that you have made several times, that this is a clinically applicable regimen. In two studies recently, the one with mofetil as the third party, and one with red, you have had three out of seven animals that when they were euthanized or died, had a lymphoproliferative disease, which means they are developing a lymphoma tumor.

Now, most clinically applicable programs do not see lymphoma within the first two to three months. Would you like to comment on that?

DR. COZZI: Yes, I think it is a very important point which I thank you. You brought this to our attention before at your presentation, and I wanted to comment, and it is good that you gave me this opportunity.

I think that what we all here in this room have to realize is that if we do an allotransplantation, not just a xenotransplantation, but if we do an allotransplantation or even if we do not transplant cynomolgus monkey, and we expose them just to cyclosporin A, we will have an incidence of lymphoproliferative disorders which can go as high as 25, 30 percent for the non-transplanted animals, which are exposed to cyclosporin A only, they develop lymphoproliferative disorder by the end of the third month, I would say by day 100, when they are sacrificed.

So, what I want to say is this is possibly something which is species-specific. I mean these animals,

these cynomolgus monkeys are potentially proved and susceptible to lymphoproliferative disorder, and even in what we consider using a clinically acceptable only cyclosporin A administration level, and there are data reported also by Professor Reitz, that all data on the initial experience with cyclosporin A.

DR. AUCHINCLOSS: Robert Michler.

DR. MICHLER: Two questions. The first is a follow-up to that in that the regimens that you have included in our booklet, the particular doses are not particularly those which we would find acceptable for human transplantation, although you continue to refer that these are clinically applicable doses.

The doses you have referred to in the documents are doses that would induce hypertension, certainly induce renal dysfunction if not renal failure in patients, and I would like to comment on that firstly, and secondly, your data is remarkably good on the issue of transgenic animals and the likelihood of developing hyperacute rejection.

What I find of interest potentially of concern is that approximately 50 percent of the animals that you have tested were not transgenic, did not develop hyperacute rejection, and therefore, is the beneficial effect of the absence of hyperacute rejection in your transgenic animals a relation to the fact that they are transgenic, or is it an

issue of the model you are using?

DR. COZZI: If I can start with the third one, which is the therapeutic doses, I think you have got a point, and I thank you for giving me the opportunity to clarify what I mean by clinically acceptable immunosuppressive regimen.

There are data here which have proven and shown that if we do an allograft, an allotransplant from baboon to baboon, if we try and use the same dose of cyclosporin A and trough level of cyclosporin A you would use in the clinical arena, it does not work.

I mean we have data in vivo and in vitro, I mean Imutran's data, there are data in the literature in vivo and in vitro which shows that the cyclosporin A trough level, you have to aim in the baboon, must be greater than 12, 1,500 ng/mL, and maybe Dr. Cooper, you want to confirm your experience in that --

DR. COOPER: In baboons, you do have to use high doses of cyclosporin, that is quite correct. I am not sure that is the case with cynomolgus monkeys. Also, your reference to the fact that cynomolgus monkeys are very susceptible to lymphoma, when they were given cyclosporin before by Professor Reitz's group, they were given very high doses, not the sort of dose that we give clinically, so I am not sure that that has been proven, the point you made about

the lymphoma.

DR. COZZI: The second question was?

DR. MICHLER: The issue of transgenic, your control group had a 50 percent absence of hyperacute rejection.

DR. COZZI: In our experience, the hyperacute rejection occurred only in 40 percent of the control, that is correct, but I think that for us the thing that was more important was to completely prevent the hyperacute rejection full stop, irrespective of what happens in the control.

We now have data generated at least by five groups around the world which have shown that hyperacute rejection is not a consistent finding when you transplant normal pig organs into primate, and this is irrespective if you are dealing with cynomolgus monkeys or baboon as recipients.

DR. AUCHINCLOSS: What do you think about that, David Cooper?

DR. COOPER: I accept that. It was a surprise to me because the old literature generally, the hyperacute rejection was pretty consistent, but I accept, as Emanuele says, there are now several centers that have shown that it is not as consistent as we once thought.

DR. LOGAN: I just had one question with regard to cyclophosphamide induction regime, and it is not a debate whether it's clinically relevant or not--we can have that

debate for another day--absent the cyclophosphamide regime, the survival is reduced, I suspect.

DR. COZZI: So, absence of cyclophosphamide regime--

DR. LOGAN: Yes, induction regime.

DR. COZZI: Can I say that in our experience, and as you realize to devise the cyclophosphamide regime, only four doses, to reach as few as four doses, we have tried every possible way to minimize the use of cyclophosphamide, and in our experience, two doses of cyclophosphamide or no cyclophosphamide at all leads to a graft lost by day five or day seven in 100 percent of the cases due to ADR.

This is our in-house experience, but I don't know what you have.

DR. LOGAN: Could you describe a little bit of what the doses of cyclophosphamide are?

DR. COZZI: Absolutely. These are on day minus 1, we--the cyclophosphamide ideally is tailored to reach a nadir in the white cell count of 2,000 cells/mL, and what we are giving to our animals in these four doses is on day minus 1, 40 mg/kg i.v. on day minus 1. On day zero, which is the day of the transplant, up to 20 if this is a heart, up to 10 if this is a kidney, mg/kg, and on day 2 and on day 4, up to 30 mg/kg in both cases, exceptionally, we have even been to higher doses, tailoring once again according to the

white cell count of design.

If this animal is leukopenic, we will not give cyclophosphamide on day 2, and we have more than 90 percent chances to lose the xenograft by day 5 to 7.

DR. LOGAN: I think to answer Hugh's question, the doses of cyclophosphamide, we use much, much less than that, and I think we are looking at two very radically different immunosuppressive regimes, although I contend there could be other differences.

DR. COZZI: I am sorry, could you speak louder?

DR. AUCHINCLOSS: Just having a little bit of trouble hearing from the microphone there. But the bottom line is very different protocols.

DR. LOGAN: In terms of hyperacute rejection in baboon model--

DR. COZZI: I am sorry, but if I can make it precise, I mean the work described by your group in conjunction with Jack Platt, it didn't hit me, it didn't strike me for substantial differences of cyclophosphamide at least on day minus 1 or on day zero. I think we are talking about similar doses.

DR. LOGAN: No, the dose is somewhere around 5 mg/kilo.

DR. COZZI: Initially.

DR. LOGAN: Yes, 5, up to 10, but that's it, no

more than 10. That's a maximum dose.

DR. AUCHINCLOSS: Now, we are going to move on Louisa's comment, and then we are going to take a break.

DR. CHAPMAN: I have listened to this discussion of lymphoproliferative disease in the presence of cyclophosphamide, and the question that keeps occurring to me, that may be relevant to interpretation of your studies, is--you are talking about this as if it is a drug-induced effect, and what I keep wondering is, is this an effect of a persistent virus whose oncogenic potential has been unmasked by the use of cyclophosphamide, so the question I would have--perhaps not to be answered now, but to be looked at in your studies--is how carefully screened are these primate models for persistent infections with viruses particularly categories of viruses that we know have an oncogenic potential like oncogenic retroviruses or herpes viruses.

I think that has got to be looked at and controlled for before you can really assess whether the lymphoproliferation is telling you about the limits of your tolerance for the drug or some other aspect of the transplant condition.

DR. AUCHINCLOSS: Thank you very much. We are going to take a break and convene here exactly at 10:45 and have a presentation from the FDA and then roughly at 11:00 or 11:10, we will start the committee discussion.

[Recess.]

DR. AUCHINCLOSS: We are going to reconvene now with a brief presentation from the FDA and their perspective on this issue of what kinds of clinical trials might be initiated in the future, Dr. Marzella presenting.

FDA Perspective

DR. MARZELLA: Mr. Chairman, ladies and gentlemen of the subcommittee, good morning.

[Slide.]

I am going to summarize the preclinical and clinical issues in the transplantation of porcine solid organs. I will introduce the questions that the agency would like the subcommittee to discuss.

[Slide.]

The first issue to be discussed by the committee is whether the quantity and quality of preclinical data is sufficient to begin clinical trials, and if not, what data are sufficient to begin this investigation.

The second issue for discussion is the potential clinical utility and risks of xenografts. Data so far, as we have heard this morning, indicate that the survival of xenografts is expected to be much shorter than that of allografts.

Given these considerations, do the potential benefits of xenografts as, for instance, a bridge to an

allograft or a short-term support of the reversible organ failure, outweigh the potential risks.

The third issue is which patients should be studied first and what efficacy outcome measures, particularly for Phase III studies, should be used. There will be a number of questions to the committee about criteria that might be used to identify patient populations for which risk-benefit would be acceptable.

[Slide.]

Now, of course, human allografts, as has been illustrated this morning, are a scarce medical resource for patients with irreversible organ failure. Patients are having to wait longer for an allograft and many die before an organ becomes available, and xenotransplantation then fills an unmet medical need, and is one of the potential means for alleviating the current shortage of allografts.

[Slide.]

For a brief historical perspective on clinical solid organ xenotransplantation, again, this is a point that has been covered this morning.

Attempts at cross-species solid organ transplantation began at the start of the century. Renal, hepatic, cardiac transplantation from non-human primates to human primates achieved some degree of technical success starting in the 1960s. Graft and patient survival have,

however, been poor, typically a few days to weeks. The longest survival, as long as a few months, were seen in recipients of renal grafts.

The most recent clinical studies of solid organ transplantation using non-human primate sources were carried out in the early 1990s, again without long-term success, and efforts are now shifting to explore the potential clinical uses of porcine solid organs.

[Slide.]

Now, for a brief overview of ongoing clinical studies or porcine xenotransplantation. Current clinical studies of porcine xenotransplantation involve primarily the implantation of cells to replace cell loss and/or correct functional deficiencies of cells. Example are neuronal cell implants or islet cell implants in patients with certain degenerative neurologic diseases or in patients with diabetes mellitus.

The advantage of cellular transplants, as we have heard, is that there is reduced immunogenicity because of the absence of the vasculature and the endothelial cells which carry xenoreactive antigens.

In addition, there are technologies, such as microencapsulation, which allow the cells to be housed within barriers designed to exclude cellular and humoral components of the immune system.

Another area of investigation is in studies of either whole porcine livers or porcine hepatocytes in patients with acute liver failure. In these studies, these devices are perfused ex vivo to provide short-term support until either a liver allograft becomes available or the patient's liver regenerates.

[Slide.]

Now, to go over to potential clinical trials, discussions between the agency and sponsors have centered around clinical studies of solid organ xenotransplants and the preclinical data that would be necessary to support such studies.

Cardiac and renal grafts, transplanted orthotopically or heterotopically, are under consideration.

Although the ultimate aim of xenotransplantation is to provide definitive therapy for organ failure with graft and patient survival comparable to that of allografts, a number of immunologic and physiologic obstacles need to be overcome before this ultimate aim can be realized.

In the meantime, our reasonable aim might be to use xenografts as temporary supports for a failing organ.

[Slide.]

I will now summarize the preclinical data. As the sponsors and others have discussed this morning, it is clear that some immunologic obstacles to the xenotransplantation

are being overcome. These issues are being addressed in pig to non-human primate, either baboon or cynomolgus monkey models. Challenges being addressed include the hyperacute and delayed vascular rejection.

In assessing the quality of the preclinical data and its ability to predict clinical benefits and risks, it is important to consider a number of factors. These factors include the clinical relevance of the immunosuppressive regimens that are used, the parity of immune obstacles, and anatomic and physiologic systems in these models.

[Slide.]

The details of the treatment strategies in preclinical models have been elegantly provided by the speakers this morning. As we have heard, there is evidence that down-regulation of complement activation and removal of preformed antibody to xenoreactive antigens contribute to success.

Immunosuppression of preactivated B cells and blocking sensitization to other xenoreactive antigens are also important considerations.

[Slide.]

To summarize the results of the initial preclinical studies, in preclinical models, the maximum duration of survival in animal recipients of life-sustaining cardiac transplants is only measured in weeks. Maximal and

overall survival are somewhat longer in recipients, in animal recipients of renal transplants.

As we have heard, significant technical obstacles, such as requirement for repeated invasive monitoring and invasive therapeutic interventions interfere with the ability to fully assess the potential risks and benefits of xenotransplants.

[Slide.]

What are then the limitations of the current preclinical data? Again, let me begin with the important advances. Prolongation of graft survival has been achieved, however, survival still falls short compared to what can be achieved with allotransplantation in non-human primates.

The preclinical studies, at least that the agency has seen, are few and graft survival is variable. The effect of xenotransplantation on subsequent allotransplantation is not clear.

The agency would like to ask the committee to discuss the suitability of the pig-to-primate model for predicting clinical outcomes. The agency also would like to ask the committee to address the clinical relevance of the immunosuppressive regimens and the parity of immunologic, physiologic, and anatomic functions.

[Slide.]

In closing, then, I will restate the issues the

agency would like to ask the committee to discuss.

The first issue is what quantity and quality of preclinical data will be sufficient to support the start of clinical trials. The second issue is the potential clinical utility and risks of xenografts. Do the potential benefits of xenograft, for instance, as a bridge to allograft or a short-term support of a reversible organ failure outweigh the potential risks?

The third issue is which patients should be studied first and what efficacy outcome measures, particularly for Phase III studies, should be used. The agency would like to ask the committee to discuss criteria that might be useful to identify patient populations for which risk-benefit might be acceptable.

DR. AUCHINCLOSS: Thank you very much.

We will be having committee discussion. As before, we would welcome comments from sponsors and/or from the floor, as well, at any point.

Committee Discussion

DR. AUCHINCLOSS: The big issue is the move toward, but not yet occurring, move toward the initiation of clinical trials of solid organ xenotransplants. Again, we are not talking about cellular transplants today.

There are two big questions which I will try to deal with here in the committee in order. One has to do

with the preclinical studies, how good are the models that we have, how serious are the limitations, and what kind of results do we, as a committee, think should be expected before the initiation of clinical trials.

The second issue will be what particular clinical trials do members of this committee think make sense or do not make sense from their perspective.

Let me emphasize what I think are the big picture features of this, but I want to the FDA to correct me, that this is a very preliminary or exploratory conversation, that we are not here today to approve a particular protocol, to say yes to this particular sponsor.

What I understand is that the FDA and the sponsors are both asking essentially what kinds of questions and what kinds of answers would members of this committee like to hear in the future when it does come time to look at individual or particular protocols.

Do I have that sense correct, FDA?

DR. WEISS: Yes.

DR. AUCHINCLOSS: So, that is where we are going at this point.

Let's start then with this issue of the preclinical studies, and I guess the place to start there is to ask the question: How serious are the limitations? All of the sponsors and several of the speakers, in addition to

sponsors, have mentioned that there are big differences between non-human primates and primates. How serious are those limitations when it comes to predicting outcomes of future clinical trials?

DR. LERCHE: I would like to make a comment or observation that is sort of relevant to the quality of some of this preclinical data that we are discussing today, and just to reinforce the comment made by Dr. Chapman just before we took a break about we have all been discussing infectious diseases from the perspective of the donor animals, but also I would just like to emphasize the impact that persistent infections can have on animal model systems and their potential as confounding variables in the interpretation of this experimental data.

The lymphoproliferative disease situation that was described to us, the entire tissue of survival of these animal model recipients, if I understood correctly, a number of the speakers said that survival was in some instances not related to graft rejection, and so this may be another area where the persistent infections in the animals used as models may have an impact.

I think this is an area that is not fully appreciated in the design of some of these studies and interpretation of data.

DR. AUCHINCLOSS: Marian.

DR. MICHAELS: This is slightly on a different topic although I certainly agree the infections to the individual patient are a problem, too.

With the PRA issues that were brought up in terms of the highly sensitized person that might be a potential beneficiary of these procedures because they wouldn't be eligible for an allotransplant, it seemed unclear to me. Some people thought that it wouldn't be a problem, and some thought it would be. I don't know if any of the sponsors wanted to address that further or whether that is something that needs to be looked at further before clinical trials.

DR. AUCHINCLOSS: I am sorry, David. I was going to ask you to comment in response, but you were saying something else. You want to hear the question?

DR. SACHS: Yes.

DR. AUCHINCLOSS: Will a highly sensitized patient for an allotransplant be sensitized for a xenotransplant?

DR. SACHS: We published about two years ago on xenotransplant patient a large series with Guy Alexander of patients with high PRA and the correlation between the antibody levels in PRA to human panel, and there was zero correlation, and the absorption of antibodies with pig left the PRA intact, and as David Cooper mentioned this morning, he has subsequently done that with an anti-Gal absorption and found a similar result.

So, while there could be some cross-reactivities, they are probably rather minor, and I think, in general, the answer will be that high PRA patients will not have any excess risk at being sensitized to pig.

DR. AUCHINCLOSS: I want to come back to the preclinical models issue.

DR. SIEGEL: I had a follow-up question about that, but I guess it addresses particularly cross-sensitivity vis-a-vis antibody. Are there any data about--since we heard a little bit about HLA and SLA cross-sensitization, are there data about that?

DR. SACHS: The cellular immune system fortunately is not as cross-reactive as the antibody, so I think we should be pretty good on that score.

DR. AUCHINCLOSS: Back to this preclinical studies issue, let me try a statement and then the committee can respond to it.

I think personally that too much is being made of the limitations of the preclinical models. The implicit suggestion I think from a number of the speakers was, gee, it's just so hard to care for these animals under the conditions we work in that when we only get to 30-day survival, that is really, frankly, good enough, we should now go to people because we will undoubtedly do so much better.

To be honest with you, I don't buy that. I really think that you should expect and that the standard should be that in preclinical studies, survival approximating the kind of survival you expect to see in patients should be achievable.

Now, there are some particular exceptions to that statement, and one example would be OKT3. OKT3 is a reagent that works beautifully in humans and doesn't cross-react on any of the non-human primates, so that it wasn't tested there, so there are particular strategies that you can make a compelling case, you have to do this in people, and it is appropriate to do it in people because of the following preclinical data in other ways.

But in general terms, I think you should be looking for results in your preclinical models that approximate what you hope to achieve in the clinical.

DR. ALLAN: I just wanted to make a comment. There is the commercially available anti-CD3 antibody that reacts with baboon. I am not saying you couldn't do an anti-CD3, I am just using an example.

DR. AUCHINCLOSS: There are many reagents that haven't been explored, I think, that are actually available that could be used.

DR. ONIONS: I found this morning's discussion very useful. Really, I am just phrasing this more of a

question because I am not a clinician.

It strikes me that cases are being made for various forms of bridges in terms of as a substitute for ventricular assist devices and also a good case for kidney where you can go back to dialysis if necessary.

What i am not quite sure about, and maybe somebody could help me out here, is there seemed to be a disagreement between the availability or the size of the patient on what would be appropriate for a bridging transplant because ventricular assist devices were not used or not available.

I wasn't quite sure, what is the ethics of using a xenotron's point here if there is an alternative, which is using a mechanical device? Could somebody perhaps just tease that out for me?

DR. AUCHINCLOSS: Robert, do you want to respond to that?

DR. MICHLER: I think that is a very good question and one which I tried to allude to in my presentation. It would be difficult, I think, as clinicians to offer an unproven therapy, at least unproven in the human clinical condition, to a patient for whom an accepted albeit not perfect alternative is available meaning the left ventricular assist device.

So, in most centers in this country, if not the world, that perform heart transplantation, ventricular

assist devices are part of their broad therapeutic regimen, and the guidelines for implantation of ventricular assist devices are fairly well established, not perfect.

There is a current U.S.-based clinical trial using ventricular assist devices as a destination therapy called the rematch trial in which patients who exceed the age of 65 are included in that trial for permanent implantation of the assist device.

So, the simple answer to the question is would I as a clinician feel comfortable looking at a patient and saying I have two alternatives for you, meaning that you meet all criteria for a ventricular assist device, and saying I would like to put in the xenograft because we have this clinical trial versus we have a ventricular assist device to put in. I think the answer is fairly straightforward.

DR. HIRSCH: But the question I think is are there individuals for whom the mechanical device is just not --

DR. MICHLER: Oh, now that is a totally separate question, that's a different question. If the question is are there a group of subset of patients for whom a ventricular assist device is not ideal, the answer is unquestionably yes, and that is really what we are addressing here.

If the question is meeting all criteria, a patient

who would be a suitable candidate for a ventricular assist device, should they be offered a xenograft, I think you would have to offer that patient in good conscience what you know to be the best available strategy at that point in time.

Now, there are certainly patients for whom a ventricular assist device is not suitable. An advanced age patient with multiple comorbid diseases for whom a ventricular assist device or even an allotransplant is not suitable, a patient of insufficient size in whom to put the device, the device is about this large around, maybe a little bit bigger, and about this thick, and the other devices are not much smaller than that, so you need a patient who weighs at least 120 pounds, and even a 120-pound individual is a little tight to get it into.

So, for these patients--and literally, there are thousands of these patients potentially who could benefit from a strategy and who are in imminent danger of death--for those patients, I think it would be a very rational approach to offer them a xenograft as a solution.

DR. AUCHINCLOSS: But I thought your question was how large is the subset, and the answer is it's small, but not tiny.

DR. ONIONS: Yes.

DR. AUCHINCLOSS: Again, I don't want to get to

which clinical studies do you think are the good ones or the bad ones quite yet. I want to stick, as your questions go, with preclinical studies, what are the limitations, what are the results that you expect from them.

Go ahead, Danny.

DR. SALOMON: I wanted to pick up on the chairman's point, not necessarily to say that I specifically disagree with what he said, but, however, to present the counter argument, as well.

So, our chairman pointed out that he didn't necessarily buy the fact that there were limitations in the animal models and that perhaps we ought to just stay with the animal models for a longer period of time. I would offer you an alternative.

First of all, there is no argument that there are novel reagents that, at this point, have been used and developed for humans that cannot be used in the animals. John's point is well taken. We could say fine, go develop those equivalence in primates and then come back and talk to us, but I just propose to you that that is a major effort and it is not as simple as just saying, oh, hey, there is already a commercially available anti-CD3 antibody.

Secondly, I think that the chairman underestimates the fact that there are dissimilar immunobiologies in non-human primates and in humans, and we could give you a lot of

different examples, but just recently they published the data in Transplantation for fetal pig islet transplants under the kidney capsule in cynomolgus monkeys, pig-to-cynomolgus monkeys, 13 days with full immunosuppression, several years ago, Karl growth in humans with half the fancy immunosuppression we have now, had measurable C peptide nine and 10 months later. I can give other examples, but I think you get my point.

Moreover, complement humoral cascades are going to be potentially very different, and it's evident to everyone here that those are major obstacles. Now, there is an underlying premise here that these complement regulatory protein transgenics are avoiding hyperacute rejection. Is that going to work in the human patient? There is a lot of money and effort going down that road right now.

Arguably, at this point, there is also the biology. I mean is the biology in the non-human primate the same? No, it is not. So, the bottom line here is I think that one can make a case for validating the non-human primate models at this point in a limited series of clinical trials. If they look like they are matching up, then, I might be perfectly comfortable with saying, okay, back to the drawing board, but if they are not, I think it is time in this field to figure that out.

DR. McGREGOR: Mr. Chairman, as someone who is

practically carrying out clinical cardiac transplantation in substantial numbers of cardiac transplantation in non-human primates using transgenic pigs, as well as the argument about immunobiology being different, the practical management of a non-human primate is so much more difficult than a human, just the practical, every-day management, the taking of blood samples, investigating the function of the organ, the therapies of immunopheresis, which really knocks a baboon, which we do routine clinically for certain diseases.

So, really, there is a huge difference in the practical management of a non-human primate receiving a xenotransplant compared to a human. So, I would respectfully submit that the bar in terms of transgenic pig-to-primate xenotransplantation survival should be lower, because it is most of our beliefs who do this work that the results in humans, certainly from a practical point of view, would be substantially better.

DR. AUCHINCLOSS: Please understand that we are talking about a matter of degree here. I do recognize that there are differences, and the question is how significant are those differences.

I would put it to you in a different way perhaps, that is you came to me and said I just can't treat these animals any longer with this protocol because it's too

complicated, I would say, all right, I can understand that in some of these circumstances, but when you come to me--or not you, I don't mean you particularly--but when someone comes to me and says at four or eight weeks our animals suffer from acute vascular rejection and lose their transplant, and I don't hear what it is that you would do differently in the human that would overcome that rejection process, I am not impressed that the time has come to go from the animal to the human trials to see if maybe it will work there.

David.

DR. SACHS: I have always felt, and I still feel, that the time to do clinical xenotransplantation is when there is a reasonable expectation that it will be successful. I have to share your opinion, Hugh, that at this point, I don't see that reasonable expectation of success meaning success on a reasonably long-term basis.

Now, the bridge I have, as I mentioned earlier, a philosophical problem with, because it really doesn't help our major limitation of transplantation, that is, the limitation in our numbers of organs, and increases the waiting list.

I guess I would change my mind on that if I thought that the bridge was being done on a tentative basis, but it seemed to me that what you are really saying when you

do a bridge is that as soon as a heart becomes available, an allogeneic heart, you are going to take that out whether it has failed or not. That is the only way a bridge would work.

So, you will never find out whether it would have worked longer, you will never be really testing the model. You won't really learn anything about the prolongation of xenografts beyond what we are seeing in the primates.

DR. MICHLER: David, you know, we had the very same kind of questions before that we had widespread application of ventricular assist devices, and the issues were (a) it is not going to be epidemiologically consequential, and (b) when do we take one out and put the other one in.

What we learned were several very important things; first, that if you put a ventricular assist device in a patient on day one, you don't want to take it out on day two or even on day seven or maybe not even on day 28. We found that these patients recovered dramatically their end organ function, so that arbitrarily, many programs around the world set a moratorium on explant of a device until the patient had recovered, and usually meant about three to four weeks.

DR. SACHS: Even if a heart became available.

DR. MICHLER: Even if a heart became available,

because we found that patients died during the explant and the allotransplant simply because they had not recovered nutritional status, functional status, end organ function, and we were dealing with renal failure and a whole host of other problems, and I think that analogy is going to be held true here.

DR. SACHS: I will hold off on my next question because I know Hugh wants to.

DR. AUCHINCLOSS: We will come back to it, I promise we will.

Louisa.

DR. CHAPMAN: You partially answered actually the question I want to ask, but in a very simple way, as a nontransplanter, it would be helpful to me anytime we are looking at survival rates in animal models and talking about a change to clinical trials, to have a sense of what the average recovery period is from the time of surgery until the patient leaves the hospital, and from the time of surgery until regaining full function defined, I don't know how, perhaps if I return to school or job or something like that, because it seems to me, in terms of quality of life, and I recognize this is more relevant for destination xenotransplant than for bridging, but in terms of survival time, it seems to me you could only count it as significant from the point where they recover a reasonable quality of

life, which I would not consider an immediately post-op cardiac transplant patient to have.

DR. AUCHINCLOSS: You don't think that a permanent transplant that lasts 30 months is likely to be good enough?

DR. CHAPMAN: I don't know. That's my question. If a patient receives an allotransplant, either a kidney or a heart, assuming no surgical complications and no significant postoperative or other iatrogenic complications, what is the average time from the time of surgery until they are ready to leave the hospital, from the time of surgery to full recovery for a heart, for a kidney? I think that is a relevant comparison.

DR. CONTE: To answer that, it is so variable. I think Bob and Chris and I can tell you we have had patients probably go home within five days after a transplant they have done so well, and others who have been so sick beforehand, whether ventricular assist devices, are intubated, have such end organ dysfunction going into it, are in the hospital for months.

I guess if you had to pick a number, it is when they are over the effects of the operation, which after a full sternotomy and cardiopulmonary bypass, is going to be in the four to 12 week period I would say. At least that is when I don't let any cardiac surgical patient go back to full activity after a sternotomy. Is that reasonable?

DR. AUCHINCLOSS: So, back to the question. How much slack do you want to cut to the non-human primate studies? David Cooper.

DR. COOPER: I just want to make one comment, two comments really. One is that although we say that it is more difficult to manage the baboons, and so on, and it definitely is, and it would be easier to manage humans, not everything is to the advantage of the human.

For example, the humans have much higher levels of anti-Gal antibody IgG than do baboons or monkeys, so we may find that the problems are exaggerated when we get to the human compared with the monkey. So, don't think that everything is going to be easier when we get to the human.

The other thing that has worried me, as I mentioned this morning, is that if you have got animals that are still showing signs of rejection, but at the same time are getting lymphoproliferative disease, lymphomas, tumors developing, it means that they are getting quite heavy immunosuppression, you are not controlling the rejection, but you are still seeing the serious effects of that immunosuppression.

DR. WOODLE: Did there animals in any of these trials get prophylaxis or antiviral prophylaxis or antibody prophylaxis of any form?

DR. COZZI: If I can comment on what Dr. Cooper

was just saying a few seconds ago, I mean if we take, for instance, a usual pig-to-primate model we have in Cambridge, okay, as I said, we have more than 80 percent of our experience developing.

If I look at what I do, for instance, in an MMF protocol, just to be impartial and talk about a molecule which I have no interest to defend, okay, when I transplant my animals, I do a pig-to-primate model xenotransplantation, what is the trough level of the compound I am trying to achieve.

I said Dr. Michler was saying earlier today you are using a very high level of cyclosporin A in baboons. This is absolutely true, and there are papers that reports that you need to aim a trough level of at least 1,200, 1,500 ng/mL of cyclosporin A to have immunosuppressive effect in a baboon.

What about in the cynomolgus monkey? In the cynomolgus monkey, we are aiming to a trough level of 300 to 400 ng/mL of cyclosporin A. Those of you who are clinicians here do know that in some patients, certainly, for instance, in some heart transplantation program, we use 3- to 400 ng/mL also in our patients.

So, cyclosporin A, we use in our animals is a therapeutic level, at least according to the level we use, to the parameter we use in human allotransplantation. The

MMF, we are aiming for a window of 3 to 6 mcg/mL, and this we are using this trough levels, not because we have data that have been generated in the preclinical setting, because these are the data that are currently being used by our center in patients who are transplanted and exposed to MMF as a drug.

Finally, the dose of steroids we are using, we start with 1 mg/kg, and we taper and go down for .20 mg/kg per day after the second week. So, if we look only at this protocol, if we exclude the four doses of cyclophosphamide, I would consider that this immunosuppression is clinically acceptable according to the trough level we are using in the department, which is 50 yards away from where I keep my monkeys.

Thank you.

DR. COOPER: Can I just respond? I agree entirely, Emanuele, that is a clinically applicable level or the levels are clinically applicable, but they are the very animals, 3 out of 7 have got lymphoma within two to three months, and yet they have still got rejection going on. So your clinically applicable dosages or immunosuppression are not controlling the rejection, but are actually, in that animal model, over-immunosuppressing to the point they are getting tumor formation.

So, it shows that there is something still needs

to be done there.

DR. COZZI: A little comment because that is very important, as well. I mean we in the United Kingdom are under a strict control and pressure from the home office, so the information that I want to bring to this is that we do not immunosuppress these animals from day zero until the day they are killed and they have their acute vascular project.

There are some stages where we are obliged to give up the immunosuppression or reduce the draws of immunosuppression because the animal is sick and unwell. I mean in the case of rat, for instance, is because we have a very profuse and severe diarrhea which we do not see in our patients.

So, what I mean, yes, we have lymphoproliferative disorders, possibly we have the existence of acute vascular rejection in that animal, but I also have to tell you I had to back up or suspend immunosuppression for four or five days before the death of the animal occurred.

DR. WOODLE: I would make the point that Hugh or Dan, and those of you that have a lot of experience in kidney transplantation, if I were to take to you today a regimen with cyclosporin, rifamycin, steroids, or maybe trachomis, mycophenolate, and steroids, immunosuppressive series of patients, and not prophylax them for antiviral prophylaxis, their incidence of CMV disease and EBV would be

exorbitant to the point where you would say no way I can do this protocol in humans.

The point that I have to make is that none of these animals received any antiviral prophylaxis, nor do you know what are the viruses that are involved in here, and what we are going to do is we are asking these companies to figure these things out and sort them out before you take this to the clinical setting.

DR. AUCHINCLOSS: I am sorry, Steve, the final point that you are making there is basically go ahead and give them the viral prophylaxis, so that --

DR. WOODLE: If they know which viruses. I mean the problem is that you have, in a lymphoma, you have a PTLD here, and I am not sure that anybody knows the etiology of these PTLDs in these animals, whether or not it is an EBV-like virus or whether it is a true cancer.

DR. WALTERS: I have a couple of process questions for FDA. One is are you satisfied that there is a standardized enough format for the reporting of preclinical data from the various groups that are doing preclinical studies?

The second question is do you have access to all or virtually all of the preclinical data worldwide on the transplantation of solid organs into animal models?

My third question is what fraction of that

worldwide data would we around this table have access to either through this meeting or through the literature?

DR. SIEGEL: I think that if I understand the question, the answer would be, as far as access, that for those sponsors that are proposing human experimentation, we essentially have access to any and all data that we ask for regarding their preclinical information, which in most cases, including drug development, not some really transplantation development, is substantially more extensive than what might be presented at medical meetings or at the literature. We may ask for a lot more detail.

However, beyond those sponsors, when you asked about worldwide experimentation, I think our access to information is pretty much the same as your access to information, what is out there in the public domain.

We will do our searches, we will ask that the sponsors do their searches and present, and also submit articles for us. I am not exactly sure about the question about the standard formatting, exactly what you are getting at or if I understood the question or maybe I answered it.

DR. WALTERS: I just wonder whether there is--I am thinking of an analogy from a totally different sphere--the recordkeeping and reporting of infertility clinics on their success rates, and there were a wide variety of ways of reporting success for a long time, and gradually, that is

getting standardized.

Is it quite standardized in terms of graft survival?

DR. SIEGEL: I don't know if we know enough to want to standardize to anything.

DR. AUCHINCLOSS: I think that there would be reason to suspect that there is information that we don't all have access to that was done in various companies.

Do you think that is a fair statement, David? Jump in now with your own comment.

DR. SACHS: I gather that what we are really asking now, Hugh, is what should the questions be of the preclinical models in order to go to the clinical trial.

I would return to my statement, reasonable expectation of success, and I think that is the only relevant question that has to be asked, any group that wants to try clinical xenotransplantation, does your preclinical data give you a reasonable expectation of success.

Then, what is the definition, what is success? Again, I would say it is different if you are talking about a bridge from the survival of the patient with a transplant.

DR. AUCHINCLOSS: That is a point that the FDA is asking, and the answer to that to me is quite clearly yes, there are different standards if you are looking for bridge compared to definitive transplant. Do you agree with that?

DR. SACHS: I agree with that.

DR. ONIONS: I would just like clarification. I wonder if David could comment. We had two pieces of data put on the table which I thought were useful. One suggestion was that, for bridges, that you should be seeing a median survival beyond 60 days I think was one comment.

In a slightly different context, I think we got a figure of--again in the bridging situation--60 percent survival of 90 days. I mean are these the kinds of figures that you would find acceptable verbiage, is that what you mean by reasonable expectation?

DR. SACHS: No, not for a bridge. I am talking about a transplant, and I think the definition of that has to be made to the investigator. I wouldn't want a heart that was only going to survive 60 days. I think that is an awful lot to put a patient through for an expectation of a 60-day survival.

If there was an expectation that it was going to possibly go on permanently, I would have a very different answer, and I have always felt that that is what you offer a patient is what you would do for yourself.

So, I think success in those terms is unlimited survival, the same as for an allotransplant, possible. That doesn't mean that it is going to happen the first few times, but if you look at the data that is available today, and ask

the very people who are obtaining that data if they feel that there is a reasonable expectation of long-term success, I will sure they will all tell you no, and yet they want to go ahead with it.

Now, if they go ahead with it, therefore, it is more likely that they are talking about a bridge, and there, if you can get over the philosophical problems about a bridge, I have no objection to it, but I myself am not sure that the bridge is reasonable.

DR. AUCHINCLOSS: Bob Michler, you had a question?

DR. MICHLER: Yes, I would just expand on your point, David, and that is that included in, inherent in the issue of survival, one must pin the issue of diagnostic and treatment of rejection, meaning that if you can get a patient without--excuse me--an animal model to exceed 60 days without evidence of rejection or 90 days with treatable rejection, that is very valuable information.

And then to just place it in the context of the patient, if we expect that a patient who is bridged with a ventricular assist device needs a good 60-day period of healthy mechanical or biologic recovery until they get transplanted, that would seem acceptable.

On the other hand, if you are looking in a cohort of patients for whom the likelihood of death on the waiting list exceeds 50 percent or 60 percent, and there are

patients like that, or a patient who is not even a candidate for allotransplantation, that one might comfortably apply that same kind of animal data to say it would be reasonable to enter the clinical arena with that information.

DR. AUCHINCLOSS: Go ahead.

MS. BLACK: I was asked to stand up by the FDA contingent. My name is Lauren Black. I am a scientific reviewer for preclinical data in the Division of Clinical Trials for trials in xenotransplantation and tissue engineering.

Consequently, I basically am put to the task of reviewing the preclinical data as it comes in from various sponsors in trying to help the division assess the risks and benefits as expressed in those data.

I wanted to pick up on--is that Dr. Walters from Georgetown--his comment about the standardized format of some of these things. It is very difficult as a reviewer to be able to access the information as is expressed in data coming in from a lot of academic laboratories when it is particularly formatted for communication to the agency when it is not under IND, for instance, in briefing packets to the advisory committee and other things.

The reason for that is that a lot of times these model data are expressed in terms of data sets that you would prepare for publication, and oftentimes don't track

down all of the reasons, for instance, for animal mortality. They don't necessarily give a full tabulation of the data from the perspective of successes and failures.

Consequently, when we review the data from 10 animals that come in, we need to know exactly what happened to each of the 10 animals in order to be able to fully assess risks and benefits, particularly from the point of view of the immunosuppressant regimens, what sort of individual differences in the animals, for instance, differences in level of expression of transgenes, differences in effectiveness of the immunoapheresis regimens, other things that may be able to help us scientifically correlate each individual animal success in a therapeutic sense, with the duration of the survival of the graft.

So, when we do the scientific assessment, we really need to know the full tabulation that goes for each animal, for the duration of its care under the clinical tracking that is done, is it the same degree that is done for patient care.

So, when we assess that, we try to make an assessment on the total data set, the same way you would a small clinical trial.

DR. AUCHINCLOSS: You catch me by surprise. I would have assumed that that would be required information,

what actually happens to each individual animal. It makes sense to me.

MS. BLACK: It's the depth of reporting issue.

DR. AUCHINCLOSS: Jay, you had a comment.

DR. SIEGEL: Perhaps it is related in some ways. Dr. Sachs twice mentioned as a standard for what needs to be shown preclinically a reasonable chance of success, and I certainly wouldn't disagree with that standard, but I am not sure it's the only standard, or if it were the only standard, I would say it would be a substantial departure from what we require of preclinical testing for all other biological therapies, as well as drugs, which is that in addition to looking in preclinical modeling for rationale, we typically require substantial testing looking at toxicology, at dose pharmacology relationships, at optimizing of regimens, whatever information we think might be relevant even if we think it has a reasonable chance of success, whatever information might be relevant to improving the safety and efficacy of initial and subsequent human experimentation with that therapy.

So, I think one might apply that principle or at least think about that, which is to say even if you thought you are at a level of a reasonable chance of success, if there were critical questions that could well be answered in animal models, if you felt that there were important

questions about what happens with retransplantation after failure of the xeno, or questions about certain aspects of concomitant therapy that could be well answered in animal models even if you had a reasonable chance of success, it would at least be a normal agency approach to say those questions should be addressed in animals if they can be suitably addressed in animals.

DR. AUCHINCLOSS: Steve, can I let David respond to that, and then we will come back to you?

DR. SACHS: I think it is a very good point, and I agree with you in terms of the FDA's answer. I guess my answer is also tempered by my concerns for the field, which I think is a different problem, but I think that there is nothing that will hurt the field more than a series of failures. So, there is both of those things that are involved in my response.

DR. AUCHINCLOSS: Steve Woodle.

DR. WOODLE: I want to take a few minutes. I wanted to ask Dr. Cozzi if he could come up, and I wanted to just ask him a few questions to try to be illustrative about one of the points that I think is really an issue here, and that is, that you can't take care of an animal in a laboratory setting the way you can a human.

Those of us who have done clinical transplants and also done transplants in large animals in the lab, have an

understanding of this, but unless you have done those, taken care of patients and taken care of animals in the lab, you don't have the first idea of how you are in the Stone Age with an animal in the laboratory.

I wanted to ask Dr. Cozzi, when one of your patients has an elevated--say, one of the animals had an elevated serum creatinine, had a kidney transplant, what would you do to evaluate that? What is your standard course of evaluation?

DR. AUCHINCLOSS: Steve, I honestly believe that people do understand that there are substantial differences in the testing that you can do for monkeys versus--

DR. WOODLE: I am not sure that--

DR. AUCHINCLOSS: If there is a particular point that you want to make--

DR. WOODLE: I am not sure that people actually understand the degree of difference that exists, and if we could take just two minutes, I will try to make this real--what you would do with an elevated serum creatinine?

DR. COZZI: I can certainly answer.

DR. WOODLE: You are worried about a rejection is what you are worried about.

DR. COZZI: I can tell you what I have done in roughly 260 out of 280 kidney xenograft we have done in Cambridge. In 260 out of 280 xenografts, which is more than

95 percent of the cases, I was working random and I was working blind, and I was not allowed to have access to what we use today in the clinic, which is the gold standard, i.e., the biopsy.

DR. WOODLE: So, you wouldn't be able to do an ultrasound to make sure that there wasn't a technical problem with the artery or the ureter, you weren't able to do a biopsy of the graft to make sure that it wasn't rejection, so you are flying by the seat of your pants in order to treat this animal who may have a problem with his ureter for rejection, which is going to predispose them to an exorbitant amount of immunosuppression, point one.

If the animal developed, let's say, a cough, were you able to make sure--how would you make sure that animal didn't have pneumonia? Would you be able to do a chest x-ray?

DR. COZZI: No.

DR. AUCHINCLOSS: Steve, I think you can make your point without going through the exercise here.

DR. WOODLE: But the point is if you didn't do a chest x-ray, you didn't do a culture, you didn't have the ability to treat with antibiotics, much less make a specific diagnosis, that most patients we would save in those types of opportunistic infections, but you are going to lose that animal in the laboratory.

DR. AUCHINCLOSS: Dr. Vanderpool.

DR. VANDERPOOL: Just three observations. First, to pick up David Sach's phrase "reasonable expectation of success," I think that is a fine phrase to work off of, and it doesn't seem to me, Jay, that you really refined it all that much by defining success as safety and efficacy because you could just change the phrase and say reasonable expectation of safety and efficacy.

DR. SIEGEL: I guess the refinement I would say is even if you had a reasonable expectation of safety and efficacy, but felt that you could improve that level by reasonable additional animal experimentation, normally, we would require that.

DR. VANDERPOOL: At this point, I am just making a rhetorical point about our rhetoric and how to think past the rhetoric itself. Success may be a shorthand term for safety and efficacy.

I think my second point would be that I think we need to consider three audiences. First, what we here together would take to be reasonable success, and we talked about that a lot, you know, in terms of what we will offer to patients, and we need to keep talking about that, but I think there are two other audiences to keep in the back of our heads.

One is what in the world would patients take to be

reasonable chances of success. I think at the point of our deliberations, we need to consider what a patient group--we have one patient with us--would take to be reasonable.

I consider things that are reasonable for me that are beyond that someone in dire circumstances would consider to be very conservative and very restrained, because as Antonio said, some patients are willing to take chances when you are in desperate straits that others won't, so I think we need to have allotransplant patients give us some feedback on what they would consider reasonable chances of success.

Third, I think we need to think, have in the back of our head, what society would view as reasonable changes of success. I think we have a lot to win or to lose in terms of social responses to initiation of clinical trials.

To put the matter in patient-centered terms, I would just ask us to keep in mind what would we be saying to patients right now, with our present preclinical data, what would we say, okay, based on the present preclinical data we have, you stand to be limited or harmed in the following way, and you stand to benefit in the following ways.

How would we fill in the blanks for those? It seems to me when we can start filling in those blanks, we are getting a fairly good handle on what we take to be reasonable chances of success from a patient standpoint.

MR. LAWRENCE: I am chiming in from the patient perspective on this. Since we have transitioned from the preclinical to the clinical to suddenly the patients begin to have some views that may matter here, I have four comments to make.

I work for the United Network for Organ Sharing, and that is an allograft-oriented group. I would like to remind the people that are gathered in this room that we have been engaged for the past 10 years in petty arguments about allocation for the simple reason that that is about all that we can do.

We are looking to perhaps the xenograft community to help relieve some of the pressure that reduces us to arguing over such small things. I remember when I first got to UNOS 10 years ago, you could take the entire waiting list of people, and I thought this was very illustrative, and you could pick them in Fenway Park, and I picture Fenway Park--I was raised in Boston--full of people, and that is how many people we are talking about.

Five years ago you would have had to move them all to Oriole Park and Camden Yards, because it was up to 40,000, and now, much as I hate to say this, you would have to get Yankee Stadium to hold the waiting list, and pretty soon we are going to Wembley for our UK friends, because this is a large group of people that we are talking about

here. Half of those people statistically will not receive a transplant, some of them will get better, most of them will die. So, that is the state that we are in.

I would like to just lay that out. I have two substantive things to say. One is to thank the FDA for including us here. I think as time goes by, we will be able to play more and more of a role in some of the decisions that you have to make.

The other is with regard to informed consent. An old law professor of mine said that in the hospital setting, informed consent reminded him of the Holy Roman Empire, which was neither holy nor Roman nor an empire. There are going to be some informed consent issues here that we can help with, and we look forward to doing that.

We urge you to proceed with all deliberate speed as we did with integration and look forward to working with you as you go along. Thank you.

MR. BENEDI: I would like to say a couple of things. One is the reasonable chance that a patient will want to take, and I think that the successes in transplantation are its own worst enemy at this point. A bill has been out 12 years, not 7 years, so when you talk to a patient and give them an option of 60 days, they are waiting for a chance at 7 or 12 years, so they need to be given a little bit more reasonable chance to live.

With these unknown entities out here, these viruses that everybody talks about, obviously, those things need to be alleviated in the general population before people really take a look at this as a reasonable alternative.

I really do think, after what I have heard here in the last two days, and the last conference that we had, that we still have a ways to go before we all feel comfortable. I really highly recommend that we all sign our donor cards before we leave. Thank you.

DR. AUCHINCLOSS: Part of the point of this exercise--again, correct me, FDA, if I am wrong--is to give both you and the sponsors a sense of how the committee might respond in the future should proposals come to you for specific protocols for clinical trials.

So, let's try a hypothetical case, that a sponsor came to you essentially with the data that we have seen over this morning's presentations and said I want to initiate a trial of definitive xenotransplantation, not a bridge trial, but definitive xenotransplantation for long-term survival.

Is there anybody on the committee who thinks that the data are sufficient to initiate such a clinical trial or that we are close to being sufficient?

[Show of hands.]

DR. WOODLE: I would just qualify my answer here

in that I think that there are subsets of patients who are facing imminent death in whom it is very difficult to put yourself in that position and say what decision you would make.

I can tell I make rounds on patients--and this doesn't happen all the time, it is very infrequent--but I make rounds on patients who I know are going to die very, very soon, that I wish there was something else that I could do for them, and I know that they would probably go for it.

We sat here, this committee sat here a few years ago and we watched a patient stand up who was going to have a baboon bone marrow, and the committee voted to go ahead and go for it, and that patient's primary motivation was altruism, so that people--not that he would benefit--but that people after him would benefit.

It's an ethical issue that Dr. Vanderpool can address, but there are people out there who may not have a reasonable expectation of benefit, but may want to do that, purely altruistically, so that people after them may want to.

DR. AUCHINCLOSS: Let me carry this exercise a little bit further.

Leave aside the question of whether you think bridging is good enough. Supposing that the indication was a bridge, cardiac bridge transplant. Would the data that we

have currently--do you want to qualify this, David?

DR. SACHS: No.

DR. AUCHINCLOSS: Would the data that we have currently convince you that is it appropriate to proceed with such a trial?

DR. SACHS: That is what I would like to speak to.

DR. AUCHINCLOSS: Go ahead.

DR. SACHS: I would like to go back then to my other question, which we were going to follow up on, that's the very point, to Dr. Michler.

That is, what would you do--and I accepted and appreciated your answer about having a period of time for the patient to stabilize and the end organs to improve--but what would you do if an organ was available after that period of time, but the xenograft was still working beautifully?

Let's say at six weeks an organ became available, but there was nothing wrong with the way the xenograft was working.

DR. MICHLER: Quite frankly, I would transplant the patient because I think it is really very, very important to show success, show success in the ability to demonstrate that the graft supported the circulation, kept the patient alive, the rejection was manageable, and that the patient was transplanted, and that patient could go

home.

MS. MEYERS: I would have tremendous reservations even about that kind of experiment based on the PERV problem, and until that is settled, I don't think that there should be organ transplants with any animal where we can't prove that it is safe.

DR. AUCHINCLOSS: I hear your concerns, Abbey, and I think that they are important concerns, but let me break the question into pieces. Let me wipe away PERV for you for a second.

MS. MEYERS: If there wasn't a problem with those viruses.

DR. AUCHINCLOSS: We are just going to talk about preclinical data, and the trial is a bridge transplant for a select group of cardiac patients.

Do members of the committee think that the data are sufficient to support such a trial?

DR. CONTE: I think when you would consider that trial, you would have to consider the success with mechanical support devices in general, and they are approaching the point where they are so good, you would have a hard time convincing most practitioners that it is a trial you would want to do. However--

DR. AUCHINCLOSS: I am going to narrow it still further. The patient is not a candidate for whatever

reason, size, et cetera, for a VAD device. So, it's a bridge and it's a select group of patients who can't get a VAD, and we have the data available now. There is no ethical issue in your mind about a bridge.

Is that data sufficient to go ahead with the bridge?

MS. MEYERS: And there is no virus.

DR. AUCHINCLOSS: And no virus.

DR. MICHAELS: I didn't hear the data or else I missed it. Do we have data on the pig to baboon or pig to cyno, and then as a bridge, taking that out and putting in an allotransplant in the primate?

DR. AUCHINCLOSS: That is a specific question from the FDA. Would you want to see that data before you said yes?

DR. MICHAELS: I would.

DR. AUCHINCLOSS: I personally am not terribly concerned, frankly, about the immunologic features of that. Let me give you a counter example--I will stop there.

DR. SIEGEL: So, you would be comfortable just providing an informed consent to the patient that this may well harm your ability to successfully receive an allotransplant when it is available, and we don't know and we haven't looked at that question in animals? I am being a little bit provocative, I understand.

DR. AUCHINCLOSS: Presumably, if we say you don't have to look in animals first, that is what the informed consent should say.

David, what do you think about this?

DR. SACHS: I think it is a very important point, and I think that it's not just from the question of the immune system, but the animal and the patients are going to be going through quite a rigorous procedure in getting them not to reject the xenograft.

They are going to be getting a lot of drugs, more drug than they would have needed for an allotransplant. There are a variety of reasons why the patient will be in worse condition.

DR. AUCHINCLOSS: I think the patient will be in much worse condition. That is why I don't favor bridge transplantation, but the question is should the sponsors do immunologic studies to determine the consequences--

DR. SACHS: Well, should the sponsors do bridging, and then give allografts is the question. Isn't that the question? Yes.

DR. AUCHINCLOSS: Incidently, I think both sponsors alluded to the--I think they suggested that they thought they should do it before they came to you, so maybe I should shut up.

DR. SALOMON: I think there is a critical

perspective, though, to return to. What disturbs me is this tacit assumption that continues on this board, that these animal models are appropriate models for the human transplant, so we talk about appropriate expectations of success, David, I respect that.

The question is have you validated that these incredibly--I mean have you pushed the animal model at this point past the limit that is reasonable? There has been a proof of concept in the animal model.

How far are we going to demand the sponsors to validate this, or is there a reason? Are there trials that could be designed based on a different premise? Does someone have to be on life and death's door to have a trial date at this point?

I would just like to propose the possibility that there are alternative groups of patients who could, under the right circumstances--I am not going to go into the clinical design trial, because I know the chairman wants to get into that in a separate discussion--but just the point.

There are people here who could have this transplant, validate the animal models, address the issue you are having, and never be threatened to die.

DR. LEVY: Just a quick comment to Dr. Sachs.

I have bridged two people with a liver transplant, and both of those patients' families were just delighted

that that technology was available, and I think that speaks for itself from the patient's perspective.

DR. VANDERPOOL: A quick question. When you say we are going to bridge this patient, I just don't know, but does that mean that you can promise an allotransplant in 30, 45, or 60 days? Bridge means going somewhere, and there is land on the other side. Can the surgeons here comment and say for this group of patients, we can bridge you there, and we can guarantee an allotransplant at the end of that time period?

DR. AUCHINCLOSS: I think that answer to that is simple. No.

DR. VANDERPOOL: Well, I thought it was no, and if it's no, then, what does the phrase "bridge" mean?

DR. AUCHINCLOSS: It means you are going to increase your chances of getting an allotransplant.

DR. VANDERPOOL: It means increase your chances. It's work in progress. I am picking up different phrases here.

DR. SACHS: I just want to respond to Marlin Levy's point. You are talking about an ex vivo perfusion of the liver, which is a standard form of therapy, and has been since the 1960s, I mean standard, but has been done effectively to tied somebody over acute liver failure. That is very different from a xenotransplant. To my knowledge,

the only time that a xenoliver has been attempted as a true bridge in the sense of a xenograft, it was a dismal failure.

So, I certainly would share your impression that any kind of treatment that will extend the patient's life long enough to get a graft, what I would call standard treatment, but I don't think we are talking about the same thing when we say do a bridge xenograft to transplant, xeno, an organ. I mean that would be actually putting a xenoliver in and waiting for a number of weeks, and I think most people are talking about it more for the heart than for the liver.

DR. SIEGEL: As I heard the comments about the bridging that you and some others made, as well, there was another issue, which was that as long as the organs remain the limiting factor, and there is no more organs to the exact same extent that you increase that patient's chance of getting an organ, you are decreasing some other patient's chance of getting an organ, and that that patient who received that organ--that organ wouldn't have gone to waste, it would have gone to another patient, so, in fact, they are delighted, but the net societal benefit--

DR. AUCHINCLOSS: Net societal loss is what you get because all you get is sicker patients going to transplantation, but that is going to bring us into our second category of questions again.

John Coffin.

DR. COFFIN: Countering that, though, I thought I heard that one of the main motivations for using a bridge was to improve the patient's clinical condition and therefore the ultimate success of the transplant.

The question is should that be also something that would be considered in the xenotransplant as to whether there was not only a reasonable chance of it surviving, but a reasonable chance of improving--

DR. CONTE: We seem to be moving towards discussions of renal and cardiac transplant, but what about organs where there are no options, there are no bridges for lung transplantation, should be bar be lower for lung transplants? Just to throw that out for people to think about.

DR. AUCHINCLOSS: Let's put that question on the table. What I am going to do is, there are two or three specific things in the preclinical area that you want us to address, and I am going to get those on the table quickly because I think we can cover them.

I am going to force you to tell me what you think about the data with respect to bridging, so that we can give that signal to the FDA and to the sponsors, and then we will move into this discussion of the larger clinical trials issue.

Your question was are there other organs. Both sponsors have I think suggested kidney or heart, stay away from the liver, the lungs. I personally think both sponsors are correct.

Is there anybody who thinks that it is time to be thinking seriously about pig livers or pig lungs, any other solid organ? No.

DR. CONTE: I threw the idea out there, not necessarily to say we should do those, but if we are going to come up with policy, I think you have to have a policy that addresses it.

If you are going to put a bar up there saying you have reasonable expectation of survival or if you put it as a bridge, survival to 60 days, so you can get a heart transplant, what about those organs where there is not a reasonable bridge available? Should we come up a policy that is all-inclusive or should we come up with a policy that is organ specific?

DR. SACHS: I think it's an excellent point because lung is clearly the most need, but it is so hard that timewise you put things backwards just getting the studies done, but you are absolutely right, there are just no available lungs.

DR. AUCHINCLOSS: Worse supply problem of them all.

DR. ONIONS: I don't want to prolong this bit of the discussion, but it seems to me that we have correctly suspended our concerns about infectious disease today, but I would just caution that I think that if you are considering or could ever consider lung transplants, there are a whole set of other real complex disease issues that I wouldn't like to get into at the moment, but I think there is a very big barrier there in terms of disease issues.

DR. SIEGEL: I would just add that I think we probably all agree that the standard should be different, not just by organ, but also by organ and setting, how serious is the patient's disease, is it bridging or whatever.

From a pragmatic point of view, we are more likely to be faced, as we all heard, in the not too distant future with proposals that we will have to decide upon in the heart and/or kidney, so I think pragmatically, that is really more important to focus on now what those standards are, not that the lung is less important.

DR. AUCHINCLOSS: One of the questions from the FDA was if you don't like pig to baboon, do you have something better. Everybody agrees that there are limitations to various degrees in pig to baboon, or pig to non-human primate in general? I don't think just baboon is what you mean there.

Has anybody got a better model? There is nothing better out there, I don't think.

I think I will withdraw my question about what happens to the subsequent--my comment about the subsequent allo after xeno, because I think everybody thinks that they ought to do that, the sponsors ought to do those studies, and the sponsors said they ought to do those studies, so I think that would be the answer to that one.

How do people feel about the heterotopic/orthotopic position issue? Do the heart people feel that having a functioning orthotopic heart is an important aspect of a preclinical study or is the heterotopic position good enough?

DR. MICHLER: I think for immunologic studies, the heterotopic position is very nice, it's simple, it's reproducible, high success rate, but when it comes to issues of confidence in order to take an organ an implant it into a human, I think it is very nice to have orthotopic functional information.

DR. AUCHINCLOSS: Does anybody want to disagree with that? They want to see survival data with a functioning organ.

Now, back there to the bridge question again. Do the data at this point, in your view, are the data sufficient that we have heard to justify initiation of

clinical bridge trial of cardiac transplantation for a select population? Tell me yes if you think we are ready to go.

DR. WOODLE: Which patient populations are we talking about? Not suitable for an LVAD, end-stage disease, about to die, with life expectancy in days to a couple of weeks?

DR. AUCHINCLOSS: So the answer to that is--who is ready to go?

DR. MICHLER: So, that would be a destination therapy.

DR. AUCHINCLOSS: Not destination.

DR. SIEGEL: I have a question to help clarify that question in my mind. We heard Dr. McGregor talk about such a potential population, not suitable for LVAD, but he also put another criteria to suggest unlikelihood that they would survive without this therapy for a graft, in fact, so unlikely that I guess he suggested there shouldn't be a control in such a study, and they included issues, such as life-threatening arrhythmias, deteriorating hemodynamics, multiple end-organ failures.

I am wondering about what we know about that population, can we identify people who meet certain criteria, who (a) we know are unlikely to survive, are as we have heard about likely to die within the next few weeks,

and who are also suitable candidates for undergoing a xenotransplantation.

DR. CONTE: I just want to make one point. There are groups of people in the heart transplant circles who think that the only people who are not candidates for an assist device are those who don't make criteria based on size alone, that there are patients who do have other end-organ damage and other systemic illnesses, however, that is just going to put them at higher risk.

That group of patients are going to be no less risk to receive a xenotransplant. I think that is very important to put that out there. So, really, what we are talking about is a mechanical issue, can we fit a pump of some type, maybe a not yet developed pump, into a recipient?

I think that is really the only issue at this point in time that limits the availability of mechanical devices for patients.

DR. SIEGEL: I guess I was not speaking of those factors with regard to availability of mechanical devices. As I understood the proposal, even if you were to exclude people--I mean not everybody who is eligible for a mechanical assist device because of size gets one, because some of them, they are doing well enough without that, that they are likely to--there are people on the waiting list presumably who have prognosis better than others, and it was

my understanding that it was trying to define a population using those criteria, not that they couldn't get a device, but who, in addition to not being able to get a device, if they without bridging were unlikely to survive long enough to get a transplant.

DR. McGREGOR: Going back on the 15-year history of ventricular assist device evolution, we with confidence can identify patients who are at imminent risk of cardiac death within 42 to 96 hours.

I think we can do that confidently, and that has been done in the past for the application of ventricular assist systems, so that is the answer to that question. W can give you hemodynamic parameters that have been worked through the NIH and whatnot for 15 years for VADs.

To get on to a second issue--and think it is a very important issue--there are relative differing opinions between cardiac surgical groups about what percent of these patients should receive ventricular assist systems.

The population that I am describing, who are at imminent risk of death, the percentage of that population who would receive a ventricular assist would vary from unit to unit, and we could discuss and argue opinions about that.

What is important is, one, the reality in the United States in 1998 is that only 10 percent of patients or actually about 12 percent received VADs, and that is

indicative of the factors, there are different opinions as to when they should be applied.

This is not an argument against that, simply to say there are clearly patients that most cardiac surgeons would feel would be appropriate for alternative technologies because the risk of VAD would be so high.

DR. MICHLER: I would just like to support that and to go on to allude to identifiable groups of patients for whom a VAD is not suitable, that, as Dr. Conte mentioned, includes size, but there are patients with valvular disease, multiple reoperations for whom insertion of a VAD is technically quite challenging, and then to think of trying to explant that and then to put in another transplant is quite challenging, and also the growing population of patients who require retransplantation for whom there is no suitable VAD.

DR. AUCHINCLOSS: For the purposes of my question, we will now stipulate that such a population even exists.

Do the data warrant such a trial? Give the sponsors and the FDA a sense of how you feel.

The answer is yes, raise your hand.

DR. WOODLE: Hugh, this is not a vote.

DR. AUCHINCLOSS: I wanted to rephrase it, suggest a rephrasing of the question. I would rephrase the question in this manner.

Given the state of the art of alternative practices, the limitations of animal models as they exist today, as we discussed here, and the state of the art as exists for xenotransplantation, what we have heard, is clinical trials such as you have suggested warranted at this point?

That is all I am trying to get at, just as an indication. This is not a vote.

So the answer is yes. Put your hand up.

DR. WALTERS: I would like to subdivide the candidates. I would like to subdivide the candidates into those who could understand the proposal and consent to participate.

DR. SALOMON: We already know from the committee that nobody understands it.

DR. SIEGEL: Hugh, do I take your--your lead-in was given such a population exists, do we mean by that, for example, given a population where we know with a reasonable certainty that they won't be alive in--

DR. AUCHINCLOSS: They will not be alive in three or four days.

DR. WALTERS: And they are capable of--

DR. AUCHINCLOSS: And they are capable of talking to you and making sound, rational decisions, and there is no PERV in the world. What else do you want me to say?

Do the data warrant proceeding with such a trial, please raise your hand if you think that that is true--

MS. MEYERS: Without any further basic research on this.

DR. AUCHINCLOSS: No, there has to be further research.

MS. MEYERS: As of today.

DR. AUCHINCLOSS: They have to be able to tell you that they have done the experiment where they have done the allo after the xeno. We have stipulated that, as well.

DR. WOODLE: I have only seen two or three hands go up.

DR. AUCHINCLOSS: Steve, your hand goes up.

DR. WOODLE: My hand is up.

DR. ONIONS: Mine was.

DR. AUCHINCLOSS: That is not what I expected to see. I had a sense that we would see much more than that.

Give them some idea of why you are unhappy.

MS. MEYERS: I think the companies have said they are not ready.

DR. AUCHINCLOSS: I understand that, Abbey, they have said they are not ready.

DR. SALOMON: To be specific, what swayed me, I believe we are ready to go for clinical trials in some areas, but what I am uncomfortable with right now--and I

would be real interested in Dr. Michler's and Dr. Conte's comment--but now we are only talking about 15 days as the best data I saw median survival with an orthotopic heart transplant.

To be honest with you, that is not good enough for me, and that is why I would not go ahead at this point. I have a lot of problems with bridge transplants in trial design, but that is off the table.

DR. MICKELSON: I agree with that completely. It was the survival data from the animal studies that we see now just don't make a bridge study worth it. You couldn't accomplish anything for a patient with that survival, if that survival time is translated into the human population, I don't see that it is worth anything to do anything like that to that patient population.

I think that there are too many unanswered questions in the preclinical data.

DR. AUCHINCLOSS: Dr. Vanderpool.

DR. VANDERPOOL: My hand is not up because I don't know. This is the first time in these meetings that I have started hearing about these populations of patients and how desperate they may be, how miserable they may be, and how they would be willing for the sake of some future cure, short-term cure, to have a xenotransplant.

Ethics is not worth anything if it is not

predicated on fact and good reason, and we all do that. Dr. Walters and I are certainly not the only ethicists here. Everyone here is an ethicist in that sense. As Robert Michler said to me, ethics is collated common sense.

But in terms of collated common sense, we need to know what those populations of patients are for whom this would be welcome, and I don't know who these people are, and I would say even if we find that population or those populations, we still have to be concerned about the effect of these trials on social response - would this set back xenotransplant science and clinical application because of the desperation of these patients and early failures would get in the news as being doctors taking advantage of patients instead of patients welcoming and pleading for this trial.

I don't know because I still have too many questions unanswered.

DR. AUCHINCLOSS: Can I put that question to the FDA, because I think it is a very important one that is on the minds of a number of us here, and that is the tremendous reluctance to proceed with clinical trials that may not work prematurely doing harm to the field because of the public's perception that we were premature. How do you take that into account as you talk with sponsors about individual trials?

DR. SIEGEL: It's an issue we certainly deal with, with a lot of novel therapies, it's an issue we discuss greatly. For example, with gene therapy, it's well known that well-publicized failures can create an atmosphere in any variety of communities that can make it very hard to proceed with what might well be promising research.

I guess I am not sure exactly how we take that into account. Usually, the sponsor investigators are attuned to that problem as we are, although occasionally we come across some less worry.

Somebody referenced a paper earlier today, the Courage to Fail or something like that, and I guess some people have more of that than others.

I think, though, in talking about that risk, we probably should differentiate amongst risks. There are different types of failures. If you do a bridging xenotransplantation and the patient dies in two weeks, that is one type of failure.

If you do a bridging xenotransplantation and the patient has a lymphoma in three or four weeks or gets bridged and then has some sort of unexpected rejection of a heart that became available a few days later that he might have well received, those are other types of failures--or if they develop some sort of xenosis--there are other types of failures that I think would have very different impacts and

really need to be thought about in different ways.

DR. ONIONS: I should perhaps state why I did put my hand up, because I was in a very small minority. I think there are two reasons. First of all, by definition, the patient population, I was struck by I think coming from the Nextran group, who said that the comparison should be with what is available, not with allotransplantation.

We have, by definition, taken a group where the prospect is just simply death within a few days. So, that is my starting point.

My second point is that for any other procedure, i would certainly want to see much better success with the animal models, but I am also impressed by comments made by several of the groups, that there are limitations to the primate models, both in terms of what we can get from the immunology, and it does strike me that at some point, one has to test whether one can control acute vascular rejection, assuming that HAR is under control, and that this does provide an opportunity in an ethical setting that is appropriate.

That is my view. However, my underlying concern, the same one raised by I think David Sachs, or was it by Harold, and that is that there is concomitant danger with this, and that is, that a string of failures could serious damage the field, and I am concerned about that, but with

that caveat, I think there is some basis perhaps.

DR. VANDERPOOL: The concern for the size certainly is relevant for concern for the biotech companies whose images could obviously be adversely affected by this.

Let me tell you one of my deepest concerns, and that is what I have heard to so far--I think I have heard it--and that is the degree to which we don't have a handle hold on acute vascular rejection.

Now, because we don't the analogy, the historical analogy that Robert Michler gave us earlier doesn't hold. One of the exciting things about the beginning of heart transplants is, sure, Christian Barnard's patient didn't live very long, the first one didn't live long at all, the second one lived a little longer, but then his patients skyrocketed to three years, and so on.

The science for this is not that. The science for this is we have a dead-end, it looks a dead-end street we are driving down. We can't see that open future yet, and that concerns me. If Christian Barnard kept hammering away at heart transplants, and they stayed at 14 to 60 days, what would have happened?

Well, it probably would have really set things back a long time. So, my concerns are shouldn't we have the acute vascular response more--should we know more about that and have it more under control before we would proceed.

DR. HIRSCH: I didn't raise my hand for a lot of the reasons that were raised here. First of all, I am not convinced of the philosophy of the bridge. I think the damage to the field is an important thing to consider, and one thing, Hugh, that you sort of told us to disregard, I think we really have to conclude with the premature data that we have that there is a potential risk of both known and unknown new pathogens being entered into the human arena, and I am not sure it is PERV.

It may be. It may be a new herpes virus, it may be something else. So, I think you can't disregard that. So, the overall potential benefits to me haven't been shown convincingly enough in the animal models to take the risks that we are talking about.

DR. AUCHINCLOSS: Can you just elaborate on one point there? Did you mean by that, that you think that the risks of heart transplantation from the pig, from an infectious point of view, are greater than the cellular transplants that are actually already underway?

DR. HIRSCH: Yes, I would think so.

DR. AUCHINCLOSS: They are. Can you explain why that is?

DR. HIRSCH: Well, it's some of the reasons we talked about yesterday, the size of the organ, the degree of the immunosuppression, and the like.

DR. ALLAN: I would like to add to it, because that is essentially the area that I was considering, too, is you can't separate the infectious disease risks even though you would like to, and say let's just put it out of the equation.

You also have to look at it in terms of bridging, and Dr. Levy really made the point, which is, well, that's not a bridge. It is a bridge. It is just outside the body, but it is still, in my view, it carries the same benefit, but it also carries the same risks, and I would like to see infectious disease data from those patients before--because realistically, a bridge actually may carry greater danger than a destination organ simply because in most cases, unfortunately, destination organs can be terminal, in other words, the likelihood of a xenotransplant organ lasting for more than a few months is going to be very small, whereas, a patient who gets a bridge may survive, and the potential agents can survive along with them.

So, i would like to see some of the data, both from the preclinical studies in the primates, and also some of these ongoing studies in terms of what is going on with the PERVs at least, you know, before we jump into some of these other major areas. As Marty pointed out, we are not sure of the benefits.

DR. MICKELSON: I just had a question. I didn't

get a sense. I stated my reasons for not being comfortable with the bridging studies, but also one of the questions I would have is I didn't really hear or get an idea of how long a bridge would have to last to assist patients who fell into this small category, who are essentially end-stage with multiple systemic damage.

DR. AUCHINCLOSS: I would have said four weeks minimum to get to that point where you have corrected end-organ damage. Is that a fair statement, Robert?

DR. MICHLER: Two to four weeks.

DR. MICKELSON: What would be their statistical likelihood them of receiving an allotransplantation after that, so that the bridge has to cover more than recovery to full function.

DR. AUCHINCLOSS: And they have to give a period of waiting.

DR. MICKELSON: Yes. To me, something that has to function as a bridge has to also have a much longer term role than, say, four weeks or eight weeks.

DR. AUCHINCLOSS: I think that is an important point, that a bridge needs to have several months--

DR. MICKELSON: At a minimum, and I think that was my major concern.

DR. AUCHINCLOSS: As soon as we get around the table with some hands that are up, I am going to throw open,

well, now we can talk about clinical trial stuff.

DR. CONTE: I think it is important to clarify that a cardiac surgeon uses a bridge for two, and only two, reasons. One is to keep the patient alive, and perhaps even more importantly, it is to make him a better transplant candidate.

Inherent in that is improved hemodynamics, so that he has better perfusion to end organs, nutritionally, he is improved, the patient can get up, and his somatic musculature is going to improve, and he becomes an overall better transplant candidate.

We haven't seen enough evidence from the preclinical data that hemodynamically, we are going to have a significant improvement although that is probably going to be true, but more importantly, we haven't seen anything that shows that we are going to perhaps make these candidates better.

We are going to put them at much higher risk of infection. They are going to be receiving catabolic medications, which is going to make their overall body condition worsen, so I think the main reason I would vote no on it at this point in time is because I see no evidence that we are going to make them better transplant candidates yet.

DR. AUCHINCLOSS: What I think I am hearing is

that we have made the transition from the preclinical to the clinical studies, and that we have moved into the conversation in particular about the value of bridge transplantation and whether that is where xenotransplantation should start.

So, that topic is now open and on the table because I can't keep it from being there, and it is where we should be at any point in any case. So, we have now moved to the second half of the questions. Clinical studies. Which trials look appropriate to you for additional clinical trials? Really, one of the key items, is a bridge the appropriate way to start given that everybody here has said we weren't close apparently to data that was sufficient to warrant a definitive trial.

Abbey, I know you had your hand up.

MS. MEYERS: First of all, I want to refer to something that Dr. Mickelson said. I think starting clinical trials at this point, even if there wasn't any viruses involved, would be using people as animals, and that is a problem.

Secondly, one of the unintended consequences of this, because we certainly saw it in gene therapy trials, is that it raised false hopes. People felt that even though it was a Phase I and the informed consent document said that it really wasn't going to help them, they all felt this was

their last chance to be cured.

So, in something like this especially a bridge, people are going to feel it automatically confers a place on the waiting list, and if they are not going to get that heart or whatever organ they are waiting for, they are going to feel cheated, and the family is going to be angry.

The other problem I have which touches on this whole thing--nobody has brought this up--is that all of these protocols, when they finally are ready to be approved, are going to go in front of IRBs who know nothing at all about this technology, and they are going to be expected to approve clinical trials on a technology that is absolutely new. There is no history for them to go on, there is nothing. There is no precedent.

I worry a lot about that. I think that it needs a regulatory authority outside of the IRB system because until we know that it is not going to be dangerous to society, it should be so closely monitored.

MR. BENEDI: I would just like to make a comment. Before I make the comment, I wanted to say that obviously, 25 years ago, 30 years ago, Bill and I wouldn't be sitting here, so there were things that didn't work then, but do work now, and the expectation of folks to live normal, long life with a transplant is real to a lot of people out there.

My question on these animal studies and

translating them over to human studies, these baboons were healthy, and they could only live 30 to 60 days. We are taking a subgroup of a waiting list of patients who are the sickest patients, and even a subgroup of that subgroup, that normally might even die with a regular transplant because they are so sick, so the data that we would get from that small group of folks that are critically ill, that may not even survive an allotransplant and getting a xenotransplant, are we really looking at data that is going to be helpful at the expense of giving hope and fulfilling these people's dreams to live a little longer? I am not sure. It is an ethical question.

DR. AUCHINCLOSS: How does the FDA deal with the problem, the ethical problem associated with bridging under the best of circumstances, and I am not sure the best of circumstances are likely to happen, but under the best of circumstances, bridging makes an individual patient do better. They get in better shape to finally get their allotransplant, and they survive better in their allotransplant.

I don't think that is mostly going to happen, and I think one could make a very strong case statistically that from society as a whole, bridging with xenotransplantation would diminish the outcome of organ transplantation across the board. Where do you put that in your equation when you

look at an individual trial and an individual patient?

DR. SIEGEL: I think that is part of what we are asking. We certainly don't have vast experience addressing that sort of question. I am not sure we have a legal or regulatory framework that would permit saying a therapy couldn't be done because it would deprive organs from patients who are not even in the trial from the potential to get organs.

I mean the scientific community may make decisions like that and may weigh them. We probably wouldn't have the legal or regulatory framework to say that.

DR. AUCHINCLOSS: The problem for us is that there is no question you would love to start xenotransplantation with bridging because you only have to go a short distance and we can learn a great deal of stuff, and we can help an individual patient, but from the point of view of presenting our effort to society, it becomes a major problem because it looks as if we are doing it to get a less good outcome for the population at large.

David Cooper.

DR. COOPER: There must be considerable information on how you plan a bridging trial because for the LVADs, that is where they started out. So, this whole business must have been gone through before, and LVADs, remember at that time were in a pretty primitive state. So,

how you deal with it from both an ethical and FDA point of view must have been sorted out sometime ago.

DR. AUCHINCLOSS: Do you want to make a comment, Robert?

DR. MICHLER: I would, and it sort of gets to two points. One, Antonio made a very eloquent statement with respect to the patient issue, and that is very important because we must caution ourselves against implanting a novel, innovative device into a patient who is already basically dead, and on one can survive that.

So, if we set the bar of entry into these trials too low, meaning that death is so imminent and end-organ dysfunction has occurred, we will set ourselves up for potential disaster.

Therein lies my point to Dr. Cooper's comment with respect to LVADs. I can recall when we first started implanting these, there was such concern on the part of our own medical community, ourselves included, that the therapy might not work, that we would reserved it for patients who were so imminently in danger of death, that I can recall many times going to the operating room doing CPR on a patient who we then had to open the chest on and put device in.

That is what we want to get away from. We just can't be setting up trials, and we made the mistake I think

in the early work with left ventricular assist device, that we set the standard of illness to a point where these patients had a low likelihood of success.

DR. AUCHINCLOSS: Certainly, in the population that we tried to define for the FDA, of people would be candidates for bridge xenotransplantation would fall under your category of worst risk individuals. We had them not likely to survive more than 72 hours, it seems to me.

DR. SIEGEL: It may make more sense, and maybe it's right way to go, to pick a population with better anticipated outcomes. I guess from the comments of the committee that if you were including patients who had a reasonable chance of a month or two of survival on the waiting list with out a xenotransplant, you would have a higher standard for what you would want to be able to anticipate your reasonable chance of success with the xenotransplant is. It is a tradeoff that is very difficult.

DR. AUCHINCLOSS: I meant to mention to everybody here, but to the FDA in addition, that I had passed out a position paper that was approved by the Joint Council of the American Society of Transplantation and the American Society of Transplant Surgeons, which is their effort to come up with a consensus statement on the initiation of clinical trials in xenotransplantation.

It has been approved by the councils of both

societies and of the Joint Council, but I would still say it is a work in progress as we try to essentially go through the same debate that has been taking place here today, but that is just one more statement for you to look at of what the transplant community thinks on this subject.

Dr. Walters.

DR. WALTERS: I am not at all sure about this idea, but I will throw it out for discussion. I am wondering if for the initial clinical trial of bridging, it would be possible to bring the clinical research effort into contact with the national system for allocating organs.

In other words, I wonder whether it would be possible to make a bargain with the participants in the clinical trial that if they are willing to participate in a bridging trial, they will go to the top of the list as candidates to receive organs when they become available.

DR. ONIONS: Wouldn't that be regarded as being highly unacceptable? You are then almost bribing people to undertake a form of therapy that is highly experimental. I personally would not wish to be associated with that.

MR. LAWRENCE: I think that would entail a number of problems that we would have to discuss in an entire separate forum.

DR. SACHS: I would have to say that you can look at the cup as half full or half empty. I think that the

progress has been made over the past few years is enormous. The data that we are looking at today is so much better than the data two years ago.

What you are really hearing is it is just not quite good enough, we just ought to work a little harder, because instead of 11 days, if we showed Marty Hirsch survivals of three or four months, I think he would say, well, gee, the benefit-risk ratio may be there.

Isn't that what you are saying, Marty? You are not saying that there is really more risk in one or the other, you are saying that you haven't been convinced that there is any benefit.

DR. HIRSCH: Exactly.

DR. SACHS: So, I think that is really what you are hearing.

DR. AUCHINCLOSS: I agree with you entirely, David, and I agree with the half full, half empty kind of look at this, but I would still phrase it differently.

First of all, I would say, oh, the data that I am seeing today are exactly, precisely the same as the data we saw four years ago in Boston. The curves are superimposable.

DR. SACHS: We had no animals surviving. We never saw an orthotopic heart at that time.

DR. AUCHINCLOSS: I will show it to you in just as

second. Essentially identical survival as four years ago when the [H.] pig was first reported at the Boston Xeno Congress.

DR. SACHS: There was no orthotopic heart until just this past year.

DR. AUCHINCLOSS: The orthotopic heart is hardly exciting.

DR. SACHS: It's 39 days, and it's the only one that is relevant, Hugh.

DR. AUCHINCLOSS: Okay. I was talking about survival of the kidneys.

DR. SACHS: No, I am talking about what we are going to be doing, which is heart transplant.

DR. COZZI: Sorry to interrupt, if I can. I was in Boston, as you were, in 1995, and these data did not exist, neither the orthotopic heart, nor the kidney. These data were not generated yet.

DR. AUCHINCLOSS: You are right, heterotopic heart.

DR. COZZI: It was a heterotopic heart with the side effects that you and I know very well.

Now, if I can also to make a small comment, because for me it is important when I leave this room to understand what exactly is the preference of this committee.

I would like to make something very precise. I

thought I had said this during my presentation. When the animal went out for 20 or for 30 days, there were--I am talking about orthotopic hearts--so when these animals were alive, these were absolutely healthy animals, eating, drinking, and jumping around, and we had a film that can demonstrate this very easily.

These animals are sustained and not just kept alive, but they do a normal live. So, as far as I am concerned, it is very important for me to understand what is the median survival of a group of this kind which you would feel necessary to have and to produce here to suggest that maybe we can do as bad--as well as we can do with an LVAD, for instance.

DR. SACHS: Hugh, it should certainly be at least as long as Dr. Michler wants to leave the heart in before he would re-transplant it.

DR. AUCHINCLOSS: So, what we heard over here was that you need two months. Is that a fair number?

DR. MICHLER: Just for the sake of argument--what would people say to 90 percent/60-day survival, and 50 percent/90-day survival?

DR. SACHS: Great. I would be perfectly happy with that.

DR. AUCHINCLOSS: That was for a bridge. The transcript doesn't record probably the murmurs of yes, I can

live with that, but I got a lot of that around here. Do people want to say, no, no, that doesn't make any sense?

DR. COZZI: Is it what was requested by--I mean when you did start the LVAD experiments, I mean I understand, first of all, I mean were there preclinical data, first of all? And, second, I mean is this the expectation that you were hoping to have, and you still hope to have when you want to bridge a patient for an allo?

DR. MICHLER: When we started with LVADs, the answer was we had isolated patients, so we had some confidence that this therapy could provide a strategy for bridging a patient.

Now, with the xenograft, I think we have to follow a very similar line and be able to give clinicians the confidence that not only with the graft survive a defined period of time in good likelihood, but secondly, that there is a way of diagnosing acute vascular rejection or at least treating it.

I think the diagnostic aspect is difficult in the animal model for the reasons that everyone has already mentioned, but at least some way of knowing that when you see it, you will be able to treat it, and hopefully, allow the human to survive.

DR. SACHS: I have seen that video, and I have to confirm entirely that it is the most exciting proof of

principle, and it is the same feeling I had when I saw the first primate who was surviving on a pig kidney with the normal creatinine and normal blood chemistries.

It proves the principle that a primate can survive on the physiologic function of the pig organ. So, again, I would return to the fact that I think this field is progressing reasonably. I would like to see it faster, as you would, Hugh.

It is progressing reasonably. I don't want to see a disaster set of results that sets it back. I do want to see it progress with full steam ahead, and I think it has enormous potential, and I think the data that Dr. Cozzi has provided with an orthotopic heart with a monkey up and eating and -- I think it was even linking, wasn't it? It was very, very exciting.

DR. WOODLE: I would just ask Dr. Michler, these criteria that you have for survival, would they apply to the patient population who are not candidates for LVAD?

DR. MICHLER: You mean as a destination?

DR. WOODLE: If you have a patient that is not a candidate for an LVAD, would you still want those types of survivals in order to conduct a trial in those patients?

DR. MICHLER: Well, in that situation, I am assuming that the patient is not a candidate for--is a candidate for allotransplantation?

DR. WOODLE: Is not a candidate for allotransplantation, is not a candidate for LVAD, what sort of survival rates would you want in that patient?

DR. AUCHINCLOSS: Are not a candidate for allo?

DR. WOODLE: I am sorry, they are a candidate for allo, but they aren't a candidate for an LVAD because of, for example, size.

DR. MICHLER: Right, so they are a bridge. So, that would be the same. If you change it around, and they are not a candidate for LVAD and they are not a candidate for allo, then, that is a difficult question, but I would feel more comfortable with that knowledge base simply because I don't think we can expect that the animal model in any way is going to parallel the human condition in the sense that we can expect 90 percent/one-year survival from this animal model. We are just not going to get that.

So, at some point in time, we have to make the leap and allow ourselves the confidence of reasonable expectation of survival and say that, yes, we can use it as a destination, and we will try and manage acute vascular rejection, but in that condition, I really want to be sure I know how to treat rejection.

DR. WOODLE: With these types of survivals, if the patient was a candidate for an LVAD, would you consider him a candidate for this trial?

DR. MICHLER: I don't quite understand.

DR. WOODLE: We have heard numbers of, say, 25 to 30 percent of patients who receive an LVAD will probably die.

DR. MICHLER: Right.

DR. WOODLE: Not come to transplant. And in these types of numbers, about 50 percent of those would have the xeno would not come to a transplant.

So, what you are asking is really that these grafts almost be equivalent to an LVAD in terms of their ability to bridge. Is that what I am hearing you say?

DR. MICHLER: I think that is a reasonable starting point, absolutely. I don't think we can expect this device to do better than an LVAD, and I certainly think that we have to have reasonable confidence that it can do as well.

DR. WOODLE: My point, then, if you are expecting the bridge, if you are expecting the xeno to provide a bridge that is almost equivalent to an LVAD, are you still going to require a patient who is not a candidate for an LVAD, to have the same criteria, the same expectation?

DR. MICHLER: Who is not a candidate for an LVAD to have--

DR. WOODLE: In other words, that patient has no other option, so are you going to require that the xeno

still get the results as you would have for an LVAD, when an LVAD wouldn't--

DR. MICHLER: I think so, because I don't think the bar is so high in the experimental model, 50 percent/two-month survival--I am sorry--90 percent/two-month survival, and 50 percent/three-month survival is not a tremendously high standard in an animal model to implant in a human condition, so if we go along with that standard, I think it is reasonable to use that as a destination therapy.

I feel a little I come on the subcommittee before Congress here. This is kind of fun.

DR. AUCHINCLOSS: I think I got your point there, Steve, that he is putting a high standard relative to the established level of care.

In your clinical questions, there are other forms of transplantation, most of which would involve definitive xenotransplantation, and one of which would involved definitive xenotransplantation in renal transplant candidates who are in no way going to get an allotransplant, but would like to.

Is there any enthusiasm here for that group of patients? I guess we have to start with the assumption that the answer is no with currently available data, so really the question would become how much better does the data need to become in that case to warrant the initiation of a

clinical trial?

DR. SALOMON: Again, I don't mind being the minority position here, but I don't agree with the chairman again. I don't believe that the data for the kidney, but based on my concern that I have already articulated and won't do it again, just my concern that the animal models may have been pushed past the limit.

However, I think that is needs to be tested and what I would propose is a very limited series of kidney transplants in a selected group of patients. I won't get into the details of that, I mean that should be a point of discussion, but 5 to 10 kidney transplants, no one has to die, it can be done on Tuesday, and it can be taken out on Thursday if they don't work, and I think if properly designed, could (a) validate these animal models to a point where this discussion then would have some assurety that I think is really required by this field at this point; and second, you might be surprised by the positive results.

DR. AUCHINCLOSS: Steve, do you want to comment on that?

DR. WOODLE: I would think that if you carefully select the patients, you are going to have patients with survival of days to weeks, and if you have in an animal model, survival already equivalent to that, then, I think you offer it out under carefully designed clinical trial,

and it's the patient's decision.

DR. AUCHINCLOSS: And I think that would be the worst thing for this field that I can imagine, to put a kidney transplant in to somebody with the expectation that it will last about 30 days with no alternative therapy.

DR. WOODLE: Why, Hugh, why?

DR. AUCHINCLOSS: Because that's not therapy for somebody, that's just a human experiment.

DR. WOODLE: What is it going to be when you have 60 or 90 days?

DR. AUCHINCLOSS: I wouldn't take 60 or 90 days.

DR. WOODLE: What would you take?

DR. AUCHINCLOSS: A year, six months in the animals.

DR. WOODLE: If you knew that you were probably going to die within six weeks, if you were a patient, and you had no alternative, you had a terrible life, you knew you were going to die within a few weeks and be miserable, if somebody offered you three months, would you take that?

Try to put yourself in that position. You don't know how you would feel when you are in that position.

DR. NOGUCHI: But the consideration--and I think we heard this before for the heart bridging, which I think is a very useful distinction, is it is very true that if you take the sickest patients, you are very often going to get

information which is only that the patient died after a certain number of days.

I think we can take some history from the history of gene therapy. There, actually, the first potential gene transfer for therapeutic purpose was for adenosine deaminase, at which point there was no treatment available, and the almost assured outcome of any intervention would have been either death or perhaps, in a particular case, going on to a transplantation.

There was an FDA approval of a drug which actually gave a safety net which helped to make sure that the first experiment that was done was not a disaster just from a point of view of just what we are saying here, a patient is going to die, and you give them something, that is not really trying to establish clinical benefit.

That is just sort of you want to do it in man for the first time, and that perhaps is not really what we are talking about, especially given the potential for the thing that we don't want to talk about, but which is prevent other viruses and other infectious diseases.

Given that aspect, I think we owe it to the community to really wrestle with these hard decisions. Maybe we should go for the first time just to throw it out, not as any position, but just as something to think about, maybe for the first heart bridging, you may want to consider

going into someone who might be eligible for LVAD.

Obviously, you need a lot cleaner preclinical data, but that would also force the preclinical data to be generated.

DR. AUCHINCLOSS: David.

DR. COOPER: I would just like to come back to the point that Dan raised several times about pushing the model to the limit. This is an extremely difficult problem to overcome, and the model is difficult.

You have to think about getting rid of antibodies and complement and all this stuff and the other, and nobody would question that, but it reflects as much on the therapy that we are trying to do, which is not quite adequate, as it does on the model.

For example, if you look at the costimulatory blockade work that has been done in primates, monkey to monkey, renal transplants, they are getting consistent survival now out six months or a year with a single drug, almost getting a degree of tolerance of a degree of hyper-responsiveness.

Nobody complains that that model is too difficult. It is because the therapy is so easy. It is a major breakthrough in therapy. If we had a major breakthrough in therapy, we would find the model would get a lot easier. So, the model is difficult because we are struggling to over

come the immunological problems which are inherent because our therapy is not yet quite good enough, just as the Imutran group have clearly shown they can get over hyperacute rejection, so that is no longer a problem, because they have a very great technology that overcomes it, but there is still a problem with the subsequent rejection episodes.

If we had an equally good therapy to overcome those, they would become easy, and the model would become easy.

DR. WOODLE: I would submit that the difference between the clinical setting, again, the difference between the clinical setting and the animal model, there is probably at least five or six therapies for an acute rejection later on that are currently available clinically, that are probably not going to be available in your animal model for some years to come - OKT3, high dose to chrome, rifamycin, MMF, IVIG.

DR. AUCHINCLOSS: Members of the FDA, I have been looking over your list of remaining questions in the Clinical Section, and in ways we have touched on most of them, but we haven't done them specifically in some cases.

Have you heard what you wanted to hear in this discussion or should I take this in some other areas?

DR. WEISS: One briefly that maybe can be

addressed very briefly is the question about heterotopic. I think Dr. Michler has said these are very small numbers that have been done and a lot of technical problems.

Is that something that should be on the table for these types of xenotransplants?

DR. AUCHINCLOSS: Sorry, I didn't mean to actually do that one. Now, you basically told us that this a mighty rare procedure and don't go there. That is sort of what I heard you say.

DR. MICHLER: I may not have been quite that strong about it, Hugh, but I think that if you are going to include the heterotopic model, which I think there are justifiable reasons why you might wish to do that, one needs to be sure that you have an experienced team that is willing to undertake that operation.

I think it would be sad to have the field set back simply for technical reasons in doing an operation. I think it is hard for the FDA to regulate that, and I think it is really an issue of the teams that are willing to undertake this procedure have some degree of confidence and experience in it, because doing a heterotopic transplant in an animal model is an entirely different operation than doing it in a human. The connections are different. So, there is no parallel there, very little parallel there.

DR. AUCHINCLOSS: But it looked to me also as if

selecting the group of patients who would be candidates for a heterotopic transplant, not candidates for an orthotopic allotransplant, or not candidates for a heterotopic allotransplant, where are these patients? How many are there? Are there any? You are down to 12 who get the procedure even from an alloheart.

DR. MICHLER: I would think that the group that proposed the heterotopic transplant should really address that question because I would tend to put that heart in the orthotopic position.

DR. CONTE: One comment on heterotopic transplantation. At least in cardiac surgery, we think of the model where the heterotopic heart is put in the chest. As a Russian surgeon who was one of the forefathers of heart transplantation showed, there are many different heterotopic models of heart transplantation that can be placed in the abdomen and in the pelvis, which we don't consider when we generally think of heterotopic heart transplantation.

That is something that could be considered and might, in fact, be an easier model than heterotopic transplant in the chest. Some of Demakoff's work, which most of us aren't that familiar with unless you want to read some very arcane literature, however, that is something that should be thrown out there because heterotopic transplantation is not commonly done, but in a situation, as

part of a clinical trial in someone who is not a transplant candidate for an orthotopic heart transplant, for example, a patient who has an elevated pulmonary vascular resistance, who would not be a candidate for an orthotopic transplant, could be a candidate for a heterotopic transplant in the pelvis. I would just throw that out there.

DR. MICHLER: But it is not an often perform operation for good reason.

DR. CONTE: Yes.

DR. AUCHINCLOSS: Dr. Walters.

DR. WALTERS: For the bridging transplants, we had some numbers proposed, the kind of data that one would want to see in the preclinical setting, are there numbers that we could proposed for renal transplants, as well, that one would like to see in the work with animals?

DR. AUCHINCLOSS: I said six to 12 months is what I think I was whispering over here.

DR. SACHS: You would probably like to see the survivals in the non-human primate equivalent to that for allos in non-human primates.

DR. AUCHINCLOSS: Abbey.

MS. MEYERS: Since no one is answering Leroy's question, is it time to talk about informed consent? Can I bring it up? I think that there are things that we haven't even touched on, and I am coming back to the real world