distinction in my mind. Given the fact that the device we're discussing today actually uses the blood as its lubricant, the anticoagulation, my understanding from physicians who have been dealing with this implant, it's a very --

You're walking a tightrope between keeping the blood thin enough to actually lubricate this device, all the while you need to have hemostasis from your surgical procedure.

So in the previous generation, you do not have this sort of mandatory anticoagulation. So you're able -- that would be part of the reason for making the decision?

DR. PAGANI: No, not all first generation or pulsatile pumps. Some of the first generation or pulsatile pumps do require anticoagulation.

The Heartmate XVE is unique and it's one of the properties. It doesn't require anticoagulation with heparin or

warfarin long term.

So that's one of the unique advantages of that particular device. But there are other devices made by other and by Thoratec that are pulsatile and do require anticoagulation in the early postoperative period.

CHAIRMAN LASKEY: Dr. Kelly?

DR. KELLY: Hi. Just getting back for a second to the question of gender and bleeding. I thought I understood Dr. Pina's data to show that there was a higher risk of reoperation for bleeding in women after the first 30 days. Is that --

DR. PAGANI: After the first, but not in the perioperative period.

DR. KELLY: Okay, thank you.

DR. PAGANI: Those causes were most likely other causes, other than the operation itself.

CHAIRMAN LASKEY: Why the triple therapy? Why the aspirin, dipyridamole and

coumadin?

DR. PAGANI: I think our initial concern was anti-platelet therapy would be an important component of the anticoagulation strategy. There is a fair amount of aspirin resistance in the perioperative period following cardiac surgical procedures.

So that was the rationale for double anti-platelet therapy.

CHAIRMAN LASKEY: Warren?

DR. EDMUNDS: Yes, but I don't think those are very good choices. Rather than tie up people in the room getting into the details of anticoagulation protocols, all I'm suggesting is that this is something that needs to be standardized, really rigorously looked at, and aspirin resistance, 30 percent of patients maybe.

But aspirin doesn't completely inhibit the platelet anyway. So a lot of confusion here.

CHAIRMAN LASKEY: But plenty of

fuel for a post-approval study recommendation.

DR. PAGANI: Okay, thank you.

MR. MIDDLEBROOK: Dr. Lindenfeld, I believe that you had a few questions regarding our neurocognitive evaluation, and why the test's baseline was at 30 days after device implant. I'd like to invite Dr. Ralph Petrucci, who is our neurocognitive expert, to come up and address that question.

DR. PETRUCCI: Dr. Laskey, panel members, Ralph Petrucci from Philadelphia, Drexel University College of Medicine. In the way of disclosures, first Thoratec neuropsychological consultant. Secondly, the FDA neurodevice panel consultant. Thank you.

We anticipated some design problems and questions with regard to starting folks at 30 days out with an initial cognitive evaluation. I might back up and just give you a little bit more of a history, and why we decided to do it at 30 days starting, and then preceding on a monthly basis after that.

Some of our earlier research, which took some 18 years for me to accumulate, actually had an opportunity to compare those patients that were being considered for heart transplant with those patients that were immediately being considered for LVAD implant, and a variety of LVADs, not just the Heartmate.

In comparing the two groups, we found that obviously the prospective heart transplant patients were sicker, and sicker than obviously other end stage heart failure patients.

However, when we compared the LVAD patients with the end stage heart failure patients that were going into prospective heart transplant, we found that they were even sicker and sicker for a number of reasons.

They were fragile, metabolically more unstable, and they were on usually double inotropes. Given that, we decided not to do any preoperative testing for the LVAD

patients, and then just consider them at a 30-day interval, and then three months, six months, and yearly after that.

It's true that they are heart patients, yes. They're different than CABG patients and they're different than heart transplant, prospective heart transplant patients. So the idea was to give everybody an opportunity to get to the gate together at 30 days, and get a good start.

Then serially test people with the same alternate versions of the measures, giving them all an equal opportunity to learn. The good news is that over time, the patients learned.

The not so good news is that it tweaks methodology and design. There's always a question with regard to why we would do this without having a pre-implant post-implant measure.

It makes it difficult from a neurocognitive perspective to administer these

tests at different institutions. You can appreciate how difficult it is to train 11 centers, and to ask the, in this case the nurse practitioners, to implement these neurocognitive tests given their other duties and responsibilities.

Given that, the nurse practitioners were able to reliably gather information under very difficult circumstances, with sometimes an uncooperative patient.

As a consequence of that, we have patients who did not want to complete the neurocognitive examination; folks that did not want to complete the quality of life scale at certain intervals; and in addition, obviously there was transplant end death as a consideration.

So there are multiple factors that contribute to this particular design. They're not easy to answer. The psychometrics are very difficult to implement. It's an annoyance, at best, to the surgeons, an

annoyance at best to the attending cardiologists, and certainly an annoyance with the patients.

DR. LINDENFELD: Let me just clarify then, and that's helpful. But the problem I have is we don't know if these patients actually were improving, or if they were just improving from the surgery.

Then you add on top of that, as you said, the learning effects. I know you said it was good, but it's not good in a neurocognitive test because it alters how you interpret the results.

You don't want the patients to learn from the last one and just do better because they learned it, but they're not getting any smarter.

So I mean we can't really say if these patients' neurocognitive function improved, separate from the fact that they clearly, a group of them went down after the surgery and we would expect them to improve

anyway. Is that a fair -

DR. PETRUCCI: It's fair to a degree, in that each patient was compared with him or herself number one, but primarily there was a between-group comparison. So it offers an opportunity for each patient to take a look at his or her own track record, and to reflect on their level of improvement over time.

Most of these patients, as I have learned, have difficulty recalling their surgeon's name at 30 days after transplant, yet alone the cognitive test.

I think that it's a valid issue, trying to recall information or the idea that information may be recalled following the initial psychometric evaluation. That's always a risk.

However, my experience with a larger LVAD population over time suggests that they continue to have memory problems, and they're not likely to remember much about the serial cognitive evaluations.

With respect to your question about time, which you brought up earlier, time's an important factor. It also is a reflection of their health, the dimensions of their health. So obviously as they improve their quality of life, their stamina and their conditioning improves, their time and performance improves.

We found this in earlier research and also with heart transplant evaluations pre- and post-, that over a period of time these patients tend to show better performance, improved strength and more adequate response.

DR. LINDENFELD: But you would agree that there's a clear learning response in these that affects --

DR. PETRUCCI: Yes, there's always that.

DR. LINDENFELD: Maybe as long as you're there, you can tell us how many of the baseline studies at 30 days were done on inpatients? How many of the patients were

inpatients at that time?

DR. PETRUCCI: I don't have that number.

DR. LINDENFELD: Again, these are difficult tests to do, and I appreciate your explanations and expertise. But I think one of the problems with some of these tests, as I said earlier, are time tests, and that depends on your concentration and your ability to function, not just on your cognitive function.

We would all agree that if the patients weren't ready to go home, they were probably still pretty physically impaired. So again, I still think none of these neurocognitive tests, the data that you've shown us, gives me any confidence that the patients actually got any better than just recovering from the surgery itself to some extent.

CHAIRMAN LASKEY: The points are well-taken, and I think we're just going back and forth. But thank you. Were there any

unanswered -- did you have another point you wanted to make?

DR. PETRUCCI: I may want to address Dr. Swain's comment about Trailmaking B as being an integral part of the cognitive evaluation. Trailmaking B is an interesting subtest and I won't belabor the point. It's been around a long time, and it's probably one of the most sensitive cognitive, single cognitive tests to be utilized.

It is complex. It requires visual motor, visual-spatial ability; it requires time, and it requires a certain component of executive and abstract functioning.

I think by itself, it's an adequate measure from an INTERMACS perspective. I don't think it should be the only measure. I think there should be more measures. But it is a powerful single little tool by itself.

We've learned over time that the more tools that we administer psychometrically in more institutions, by different people, the

more likely we are to respond to occur, for unreliability to occur.

DR. LINDENFELD: Is there a learning function in the Trailmaking B?

DR. PETRUCCI: There is.

DR. LINDENFELD: So this is going to be repeated on multiple occasions. So each occasion has a learning function?

DR. PETRUCCI: It does.

DR. LINDENFELD: So it's not just from one to two but two to three and three to four. So the expectation is that it would improve in any group of people, all of us sitting here would improve a month from now if we took it today; is that correct?

DR. PETRUCCI: Hopefully, yes.

(Laughter.)

CHAIRMAN LASKEY: Thank you.

DR. LINDENFELD: After this, I may not.

CHAIRMAN LASKEY: Thank you. Okay. Let me put this to rest, but you can --

DR. EDMUNDS: Dr. Petrucci, as you work out the post-market protocol, are you comfortable with having nurses do these tests? I'm told that it's usually better to do it by a neurologist. Can you create a control group? Aging has been shown to be not improved cognitive function. Let's just put it that way for diplomacy.

DR. PETRUCCI: Preferably, I would like to have neuropsychologists at each institution perform the test. This is not the real world, however. Out of the sites that we surveyed and worked with, two sites had neuropsychologists. One site had speech pathologists.

Those three sites were extremely accurate and required very little follow-up. They did very well by themselves. However, the remaining sites required continued tutelage.

So I would suggest that in the ideal world, we'd like a group of well-trained

cognitive neuropsychologists to be doing that.

DR. EDMUNDS: If I could interrupt. I don't think you need to solve the problem here now. I just was trying to point it out, that I think it ought to be developed in your post-marketing protocol.

DR. PETRUCCI: Okay, thank you.

CHAIRMAN LASKEY: Thank you.

MR. MIDDLEBROOK: I would just like to invite Les Miller back up to the podium for another brief comment.

DR. MILLER: I just wanted to respond to Dr. Page's question. I think the inference was that we'll have both on the market and they'll kind of keep pace together.

If it's a patient preference, it will be an overwhelming transition to this type of continuous flow pump. On a side by side comparison of size, and this is noiseless operation versus the sound of the valves clicking and the gas exchange.

So I think you need to get the

sense that if this were to be approved, it's the first of a series of this type of design pumps, which I think will become state of the art in the field in a very short period of time.

DR. LINDENFELD: Not to mention durability.

DR. MILLER: To be sure.

DR. EDMUNDS: Thank you, and that was indeed my question, and perhaps if Dr. Lindenfeld could estimate, for me at least, what she thinks might be the penetration of this technology versus the previous in your own practice, if this were available.

DR. LINDENFELD: I think the majority of the patients will very quickly switch to this technology, assuming that bleeding problems, we don't see some of these bleeding problems.

DR. EDMUNDS: So might it be that the alternate technology might be reserved for cases where bleeding was an issue,

anticoagulation compliance might be a problem?

DR. LINDENFELD: Long term anticoagulation, yes.

DR. EDMUNDS: Thank you.

MR. MIDDLEBROOK: I'd like to ask Dr. Pagani to come back up and maybe add some more comments to Hank's question.

DR. PAGANI: The one thing that I would want to say is that is -- the problem with bleeding is not unique to this device, and the problem with uniformity is that we really don't know.

There's a lot of experts in the field. We really don't know what measures are important to monitor post-operatively or interoperatively.

There have been a lot of, as you know, using utilization of TEG to be helpful and there's a lot of disagreement about the utility of TEG to help make interoperative decisions.

So there's not agreement on a

methodology by which we should monitor bleeding, or there's not uniformity on the methodology by which we can solve the bleeding problem. So there's some of the difficulties in trying to incorporate that into a post-market follow-up study.

DR. EDMUNDS: Well that's exactly what I'm trying to point out.

DR. PAGANI: What I'm saying is, I don't think anybody has the correct answers, in terms of --

DR. EDMUNDS: I disagree with that. I don't know anyone has an optimal answer, but a lot of people have a lot better answer than you have now. That's the point I'm trying to make.

You don't know about plasma tissue factors circulating; you don't know about F1.2 or D-dimer, getting these measurements. You don't' know the platelet inhibitor. You don't know about the HemoSense Test of Coumadin Anticoagulation, and TEG has never been

validated.

DR. PAGANI: Correct.

DR. EDMUNDS: Yet the company is making millions over a device that's useless.

DR. PAGANI: Correct.

CHAIRMAN LASKEY: Thank you, Hank. Dr. Kato?

DR. KATO: You know, one other problem with some of the data, and again this is going to be a center thing, a surgeon thing, a patient thing, but you know, you look at the volume mortality relationship by center, and it's an absolute scattergram.

I mean the results are all over the place. You've got high volume places doing great work; you have high volume places doing, you know, with low success rates. You have low volume doing high success rates, you know, and I was talking to some of the other surgeons about this.

They said well, you know, it's all patient selection. It's maybe something we're

doing in the operating room.

But one of the things about this new technology, in which I think I'm actually very optimistic about this technology, is that its widespread use without more uniformity, as Dr. Edmunds is talking about, is going to create, you know, even worse scatter and probably worse outcomes, unless there is some consensus and standardization within the group of people that you're going to promote this device with, at least initially, as the technology and experience spreads out.

DR. PAGANI: I certainly agree with all these comments. I think they're very valid comments. But I think also that's part of what the purpose of INTERMACS is, that we learn some of these things and do it on a global fashion.

I don't think we can incorporate a lot of these ideas necessarily into one little post-market surveillance study. I think these are major issues that have to be attacked

globally with many centers, and looking at multiple devices.

So I don't think we can answer, we can solve the question of bleeding with a post-market surveillance study. I think it's totally impossible. I think it's a broader problem that requires more data than what can be gathered in 70 or 80 patients.

That's why I think the INTERMACS would be very important, because it looks at this problem for multiple centers and for more devices.

DR. KATO: And I'm sorry, one other question, since you bring up INTERMACS again. How is that data going to be disseminated? Is that -- how transparent is this organization?

DR. PAGANI: This organization is public, so the data is publicly-available. So you can actually -- my position in INTERMACS is I'm the chair of the Data Access and Analysis Committee.

So that we are promoting access to the public, not raw data, but suggesting scientific questions to be answered. We would analyze the data and make it very public.

DR. KATO: So much like Massachusetts, New York, some of these full reporting states for bypass surgery, the anticipation is you're going to be publishing this data on an annual basis, center-specific, maybe surgeon specific?

DR. PAGANI: Not center specific, and certainly -- again, Dr. Naftel can speak to the specifics of that, but not to that level. There has to be some priority given to blinding specific devices too.

DR. KATO: Well, it sounds like you're potentially, forgive me for saying this, blinding the public rather than blinding the devices.

I mean I think that if you're going to be a registry and you know, you are in favor of public access and transparency, then

the right thing to do is to make that data published on an annual basis, and make it center-specific as well.

DR. PAGANI: But there is also some concern, and I'll let Dr. Naftel speak to this, but there's also some concerns if the data's going to be used as a means of post-market surveillance, or eventually hopefully be used as a way of monitoring devices in a trial, that components of that data cannot be made available to the public, especially if it's trial data, until the trial is completed. So those are potential concerns with --

DR. KATO: But after today, if this gets PMA approval, then we're out of the trial phase.

DR. PAGANI: Correct.

DR. KATO: So with all due respect, you can't hide behind that excuse.

DR. PAGANI: No, we're not. No, we're not hiding behind that excuse.

CHAIRMAN LASKEY: Norm, I think the

way the registry is run and the dynamics of it and the politics of it are beyond the scope of our discussion. We should get to the questions and the order at hand. But unless Dr. Naftel, you have a --

DR. NORMAND: I do have a question that wasn't answered, so I just --

CHAIRMAN LASKEY: Let him speak to the one burning issue here, which is concerning Dr. Kato.

DR. NAFTEL: I'll be very brief. First of all, please go to intermacs.org, and you'll see the most transparent process you'd ever want to see. The reports that we've generated so far are there, and everything you want to know. All the data elements, everything we've done, all the presentations.

We do have a quarterly report that goes out to the federal partners. We produce reports to all of the companies, industry, and to each individual institution. They get an analysis.

We have not elected to provide the per institution analyses to the public yet. Certainly, that's something we can discuss. But as you can imagine, the number of devices per institution is actually pretty low for any sort of analysis, where you'd start to want to rank institutions.

But it's all in place. Please to go to intermacs.org. That sounded like an advertisement.

DR. MASSIE: Don't step down yet. I do want to ask a question. In terms of post-market surveillance and post-marketing approval studies, what are the road blocks to comparing this device to other devices in the registry?

I know that the Heartmate II is not in the registry now, although you're prepared to capture the data once the device is approved, I think.

You could then, of course, compare those data to some other device, where the

data are in the registry, a contemporaneous device.

DR. NAFTEL: Absolutely. As we've said several times, there are five approved devices, and all of those are going in now.

As soon -- if Heartmate II, as soon as it's approved, those patients with this approved device will go into INTERMACS, regardless of the decision here about using INTERMACS for post-market surveillance.

DR. MASSIE: But what is the limitation, is there is one, based on privacy or commercial things, to comparing outcomes of these 194 or 200 or whatever it is people in the United States, whose data exists for the Heartmate II device to Heartmate XVE, put it in the same time window and other devices.

That's not -- and then going forward, one would really like -- everybody's been saying where is the comparator? Well, you've got the comparators. There may be adjustment things that will be complicated

statistically, but will that be available?

Because right now, there is some proprietary limitations, right?

DR. NAFTEL: The answer is shorter than the question. There are no roadblocks. We see none at all. All the patients are consented for their information to go to device companies, and I don't see any roadblocks.

DR. MASSIE: I guess the FDA gets it, I guess.

DR. NAFTEL: FDA's right in the middle, yes.

CHAIRMAN LASKEY: I guess that's how a registry should work. My main concern about the registry is what if you don't get the money to support it? You know, we're left hanging here. I mean we all hope that doesn't happen, but funds do dry up.

I'm part of a registry at the moment where the NHLBI funds are no longer available, and now what?

DR. NAFTEL: Yes. Certainly, that's a real possibility and I couldn't dare speak for NHLBI. We believe that it will continue. But even if it doesn't, we have a committee in place to work on a business plan and to do everything it can to extend this.

We feel sure it will not go away, since CMS is requiring this. We believe we have the support of NHLBI and FDA and industry. So we don't expect it to, and we certainly are committed to keeping it going.

CHAIRMAN LASKEY: Thank you. Dr. Normand.

DR. NORMAND: Yes. I had a question that I had asked, and it was regarding the completeness of follow-up for the various quality of life measures and the six minute walk and the neurological tests, about missing data and about how many.

I wanted to get some -- because right now, it's impossible to interpret those data. I think I just heard that there were

41, the slice of 37. Maybe you're talking about the September follow-up.

But at most with the complete data, which I'm not arguing you should use, there's only 41 people. It's really difficult to interpret the information from those particular instruments, without knowing how many died, how many couldn't respond and how many just refused.

Perhaps you just didn't have time to pull that together, which would be imperative to have in order to interpret the data.

DR. MILLER: It is the truth. You did mention the competing outcomes, is that when I looked at six month data, 40 percent had been transplanted; 20 percent had died.

So when we looked at the number who really could be eligible to have that, it looked like we had about 75 to 80 percent of the data collected.

As Dr. Petrucci alluded, that some

patients just elect to not have that data completed or take that test again. But it's for a fairly high percentage of these patients we have this consistent data.

DR. NORMAND: So again, I just -- it's really difficult to interpret the results as they're presented, because the small number that died are very informative to your output. So I don't think you can answer that today, but thank you for --

DR. HEATLEY: I think I can answer or at least I can try to. Was there any particular measure you were interested in?

DR. NORMAND: I wanted to see the analysis that uses the longitudinal missing and random assumptions. But right now you're not. You're just doing complete case means and ignoring that. So I don't think you can pull off analyses right now. Do you have that analysis?

DR. HEATLEY: That depends on how complete the data was.

DR. NORMAND: Well, I wanted to know how many we're missing at random, and how many died, how many are left in, in terms of actually --

DR. HEATLEY: I'm not prepared to answer that.

DR. NORMAND: Yes, I figured. Thank you.

DR. ZUCKERMAN: Dr. Normand, again I think your comments were just very helpful. Number one, there were no prospective hypotheses for these QOL end points to, as you point out, there are multiple problems with missing data.

So at the end of the day, while this is somewhat explanatory and hypothesis-generating data, etcetera, the question the FDA would really want to know is whether any of these data are of sufficient quality to be put in the device label, and maybe we can attack that when we get to the labeling.

DR. NORMAND: Just to follow-up,

Dr. Zuckerman, the reason why I was asking that is it would be terrible -- well, sometimes data can be presented in a way that are more harmful than helpful, by presenting simple summaries.

So I'm just a little concerned about having data, where I really don't know. It may look good, but I have no idea if it's the right way. So that's why I was asking that. That wasn't a primary --

DR. ZUCKERMAN: Absolutely. I would agree completely, and would perhaps suggest therefore that these data don't belong in any device label.

CHAIRMAN LASKEY: And I think we're helped along by the fact that they weren't pre-specified, and so we needn't spend a lot of time on this. Yes sir.

MR. MIDDLEBROOK: Okay. There was one final question that was posed before lunch. I'd like to bring up Dr. Stuart Russell to answer that question, and it has to

do with the change in renal and hepatic function from baseline.

DR. REICHENBACH: This is a question that actually went to the FDA, when you were asking about pulsatility and the effects of continuous flow.

We have presented data in abstract form at both the ISHLT and the HFSA on first the original patient cohort, and then additionally with CAP cohorts, looking at baseline data for creatinine, BUN, T. bili and transaminases.

You know, the baseline creatinine was 1.4. It went down to 1.1. We also split the group into half, based on above or below that baseline, and in the high group, it was 1.7. They also came down to 1.1. With creatinine, we saw similar changes, with the BUNs going from about 60 down to about 30 at six months.

T. bili started at 1.3. It was actually a slight uptick to about 1.7 at 30

days. It came down to .9 at month six and for the transaminases, it was about 70, came down to about 30 by six months. So both liver and renal appeared to improve with this essentially continuous flow.

MR. MIDDLEBROOK: Dr. Laskey, excuse me. There was one more question we did not get a chance to answer before the break, and that has to do with there were ten patients that were not listed 1A or 1B at 180 days, and we talked about the outcome of six of those patients.

There was a question raised regarding the four remaining patients that are ongoing, and I'd like to bring Laura Damme up to answer that question.

MS. DAMME: Okay. So the four patients, one of them was a 63 year-old female that was implanted, and she decided it was her preference not to be listed. She actually lived a little bit further from the center, did not want to relocate closer for the

transplant.

She continued to be ongoing very well, very active and had a total duration of 796 days. She did end up expiring. She actually ended up expiring with a pump pocket infection that she did not want anything done with.

Another one of these patients that was a patient preference was a 63 year-old female. She was implanted and had decided not to be listed. She was very active in camping, fishing, boating. She ended up getting transplanted, with a duration of 635 days.

The two last patients are actually not listed due to compliance reasons. There was a 34 year-old that was entered into the study. He had a history of non-ischemic alcoholic cardiomyopathy.

He was implanted and then did unfortunately go back to alcohol abuse. He went through detoxification, etcetera, did get delisted, and continued to kind of go through

therapy for that.

He continued to be non-compliant, and he did actually on Day 347, he actually had an incidence of hemolysis, for which they gave him some TPA, and he did subsequently have a hemorrhagic CVA.

But it was moderate. He did recover from that, and they actually fairly recently explanted him for recovery, at Day 558.

The final patient is a 42 year-old male, again a non-compliant patient, unfortunately, due to drug abuse. He is not currently listed. They keep rescreening him. He's doing well, very active, but he has not passed his drug screen yet, and they keep trying to get him to pass, and hopefully then he will get listed and get transplanted.

His duration -- I thought I had his recent duration -- the duration actually as of July 13th, when we put this together, was 416 days. So add another six months to that. Any

questions?

CHAIRMAN LASKEY: No. Just a vote of appreciation for that very thorough follow-up. We can only hope that such completeness is available for the registry, because this is very, very helpful.

We have a competing risk problem up here. It's not late but it is getting in the hour, and there are people that need to make arrangements for transportation and so forth.

I would suggest we take a ten minute break now, and then I'd like to reconvene for the panel questions and move on to the vote. I think on that schedule, we can get everybody where they need to get by 4:30.

So we'll see you in ten minutes. Thank you.

(Whereupon, a short recess was taken.)

CHAIRMAN LASKEY: Thank you very much for honoring the spirit of this process.

As we round third and head to home, we can focus our discussion on the FDA questions, and Eric, if you can tick them off for us, we'll try and summarize the sentiment up here.

MR. CHEN: Okay. So the first question involves the evaluation of safety and effectiveness is please provide your clinical and/or statistical interpretation of the results from the Heartmate II study, and whether the results demonstrate a reasonable assurance of effectiveness, even though the data did not meet the performance goal.

CHAIRMAN LASKEY: So I think that you've heard over and over again that we're all disappointed with the nature of the construct of the study.

However, there was a pre-specified hypothesis. There was a study design. The study failed, quote-unquote, to meet the set criteria of a lower bound for a confidence interval.

But I think that moving past the

failure of the study to meet its -- the pivotal population to meet the primary end point, we have discussed the importance and the relevance, and the implications of looking at the ensemble of the data that's been presented to us here.

That is not only the pivotal group but the continued access protocol and the small size protocol.

I think that looking at the composite of that population, I think the sentiment here is that we have met reasonable assurance of effectiveness, despite the fact that the data did not meet the pre-specified performance goal. Do we have agreement on that, in terms of an answer for the agency?

DR. MASSIE: I would just -- I circled in this, because it's not a simple question as it evolves, the "reasonable" in the question, and seizing upon the reasonable, I would concur with what you just said.

CHAIRMAN LASKEY: Underlining the

"reasonable." Yes, good. Thank you, Barrie.

DR. ZUCKERMAN: Okay. That's what the law says, reasonable, and that's why it's there. Can I just ask for a little bit further clarification, Dr. Laskey.

You stated the composite of the three clinical trials, and it's important for the agency to understand what that composite means.

As the prelude to Question 1, we would consider indicating by itself Trial No. 1 or the so-called pivotal trial, and then have concurrently results summarized for those other two cohorts that you stated.

As opposed to the way that the sponsor this morning showed effectiveness, where they already in a post hoc fashion have just added up 194 patients.

DR. MASSIE: I'd be happy to comment on that. I think that it needs to be that way, as he talked about it. It is a pivotal trial. I think part of the reason I

say "reasonable" drives my boat is that we do see some confirmatory data elsewhere.

But I think what we're really talking about is the 64 percent in the pivotal trial, as opposed to the 65 percent. I think the other data help us, help me at least, to decide that there's reasonable evidence with 64 percent and other findings.

CHAIRMAN LASKEY: I think the terminology here, you're quite right Bram. We have to be extremely careful about our nomenclature, that the clinician view of a composite is not a statistician's or a methodologist's.

We're not ignoring the data. We're dealing with the data on a supratentorial level, and working with that composite, that that is not a statistical pooling and it is not any sort of amalgamation of the populations.

The pivotal trial must stand on its own, as we are recommending. But all of us

have grappled with the implications of the other two populations, and feel that it does provide a signal of consistency.

DR. EDMUNDS: Well, should we delete and/or statistical from the statement, just leave it as clinical?

CHAIRMAN LASKEY: I'm not sure I have the answer to that, Hank.

DR. ZUCKERMAN: That's okay, Dr. Edmunds. The question asked reasonable assurance of effectiveness. We don't have a requirement in our law that the P value be less than .07, .05, what have you. What we needed to hear is the very good discussion that we've just had.

DR. SOMBERG: I would just hope the FDA would consider some of the provisos that were put into this study, maybe be considered for future studies and for future reanalysis of this work, because things like whether you're a transplant candidate or not.

There were certain issues that I

think a priori sounded very useful, but maybe inhibit things, especially in light of the fact that I don't see this as purely a bridge to transplant. This is sort of like grasping for a straw or a rope when you're falling.

Then once you're somewhat out of the urgent emergent situation, then you try to make decisions. I see people making very major life decisions, whether they want to go to transplant, whether they don't, whether they want to change their lives, move next to a center, etcetera.

These are tremendous problems. So I think having some sort of concept that you had to be ready for transplant to be considered that this bridge works is not correct. I think that is some of the problem here.

I don't want to get into whether you should evaluate those patients one way or another, but that's an important consideration in the future.

CHAIRMAN LASKEY: Next, Eric. Question 2.

MR. CHEN: Please provide your clinical and/or statistical interpretation of the results, as to whether any class of serious adverse events, that is to say infection, bleeding or neurological event, raises clinical concerns for a left ventricle assist device in bridge transplant patients.

CHAIRMAN LASKEY: So I think what we've heard today is that (a), in the absence of a comparator population that's contemporaneous, it's difficult to make such statements about statistical similarity.

But what we heard from the FDA's review of the literature and what is presented in our panel pack would lead me and I think others to think that these rates are not much different to a clinician's way of thinking, from the bridge to transplant population. Is that a fair statement? This is what people are seeing around the country in patients like

this?

DR. LINDENFELD: No, I think that's a fair statement. The bleeding may be -- I think the bleeding's comparable too, although particularly we'll talk about it later in women. I think we have to be concerned it might be higher.

DR. EDMUNDS: Well, I'd like to make a comment. You don't make progress standing still, and I think it's time to move on in the bleeding and thrombosis area.

I think that I can't agree to that at all, and I will vote against it, unless there are better protocols developed for managing both bleeding and thrombosis.

CHAIRMAN LASKEY: And Hank, you'll have your opportunity to add those suggestions to the post-approval study, which we're clearly moving towards.

I think the sepsis issue is of concern, but it has been of concern since Day 1. I don't think it's any different here, and

whether that raises issues of immuno-suppression in these people, I guess, is for others to decide.

But it needs to be grappled with as well, and how clever people are with the registry design remains to be seen. But I think we can answer you Bram here in saying that -- I'm sorry.

DR. NORMAND: I guess I could have just e-mailed in my response, but I do have some comments regarding some of what I heard the FDA did say, and I may be mistaken by this.

But it was my understanding when the FDA did look at the literature, it was very difficult for them to define serious adverse events from their literature review. If that was the case, I just want to make it clear, at least in my mind, I can say something clinically.

I can't understand some of the decisions made around the table, but it's my

understanding that there isn't any historical evidence about serious adverse events that are comparable.

So I just want to make it clear that right now, it's basically we don't have the historical data to compare the adverse events.

I mean I obviously trust the judgment around the table, but I just I think Dr. Laskey, you might have said something that the FDA -- my understanding is the FDA said they could not verify that, because the definitions weren't comparable and defined.

DR. VASSILIADES: Excuse me. I want to clarify that statement that's up there, to make sure that I understand. We're not talking about the Heartmate II in this question.

We're talking about a left ventricular assist device in the generic sense for bridge to transplant, compared to what? I mean I would have concerns about all those

events. But I mean --

DR. ZUCKERMAN: I'm sorry. We're talking about the specific device that's being evaluated today.

DR. VASSILIADES: Okay, all right. Well, it's not worded that way, okay. So I just want to be sure that we're talking about, because it's worded in a generic sense for a device being used as a bridge to transplant.

CHAIRMAN LASKEY: That's true, Tom. I think, as you can see from the title of the series of questions, that we're going to confine the discussion today to Heartmate II. Sharon, of course what you say is absolutely correct, that it's hard, when definitions vary all over the place.

But again, the clinicians feel that this is pretty well what they're seeing in their line of work. It may not be published at the moment, but I think we need to rest assured with that level of input.

DR. MASSIE: Did we not have some

comparative data, at least with the XVE? No?

CHAIRMAN LASKEY: I'm sorry. Can you come forward?

DR. PETRUCCI: There was five serious adverse events between the Heartmate VE data presented and the Heartmate II study. Those five serious adverse events had common definitions.

They were right heart failure requiring RVAD reoperation for bleeding; percutaneous lead infection; other neurological event; and stroke. They were common. What slide number?

MS. DAMME: Slide No. 73.

DR. PETRUCCI: Slide No. 73. So those serious adverse events had common definitions between the two data cohorts. So we prepared an analysis of those, a comparison of those events.

CHAIRMAN LASKEY: But admittedly, this is a tough one with so few N to compare.

DR. PETRUCCI: Correct.

CHAIRMAN LASKEY: I think the implications of the question are larger. But you're quite right. Thank you. Bram, are you satisfied with that?

DR. ZUCKERMAN: Yes.

MR. CHEN: Please provide your clinical and/or statistical interpretation of the results for the small patient cohort, but a body surface area BSA less than 1.5 meters squared, and greater than or equal to 1.2 meters squared, and discuss whether results from the primary study cohort can be extrapolated to the small BSA patients. If not, please discuss what concerns you may have.

CHAIRMAN LASKEY: So whether Sharon is in the room or not, we would all agree that there's an inadequate sample size here to make any statements of number one. I think that was recognized.

Certainly, treating it as its own subgroup was one of, I guess, the reasons

behind the FDA requiring you to split this out from the whole, from the other 126 patients.

So can we make statistical interpretation of the results? Of course not. Can we make clinical interpretations, how clinically relevant is this?

Given the interaction of size and gender, it's terribly important, terribly important. I would guess that that will be a key part of the construction of a series of questions for the post-approval registry.

Beyond that, I'm not sure that we can say with any certainty whether rates of bleeding are higher or lower, or rates of stroke are higher or lower in such a small sample.

But it's a group that needs intense scrutiny, and I think we would congratulate Thoratec for taking this on. This is a group that can't be ignored. We just don't have seven to ten patients total. There's no way that we can make reliable statements.

DR. ZUCKERMAN: Okay. Maybe we could get some more input from the cardiothoracic surgeons on the panel, because there's a broader issue here. If you go to the current labeling for the new Thoratec device, the Heartmate II LVAS is contraindicated in patients whose body surface area is less than 1.3.

So on the one hand, we have a label that says part of this population could be theoretically contraindicated.

On the other hand, the panel has indicated that BSA per se, as opposed to looking at the patient and seeing whether the device can fit, or in a surgical sense would be a better way.

So can the surgeons here help us as to how this device should be sized for a patient? Is the BSA criteria the appropriate way?

DR. EDMUNDS: I have to defer to Tom. He's actually doing it and I'm not.

DR. VASSILIADES: I think it's a reasonable start. I have no experience obviously with this particular device. I don't know what other additional factors there may be.

But I think it's certainly reasonable, and this is a patient subpopulation that you would want to see it used in.

DR. ZUCKERMAN: Okay. So how would you consider the following patient, who has a BSA of 1.25, say as a hypothetical. It's contraindicated in their labeling, but yet we have these data. So what would make you go one way or the other, in terms of deciding upon potential device placement?

DR. VASSILIADES: I think if it's technically feasible to implant the device, based on whatever size measurements you use initially for BSA and then other interoperative factors, if those are favorable, then it doesn't appear to have --

there doesn't appear to be any contraindications in terms of what the clinical data show in the experience.

So you know, I don't see any red flags, to be honest with you.

DR. MASSIE: Wouldn't it be possible to say that in the label, there is no experience --

DR. LINDENFELD: Yes. That's what I think it should say instead of contraindicated.

DR. MASSIE: -- with patients less than that, but I don't think you want to say it's contraindicated.

DR. LINDENFELD: You don't have any data that it's contraindicated. You just don't have any experience.

DR. VASSILIADES: Right, right. That's right. So on the one hand you don't want to say that it clearly can be used, but on the other hand you don't want to say that it shouldn't be.

So I think that in one of these instances, I mean I think you should leave the door open, to allow the clinician to make the decision, that we don't have data to suggest that this device is going to be formed differently, independent of the size issues.

DR. ZUCKERMAN: Yes. From a regulatory viewpoint that would be the way, to use the correct phraseology of the clinician experts think, that that is the actual case with respect to the data, that we have no data that says right off the bat you shouldn't do it.

CHAIRMAN LASKEY: And did I hear earlier, probably during the FDA's presentation, was there some suggestion perhaps obliquely about using BMI, or is BSA the standard in the industry here? Can there be some wiggle room with BMI, or doesn't it help? No? Okay. I saw that data.

DR. MASSIE: I would say speaking of contraindications, the one I did hear is

that it's contraindicated in a patient who's not eligible or appropriate for anticoagulation.

CHAIRMAN LASKEY: Right. That's another story. We were confining ourselves to the small surface, yes. Eric, number four.

MR. CHEN: This is the first labeling question. With regard to the indications for use labeling and clinical data, please comment on the following.

Question A. Please comment as to whether the indications for use adequately reflect the Heartmate II study patient population, and for which the device may be marketed.

Question B. Please discuss whether the device should be contraindicated for patients with less than BSA of 1.3 meters squared, or if the decision to implant the device should rather be based on an individualized assessment of body habitus and device fit.

CHAIRMAN LASKEY: Well, I think we just tackled B. Not that it should be contraindicated, but there should be language to the effect that there's no information on that group.

With respect to A, indications for use adequately reflect the study's patient population. This in some ways blends with the construct of the post-approval registry study that we would suggest.

But can I have some discussion on the specific answer to 4A?

DR. EDMUNDS: Well, why did you change -- excuse me. Why did you change it from 1.2 to 1.3?

DR. ZUCKERMAN: That's the manufacturer's initial proposed labeling or IFU. The agency didn't think that it necessarily made any sense. That's why we would like it discussed.

DR. LINDENFELD: There weren't any patients under 1.3, I think, were there? I

don't think there were any under 1.3.

DR. EDMUNDS: It's not something to send a surgeon to jail for.

DR. ZUCKERMAN: Absolutely.

DR. KATO: Well, I don't think, you know. If the surgeon does it below, with a BSA of less than 1.3, it's just off label. I don't think that's going to be a reason not to do it.

On the other hand, I think that the language by Dr. Lindenfeld is more than adequate to cover that situation.

DR. SOMBERG: May I ask a question?

CHAIRMAN LASKEY: Yes.

DR. SOMBERG: There's a day and a half training program. Clearly, this is a complex issue. Your body surface area doesn't necessarily mention, I mean measure this cavity where this type of device, that has a peculiar configuration, is going to be placed.

I would like toknow what they teach in that one and a half day. Or actually I

don't want to know, but it needs to be -- that has to be -- that instruction, I think, should be in the IFU, so it's clearly stated what are the recommendations. How does one size it up?

You know, I mean it's like palpating the abdomen. You feel a mass, you don't feel a mass, you know this is the right place, this is the wrong place. I think those are important considerations.

DR. KATO: Yes, and just to tag along on that, I mean body surface area is a function of height and weight, and I assume that some of these people are going to be fluid overloaded for whatever reason. So what is their true BSA supposed to be?

So I think that's where you're going to have to allow a lot of flexibility on that. But what John says I think is correct.

CHAIRMAN LASKEY: Yes, Cindy.

DR. TRACY: Just looking at the proposed labeling, it states in here the Heartmate II blah blah blah is intended for

use as a bridge to transplant in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure.

It's probably not that critical to make a big distinction here, but some of these patients, I forget exactly how many, did have improvement in ventricular function, have the device removed.

So that maybe should state presumed non-reversible left ventricular failure, rather than just stating non-reversible failure?

DR. ZUCKERMAN: Okay.

CHAIRMAN LASKEY: I'd like to get us back to A, and specifically Bram, I guess you're trying to get us to deal with the Thoratec proposed label, and to modify that accordingly?

DR. ZUCKERMAN: Right, and Dr. Tracy just read the indications for use. It's in your second notebook, page ten, Section

9.1.

(Pause.)

CHAIRMAN LASKEY: What page are you on Bram?

DR. ZUCKERMAN: Page ten, Section 9.1.

DR. PAGE: In our booklet is it 2.0 indications per use?

DR. ZUCKERMAN: Yes.

DR. PAGE: It's 2.0 in our booklet on page ten.

CHAIRMAN LASKEY: And would we agree that the study's patient population, at the least the pivotal trial, probably the continuing access trial, that patient population matches what the language is, appears to be?

DR. NORMAND: Can I just ask about the age? Are there any age restrictions that we need to, or is that just not an issue? It's not an issue.

DR. ZUCKERMAN: I don't think so.

DR. NORMAND: Do we have experience with a certain age group?

CHAIRMAN LASKEY: That's a good point, Sharon. There's nothing in there that speaks of contraindications. But I think we would need to go back to the company and see whether the company wants to have that information in their label.

DR. SOMBERG: But it's a function of size. You know, if someone could handle this device and have those sort of conditions, why would one want to put in additional limitations when we don't know, and this is a dire situation?

CHAIRMAN LASKEY: I guess the practical side of that Sharon is that above a certain point, people are not considered transplant candidates. So by definition, bridge to transplant doesn't apply to the elderly.

DR. NORMAND: I'm just saying typically you describe the patient population.

I think you're telling me, using that descriptor, it's fine. You don't care about age; you only care about the body surface area and whether or not it's going to fit?

DR. KATO: Well, I think you also care about -- I think the other key word is bridge to transplant in a clinical transplant candidate, only because most transplant programs do have an age cutoff.

Whether you want to make it 60, 65, but it's center-specific. So I think as long as that, this is -- it's understood that the intent is a temporary device leading to transplant.

Now granted, there are some people who want to go to destiny with this, and that's their right to do or they are going to be prolonged waiting times. But at least the intent going in has to be that this is a temporary device leading to cardiac transplant.

DR. MASSIE: I think that's

critical, because if you look at all the exclusions from the trial, they're largely designed to define that in some -- it's always a relative decision, but you know, people who have cancer, who are imminent, you know. There are things.

So I think you have to say in somebody who is a potential candidate for transplant, so you don't get somebody who's got -- well, if they had one adenocarcinoma, didn't they, in this one, you know, that's advanced and they died of that.

So I think it would be crazy to put it in somebody, although we just did in our journal have three case reports of people with cancer, who had LVADS and did well for three months.

DR. LINDENFELD: I don't think we can specify age and I'll have to find it. But somewhere in here there was a differential adverse effect that was substantially higher than those greater than 55. So when we talk

about post-marketing, we need to come back to that.

CHAIRMAN LASKEY: Yes. So age is probably an implicit cutoff, rather than anything else. Norm?

DR. KATO: I'm still concerned about the scattergram of percent success with, you know, with volume. I don't know whether it's a patient selection issue, a center effect or a specific surgeon effect.

I guess personally I would like to see a tighter definition, I mean if there could be one, only because -- just to try to narrow down the variability and success rates, if that's even possible.

CHAIRMAN LASKEY: You should have brought that up on Question No. 1, but it raises a very critically important issue, but do we have enough sample here to look at a volume outcome relationship? I'm not sure we do. I mean it is all over the place, but I'm not sure we can construct what we'd like to

see, which is an inverse relationship between, you know, outcomes and volume.

But hopefully, that will come out of a registry with more sample. At the moment, it is all over the place. It's hard to make sense of. But it's a small number for each site. Tom?

DR. VASSILIADES: No, I think you're dead-on with that. I think you're absolutely right. There's really not much more we can say about it, I think.

CHAIRMAN LASKEY: Okay with four?

DR. ZUCKERMAN: Yes.

MR. CHEN: Please discuss whether you think that additional warnings, precautions or contraindications should be included in the labeling to assist practitioners in using the Heartmate II.

For example, please comment on the use of anticoagulation, given that the device is axial flow pump.

DR. PAGE: Before we address the

anticoagulation, there are a couple of issues I'd just like to ask or raise, issues regarding the labeling. Page seven, third bullet down, it says to the operator "Do not overtighten thread protectors."

You never want to overtighten anything. But if that can have an important impact on the success of the implant, might you consider a torque wrench or something?

I guess my question is, is that a critically important part of the surgery, and if so, are there ways to work around that? Because now you're going to be opening this up to other surgeons, who will not have your level of expertise perhaps.

For example, in pacemakers, there is a torque wrench that keeps the operator from overtightening the set screw.

DR. PAGANI: The proper construction and preparation of the pump is what is taught as part of the training course. So that's a key element of the training

course, and a lot of time is spent on pump preparation and how to implant it. Those elements are discussed in the training.

DR. PAGE: So you're satisfied with that alone?

DR. PAGANI: Yes.

DR. PAGE: Okay. Next, on page eight, fourth bullet down, if there's an ICD or a pacemaker, it should make sure that there's not interference, if there is interference, it says that you should replace the ICD with one that is not prone to programming interference.

Do you have any data on which devices are prone to programming interference? That might be something that could also be looked at in post-marketing.

Finally, on page 58, the issue of the pledgeted mattress, the issue, there are specifics about the technical procedure on putting this in. There were two malfunctions related to pledgets.

Do you feel -- four, I'm told. Do you feel like the training program and experience now is such that you can teach adequately new operators this procedure?

DR. PAGANI: Well, I think it has nothing to do with the -- I mean I can speak to one of those episodes, because it occurred at our institution.

A small piece of pledget fell into the operative field and was sucked into -- it moved into the left ventricle and was sucked into the pump.

So it had nothing to do with the preparation or training of the pump. So I think it was an aberrant event, and not related to the pump implantation. It could happen in any particular operation.

DR. PAGE: But with four in a relatively small series, it seems to me there needs to be some sort of vigilance to keep that from happening the next time.

DR. PAGANI: There were just two

events listed. Just two events.

DR. PAGE: One of your colleagues was holding up four to me.

DR. PAGANI: No, no, no. Just two events.

DR. PAGE: Okay.

DR. DOMANSKI: Maybe I could -- I'm just kind of curious about the business of the programming interference, and I'm bothered by that now. I don't put in ICDs, but I'd like to know what guidance there is about that.

I mean which ones do interfere? Have you seen that? What did you do about it, and what guidance do you offer in your course to deal with it?

DR. REICHENBACH: We have observed that in one case, and thus far it's been interference with one manufacturer. It's interference during programming.

Some centers have been able to work around it, but we want people to know that up front, so they make sure they can do that, and

make sure they can program beforehand.

CHAIRMAN LASKEY: But just in case it might happen again, should that not be a precaution rather than buried in the IFU?

DR. REICHENBACH: I think it's something that should be --

DR. ZUCKERMAN: The answer is yes.

DR. REICHENBACH: Yes.

DR. ZUCKERMAN: It is a precaution in the IFU.

DR. EDMUNDS: In your training, I think it's very important to emphasize that the INR need to be between two and three and very carefully monitored, much moreso than with a prosthetic and mechanical heart valve, because your bearings need the lubrication, and the patient doesn't need a hemorrhagic CVA.

CHAIRMAN LASKEY: I think that is the guideline for the measure of INR, though. There's a protocol.

DR. SOMBERG: Well you know

unfortunately, it's really not known, because there's not a study done. I mean the numbers are too small. There's no variable. I don't know. Maybe it should be 2.5. Maybe it should be 3.0 or slightly higher.

So that I mean we don't know that, and what about low molecular weight heparins, where you may not need to measure the INR here.

So I mean I don't think these things should be written in. I think we have a very formative device that seems to have some clinical benefit, and that we're getting very picky on.

I think a lot more data is needed in almost all these areas before we make a recommendation, which people are going to read. They'll say okay, that's settled. We don't have to go on.

CHAIRMAN LASKEY: No. I think that we need to be somewhat more helpful if not specific with guidelines for anticoagulation

in the label. The general default here is use it as it was used in the trial.

Now you can get additional information, and by the way, I don't know anybody that uses low molecular weight dextran, even heparin.

So I think we have to go with what was in the trial, which was between two and three. We can look at it.

DR. SOMBERG: Do you know how many patients were at that range above it or below it, what the complications for bleeding? Were they high, were they low, how often was it measured?

I mean there's so many loose ends here, to put these things. You can write down yes, you know, obviously in teaching the course. This is the goal we kept people on. But why they did that, I don't know. You know, everything's picked sort of *a priori* and are not really followed up on.

CHAIRMAN LASKEY: Well, we need a

recommendation in the label for the use of warfarin here John, so you're going to have to come up with something better than what was in the trial. But these patients need to be anticoagulated.

DR. SOMBERG: Well, I think you say this is what was -- this was the goal in the trial, and this is the goal that we're teaching people to do. But we don't have adequate data to support that.

I mean a lot of people have said, you know, how long we give clopidogrel in a certain instance and in another device. It's the same thing here. We just pick something and we don't optimize it.

I would like to highlight. By the way, I would highlight that there are problems that should be highlighted. One is infection and the other one is bleeding, and that more care has to be given to each area.

I think it's to each center to try to come up with protocols to try to optimize

situations, and only time will tell what's the best one.

CHAIRMAN LASKEY: We may be hearing something about anticoagulation protocols here. That would be very helpful.

MR. MIDDLEBROOK: Dr. Laskey, I just want to refer the panel to Section 13.3 on page 73, in the second book, the binder. It's Section 9.1, where we do define the anticoagulation therapy requirement.

Yes. It's Section 13.3 on page 73, in the second binder, the smaller of the two binders.

DR. SOMBERG: Mine doesn't go to 13.

MR. MIDDLEBROOK: It's in Section 9.1. I apologize for that. But it's in the patient management guide at Section 13.3, page 73.

DR. YAROSS: Page 73.

(Pause.)

DR. SOMBERG: I can't find that

section at the moment. You're going to have to -- I'm sorry.

DR. YAROSS: It's 9.1.

CHAIRMAN LASKEY: Maybe we can share that with you, John. But getting down to the --

DR. YAROSS: Tab 9.1, which is the second tab of the smaller volume, page 73 of that tab.

CHAIRMAN LASKEY: It is explicitly stated there. So there is a protocol. Yes?

DR. PAGE: My one question on page 73 is it says "For sustained low pump flow states, consider increasing anticoagulation to upper limits of normal."

Do you mean upper limits of therapeutic? I assume that's a low flow state, so we don't want upper limits of normal. We want upper limits of the therapeutic INR, translate to three or above. That just needs to be changed for the record.

DR. EDMUNDS: Well, most of the

weaning protocol, the INR is at the bottom of that 13.5, that 13.3 section under number five. 2.0 to 3.0.

CHAIRMAN LASKEY: Right, as was mentioned earlier. But the point about weaning, when we're getting low flow states, presumably this is not an optimal situation. The only one that might qualify for that would be the weaning.

Should we have specific recommendations for handling the anticoagulation?

DR. EDMUNDS: I think the people in the OR have got to handle that one, because it's going to be very individual in what the coagulation defects that they're dealing with at the time. The amount of bleeding and everything else is going to play a factor as to what they decide to do. But that's a transitional state.

CHAIRMAN LASKEY: John?

DR. SOMBERG: Reviewing this

carefully, I read an agenda here, is you're using the degree of anticoagulation for a hemodynamic factor, and you're going to have a side effect of bleeding.

There are other ways to change the rheology of the blood besides anticoagulation. There's another area that needs to invest in. I must say I read this over, but I didn't think of that beforehand.

But the degree of hydration, other pharmacologic agents can affect that as well. So you have a competing thing here, because yes, you're using the blood as a lubricant and you want to be at a certain lubrication and it's that.

But it's also, by changing that, you're going to change the rate of hemorrhage. So someone has to think of, and I don't want to do it standing on my -- sitting down here at the moment, but someone has to give thought to how to separate those two factors.

CHAIRMAN LASKEY: Yes Gene?

DR. BLACKSTONE: Going back to Section 4, the label, pages really 11 through -- yes, 11 through 22, I believe, need to be modified to reflect the pivotal trial and to use the language that we have agreed to today, none of which is contained in this section.

CHAIRMAN LASKEY: I think we would agree with that, pass that on, that it should reflect the pivotal trial and not the --

DR. TRACY: Warren?

CHAIRMAN LASKEY: Cindy.

DR. TRACY: Sorry, but there's one -- back to the question on the labeling for contraindications. There is one contraindication that we kind of mentioned but it needs to be stated explicitly. The patient cannot have this device if they cannot receive anticoagulation. That needs to be stated as a contraindication.

I think some of the other absolutely contraindications are implicit in the initial indication, which states that the

patient is otherwise a transplant candidate, which precludes somebody with metastatic cancer and so on and so forth.

But I think in terms of a specific contraindication, that just needs to be put in there.

DR. LINDENFELD: I'm not sure. I just was interested to read that pregnancy is another one, but I don't know how much that needs to be up front or later on. But there's a paragraph in there that states that pregnancy is likely to dislodge the lead, and I don't know up front that needs to be in the labeling.

But I think that since this is going to go into young women, somewhere that needs to be emphasized. It was something that I had not thought of in the past, although maybe it's obvious to everyone else.

DR. EDMUNDS: I would slightly disagree with you, because there may be circumstances where you would have someone who

really couldn't be managed by coumadin.

You might try to manage them with a low molecular weight dextran, I mean heparin, or some other anticoagulation protocol under a special circumstance. So I wouldn't tie the clinician's hands.

DR. TRACY: No, I'm not saying that. I specifically said they're not a candidate for anticoagulation, not stating not a candidate for warfarin.

CHAIRMAN LASKEY: That sounds reasonable. JoAnn, get back to your point, that there should be a contraindication for --

DR. LINDENFELD: I'm not sure it should be a contraindication. I was just surprised to read through there that this shouldn't be put in anyone who may be pregnant or may become pregnant, because it may dislodge. The growth of the fetus may dislodge the lead.

I couldn't tell what data there was there, if that was presumed or if it had

happened. But I just wasn't aware of it, and I just think it ought to be somewhere, where people are aware, especially a device that can go on for some time, that's likely to be put in young women.

We ought to be sure that clinicians understand that. I don't know what, I don't know that we even need to go into that, what data you have for that. But I was just struck with that.

CHAIRMAN LASKEY: Well, nobody in the trial was pregnant. But I think we're in no man's land with the effects of non-pulsatile flow on the fetus.

DR. LINDENFELD: But the specific indication here says that the fetus may dislodge the pump. I have no idea how strongly that's felt, but maybe it just ought to be somewhere where it rises to people's attention.

I don't think it should be a contraindication, but I was sort of surprised

to read that, and I consider young women all the time.

CHAIRMAN LASKEY: Okay. I think we can move on.

DR. KATO: Just one more minor point. It says the Heartmate II is intended for use both inside and outside the hospital. I don't think anybody would disagree with that, or for transportation of VAD patients via ground ambulance, fixed wing aircraft or helicopter.

I'm not sure that that was proved, or is that a general statement within other package inserts for other VAD devices, or is that some specialty type indication that the sponsor's going for?

Because otherwise, since no data was presented, I would recommend that that last part be stricken, as far as the transportation mode.

MR. MIDDLEBROOK: This is Don Middlebrook. We did provide data to support

or validate the use in air ambulance, and air transport and in ambulance.

We did provide that as part of our verification, part of the engineering section data that has been provided to the FDA, and Eric has indicated earlier that there were no concerns raised for that information.

DR. KATO: But is this a specialty indication that you're trying to get for Heartmate II, compared to the --

DR. ZUCKERMAN: No. It's a standard part of the bridge to transplant label, and as Don pointed out, that can be qualified through appropriate pre-clinical engineering testing.

CHAIRMAN LASKEY: Okay. Number five.

MR. CHEN: Okay. So we've had a lot of discussion on the post-market, so let's go through each bullet. With regard to the post-approval study, please comment on the following.

Based on the clinical data provided in the panel pack, please comment on the design of the post-approval study proposed by the sponsor. Is follow-up up to one year post-transplant with data collection for adverse events and functional assessments appropriate?

CHAIRMAN LASKEY: I think we have an all unanimous yes, if not longer. But at a minimum, yes. Discussion?

DR. MASSIE: Well, I think that -- I mean I've heard mixed feelings from the people on the panel about the INTERMACS versus others. But I do believe INTERMACS is a good vehicle, but what I've heard is not a good and adequate study, in terms of numbers.

If in fact what David Naftel said was true, I think there are all sorts of things that one could pre-specify such as comparative analysis with other bridge to transplant devices.

It's post-marketing, but now we

could actually specify we'd like a comparison with what's been going on during the same period as this trial with other devices, because those are in the database. These will -- the Heartmate II will be added.

But then going forward, I think we also need it. But I don't see, given the vehicles existing and all these people being entered registry-wide, that we should be parsimonious. Why not hundreds?

CHAIRMAN LASKEY: Well, I guess I'll just -- you know, it's important, it's terribly important that they be consecutive or nearly consecutive, and I didn't hear that today. But I think maybe everyone understands that in the registry. Otherwise, it's not very good.

DR. EDMUNDS: But Warren, I think our discussions that we've had before about changing protocols and beefing them up should be continued in the follow-up period, or at least evaluated.

CHAIRMAN LASKEY: That's a different issue, but we're asking for consecutive enrollment or nearly consecutive enrollment of everybody with a device from henceforth in the registry.

Now what we do when they get in there, what study they fall into or how they're stratified is yet to be determined. So we can hopefully articulate that today.

DR. PAGE: Yes. I'd just like to say to the sponsor, I was really surprised by the post-market, the post-approval study that was put forward at 50 patients. That seemed awfully low, and I would have anticipated a good faith effort to really look at some of the questions that you all know are still outstanding.

For example, if statistically one in four patients is a woman, and if 50 were studied, then we'd only have 12 more patients. So I've got to say as I read this, just kind of give you feedback, it disappointed me that

a greater effort at really addressing -- I realize that companies always come with a plan, and the FDA ends up negotiating.

But we're all out to get the information. We're all out to identify safety in this device. While I think, I compliment you on putting together a very nice packet for us, I was troubled by the study as it was put forward.

MR. MIDDLEBROOK: Warren, is it okay if I make a comment? Yes, I appreciate your comment, and as I indicated before, we put it forth as a starting point, because we didn't know at the time what the issues with the PMA data would be.

So we put forth the protocol. We did propose the INTERMACS, because I think it's important to point out that even though we proposed a relatively small number of patients, that it's our anticipation that INTERMACS will continue to serve as a registry and capture the data on all of these patients

continuing to go forward, from now until perpetuity, in the unlikely event unless they somehow run out of funding and nothing else happens.

But I think that is really a remote possibility that that will happen. So the idea was to kind of come in with a finite, relatively small number, and the reason we did that really was based on the fact that with 133 patients and the additional 280 patients in the CAP study, that we had such a large body of valid evidence collected during the clinical trial, and with the INTERMACS sort of safety net there, that we wouldn't need a very large post-market study because the data would continue to be collected and analyzed going forward.

DR. TRACY: Do the data that you propose in your post-market surveillance correlate with the INTERMACS data fields, what the actual fields are in the INTERMACS database?

MR. MIDDLEBROOK: I think that's an important question, and I want to make sure the panel understands it too, as you kind of contemplate the post-market study.

As we proposed our post-market study, we proposed it, that INTERMACS would be used to collect all of the post-market data. The reason for that is that the VAD coordinators are already very well overloaded with a lot of stuff to try to do.

The INTERMACS is already IRB-approved. There's already an informed consent. So to facilitate, there's electronic data entry. There's a lot of things in place that facilitate the ease of collecting this data. That's why we wanted to stick with that in its totality, because adding anything else onto that would require additional informed consent, additional IRB approval. It could depend on what you decide on. It could involve a core lab and other things that would really complicate the post-market study.

So we wanted to kind of keep it within the construct of INTERMACS, and that was the rationale for what we did.

CHAIRMAN LASKEY: Dr. Normand?

DR. NORMAND: Thanks. I guess I'm not so concerned. I guess I don't want to be fixated on INTERMACS versus not INTERMACS. I think the idea should be one of what would be the post-market study?

Will you provide, collect elements that are going to be comparably defined in your earlier studies? Otherwise, we can't use the information in the earlier studies.

So if INTERMACS serves that purpose, great. If it doesn't, too bad and you're going to have to go for it with something else.

So I guess I'm not -- I hate to be tied to a particular registry, and if you're stuck with the way they collect the data and you can't sort of capitalize on the good data you've collected already.

But the reason -- I have a couple of questions and I guess concerns. So the thing is I too was disappointed by the very, very small sample size, and again, these sample sizes are pulled out of the air.

I think what one should do and I'm sure FDA could work with you on this, is what is it you're trying to estimate. If you're talking about the adverse events, let's talk about the actual adverse event rate you expect.

The fact that we don't have any concurrent controls I suspect means that if you do use INTERMACS, even if you don't, that we should probably have some concurrent controls that we could capitalize on.

So I would start off by saying that that 50's too small. I don't know what you actually want to estimate. If you want to estimate an overall rate, a combined rate, if you want to estimate bleeding, whatever. But we need to determine that, and that we do need

some, I would argue again, concurrent controls to do that.

CHAIRMAN LASKEY: And that's on the next page, so we'll get to that. But to the specific question is a follow-up one year post-transplant appropriate, we would all agree to that, irrespective of the end.

DR. NORMAND: So you're saying one year's long enough to see the adverse events?

CHAIRMAN LASKEY: I didn't say that.

DR. NORMAND: Oh, sorry. At least one year is needed to see it.

DR. MASSIE: Well, this is one year post-transplant. So this could be two years.

CHAIRMAN LASKEY: Right. That's correct.

DR. LINDENFELD: One year after the device is removed from the patient.

CHAIRMAN LASKEY: I think this overlaps with our recommendations for a post-approval construct, that I think we're getting

the concepts out now, and we're sending a loud signal that 50 is not appropriate.

DR. MASSIE: What is INTERMACS' follow-up post-transplant? I mean before we say this, this may be --

DR. ZUCKERMAN: Dr. Massie, I think it may have to be whatever the FDA advisory panel recommends. I would go back to Dr. Norman's key points.

We're really looking for your advice on what are the key questions, so that we can then seriously discuss with the sponsor a post-approval registry that definitely needs to be completed in a timely fashion.

If INTERMACS can be a part, that's fine. But we need to define the key questions which are in Part B of this question set.

CHAIRMAN LASKEY: Can we move onto B? Are you okay with the answer to A?

DR. ZUCKERMAN: Yes.

CHAIRMAN LASKEY: All right. Separate subgroup analysis for women and small

body habitus patients, recognizing that there's substantial overlap.

I think we've said over and over again that we need more data in this group. So there's no question. How you deal with that in the registry can also be discussed.

But there should be a separate subgroup analysis, either comparing men to women or small to large. But there ought to be a mechanism to look at this issue.

DR. SOMBERG: Also age, age would be appropriate to look at.

CHAIRMAN LASKEY: Yes. But again, to keep us focused on the question at hand, the separate subgroup analysis, which I think will be incorporated into any recommendation that we have for a post-approval study.

DR. TRACY: I believe that's actually in there, in Section 8, 5.1, Patient Assessments. I do believe that that is what they propose to standard demographics of age, gender and patient's described ethnicity will

be recorded.

Maybe it just needs to be fleshed out to say that comparisons will be made. But they do intend to have that data.

CHAIRMAN LASKEY: Yes. I mean there's a big difference between entering that in the database and then looking at it in a more critical way.

DR. ZUCKERMAN: Right. The point of B is to ask the advisory panel should these two subgroups be prospectively identified and studied in a serious prospective manner, as opposed to, as Dr. Tracy was saying, there will be women entered in the registry.

We'll describe the percentage of women; we'll look at some exploratory features as we did in the pivotal trial.

DR. TRACY: But I think chances are you will find a lot more in this data as time goes by.

So it all has to be collected. Yes, those have to be separated out. But I

think there's always going to be something more that you don't anticipate at this point.

DR. ZUCKERMAN: Sure. But there's a difference between a prospective look versus retrospective. We're asking the advisory panel should this be prospectively identified as two key subgroups.

DR. LINDENFELD: Yes.

DR. ZUCKERMAN: Thank you.

CHAIRMAN LASKEY: What measures, I guess you can get more information on in the specifics of the registry. C?

MR. CHEN: Please comment on whether or not the success criterion for device effectiveness is adequate for a post-approval study, or if instead it would be more appropriate to utilize a concurrent control group in order to assess post-market effectiveness.

CHAIRMAN LASKEY: And in fact we've said over and over again that yes, we would ask for a concurrent control group, the nature

of which we can specify.

Again, as we get to conditions for approval, although Sharon, did you want to share any ideas at the moment? Sharon? Concurrent control groups?

DR. NORMAND: Yes, I agree. There should be concurrent control groups.

CHAIRMAN LASKEY: Any suggestion of the nature of such?

DR. NORMAND: Well, I guess depending on the subgroups. So if you wanted to go prospectively and do some match sampling of women with TAXUS -- I don't know if they still want to do the same -- forgive me.

I was thinking about a discussion we had yesterday, where concurrent control groups was voted down. But in terms of looking at -- I don't know. I think the clinicians need to decide if it needs to be the same, if we want to use the XV, the VE or not.

So I don't know if you're asking me

what the comparison group should be, versus how to actually do that.

CHAIRMAN LASKEY: There are choices. This is the point, that there are a number of possibilities.

DR. LINDENFELD: I think clearly one concurrent control should be a device with a slightly different level of anticoagulation, since bleeding is a problem here. We ought to be sure that that comparison can be made, I think.

DR. TRACY: There is a problem, though, looking at a concurrent control for small sized people, because there is not another device that would be a concurrent control for that group of patients.

DR. LINDENFELD: No, but there are plenty in the women in the 1.5 to 1.7 or 8 range, because women are more susceptible to bleeding and the effects of anticoagulation. I think just that's one thing that concurrent controls should help.

We should be sure that we can establish that, because there is more anticoagulation in this protocol than in some other devices.

CHAIRMAN LASKEY: So we would come down on the side of advising the control group inclusion. Yes, Gene?

DR. BLACKSTONE: I would suggest that the wording that says "This success criteria" also be revisited, because I believe this is not a good success criteria.

That instead one should have as success criteria some specified point in time, and a time-related method should be used for that and not these methods.

CHAIRMAN LASKEY: And again, I was going to bring you into that discussion for the specifics of the nature of our recommendations for the post-approval study. But I think your point is well-taken, and we could probably just delete the "this," not knowing what "this" is going to refer to once