that have ICDs implanted for appropriate clinical indications, who have severe congestive heart failure, and are at the end of the road, and have had CRT therapy, and might provide an appropriate population in which to begin to do some of these studies--if the question of arrhythmagenesis remains high on the list.

I understand that that involves compromises in terms of imaging. Nor do I mean to

suggest at all that that be the only group in whom one ought to consider appropriate trials.

DR. BORER: I think that several important points have been made, and I'd like to comment on three of them.

First of all, I agree with what Jeremy said about conservativism in doing these studies, and would just amplify by saying that arrhythmias--potentially lethal arrhythmias--could occur at several points after the administration of cell therapy, and the mechanism in each case could be different. So you have to watch at many points in time. I don't know when the watching needs to end. Again, it may be beyond the scope of this meeting, and maybe in the too-hard box.

But the important point is that there is the potential for problems with the initial mechanical perturbation, with the initial physical injury of the myocardium. Then, subsequently, there are problems when the cells begin to grow before they have fully defined their interconnections with the surrounding tissue. And then there are other problems that could occur when they have made those connections.

So one has to monitor. And I would

suggest that we do need that information.

I think that Jeremy was absolutely right in indicating that the availability of ICDs reduces the risk compared to what it might be, but there a couple of points that we have to keep in mind--without negating in any way what he said. I think Dr. Lederman's point is a good one. If you use that population, you can minimize the capacity to make certain measurements you want to make.

But, more importantly, the fact that an ICD is in place doesn't mean that someone has been made immortal. [Laughs.] So, if you create arrhythmias and they are sufficiently severe, they may override the ICD, and we wouldn't want to do that. So we'd want to know if that was a potential problem--number one.

Number two, even if the ICD was successful, people don't like to be shocked. I mean, it hurts--they tell me. So, you know, one would like to know about that problem. And, you know, I'm not saying anything different from what Jeremy said--and he could say it better than I. But I think you have to keep that in mind.

So we'd still like to know about the arrhythmias, their likelihood, etcetera.

Now, how much do we know because 60 to 100 patients have been studied? I have a statistician sitting two seats to my right, and he should answer this. But I think--and you'll correct me if I'm wrong Dr. Tsiatis--that the power we have from zero out of 100 doesn't rule out a heck of a lot. There could still be a lot of events. And so we should have, I think, some preclinical data to help us in this situation.

So I think those are just three observations on the important points that have been made.

CHAIRMAN RAO: Dr. Schneider.

DR. SCHNEIDER: In part, to follow up with Jeff's cautionary note in terms of the numbers--I think it's either naive or disingenuous for someone to suggest, as Dr. Lederman did, that it would harm patients for any of the conservative precautions being imposed as they're being discussed here.

Since Phase I trials haven't been done there's no proof yet of safety in humans in the U.S., much less of efficacy in humans. So to wrap yourself in the mantle of protecting patients by speeding the trials along is preposterous.

CHAIRMAN RAO: Let's see if I can try and

summarize and see whether we have some consensus on some basic statements here.

So, it seemed to me from just listening to everyone was that everybody thought that one needs animal studies. And since this is with the device, it seemed very clear that one needed animal studies in a large animal--of some kind, right?

And that you couldn't extrapolate from one type of delivery to another, because there were issues with it. And you couldn't extrapolate from one type of catheter to another, because there are issues with doing that, or if you're using it in a different way than what it was supposed to be used.

And that if people in different centers used one device, they should have some sort of hands-on experience, because things change when you're using it in a different fashion--if I have paraphrased that right.

And that once you deliver cells, you really need to look at the function of the cells as they've been delivered, and so that they need to be delivered in vivo in some fashion because simple models will not be adequate in terms of doing it.

And you have to look at their behavior where they've been delivered; and that monitoring

has to be of a reasonable length of time, in terms of that behavior in terms of safety of what you'd look at.

And that during that process--especially if you're doing it into arteries and veins, that there are issues of monitoring because of what's known about micro-emboli and what's known about that; that you need studies to look at whether that's going to cause ischemia or an infarct, or it's going to cause arrhythmias, and that that needs to be monitored for at least some period of time in a critical way; and those would be unique or specific to delivery via the cardiac route.

Does that seem like a--have we missed something? I mean, there was some issue that we did not really look at in terms of long-term follow-up, and that wasn't absolutely clear. Dr. Borer seemed to point that you might need to worry about it on a longer basis, and one might need to.

DR. BORER: Can I just come back to the point Richard Cannon made? And I'm asking a question here. I don't know anything about cell delivery to the brain, or whatever.

But I think there may be an important difference between delivery of functional

progenitor cells to the brain that might cause a benefit, and delivering a bolus of something that might obstruct an artery, even though it couldn't grow into a new part of the brain.

So I would continue to have Richard's concern about the embolization--the importance of potential embolization to the brain, despite the fact that, apparently, the neurologists have a hard time developing a therapy by delivering cells that way.

Am I wrong about that? Is that--

DR. KURTZBERG: It can't cross the blood-brain barrier--okay?

DR. BORER: But you don't have to. All you have to do is block an artery.

DR. CANNON: I'm worried about plugging the microcirculation, much as the microcirculation of the dog heart was plugged by these cells. And these are large cells. They're not like stem cells that are small and deformable and that circulate very easily. These are large--I'm talking about the myoblasts, now, not the stem cells.

And, certainly, we send patients to surgery, and even to the cath lab, and they sometimes come back differently because of things

that are dislodged during the course of the procedure that make their way to the brain. So, certainly, the circulation can carry debris to the brain.

It's just a concern. And I would think an animal model, perhaps--just injecting the cells into the cavity of the left ventricle to see if they do, indeed, lodge in the brain for a period of time that might be anticipated to cause some damage would be a worthwhile thing to look at--for the large cells, not the mononuclear--the stem cells or the peripheral blood mononuclear cells. I don't think that's a concern. It's the large cells.

CHAIRMAN RAO: Dr. Grant, you had a comment?

DR. GRANT: Yes, I just want to just speak to this third point, the injection of cells into systemic circulation.

And the question that would be consequent to your discussion is: do you think that an animal study--that an additional animal study needs to be done in which the cells are specifically injected into the systemic circulation to see about the systemic effects? Or do you think that these kinds of effects that you're worried about would be

picked up in the other animal model--in other animal studies?

Because there would be enough systemic distribution we'd need to do additional studies? That's, I think, what that third question was about.

CHAIRMAN RAO: Let me see if this was summarized from what people said: is it depended on the cell type; that bone marrow cells, we have a lot of experience with in terms of putting them in systemic circulation, but that's not true for, say myoblasts, or for some of the other cells.

And for myoblasts, maybe we have some experience because that's been done in some of the animal models already, but that's not true for some of the other sorted cells or the passage cells.

DR. SCHNEIDER: Michael Schneider--but to deal with Dr. Grant's question specifically, it would be my expectation that the kinds of information that would be useful to address this point about embolic risk would come about as part of the natural dose-ranging studies that would occur. I don't envision that it would scientifically advance a protocol to inject non-physiological numbers, or non-therapeutic

numbers of those cells into the systemic circulation to see what happens.

And I share Dr. Cannon's cardiologists's view of the nervous system as a sponge that vessels go to.

[Laughter.]

DR. TAYLOR: I just want to make two quick comments--oh, I'm sorry.

One is that myoblasts are not the only large cells we're talking about here. Some of the mazenchymal cells are as large or larger than myoblasts, and we need to keep that in mind.

VOICE: [Off mike] What's--

DR. TAYLOR: 10 microns. Yes. Rounded.

But the other issue is that we did studies for different reasons, where we injected many of these different bone marrow-derived cell populations intravenously to try to treat vascular injury. And we found that there were some negative effects of some of those cells, and positive effects of other of those cells. And we didn't expect that.

And I think what we have to say is if intravenous is going to be your preferred route of administration, then obviously you have to do that.

But, otherwise, I think it's a waste.

CHAIRMAN RAO: Dr. Borer.

DR. BORER: In response to Dr. Grant's specific question, I do think it may be worth doing a specific animal study. I think Mike is right, that the information may well fall out of the studies that are done with dose-ranging in the normal course of development.

But the problem I see here is that we don't actually know how many cells are escaping into the systemic circulation with the various of routes of delivery we've been talking about. And, therefore, we may miss the information that we want.

Doing what Steve said, which is to inject some cells into the left atrium and, you know, see what happens, seems to me to be a good idea because ultimately what you wind up with is the lower bound at which problems might be begin to develop. And if, in fact, the lower bound of injectate size at which problems would develop is above the size of anything you're injecting, then it's a non-problem and you don't have to worry about it anymore. If it's not, then you have to worry about it a little bit more, and maybe the strategy would change.

So I think it may be worth doing a specific study to determine what happens to these large cells.

DR. CUNNINGHAM: I also want to comment that for when we do this in patients, that it's going to be a risk they would at least want to know about; that there was going to be a cognitive change. That's something people tend to care a lot about; either whether it's in themselves or it's in a family member, that it's not a simple thing, and you at least would want to know that was a risk, and you might not choose to have the therapy if that were going to be something you had to endure.

CHAIRMAN RAO: Quick comment, Dr. Lederman.

DR. LEDERMAN: Unfortunately, yet another question.

If we are administering locally cells derived from a patient by leukopheresis, for example, how important are the questions we've been discussing about systemic distribution, or mal-distribution of cells themselves recovered from the circulation?

CHAIRMAN RAO: I mean, I thought we tried to cover that, because we did try to point out that there might be different criteria--you can have a

standard criteria on the cell type. But even if it's a cell which is endogenous, you know, if you put RBCs back, there is an issue of the concentration at which you're putting it relative to the concentration at which they're circulating. And that's always been an issue.

And so I don't know if it would change specifically for leukopheresis versus any other method, but I would still want to know what happened when we put in cell by a particular method, and how they went, and what they did.

DR. KURTZBERG: I mean, there is data about the upper limit of safe cell dosing when you give leukopheresed cells. I mean, it's way, way, way above--it's logs above the doses that you're talking about for these injections--even if the whole injection escaped into the circulation. I mean, we're talking 5×10^{10} to 10×10^{10}. And there are rates per kilogram to infuse them to not have leuko-agglutination. But you're two to thee logs below that in the numbers that you're talking about.

The other thing is that, I mean, in leukemia, people have circulating blasts that are large cells. They may be 20, 25, 30 microns in

diameter if they're certain kinds of blasts. And, in general, they have high numbers of those cells, and they're not clogging things--until the white count gets very high, and then they do clog--you know, decrease CNS perfusion.

But, I mean, you can learn some lessons from those kinds of cells that may help sort some of this out.

CHAIRMAN RAO: To me, the sense is that the committee's telling people that one should be cautious, and that testing is required.

Does that seem like a short summary?

And I'm going to ask the FDA--did they feel that they had a sense for the kind of issues that one needs to worry about?

DR. GRANT: Yes, we're ready to move on to the next questions. But Richard had something he wanted to say.

DR. McFARLAND: I don't want to spend a lot of time on this, but one specific question--just as a ballpark--for the studies that are to test safety of catheter administration of a cell--I don't--at this point it doesn't matter which cell--how long would one expect the studies to go out? Three hours? Weeks? Four weeks? Three weeks?--not

dealing with, necessarily, the biological properties of the cells, but just the safety related to administration.

CHAIRMAN RAO: Let me take a stab at this, and then see if the committee aggress.

So, there are a whole set of studies that we talked about which are related specifically to cells--right? And those are really in terms of the safety of the cells and the long-term effect after they incorporate and what happens with them. So, really, when you're thinking of a combination of cells with a device, you're looking at the short-term effect of delivering those cells, and the complications if they go to an inappropriate place.

My feeling would be that that's the issue that you would want to look at, which is relatively short term rather than long term, in terms of looking at it.

Does that seem like a reasonable--

DR. BORER: I think that's reasonable, but I would just--you know, you're talking specifically about device-related injury, I believe.

DR. McFARLAND: Correct.

DR. BORER: You know, my understanding of

this situation--and you'll correct me if I'm wrong--is that if you create a physical injury, it takes a couple of weeks for the necrosis to be maximal, and the scar to begin to form; and, you know, a little bit longer until the scar is fully mature.

It seems that those kinetics would define the time--the duration of the observation period, because we are talking here about creating a physically-mediated injury.

So, you know, just as a stab, if you looked at some set of animals, or some experimental preparation--whatever it is--for a month, I think you would encompass all the device-related problems. Probably you could do it in less time, but I would be thinking about the kinetics of injury, tissue necrosis and scar formation as the basis for making that decision.

DR. SIMONS: I think I would be looking at a much shorter time frame. I think the injury from the needle-based devices is minimal. We have pretty extensive experience with the devices in animals. They're really benign, all of them.

And after what we did--you know, to hearts with lasers, what we can do with a 27-gauge needle

does not even come close. I would not really be worried about the acute safety of a needle-based device.

DR. NEYLAN: And I'd just like to revisit my sidebar issue of the need for close communication between the divisions at FDA, because this is an example where I think we would not like to see one set of experiments go forward that describe device-related safety, and another about the delivery of the cells.

So I think it would be much better if we create one set of experiments that answer both questions.

DR. McFARLAND: No, I agree, and that was part of the impetus for asking the question, so that TDRH and CEBR can have a basis for discussion.

CHAIRMAN RAO: Now that we've talked this one through, shall we move on to the--I guess the clinicians have been waiting for this, I guess--in terms of the clinical aspects of these questions.

So I'm going to read out that question, and then I'm going to just let people make individual comments, and then see whether we can put that together.

So the question was: Please discuss the

appropriate frequency and duration of follow-up. In addition to any other events, please consider the following potential adverse pathological and clinical events in your discussion items: scar formation, left ventricular dysfunction, ventricular arrhythmias and neoplasia.

And I guess, here, I just want to make sure that we are clear on this, is that we're thinking about early clinical studies that will be done, rather than looking at animal models here. So this would be some kind of clinical study where you've done it, and you want to worry about whether this makes appropriate sense, and what kind of follow-up should one consider, and what are the issues related to this?

VOICE: [Off mike] [inaudible].

CHAIRMAN RAO: Yes, I think that's an important point, given what we've already heard. That's another important issue to worry about.

DR. CUNNINGHAM: How about cognitive function, since we just discussed that; and also stenosis.

CHAIRMAN RAO: Okay.

Go ahead, Dr. Borer.

DR. BORER: I'd like to focus on left

ventricular function or dysfunction here. I mean, we've talked about arrhythmias and the duration of observation that might be necessary for those. But I want to point out something that has an impact here.

If you replace an aortic valve in a person with aortic regurgitation, it takes three years until left ventricular function has maximized. If you replace a mitral valve in someone with mitral regurgitation, it takes three years for left ventricular function to maximize--systolic function to maximize.

Now, forgetting about the whys and wherefors, there are lot of processes--and as Steve said yesterday, we don't understand them all, but the cells do. The fact is that a great deal of remodeling goes on after you change the milieu; the exogenous hemodynamic milieu and, I would suggest, perhaps the cellular milieu in the scar, because what you do in the scar is going to impact--if it's effective, it's going to impact on what's happening in the non-scarred areas.

So, with that as a preamble, I would say that at some point in some studies, you've got to look for a long time to know everything that may

happen. Is it necessary to look that long before you approve a product? No, of course not--at least I don't think so, not if there are sufficient animal studies and early clinical experience that suggest you don't get deterioration. If you get some improvement that's clinically relevant, you know, at six months or whatever the time point you're looking at is, one might approve a product.

But in terms of the duration that we should make observations, ultimately, at some point, either before or after approval of a specific product, you have to look for a long time if you're going to see the effects. And we don't know the process that's going on here. We're injecting cells. The cells may be re-differentiating, transdifferentiating. They may be doing all kinds of stuff. We don't know the kinetics of those changes. We don't know what that means. We know that--I have to infer from the data I saw yesterday that important changes in the interaction between myocytes and extracellular matrix is going on during this period; the kinetics of extracellular remodeling is much slower than the remodeling of myocytes--on and on and on and on.

In order for us to fully understand the

biology here, if we're just talking about mechanical function, it's necessary to look for a long time. Again, that may not be necessarily in order for a product to be approved--there are other issues there--but to know the biology, monitoring has to go on for a while. And although it's not my field--and Steve and others may want to comment on this--I think the same thing is probably true of the angiogenesis-arteriogenesis issue.

CHAIRMAN RAO: Before you cede the mike can you say, well, what kind of monitoring? I mean it should be Holter monitoring for one month or, you know--

DR. BORER: Well, in terms of left ventricular performance, you know, there are a number of non-invasive techniques that easily can be applied periodically over time; you know, echocardiography, radio nuclide angiography, MRI if you happen to have it available and the patient can undergo MRI. There are a lot of techniques.

But there are global, left ventricular function assessment techniques, and that's what we really care most about. If we see improved wall thickening someplace but the heart's not putting out more blood and not pumping better, who cares?

So I would say that there are a variety of standard, non-invasive techniques that can be used to evaluate mechanical performance of the heart.

In terms of electrical performance, as long as you're looking at the mechanical performance, you may as well look at the electrophysiologic aspects of what's going on--and there, yes, I think a Holter and a standard 12-lead electrocardiogram would be the minimum.

In earlier studies--as Jeremy pointed out before--during the first few months after an intervention--now I'm talking about animals, because you wouldn't re-do this in people--I think standard electrophysiologic testing--invasive electrophysiologic testing--would be very important. In people, I can't imagine that you would want to do that very often. People don't like to have that done to them.

I don't think you'd want to do standard electrophysiologic testing very often. There might be some subset--and, you know, Jeremy should comment on this--in whom a pair of standard electrophysiologic studies might be done, separated by an interval of, you know--whatever the interval is; whatever the preclinical data and the 24-hour

ambulatory electrocardiogram suggest is correct; maybe a month, maybe two months--I don't know.

But I think you do have to look at certain aspects of the electrical function of the heart. It's simple to do that with electrocardiography, because if the electrocardiogram's okay, if you're not seeing arrhythmias, then, again, who cares about what's going on in the substrate? And as long as I was looking at mechanical function, I'd look at electrical function by these simple means.

CHAIRMAN RAO: Joanne?

DR. KURTZBERG: I would think it would be important also to, if possible, require or strongly suggest an autopsy for any patients who die--given that you're saying this is such a high-risk population. Because you may learn something about the anatomic and histologic things you find in the heart, even three years later, that will help you optimize this.

DR. RUSKIN: I think, with regard to follow-up, the issue of safety with regard to ventricular arrhythmias is a very difficult challenge. I think if we've learned one thing in the last 20 years it's that you don't follow ventricular arrhythmias. You either stay out in

front of them, or people die.

And Holter monitoring, I think, in this population is a waste of time because the prevalence of spontaneous arrhythmias in this patient group is somewhere between 60 and 80 percent--talking about non-sustained ventricular tachycardia. And the question then arises as to what you would do about it if you saw it, because anti-arrhythmic drugs--talk about Dr. Epstein's Janus effect--you know, we might just as easily kill people with the drugs that we use to try to suppress these things as help them. And that's why it brings me back, I think, to the issue of having a group as protected as possible at the time that they get the therapy, with an implantable device--at least early on; not that it's perfect, but at least it offers a high level of protection against anything other than an incessant VT or VF.

And I think that's really what the follow-up is. It's having a protected patient with a monitoring device that records events 24 hours a day, seven days a week, 365 days a year. But the real lessons will be learned from outcomes and, I think, from the preclinical work that gets done. And it's not going to get answered by ECGs and

Holter monitoring and other simple forms of observation.

There are host of other risk stratifiers--like T-wave alternans, signal average DCGs, and a number of other things--all of which would be of interest. The problem, again, will be that the positivity rate is so high in this population, even without the therapy, that I think it's going to be very hard to distinguish the treatment groups from the non-treatment groups--even if there's a pro-arrhythmic effect.

CHAIRMAN RAO: I'll ask this in a more particular way, and it's really part of Question 7, which sort of segues into this, and you've already raised that as a point.

So, once you've chosen a patient population--and there's a caveat on how you choose the population from the points of the worries that one has with any kind of new therapy--you have to worry about monitoring them, and there's going to be a certain basis of monitoring which is dependent on the disease or the underlying process that they have.

And then you want to have some kind of additional monitoring--maybe--which is specific to

the therapy that you've now introduced. In this case is there anything which is new or unique that has to be added on, or can one simply say that, well, you've chosen this patient population. You're going to have to really be doing massive monitoring anyway. Do you need anything else.

And, you know, Joanne pointed out that even if you do all of this, one important thing one should suggest is that they also do an autopsy, which is not really monitoring on side effects but is learning after the fact; and that one should be looking at closely monitoring improvement in some fashion, or at least it's function of the cells, by looking at left ventricular ejection fraction in some fashion, or left ventricular function in some fashion.

Are there other sort of additional things that one can use, and which would distinguish between, say, the therapy--like you pointed out--versus the underlying disease?

DR. SIMONS: If I can attempt to begin to sort of address these issues--and it really takes us into, I think, Question 7.

As Dr. Ruskin points out, there is a very high frequency of all sorts of events in these

people, given what these patients are. I really think the only way you can find out how safe these kinds of therapies are, if you do double-blind randomized trials, and you have control group--not to assess efficacy but to actually assess safety, because there will be a number of adverse events in this patient group, and we will not be able to say whether that is because of therapy or because of natural history of disease if we don't have a control group.

CHAIRMAN RAO: Dr. Perin.

DR. PERIN: In talking about monitoring LV dysfunction, I think we probably should start from the beginning, which is really--obviously, we need to see these people pretty often, in terms of clinic visits because I think symptoms, even though are not completely objective are an important thing to assess in these people.

And in our limited clinical experience we noticed that people really had a change in improvement--we presented this at ACC--around the seventh and eighth week. So that's something that you might want to know.

Also, I think that echocardiographic evaluation is simple--because there is a problem of

doing MRI, because a lot of these people are going to have a problem with having MRIs.

One other thing I would like to take note is the issue of global versus regional improvement. I think that--I don't agree with what was said. You don't have to have--the meaning of global improvement, it's great to have LV global improvement, but we've seen patients that have regional improvement and this may translate in a function way into a very significant improvement.

And so another way of looking at LV function is really--and I had said this before--is exercise capacity. And I think we need to be evaluating these patients functionally as they go along--and this is a translation. So maybe if we injected part of the heart we don't see a global improvement in LV, but that patient may be able to walk a lot further on a treadmill, be able to exercise more, and that's important, as well.

DR. BORER: Yes, I think Dr. Perin's points are very well taken. I didn't mean, in what I said before, that in any way a clinical evaluation should not be done, or should be precluded. Obviously, that's the name of the game. The patient has to feel better and/or live longer, or

you haven't done anything useful--no matter what the ejection fraction turns out to be.

So I would absolutely agree that clinical evaluation has to be the key, and it's a given in the follow-up of patients getting these kinds of treatments.

I would also agree that there could be clinically meaningful regional improvement without much change in global left ventricular function. I'd sort of doubt that it would be very meaningful if there wasn't any change, but I was thinking more in terms of the kinds of echo studies that show that with sonomicrography--the ultrasonography, you can see thickening in one small region. That doesn't mean much to me.

But the point is well taken that you made, and I don't disagree with it at all.

There's a sort of a more overarching issue here about the various modalities that we might use to evaluate patients. And, you know, Jeremy, of course, is an expert in this area, and he's undoubtedly absolutely right that the yield from simple rhythm-monitoring studies would be pretty low in people who are as sick as these people are, and maybe that's the wrong example for me to take

here.

But, you know, in general if you don't look you don't find something. There are simple means of following patients, and I like Dr. Perin's suggestion--which I think should be part of any follow-up--clinical follow-up of people with heart failure--that is to assess exercise tolerance formally.

There are lot of simple things that you can do that are sort of part of a standard armamentarium of researchers and clinicians who follow patients who are very sick that I think should be done. They may not show much, but unless you look, you don't know.

So I just offer that. If, you know, it gets back to we-know-what-we-know, we-don't-know-what-we-don't-know, as Dr. Harlan said before. Better to look with a wide compass when our knowledge base is relatively small, then we can eliminate things as we go along.

CHAIRMAN RAO: Dr. Ruskin.

DR. RUSKIN: Just a quick comment.

Jeff, I agree completely, and I didn't mean to suggest that we shouldn't do the Holtering or the routine ECGs. We would certainly do those,

and it's possible one might see things that were very surprising.

The issue that I raised really related to safety; and that is that doing Holter monitoring as a safety maneuver is not productive in this patient population because, clearly, it's an icepick in time, and you may see absolutely nothing and have a dead patient 12 hours later, or see florid arrhythmias that purport nothing ill with regard to long-term outcome.

So the data would, I think, be necessarily obtained, but it couldn't be used to ensure safety. And that's really the reason for making the plea that early on one consider populations that have protective devices. They're not perfect, but they're a lot better than not having them.

CHAIRMAN RAO: How about, you know, monitoring for potential complications. I mean, should people be worried about "We are putting in cells. There might be an inflammatory response because of all the necrotic material." Should one be looking at C-reactive peptide? Is that something which should be over and above what one would normally be doing in a sick patient?

Are there any other such tests that you'd

want to do, you know, to look at--?

DR. BORER: I think you'd do whatever you can think of. It may not be worth anything. But, again, if you don't look you don't find out.

I wouldn't particularly have picked C-reactive protein, but it's fine. You know--sure. Why not look at systemic inflammatory markers?

Steve Epstein made the point yesterday--I have to backtrack for a moment. I've referred to Steve at least 20 times here--and as you look around the table--well, one of them just left, but there are three generations of Steve Epstein trainees or underlings sitting at this table. So it shouldn't be--and, unfortunately, I am now the most senior of those three.

[Laughter.]

Which, as Steve would say, what does that make him? But--what was I originally talking about? [Laughs.]

[Laughter.]

There was a point here. Oh, yes--about atherosclerosis. You know, the inflammatory milieu--this is important because, remember--I mean, your point is very well taken. Steve pointed out that some of these treatments we give could be

good for the myocardium but, depending upon how we give them, they could be atherogenic. That's very important.

You know, undoubtedly, that the event rate--coronary event rate--is substantially higher--two- to threefold higher among patients with rheumatoid arthritis than among patients without rheumatoid arthritis; that is, among patients with rheumatoid arthritis with positive markers of inflammation.

So there's some evidence that a systemic inflammatory milieu somehow potentiates the development of coronary disease.

Now, I don't want to talk about mechanisms because we don't know them--or at least I don't. But I think, therefore, if we believe that there is a likelihood that we're going to stimulate an inflammatory response with what we're doing, we should be looking for evidence of that so that we can relate that--even if retrospectively--to other events that occur in this population. So I think the point is very well taken and we should be doing that.

CHAIRMAN RAO: Given that this is a sick population that would be the first sort of

candidates for this, irrespective of how you select them, would be anything you'd suggest which will change the frequency of monitoring from what you'd normally do for a sick population of this sort? Or would it be more frequent? Or would it be longer, in terms of the anticipated complications? Or anything that one might imagine?

DR. SIMONS: I actually don't know what patients--or the population that we're talking about. Because as we discussed several times, there are really two different patient groups here. One is an acute myocardial infarction patient, and one is a patient who is chronic heart failure. And I think you would monitor differently in these two different groups because in acute MI, the patients--the risk is early. And once it's been successfully treated, that's a pretty low-risk group, with a very low mortality rate.

While, you know, Class IV heart failure patient, who has a 20 percent ejection fraction has a pretty high mortality rate. I think you would sort of treat those things in a very different manner.

CHAIRMAN RAO: Either of those groups--so, you know, you take acute MI, and you're trying to

treat it with, say, bone marrow cells, and you would monitor acute MI in a particular way.

Would it change now that you've added cells to the therapy?

DR. SIMONS: Probably would--you'd probably want some sort of non-invasive imaging such as echo. During the first two weeks you'd probably want it several times to see there's no pericardial effusion, and there's--if the left ventricular function is not changing in sort of adverse ways--there's some adverse left ventricular sort of remodeling.

But after two weeks I would go back to pretty normal schedule; three months, six months.

CHAIRMAN RAO: If something changed, it would change acutely.

And in a chronic disease model, would there be anything that you'd change?

DR. SIMONS: Once again, if this is a catheter-based delivery, I think you need to monitor more intensively within the first couple of weeks.

CHAIRMAN RAO: Dr. Borer?

DR. BORER: Yes, I agree with what Dr. Simons says. But I think you have to be aware--you

say, "Should there be a difference compared with what we usually do?" There is no "we." You know, what someone who is working in an academic institution, collecting data in a research milieu might do is very different from what one might do in private practice, or in primary care, or what have you.

So what I would say is that we should pre--that people who set up these protocols should pre-specify regular evaluation--by objective techniques that we've all talked about here, at some appropriate frequency, be it, you know, every month for a few months, every six months after that, every year after that--whatever it is. I don't know how the patients will live.

But I think that that kind of monitoring probably should be continued for many years--again, given the fact that remodeling takes a long time.

CHAIRMAN RAO: Dr. Cannon, and then Kathy.

DR. CANNON: I would second Dr. Borer's comments about long-term follow-up because, particularly in thinking of this approach for the chronic, intractable anginas, sort of an angiogenesis or neovascularization approach. It's conceivable to me that you could have a short-term

benefit, but not just a late failure, but maybe even a worsening of the situation over time.

So perhaps putting cells in, either directly or indirectly, stimulates new vessel growth. But that may not be permanent in that those cells will have to be replaced in time. The don't live forever. And if that person's own progenitor cells are very poor in function and few in number, then the growth that was stimulated by putting in a large number of perhaps activated or genetically modified cells, or what have you, that effect may go away in time, and the patient doesn' have a way of replenishing or replacing the cells that compose the new vessels. They could fail fairly quickly, perhaps.

It's conceivable--it's like the movie Charlie. You know, there's short-term great benefit, but then a deterioration that actually makes the individual worse off than were had nothing been done at all.

CHAIRMAN RAO: do you feel we have enough information to point out how long?

DR. CANNON: No. No. I just raise that as a possible concern, or a justification for following them longer and perhaps more closely tha

you ordinarily would someone with chronic stable angina.

DR. HIGH: I just wanted to raise a question to the cardiologists about one other method of data capture, and just get your response to this.

But, how often are these people re-instrumented, or re-angio'ed, or whatever? And how much risk is it to do an endomyocardial biopsy if they are?

CHAIRMAN RAO: Dr. Epstein, do you want to take that?

DR. EPSTEIN: Well, my question was going to be directly related to that.

I would like to raise a difficult question, because it's very expensive. Given the Lancet article of two weeks ago that was called--it was a very small number of patients, and I don't know how much credibility to give it, but it raises the interesting question that infusion of cells into the coronary artery that had been harvested after GCSF stimulation seemed to be associated with a much higher incidence of re-stenosis than would have been expected.

Should patients receiving cell therapy at

the time or shortly after angioplasty--should they have a repeat coronary angiogram in six months to rule out this very important possible adverse effect?

What do you think, Richard?

DR. CANNON: You know, with the new drug-eluting stents, it may be that that will not be an issue in sort of the current environment now that it was with the bare metal stents used in that. So perhaps following more for ischemia--non-invasively, perhaps--would be more acceptable.

Doing repeat cardiac catheterizations serially--

DR. EPSTEIN: It's expensive--

DR. CANNON: --it would obviously add to the expense--

DR. EPSTEIN: --and it's--but that is, you know it's a good question. And, you know, given that recent study, you know, it's a very relevant one.

CHAIRMAN RAO: Is biopsy dangerous, though?

DR. EPSTEIN: Oh, yes, I wouldn't think about biopsy. And, also, I think you'd have a sampling. You couldn't be confident that you were

getting tissue in the area where you think you've done some.

DR. HIGH: [Off mike] Well, no, he said he could do it within one micron--

[Laughter.]

DR. EPSTEIN: Well, but Mike he was just joking.

[Laughter.]

DR. RUSKIN: You know, about the--if there were a credible scientific question to ask from repeat catheterization, I think the primary question you're asking is: does the risk preclude doing it?

The risk of a cardiac catheterization for a major event, among all comers, is one in 500. Now, it may be a little higher in a very sick population, but, you know, I think that that risk is--not death, but some major event, stroke, MI, death, bleeding, infection--one in 500.

I think that if we had a credible scientific question that was very important to answer--and I'm not sure that we do. I think Richard's point about doing non-invasive assessmen might suffice for the question about re-stenosis. But if we had a question, I think that the risk

would be supportable, or could be supportable, given what I've just said.

In terms of biopsy, in fact the biopsy data suggests that, in experienced hands, that's reasonably safe, too. The big concern I would hav is exactly what Richard said--you know, the sampling error. I mean, a catheter-based biopsy i a right ventricular biopsy. It's not anywhere nea where we're looking--where the problem is, where the cells were put in. To do it on the left side would be very dangerous, I think.

So I would be concerned that we wouldn't be able to get the information that we want to get And I would be interested in--just with regard to your question, which I think is a very good one--applying non-invasive methods, like MRI if it were possible, or perhaps PET scanning to ask some of the questions that you might have wanted to ask with a biopsy.

CHAIRMAN RAO: Dr. Perin?

DR. PERIN: If we look at the population of patients that are the chronic ischemic end-stage patients, the reason they got there is they've got horrific coronary disease, have very aggressive coronary disease. Their coronaries are already all

stopped up.

So I think it's really hard--and we've done this--but to re-angiogram these patients, it's really hard to differentiate what's progression of disease that they were going to have anyway; what's do to the stem cell injection. So it's very difficult to evaluate--and which is completely different in the acute MI population, where that may actually be something that's important to look at, because you have a target vessel, and a lot different coronary situation.

DR. BORER: I think that that's a very good point that leads to the point Dr. Simons made a few minutes ago, and that Jeremy made yesterday, which is Question 7, about controlled studies.

I think, Jeremy, what you said was that from the earliest studies they should be controlled. And I agree with that.

I think there's absolutely no way to interpret the data in a very disparate, very sick population--very heterogeneous population. I don't think that it's possible to interpret most of the data that are of interest to us without some comparator.

And I would go back to Dr. Murray's

earlier point. You know, you can not ethically justify studying human subjects unless you can interpret the data.

So I would say that Jeremy's point is a very important one. I think controls have to be built into these trials, even from the earliest studies, and that probably it's not worth a heck o a lot to do observational studies with no comparator in most situations.

You know, the type of control could vary. There are active controls, there are placebo controls--if you want to call it that. There are dose--different doses, in a dose-response design, that could be used. But I think you do have to have comparators.

CHAIRMAN RAO: That's an important point, and I think it came up a couple of times before in the past, too, and I'll just try and summarize those few comments and then turn it over to you.

So, there seemed to be consensus in the field--in fact, almost everybody who talked about it said that controls are important, or that placebo controls are quite important.

And then I asked this question yesterday was that is it possible to get controls. Will it

be possible to recruit them? And the answer was yes--as long as there was some kind of cross-over option. And that seemed to be a possibility, so that that wasn't an absolute limiting factor that was there.

And you've reiterated that point, that it would be very hard to interpret these in small studies without any kind of controls. So it seems that that's one important thing that one should keep in mind in any kind of clinical study that's going to be done--right?

Go ahead.

DR. MURRAY: From the point of view of ethics--and science, here--there's one absolute requirement: namely, the study would have to offer interpretable results--right? We've talked about that. You cannot justify doing trivial things to human subjects if the design is basically never going to yield anything of any value and you know that going in.

The other thing you want to do--and as I'm understanding the situation, is it's going to be very difficult to get a good signal-to-noise ratio so that you can actually pick out what the actual effects of the intervention are. So there's a nee(

to maximize sensitivity to be able to pick those out, and the discussion that's gone on about, you know, what to look for here has been very helpful for that.

Even in small numbers you'd want to have some sense--we don't usually do power calculations on small sizes, but we probably--we ought to do th best calculations we can in these so, again, so that we have some assurance that we will have interpretable results.

I don't think it will be easy to design studies that will be ethically clearly acceptable with the placebo design Phase I studies here. But I suspect it's the way we have to try to go. And I'm going to count on the creativity of the investigators and the courage of the subjects.

CHAIRMAN RAO: Go ahead, Dr. Borer. I thought--did you want to make a comment?

DR. BORER: About placebo, I did.

The issue of doing a placebo-controlled study and then offering, as the benefit, a crossover--or I would--it's not a crossover, it's a dropout--at the end of a certain period of time, if the treated group actually shows benefit is very attractive, but we may not have information that

would support doing that from early small trials, or early small studies. So I'm not sure that that would be the out.

I think that one has to think creatively about some other types of controls. And I do like the multi-dose design, because that does allow you to know, if you see a dose response, that, in fact, there is, by definition, an effect. In that situation, you know, everybody gets something. And, of course, we don't know going in what's better and what's worse; whether there is a dose relation, whether there's a maximal dose that's effective and above that you have safety problems. You don't know that.

So I think that that might be some--a creative approach to dealing with this need for comparators. And maybe a placebo-controlled approach would be the appropriate way. I don't know.

I'm just suggesting that we have to be more creative about the thinking about study design to provide appropriate comparators. And then I'd get back to what we all discussed before, which is that since multiple small studies will be done with these agents, the designs and data collection

strategies should be compatible--sufficient compatible--with one another so that you can pool some data and eventually come up with some information that might be more interpretable than the data from any single study alone.

So, just sort of overarching thoughts.

CHAIRMAN RAO: In some ways we've been trying to answer this question but it's been a little bit different from the way it's been set up there.

I mean, it seems to me that, listening to all the experts in the field, is that they seem to feel that selection of patients, and the design of the experiment, in terms of the controls, or the placebo used, was really as critical as sort of the readouts. And, in fact, nobody seemed to feel that there weren't enough adequate readouts which were non-invasive and that it would not be possible to design them. It was just simply that you will have to design them adequately, depending on the type of patient you chose and the kind of, you know, disease you were treating.

And I think the two points that were made to me which were really important was that you're going to have to follow up for certain things for a

long time. It's not an aggressive follow-up, but you need to follow them up because you have to learn something from these things. And that the other was that in this trial itself there should be some urgency, or some selection so that you could have the option of performing an autopsy because that might work really well, given that the choice of patients is such that they are relatively sick, and that that might be a really important thing to keep in mind.

Does that seem to capture? Does the FDA think that that addresses some of the issues on the clinical trial?

DR. GRANT: Yes.

CHAIRMAN RAO: In that case, it's amazing. We actually finished on time.

[Laughter.]

Well, thank you for all the people who stuck out here to the bitter end. That was useful And I thank all the experts who gave the time to come to this. It couldn't have been done without them.

[Whereupon, at 3:00 p.m. the meeting was adjourned.]

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CERTIFICATE

I, **SONIA GONZALEZ**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

SONIA GONZALEZ