it might be a reasonable comparison.

However, dissecting the remainder of the adhesions, the right atrium from the right pericardial wall, the great vessels apart, and whatnot, would have been totally unrelated to what was happening from the study. So in the clinical picture, it may be a totally meaningless aspect.

CHAIR YANCY: Other inputs? Please, Dr. Jeevanandam.

DR. JEEVANANDAM: Or at least acquainted this. This was the time from skin incision to the placement of the sternal retractor. So, this is the time where they have gone through the anterior mediastinum and the posterior chest wall and put the retractor in. So this isn't the time for their entire dissection or for going on pump and, you know, setting up the right atrium, etcetera. So, this is theoretically the area of "protection" that they have gone through and put their external retractor in.

CHAIR YANCY: My sense -- oh, I'm sorry. Dr. Page.

DR. PAGE: My only comment is I think Table 5 is consistent with what we saw in terms of primary endpoint. I remain very concerned about this clinical, Table 6 and the one clinical outcome that would have hoped to have seen is going in the wrong direction.

Overall, I don't know what to make of these secondary effectiveness evaluations.

CHAIR YANCY: So if I can make an attempt to paraphrase what I have heard, the only component of the secondary effectiveness with which we have some degree of quasi-comfort is the reduction in the severity of adhesions. But we are all confounded by the dissection time data and essentially reject it as not being contributory towards secondary effectiveness.

Have I overstated that? Are there contrary viewpoints? Dr. Hirshfeld.

DR. HIRSHFELD: I think we have to, I don't think we can just reject the data and ignore it. I think the fact is that the data move in the wrong direction and that may be a signal that there

is some other thing that is operating here.

CHAIR YANCY: Dr. Zuckerman, is that enough information for you on question three?

DR. ZUCKERMAN: Yes, but I would like to ask you to summarize the panel on one other point.

You've had a thorough discussion of the secondary endpoint effectiveness data. Would it be fair to say, as a panel conclusion also that it doesn't help one anymore extrapolate to the larger intended indication?

CHAIR YANCY: I think several panel members have spoken to this issue of extrapolating these findings to a larger domain that would include adults. We've heard about comorbid conditions. We've heard about different kinds of surgical operations. The presence of eye main grafts I think Dr. Weinberger and Dr. Hirshfeld have made some comments on that, Dr. Zuckerman. But if someone wants to respond specifically to that comment, I would welcome that.

DR. HOPKINS: I'm not sure that that's

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what we said. I think what we said was that A, B, and C, no. D, yes and that is contributory to the evaluation of this product, this device.

In other words, D says the percentage of patients with the worst degree of adhesions was improved by the use of this device and I think we're all saying we agree with that. The consequences of that are we're having a problem in terms of the clinical impact that that has.

But in terms of the definitions of the secondary endpoints, what I heard is that we all agree that 3D was met, but 3A, B, and C, and Table 6 were kind of un-interpretable because of, for various reasons. Either they are underpowered or Table 6 may be measuring 15 other things and have absolutely nothing to do with the severity of the adhesions from which you could extrapolate a utility for this device.

CHAIR YANCY: So that is the message we have just given FDA. But now they have responded, whether or not he message we have given, even with regard to the one component to which we have

tentatively embraced, 3D, do we believe that can be extrapolated to a larger population?

DR. HOPKINS: Are we going to discuss that under labeling or you want to discuss that now?

CHAIR YANCY: Well, labeling is next, so we can't avoid it.

DR. HOPKINS: No, that's very --.

CHAIR YANCY: Dr. Yaross.

DR. YAROSS: Yes, I thought we were coming to this under question four also, but I guess the challenge I see, and this was alluded to this morning in terms of whether or not the sponsor is between a rock and a hard place, because in FDA's own summary, it says that this was a reasonable model and it's been alluded that this is probably the only executable study design and yet the challenge comes back about extrapolation.

You know with respect to Dr. Domanski's earlier point, the panel has to use their clinical judgment if this is the important indication for which studies and effective devices are sought, we

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just need to make sure that reasonable study designs are accepted.

CHAIR YANCY: So that we can be somewhat structured, let's go ahead and introduce question four. Can you bring that up?

The additional language is at your place, but the focus of the question is to discuss whether the data provided, in aggregate, can be used to extrapolate the proposed Indications for Use from pediatric to adult patients who may or may not have a planned re-operation.

The fact that we're discussing this as a point of information does not mean that we have de facto approved the PMA, but this is part of our deliberation.

Dr. Zuckerman, I think you had your hand up and I didn't recognize you.

DR. ZUCKERMAN: You know, I just wanted to clarify one thing. You know, FDA wrote something in executive summary that said a, b, and c. But the point of taking things to an advisory panel is to get advice from experts. And while FDA

didn't see perhaps yesterday a way for it regarding extrapolation to the biggest or different alternatives, I wouldn't necessarily assume that that's true now and would like the panel to go into the organized fashion that you have directed us, Dr. Yancy.

CHAIR YANCY: So in that context, I think we do have to be clear about resolving question three. Because what FDA would like is our advice about whether our tentative embrace of the one secondary effectiveness measure, fewer worse adhesions, has enough veracity that we're comfortable with that benefit being extrapolated to a broader patient population. And I think Dr. Hopkins started off with no. Is that correct?

DR. HOPKINS: Well, there's two different questions. The question is do we accept that outcome as being highly likely? And the answer is yes.

To be able to extrapolate to other populations may in fact fall under, and this is where when we start to talk about labeling

indications, it's really two separate questions. The extrapolation may fall into the area of clinical judgment, which gets into the whole area. Usually, it's the reverse that we're talking about, in terms of off label use. It's approved for adult use and we use it for kids. Here we're talking maybe it should be restricted to kids. And does that mean a clinician can't use their judgment and use it for adult? No.

But what we're talking about is the labeling that we can comfortably do, based upon the evidence that we have.

So, if you ask me about extrapolation, I would say no. But I would say the first part of the question, has the percentage of patients with the worst degree been proved to my satisfaction? The answer to that is yes.

CHAIR YANCY: And I think the panel in general has resolved that the answer is yes.

Dr. Domanski and then Dr. Page.

DR. DOMANSKI: Yes, I would underscore your answer, in fact.

The thing that I would add, though, is once these things are out there, of course, they can used off label. I think that somebody using this particular device off label is at real risk because here it's not just oh, they haven't you know, done a complete study. There really should be some considerable concern that there might be a problem in adults.

And I think, given the indication by the FDA, if, you know, assuming we go ahead and recommend approval in the kids, I think somebody extrapolating and using it in adults who then has a misadventure will have the warning of the FDA as, you know, in this panel, that is, a certain sort of legislative history if you will, to this. I think we should do whatever we can in the labeling to encourage not doing that, more so than with other devices that one sees coming through here.

CHAIR YANCY: So from my kind of Texas mind, let me see if I can really hone this down. So do we believe that if this device were used in an adult, that we would see fewer worse adhesions?

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That's really the frame up here.

Dr. Page.

DR. PAGE: Yes, the --

CHAIR YANCY: That's a yes?

DR. PAGE: No. That's an absolutely no.

CHAIR YANCY: Okay.

DR. PAGE: The model, while I think it probably is the best, and maybe the only model to assess re-operation and adhesions in a re-operation, let's keep in mind, these are three kilo babies. The average age was 12 days. Seventy percent had their chest open for two to five days before this. So the whole healing process is completely different from what happens in an adult, as opposed to eight to twenty years for the average re-op in an adult.

So in terms of efficacy, we have no data. And we have a model that I don't think follows.

CHAIR YANCY: So your answer is no.

DR. PAGE: The answer is no. But also,

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are we going to get a chance to discuss safety? Because safety is key. And as I look through the documentation, there are a total of 11 adults who completed a protocol, 11 patients for safety data. And that -- safety first.

CHAIR YANCY: We will get to that when we have a discussion about a potential post-approval study, if we decide to do that. Dr. Somberg.

DR. SOMBERG: We really don't have the information. So I don't think we should, as a panel, say that we have an expectation that there would be toxicity in adults. We don't know that. We, at the same time, I'm glad most of my colleagues are worried about the adult side. I saw that. You know, I was concerned that that would not be an issued raised.

But we have to also say that the sponsor does have a lot of information in the preclinical models, where you're looking at this issue and there are other barrier devices that have been brought forward as well. I understand two of

them are approved. One of the slides stated that. So, I think that we have to say that we really don't know. And I must disagree with Dr. Domanski it's that we have to anticipate that those two lesions will become three plus to the power of four or something. I think we just have to say there has to be some caution.

And as in cardiology and cardiothoracic surgery, people explore and hopefully they explore within the confines of studies and registries. But I wouldn't want to go so far as to say that we expect to have adversity. We just don't know.

CHAIR YANCY: Dr. Zahka.

DR. ZAHKA: I guess I haven't heard enough today to know how to answer the question. It strikes me that if in adults there are two devices that are already approved for this purpose, then that means that there is a clinical problem in adults. And that it's not a moot point and that somehow a study was done to prove effectiveness and safety of those devices.

CHAIR YANCY: This is a panel only

discussion. We'll yield to you. Panel only discussion right now. I appreciate your desire to speak and we will get to that point.

DR. ZAHKA: And this device, you know, I believe has been shown to reduce adhesions. So it's not illogical then to say that in the adult population there is a problem, it's been recognized, and this device has a potential to help adults. And these data support that in humans, that this device may be helpful.

CHAIR YANCY: Dr. Yaross.

DR. YAROSS: Yes, I would just ask Dr. Zuckerman for clarification. I had understood that there was no device that was specifically indicated for cardiac surgery.

DR. ZUCKERMAN: Yes, but the clarification I want to give to Dr. Zahka and other members of the panel is to remember that this is a PMA device that we're discussing. So regardless of whether there is another approved device on the market, each PMA must stand on its own. You must individually look at the data for safety and

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effectiveness and make a risk benefit profile decision.

CHAIR YANCY: I thank you for that clarification. I think we are, in fact, blending these discussions. So, ostensibly, we are discussing question four. So, this is an opportunity to continue to develop our thoughts about whether or not we can extrapolate the aggregate database we have seen today from the pediatric to the adult population.

Dr. Neaton, please.

DR. NEATON: Could I just ask maybe a question, because there's an element of this that I don't fully understand.

So one part of the extrapolation is going from a little body to a big body. But the other part of the extrapolation is going from a repeat procedure five to six months later, to one that's going to be many years later. And so, if this device doesn't really kind of reduce to zero adhesion, it's just reducing severity, I mean, how would one expect those to evolve over time? I

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mean, is the time element here another important consideration?

CHAIR YANCY: Dr. Jeevanandam.

DR. JEEVANANDAM: I had a comment to make, but I think I could try to answer your question. So when you talk about the many years between re-operations, what we find clinically is that the adhesions are probably worse at about six months where they are vascular and there is a lot of inflammation and there is edema. And then over a period of time, they actually do mature. And if you do operate on somebody 10 years, 15 years later, the adhesions tend to be a lot less vascular and somewhat easier to go through and you have less of your catastrophe.

But it's not uniform that you do have some patients who would have a lot of adhesions. But then if you track them back, they probably have had some event in their primary surgery, such as a bleed or an infection or something else going on.

I guess you know, so to frame this question, it says, okay, this device decreased

adhesions. And I think there is, in this population, yes, it decreases adhesions. Then the next question was, will it decrease adhesions in an adult population?

And first of all, we don't have any data on that at all. The only thing that we have is a couple of adult patients and when we talk about the adult population, these VAD patients are a group of patients who are going to have a planned re-op. Okay? They are going to have a planned re-op in about six to eight months. And so they are not that much different than the Norwood patients.

Now, I know this device went into two patients and they did not have good outcomes. And the idea was that the membrane itself breaks apart because of these grafts. Now, these grafts don't all have to be placed right on the anterior mediastinum. A lot of people actually put them out on the right side, so theoretically, these grafts should not be, I don't know, squashed or however it was described, or destroyed by these grafts. And so, it does give me a little concern that the two

patients that they did go back on in adults had adverse events and have adhesions.

So I don't think you can automatically just project that because this worked to decrease adhesions in neonates that it's going to work in adults. And I might actually caution against that.

CHAIR YANCY: So you are not comfortable extrapolating these data from the pediatric population to the adult population.

DR. JEEVANANDAM: That is correct.

CHAIR YANCY: All right. That is the focus of question four.

Dr. Somberg.

DR. SOMBERG: Well, I agree with your conclusion. But I just want to say that I've heard two individuals, two surgical colleagues here say that oh, as the adhesions mature, they become less problematic. That might be so in the natural history. But if you change the natural history by pushing it up front to the mild adhesions, those mild adhesions, over time, might become more dense and fibrous at a later date. And they may not

mature as the natural history does.

And I'm not saying that's for sure. I'm just a guy who bets on weird scientific outcomes that sometimes occur.

But I'm just saying that should be revealed. And I think what my sense is of what I've heard from people is that there is going to be a need for, I mean, based on two patients, what can you do? So there is a need for a larger experience in adults, before it's used in adults.

CHAIR YANCY: Dr. Hopkins?

DR. HOPKINS: Yes, I think all of those comments are well taken. Where I would be interested in using this in adults is a third or fourth time redo in an 18 or 20-year-old where the risk benefit ratio would be very, very favorable. I would be less inclined to use it in a 60-year-old coronary who is a diabetic.

So I think there is all of those, none of that has been investigated here. So just a straight extrapolation that this is useful in adults regardless of other factors is a little bit

difficult. And so you're talking about labeling, it becomes very kind of misleading.

In terms of the biology that you suggested, the biology of wound healing would suggest that that scenario would not occur, the blocking. But it would be more likely that blocking mild adhesions is a good thing. But nevertheless, there is no data here to extrapolate.

CHAIR YANCY: But it sounds like you're saying that there is at least a limited possibility that you would extrapolate these data to a certain segment of an adult population. Is that correct?

DR. HOPKINS: Absolutely. I think there is potential utility of the adult population.

CHAIR YANCY: Okay.

DR. HOPKINS: We just don't have the data to say that without any codicils.

CHAIR YANCY: All right. So other comments on this issue, that is, extrapolating the aggregate data in the pediatric population that we've seen today to the adult population? We've heard from Dr. Page, we've heard from Dr. Hopkins,

we've heard from Dr. Jeevanandam, we've heard from Dr. Neaton. Are there any other comments the panel wishes to make?

Dr. Hirshfeld.

DR. HIRSHFELD: Just one thing. My sense is if the device is approved, and is approved in an adult indication and there is a post-market surveillance study, that unless that study involves some sort of an efficacy assessment, we will never know whether this device is of any benefit in adults.

CHAIR YANCY: I may need clarification from FDA at this point, because the post-marketing or post-approval study typically is to capture real world use experience, look for any uncovered, unanticipated adverse events, and to derive data on longer term performance, but not primarily on efficacy. But I don't want to misspeak.

DR. ZUCKERMAN: That's correct for the intended indication. I think perhaps we've gotten off track a moment.

I initially asked the panel to

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elaborate a little bit more on whether the secondary endpoint effectiveness data could be extrapolatable to the adult population in preparation for the next question. And I think there has been a range of views and a healthy discussion.

Regarding post-approval studies, the way I would suggest that the panel always look at this is never jump the gun. Point number one is to figure out if you have reasonable assurance of safety and effectiveness for an intended labeled population. Make that discussion and then once you have perhaps chosen the appropriate population, post-approval studies, as Dr. Yancy has pointed out, have a certain niche and we'll go over the particular slide that tells us what the potential uses of a post-approval study are.

That's correct, Dr. Yancy.

CHAIR YANCY: Thank you. So let's do this so we can stay on track. With regards to this specific query of the secondary effectiveness data and extrapolating that specific point to a broader

population, the panel was equivocal. We didn't have a strong statement yea or nay or as an aggregate, but individual members had strong feelings.

On question four, where we were discussing in bullet point A whether or not we can take the aggregate information and extrapolate that, in general, from the pediatric to the adult patients, we have strong opinions expressed in the panel that that is at least problematic, if not unacceptable.

Am I misstating that at all?

(No response.)

CHAIR YANCY: So we need to go on to B under question four, which is, "Please discuss whether the proposed labeling accurately informs physicians as to how to use this device and if the device can be indicated for placement between pericardial surfaces."

This is an issue that Dr. Katz spoke to several times. Do you want to start this discussion?

DR. KATZ: I would love to. Unfortunately, I think we don't have enough information to make the statement that this device would work in between pericardial surfaces. In the information that we have here, the study was very limited. Also, as far as how to use this device, again, it's in such a limited area, I would be a little bit uncomfortable extrapolating it. The --

CHAIR YANCY: Marc, let me help you. I may have misdirected you by not taking the time to read the proposed labeling language. Because the question is in the context of that language, whether or not this language gives the practitioner sufficient information. And it goes as follows.

"REPEL-CV is a surgical adjuvant indicated for reducing the incidence, severity, and extent of post-operative adhesion formation in patients undergoing cardiac surgery via sternotomy." And then there's a contraindication statement. "REPEL-CV is contraindicated in patients in whom a Ventricular Assist Device (VAD) is implanted."

And then the question that we are addressing, 4(b), is whether or not that language that I just read accurately informs physicians as to how to use this device and if the device can be indicated for placement between pericardial surfaces.

DR. KATZ: In that case, I'd have to say no. Because that statement, if just reading that one statement would give me the sense that it would reduce the incidence, and severity, and extent of adhesions anywhere it was placed.

CHAIR YANCY: And I think that we've already determined that the incidence is not affected or that's our feeling. Is that right? Okay.

Dr. Jeevanandam.

DR. JEEVANANDAM: Can I make a comment on the labeling itself? Because I think the labeling itself needs to be changed, right? Because we're not saying it's going to be indicated not for reducing the incidence, but indicated for reducing the severity and extent of postoperative

adhesions.

CHAIR YANCY: So that's an acceptable statement.

DR. JEEVANANDAM: And then it says in patients undergoing cardiac surgery via sternotomy. And I think that's where there needs to be a limitation in maybe pediatric patients or in this particular group, you know, neonates undergoing cardiac surgery, but we can't expand that to adults undergoing cardiac surgery as well --

CHAIR YANCY: So what I'm hearing --

DR. JEEVANANDAM: -- with the data that we have right now.

CHAIR YANCY: So Vall, what I'm hearing you say is it should have the incidence struck and then you're saying that it should have pediatric patients added. Not just patients, but "in pediatric patients." Is that what I'm hearing?

DR. JEEVANANDAM: You know, pediatrics, that's a wide range. So, --

CHAIR YANCY: So give me better language.

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DR. JEEVANANDAM: -- if it's an 18-year-old, --

CHAIR YANCY: So neonates, is that what you're --

DR. JEEVANANDAM: Well that's what this study showed. It was for neonates.

CHAIR YANCY: Dr. Zahka.

DR. ZAHKA: You have to remember that after the second stage, at six months, give or take, they have to have another operation at 18 months to four years. I think it is very reasonable that if we're comfortable saying that it works as a newborn, it leads you out to six months, we have to be comfortable with the next step in saying it should be useful at six months, to allow you to get to three or four years. Yes, we don't have the perfect data, but to just make it in neonates, I think is too restrictive.

CHAIR YANCY: So your input would be pediatric rations.

DR. ZAHKA: Yes.

CHAIR YANCY: Other comments, please.

Just a minute. Dr. Weinberger, please.

DR. WEINBERGER: I think that what captures your feeling and what captures mine is that there has to be an expectation of a repeat operation within 24 to 36 months. If there's no expectation of another operation in the near future, I don't think that we're on any kind of strong basis to recommend the use of this product or to use that indication.

CHAIR YANCY: So your contribution to this labeling statement is that patients and surgery need to be further modified as an expectation for a repeat surgical procedure.

Just as another point of clarification, are we going in the direction that FDA wishes by dissecting this?

DR. ZUCKERMAN: Yes, but let's take a step back a moment. I think we're jumping ahead to D, which is perhaps construction of a more appropriate labeling, 4D. So let's make sure we answer. 4A, you've summarized, Dr. Yancy. 4B, we've heard comments.

CHAIR YANCY: 4B, specifically, is running 100 percent no, so far, because everyone has had a modification of what they see and indicating that it doesn't completely inform the practitioner.

DR. ZUCKERMAN: Okay, 4C.

CHAIR YANCY: We haven't gotten there yes. You're jumping the gun, now.

DR. ZUCKERMAN: Oh, okay. And then I'd like to discuss what an intended use statement should comprise when we get to 4D.

CHAIR YANCY: Terrific. I think we can address 4C. Doctors Blackstone and, I'm getting tired, --

DR. JEEVANANDAM: Jeevanandam.

CHAIR YANCY: -- Jeevanandam. I like to call you Vall.

DR. JEEVANANDAM: That's fine. It's easier.

CHAIR YANCY: If you could address 4C for us, succinctly, that would be great.

"Please discuss if the data obtained

from experience with Ventricular Assist Device patients is applicable to patients with other types of prosthetic devices."

DR. JEEVANANDAM: I think they're putting a contraindication on this device with the experience with two patients. And you know, with a graft that went straight up the sternum where a lot of times we put grafts around the sternum. You could put a membrane like this over the right ventricle and that's what you want to protect during your re-entry. And then you have other types of prosthetic devices. Now, does that mean with any graft, with any valve? And I think that that is not appropriate.

And I think the other problems, in terms of ventricular assist devices, this experience might have been with a HeartMate, it sounds like it was in the early 2000s, so it's probably with the HeartMate VE. And there are other devices that are coming out now that have much smaller grafts. They have grafts that go in different places. You know, the Jarvik goes down

to the descending aorta. So I think if you just ventricular assist devices, that may be way a broader spectrum. But on the other hand, --

CHAIR YANCY: So your answer --

DR. JEEVANANDAM: -- we're saying that we can't go to adults anyway. So I don't know if this matters.

CHAIR YANCY: Well, no. We have to frame it up. We can't quite do that. So what you're saying is that not only does it not apply to contemporary ventricular assist devices, but it also would not apply to other prosthetic devices.

If there is no variance on that, then I would like to keep going to D, because we were already framing that up.

Are you comfortable with that, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. Okay, in looking at 4D, which gets to the heart of the matter and IFU statement, I'd like the panel to be cognizant of two features. Number one, we're talking about a hypothetical here. If you engage in a discussion

about an appropriate IFU, it doesn't mean that you have to vote yes.

The second point is that in a primary indication statement, we want to truthfully label the intended patient population. And I would like to remind the panel that when we put the word pediatrics in a regulatory context, that's I believe, up to age 18, which may or may not be appropriate here. Some other wording may be appropriate.

And the second thing that I think that panel members have already gotten to is that we want to see if we can simply state what the product does in the intended patient population.

Thank you.

CHAIR YANCY: Thank you for that direction.

So, if I capture what we said previously and we're addressing 4D, "Please discuss whether there are any other issues of safety or effectiveness not adequately covered in the proposed labeling."

What I've heard so far is to strike "incidence," to modify patients by language that Dr. Zuckerman tells us that we need to craft more carefully, and to also modify surgery, i.e., with the intent of or the expectation of a repeat surgery. If that is correct, then we can continue to morph this.

Please, Dr. Hopkins?

DR. HOPKINS: For a number of reasons, I would probably prefer not to see the term pediatric in the labeling statement, but rather just restrict it to patients undergoing surgery via sternotomy who are at elevated risk for needing another sternotomy in the near future, or within six years, of something like that. That gets rid of all the elderly people right off the bat. So you almost don't even have to say that.

The ventricular assist device, I don't think we finished that. I think we do have data that suggests that it may be contraindicated for placement between a rigid prosthesis and the sternum, or it is not suggested for that. And is

it possible to put that it's not contraindicated in adults, but effectiveness has not been proven yet. Can that be an asterisk to the labeling statement?

DR. ZUCKERMAN: Okay. A contraindication statement is usually put in when there are definitive evidence, when there is definitive evidence that you would not like any of your cardiac surgical colleagues to ever do this particular maneuver. Given --

DR. HOPKINS: Me or the sponsor?

DR. ZUCKERMAN: Excuse me?

DR. HOPKINS: Me or the sponsor?

DR. ZUCKERMAN: No, the sponsor is out of the picture right now. You have a very important job here this afternoon, as you know. And given that you are understanding gravity of the situation, is it appropriate, based on the data that we have, to say that we should never do this in a contraindication statement is the point on the table.

DR. HOPKINS: I don't think you can say that.

CHAIR YANCY: So, Dr. Hopkins, can you respond within that context?

DR. HOPKINS: I would say you cannot say that, based upon the data that is here.

CHAIR YANCY: And Dr. Katz, you had a comment.

DR. KATZ: Well, that's where my question came from earlier today, is that I'm not sure I understood how that got to be a contraindication from the information that I have. It was used in two patients and it was not effective. But not being effective does not make it a contraindication.

CHAIR YANCY: But let me just remind you that this language was brought forward by the sponsor, as proposed language.

DR. KATZ: It makes me wonder that there is information about other issues that came up as to why it would have been made that way, I guess. From the information I have, I have no reason to think it should be a contraindication.

CHAIR YANCY: There are comments here.

Dr. Domanski, then Dr. Somberg.

DR. DOMANSKI: Yes, I certainly agree. I don't think we have the basis for saying it's contraindicated. But I do think we have the basis for saying that the indication should be limited to very early in life. I mean, we can argue about whether it's neonate or not, but I think pediatric is too broad. I don't think you've demonstrated safety and effectiveness in adults.

And I don't think you've demonstrated in a pediatric population at the upper reach of that. So, of course we haven't demonstrated a contraindication, but I think we ought to be very clear that it's indicated only very early in life and for a specific purpose, because that's what they've demonstrated.

CHAIR YANCY: So with regards to this question, Mike, would you strike the contraindication statement?

DR. DOMANSKI: Yes. I would be very cautious on the basis of two patients about putting in a contraindication statement.

I know the sponsor said that, but you know, we're happy to disagree with them about other things. I don't think we have a strong enough thing to put a contraindication in. Because you know, there may be somebody who needs to use it or feels that they need to in some case that I can't come up with, necessarily. We don't have the basis for saying don't ever do it.

CHAIR YANCY: Dr. Somberg.

DR. SOMBERG: Well, I thought that the sponsor's statement that in those two patients with that particular device which has the constant motion, there was a rapid breakdown of the material. It wasn't made to handle that. It was very demonstrable and I think we should give deference to that observation. I don't think anyone has ever forced someone to study something when, you know, in two consecutive cases the material disintegrates. And that's the point they were making.

So I think that's important. It should be left in there. If you don't want to call it a

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contraindication, you can call it that it does not work when it is constantly vibrated against, etcetera. But it wasn't a, you know, very marked vibration.

I must say I do agree with the people who said pediatric because that's the overwhelming experience here. And to go beyond that, I think we need to see some patients.

CHAIR YANCY: So, if I can attempt -- yes, Dr. Zuckerman?

DR. ZUCKERMAN: No. And that's, material like that, Dr. Somberg, can be put in a warning statement in the labeling.

CHAIR YANCY: So if I can attempt to frame up what we've said about 4D and keep us on task and on time, "Please discuss whether there are any other issues of safety or effectiveness not adequately covered in the proposed labeling." And we all have the labeling before us.

The panel would advise that we strike "incidence." The panel would advise that we modify the term "patients" and use something that captures

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early in life or pediatrics. And the panel would advise that we do something or say something that suggests patients at risk or at high risk for a repeat operation. And the panel would advise that the contraindication may not be precisely correct, but there should be language to reflect a very very limited experience that was not positive in patients with the VAD. Is that fair?

(No response.)

CHAIR YANCY: There's enough head nods. I think the panel is okay with that. Is that acceptable, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. But because this is an important point, just truth in labeling, I have two questions. Perhaps the sponsor wants to clarify again why they think this might be a contraindication.

The second question I have about just the general construct of the labeling, which is the point of 4D, is if you go to Section 10 of your panel pack, which is the proposed label, there is no discussion of the first three small feasibility

trials, which do have some additional safety data. They do have the experience of the two LVAD patients. Would the panel recommend that in addition to the pivotal trial that we've discussed here this afternoon, that that data be put in the general clinical section and safety result section?

That's been our general policy for labeling, that we describe the whole PMA experience.

CHAIR YANCY: It seems to be a fairly straight forward administrative question. Is there any disagreement with that?

Dr. Blackstone.

DR. BLACKSTONE: I think if you just broadly say LVADs, that is misleading. I think that you have to either say what kind it is and how it was rooted or something because I think it is applicable historically.

CHAIR YANCY: Dr. Katz?

DR. KATZ: Dr. Zuckerman brought up the point of asking the sponsor about why they came up with the term contraindication. That would be

helpful for me because I think that is the one adult population where, if this were approved, that it would be most likely used.

CHAIR YANCY: As a point of protocol, are we able to allow that response now or request it after the break, when the sponsor has a chance to respond to everything?

DR. ZUCKERMAN: To keep continuity, let's have them talk right now.

CHAIR YANCY: If you could have a limited discussion about that specific point, please.

DR. PINES: The contraindication was placed in the labeling precisely for the reason that Dr. Somberg mentioned. We have over the past eight years worked very hard and spoke to a lot of people about doing clinical studies in post-operative adhesions. You can be sure that if in fact there was a patient population other than pediatrics, we would have pursued the adult population. Everyone that we had spoken to essentially told us there is no clinical model

that, in a practical time window one can assess post-operative adhesions. So that's number one. The pediatric is exclusively the only model available for assessing efficacy. So that's number one from our perspective. And I can assure you, as I said before, we wouldn't have done a study in the pediatric population that has all these difficulties that I think we all heard about, unless there was no other option. Okay?

With regard to the LVAD, there were two LVAD patients and, in fact, we had spoken back in 1998. In 1998, the LVAD that was used was the HeartMate LVAD. The graft was essentially this wide and it went right across the mediastinum. That's the only experience that I'm talking about. There were absolutely no safety concern. There was no adverse events. What the patient had was a lot of adhesions because the barrier was not in place for the time required.

As you know probably much better than I do, LVAD patients have extensive adhesions. Okay? So I think the fact that two patients had lots of

adhesions, does not make a story with regard to LVAD.

If in fact there are LVAD devices currently that are marketed that we can use that are not placed across the chest, if you will. And if in fact the patients come back in a reasonable time, that's something that we would certainly want to consider.

The only reason we took the LVAD out and put it as a contraindication because for us, it was an easy decision. The product does not work in cases where you have all these pulsating movement.

And it would not be productive to put a warning. We wanted to be very clear. You're not going to achieve the kind of efficacy that we think you get with pediatrics in the LVAD patient population.

And that was the reason. Strictly based on efficacy and to the point that Dr. Somberg raised.

CHAIR YANCY: Any focused comments or anything in response to what we've just heard?

Thank you.

Dr. Katz?

DR. KATZ: Just actually as a quick question, so I'm absolutely clear. It still seems to me is that what you're talking about is a lack of effectiveness, not a contraindication.

DR. PINES: Correct. Absolutely correct.

DR. KATZ: Okay, thank you.

CHAIR YANCY: Thank you again. Dr. Somberg?

DR. SOMBERG: I just wanted to say that from my point of view it's not that you were told that the pediatric was the only model and therefore, you should be punished for using that model. It's just that that's what we have, it's my impression, that's what we have the experience with and, therefore, the indication would be for that. And as we get more experience with other populations, there are many ways to get experience, by the way, you should certainly broaden the indication.

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But right now, when we have like 150, 160 patients all together exposed to this system, probably 95 percent to 99 is in the pediatric, very pediatric age group, I think that has to be noted in the indications.

CHAIR YANCY: Dr. Zuckerman, my sense is that we've addressed for A, B, C, and D and that we are less enthused about a specific contraindication but think language needs to be there to address the experience. Language which can be strengthened by the inclusion of the entirety of the preclinical data in the label packet insert that describes specifically what the LVAD experience was in the context of what we just heard.

DR. ZUCKERMAN: Good.

CHAIR YANCY: Let's go to the final question. And I appreciate the panel's patience with this process.

This is post-approval study and there are three bullet points under question five. We have the question before us. We heard FDA and we

heard sponsor present comments on the post-approval study.

The questions are A: "Please discuss the appropriateness of mediastinitis as the primary endpoint versus a composite primary endpoint;"

B: "Please discuss if a 4 percent non-inferiority margin is clinically significant and an acceptable margin of difference;" and

C: "Please comment on the appropriateness of the length of follow-up to evaluate long-term safety."

If we can start with A so we can keep these things framed on compartments. Dr. Neaton?

DR. NEATON: I think Dr. Zuckerman wanted to say something first.

DR. ZUCKERMAN: Yes. Just for the panel's ease of reference, they may want to go back to slide 61, which points out the reason for post approval studies from a regulatory perspective.

CHAIR YANCY: Is it possible to project that slide?

DR. NEATON: Maybe while they are

looking for the slide I can make a general comment.

So I actually was intrigued by the sponsor's study, the pivotal study, and I think made strong arguments in a tough population to kind of choose one to demonstrate efficacy. And where I kind of sit primarily is with still some uncertainty about safety. And we've had a lot of discussion going back and forth in the adult population.

And I guess these are three questions which are reasonable, but I guess I would like just for the record say that I think that it doesn't make any sense to me at all to address this question, to address the question of safety now in an observational study. We've already heard arguments about using the historical data from the registry which is probably not even suitable. I think a trial is needed here. You can't, you're simply, the risk of bias when you're looking for differences as small as what are being hypothesized is so great in an epidemiological or observational study, that I think, you could just be overwhelmed.

And so, I think you need to do a trial in adults to understand their safety in the short-term.

And I think you know, one of the outcomes clearly should be the one that is proposed here, but it probably should also include other kind of a broader set of outcomes to kind of ensure the power is adequate.

CHAIR YANCY: I don't want to put words that were not intended. So are you rejecting the post-approval study?

DR. NEATON: Yes. I don't think it makes any sense. I think from the point of view of both what we've heard from the registry, as well as from the point of view of I think of where we are in sitting with the uncertainty around safety, particularly in an adult population where it hasn't been studied.

And to me, the idea of extrapolating the efficacy to adults and becoming more convinced about that, that there's the uncertainty about the safety that I'm still concerned about and I want to see that demonstrated in a proper trial.

CHAIR YANCY: So is it perhaps appropriate to say that especially when you view the tenants on this line, that you don't reject the notion of a post-approval study, but this study as intended, particularly to capture the broader population?

DR. NEATON: Yes.

CHAIR YANCY: Dr. Blackstone.

DR. BLACKSTONE: I agree. That was going to be the question I was going to say because I don't want to answer these three questions. Because I also don't believe this is a right trial.

CHAIR YANCY: Dr. Jeevanandam.

DR. JEEVANANDAM: I have a question about a post-approval study. Right? So is this implying that we are approving this for adults and we're testing this in adults? Because we -- or is this a post-approval study just for the neonates?

Because if it is, then I agree with them. Then this is really not a post-approval study, this should be a separate study.

CHAIR YANCY: So before we lose our

direction, let me get two inputs from FDA. Matt.

MR. HILLEBRENNER: Yes, I just wanted to clarify that in case this was not clear, the post-approval study can only include patients who are included in the indicated use population.

So, and I don't want to put words in anyone's mouth, I heard more or less overwhelming evidence that this indication would be limited to neonates or pediatrics, or something other than including all comers for cardiac surgery. So the proposal that was made by the sponsor was based on their proposed indication that included all of those patients. The eventual post-approval study would only be in the eventual approved indications for use.

So, I think --

CHAIR YANCY: So then, if the label is modified to say early life or pediatric, then that is the only population in which the post-approval study can occur. Okay.

Are we then comfortable addressing these three questions in that context?

DR. SOMBERG: I must say I'm not, not to believe your regulatory interpretation, but I think post-marketing studies can also be used to broaden a population and it depends on how you slice this. But for instance, if you had a study that looked at ventricular tachycardia, you might have a sepsis one study that looks at polymorphic ventricular tachycardia. So if you have a study that looks at one age group, you know, it's not their dichotomous, pediatrics are so different than adults, but it hasn't been shown -- it's more of a chronicity issue here of when you would look at it. And there is also an issue of when you could, you know, the type of study you would have to do.

So, a post-marketing study could possibly look at a population that was broader than the initial approval.

CHAIR YANCY: I think this is an issue of language because this does not exclude doing the kind of trial that Dr. Neaton has suggested, that is a structured trial in a different patient population. This is a post-approval experience.

MR. HILLEBRENNER: Right. So the trial that we're discussing here would be done as a condition of approval under this PMA.

The trial that you're talking about and the trial that Dr. Neaton talked about would certainly be doable and technically would be post-market in that it would be subsequent to approval and the final decision. But that would be done under an investigational device exemption, separately from the PMA. That would be a new IDE and later a new PMA marketing application.

CHAIR YANCY: Dr. Zuckerman, --

DR. ZUCKERMAN: Yes.

CHAIR YANCY: -- steer us clear here.

DR. ZUCKERMAN: I just want to again emphasize that of course the FDA wants to see more data on this technology and other technologies, but you really have to understand the point of a post-approval study. And again, I need you to think hypothetically.

If the panel does think that there is a more appropriate limited indication for the early

age group, what would be appropriate, given that these are the reasons why we do post-approval studies.

Now, certainly if the sponsor also wants an adult indication, we would be more than willing to design an IDE trial along the very appropriate lines that Dr. Neaton indicated. But that's not the question under discussion right now.

CHAIR YANCY: Any comments from the panel?

Dr. Hopkins.

DR. HOPKINS: This is a question. Let me make sure we're clear. If in fact the label says or the labeling is restricted to pediatric uses under the age of 18, then the point of the post-approval study would be to gather more information on things like mediastinitis in which the pre-approval studies were inadequately powered. It would be a separate study that would be proposed to extend the indications for adults or other purposes. Is that correct?

DR. ZUCKERMAN: Not quite. So, let's

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take it a little step further.

Suppose hypothetical you think that the approved indication is for the early age population. As you pointed out, this study was done at perhaps the 15 best centers in the United States. So we look at our chart over here and we want to ask the question, do we want to make sure that community performance can get the same safety results in the labeled population at different centers? And now we have a certain control safety rate from this study done at excellent centers.

But what you posed Dr. Hopkins, is the hypothetical if we don't believe that there's reasonable assurance of safety and effectiveness, can we somehow get that data in the post-approval study? And the regulations are clear on this. The answer is no.

This for the points listed on the slide. So I need the panel to think about what are the appropriate reasons for doing a post-approval study here.

CHAIR YANCY: So under the auspices of

a more limited patient population with all of the provisos we have collectively agreed upon for the label language, if this were approved and if it were approved with a contingency of a post-approval study, we still have three bulleted points we need to address.

Dr. Somberg.

DR. SOMBERG: I think one reason to do the post-approval study would be to broaden our understanding of the safety. And certainly the end was inadequate to study things like mediastinitis, etcetera.

The other thing would be to broaden our understanding of the inter-operative interval, which I think is most important. And there are cases where you might intervene. My colleagues do a procedure. It's delayed for a while, it's poor growth or something or other and you get a greater chronicity of that. And there might be valve cases, etcetera where you come back or tectologies you come back in when they're a certain age, you might do that.

And therefore, I worry about us limiting ourselves to saying oh, you can do this under a post-approval study and the other one you have to get another IDE and do a PMA application, when we're talking about broadening a population in a very special group where, you know, for years the FDA told the sponsor that the pediatrics are the only people who are going to be re-operated so that's the only one to do a particular study on. So now how are we ever going to -- are we not blocking ourselves, everybody here, is blocking themselves, painting themselves in a corner, and will never be able to make a statement beyond this very small group.

So I think what we can do is we can look at safety in a broader real-world situation and we can also look at increasing the age of the patients.

CHAIR YANCY: I think we all accept the premise that a post-approval study will provide more information regarding adverse events, expected and unexpected.

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But if we think about an unlabeled patient population, let's be very precise because the hour is running late. Is it appropriate to use mediastinitis or some other composite primary endpoint in a post-approval study. That's the precise question right now. Is there enough concern about mediastinitis that that's a primary endpoint for the post-approval study in an unlabeled population exposed to a post-approval study or is there another endpoint?

Dr. Domanski.

DR. DOMANSKI: Yes, I mean, there's been a lot of discussion about mediastinitis. It seems to me that it would at least be a component of a composite endpoint. So I guess the answer is --

CHAIR YANCY: Would you prefer it as the single or primary endpoint?

DR. DOMANSKI: No, I always prefer it as a composite endpoint.

CHAIR YANCY: And what else would be in that composite?

DR. DOMANSKI: I think, I guess death would be part of that. It may be that, you know, I think maybe referring to the other elements, I'd rather refer to the surgeons who were facing the complications of this. So let me punt that to those guys. But death should be one of them.

CHAIR YANCY: So additional input on this endpoint.

Dr. Jeevanandam.

DR. JEEVANANDAM: So again, so this is going to be a post-market study on the approved patient population?

CHAIR YANCY: Yes.

DR. JEEVANANDAM: I mean, I don't know if it needs to be done, but if it needs to be done, I would propose a composite primary endpoint including mediastinitis and bleeding and perhaps take back for tamponade and death.

CHAIR YANCY: And so you are correct, when we get to the point of casting a vote, we may or may not approve a post-approval study needs to be done. If we vote yes, we may say yes with or

without. So you are right. In the context of the hypothetical circumstance where it is approved and we vote yes for post-approval study, then the endpoint you're suggesting is a composite of mediastinitis, bleeding, and death. Is that right?

DR. JEEVANANDAM: That's correct.

CHAIR YANCY: Okay. Dr. Blackstone.

DR. BLACKSTONE: But I think death that you're talking about is death at the re-operation. Isn't that true? Okay, not death in general.

CHAIR YANCY: Okay. That's an important clarification. Thank you.

Anybody in variance with what I just said on 5A?

(No response.)

CHAIR YANCY: 5B is, please discuss the non-inferiority margin. Is it clinically significant?

Is there someone that can bring us to that answer quickly? Dr. Neaton? Dr. Blackstone? I'm willing to bag.

DR. NEATON: I don't think there's a

quick answer to this, but you know, and also, it keeps coming back in my mind to what is the comparison group. Not inferior to what? And so I just would prefer, at this point, not getting into any details. And that's something that requires a lot more thought than I can give at this panel meeting.

CHAIR YANCY: So we can certainly defer that if that is in fact the way we need to go.

Dr. Blackstone?

DR. BLACKSTONE: Yes, I was going to say, I was asking the same question. And that is, what would be that standard? But then I would also go one step further and say that the FDA, for valves and others, have objective performance criteria mechanisms that is not necessarily based on a delta, but is based on other criteria. And I would think one that is consistent with the criteria that you have been using for other devices would be reasonable here.

CHAIR YANCY: Well the one thing --

DR. BLACKSTONE: We could go that

route.

CHAIR YANCY: The one thing that I saw today was that you could surmise a soft rate of mediastinitis based on what we saw in the afternoon analysis that FDA did for us.

And so the question would then be, if we take that rate, I think it was about five percent, what is the range around that rate that would be acceptable for non-inferiority.

DR. BLACKSTONE: I just don't know what it would be for the composite endpoint that you're talking about.

CHAIR YANCY: My sense is that this is specifically about the mediastinitis component of the composite. I think that's a yes. Yes, it would be specifically about the mediastinitis component of the composite.

DR. ZUCKERMAN: Okay, Dr. Yancy, would you like some more clarification on that?

CHAIR YANCY: I would love it.

DR. ZUCKERMAN: Okay. You know, certainly again, at the beginning of the day, the

Agency and sponsor had a certain construct based on where we were. We have moved a long distance today.

I think what I've heard the panel indicate is that you would be willing to live with a relevant important composite safety endpoint as the primary endpoint. Consequently, our usual construct, Doctors Neaton and Blackstone, would be to compare that safety data with the recent data generated in the pre-approval pivotal trial to see if in a new set of centers we were in the same ballpark in terms of safety, that general construct. And would that be okay with you, as long as both the sponsor and FDA could come up with a clinically meaningful delta that the sponsor could show that aren't above is where we're at.

CHAIR YANCY: Response from either Doctors Neaton or Blackstone, please.

DR. BLACKSTONE: And how would you construct that delta? You have constructed on it on the basis of confidence limits for valves. Why not do the same?

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DR. ZUCKERMAN: We can always generate an OPC from the literature. But here, as Dr. Neaton pointed out, we have recent relevant historical line data that could be used as a control. We have a new prospective data set. And the opportunity would be there to construct a non-inferiority hypothesis with that recent relevant control, rather than utilizing a journal article where often a lot of the data that both the sponsor and FDA would like to know isn't published in the journal article.

But that, generally, is the question on the table now. What would you use as the control and any other general recommendations?

DR. NEATON: I mean, just, I mean, again, this requires a little bit more thought. But I would not use the data from the randomized trial because I think there's enough concern that maybe the rates there are high. And so, you don't want to kind of -- the issue is is whether or not the trend and, I don't know if I want to call it a trend, but are the concerns that have been

expressed today about mediastinitis kind of real and put some bounds on that.

And so, I go back to the idea, I don't see how you can establish that without a randomized comparison. But if I were going to establish an historical control, I'd probably use the literature to get a more stable estimate of what that incidence rate is, as opposed just to three or four cases from the study.

DR. HOPKINS: I think the problem with that is that the literature is a moving target and is always five years out of date. And this is the incidence of mediastinitis is really changing rapidly.

I think as we discussed earlier, STS doesn't have that data, but the Congenital Heart Surgeons Society does. So there are databases out there that we could get relatively concurrent data on which to construct a non-inferiority trial.

So I think that to answer your question very specifically, I think it could be stated such that in the first instance, you'd compare to the

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control arm of the randomized study. And in the second instance, you'd compare to some kind of concurrent database that is appropriate, such as the Congenital Heart Surgeons Society. And thirdly, in terms of the delta, I would propose three percent.

CHAIR YANCY: So what I'm hearing from the panel is that we are very tentative about really prescribing a margin. And we really need to understand the reference population and the origin of those data. And that this something that would take more time to evolve. Is there a brief comment on this, Dr. Somberg, specifically on this issue?

DR. SOMBERG: Yes, specifically on the issue. And I think we're pushing too hard to develop a non-controlled study and I think there should be a control, but a controlled study. One proposal was for a randomized one and we could have a registry with a non-randomized where you would have real world experience, you would have people entered into it who would have the device who have it -- you could look at toxicity, side effects, and

you can also look at some efficacy, a simple efficacy endpoint.

So there are a number of alternative designs than what just we summarized.

CHAIR YANCY: So that we can maintain some progress, let's also discuss 5C. "Please comment on the appropriateness of the length of follow-up to evaluate long-term safety."

There are several panel members from whom I have not head in the last several minutes, so please feel free to give us your thoughts on the appropriateness of the length of follow-up.

Dr. Jeevanandam.

DR. JEEVANANDAM: I mean, I guess in the context of a post-approval study for this pediatric population that we're anticipating them having another re-operation, obviously when they have their re-operation, they don't need to be followed up there. So, you probably need to follow them up until they get their re-op.

CHAIR YANCY: Well the language now says an eight week follow-up.

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DR. JEEVANANDAM: I think that would --

CHAIR YANCY: Is that acceptable or not?

DR. JEEVANANDAM: Well, you know, from an efficacy point it's not going to be acceptable. But I guess if you're looking at it purely from a safety point of view, you would get all your endpoints, which are mediastinitis and bleeding. You won't get your endpoint of mortality from the second operation, but you'll get your other endpoints, if you're going for eight weeks.

CHAIR YANCY: Other comments on the appropriateness of length? Dr. Hirshfeld.

DR. HIRSHFELD: Yes, I would agree with Vall. I think we're talking about now a study that's entirely different than the one that was conceived when this document was written. And I think that the outcome of the second operation is a critical portion of both the safety and the efficacy endpoints. So, I think that should be included.

CHAIR YANCY: So if I can, unless

there's a burning -- Dr. Blackstone?

DR. BLACKSTONE: No, it's exactly his point. And that is, that the eight weeks after the initial thing doesn't capture anything about the re-operation, which is what we're concerned with. So I think it would have to be both early, but then after the subsequent re-operations, and if it is put in again, there may be multiple per patient, in fact.

CHAIR YANCY: Okay. So that's good input. So, Dr. Somberg?

DR. SOMBERG: We did see a mediastinitis at 120 days, if I remember correctly, in one case. So, I think you have to, and we're talking about six cases all together, so I wouldn't -- 50 something days, 56 days, is not 120 days. So I think that should be taken into account.

CHAIR YANCY: So based on the paragraph that is stated in item five, if I can again put together what the panel has said, this would be an on-label population. The control arm would not be the society of thoracic surgeons registry, but

would be another relevant database. The length of the follow-up would have to be inclusive of a time that captures the second operation.

The endpoint would have to be a composite of mediastinitis mortality and bleeding. There are secondary endpoints listed that in general should be the singular components of the composite and we are not yet prepared to assign a non-inferiority margin. But there has been one suggestion by one panel member on what that might be.

Does that capture the flavor of the panel?

(No response.)

CHAIR YANCY: Dr. Zuckerman, is that a satisfactory response?

DR. ZUCKERMAN: Yes, that's very helpful information, in terms of where we are right now.

CHAIR YANCY: Great. I would recognize that this has been a very detailed and deliberate discussion. I want to thank the panel members for

that.

We cannot yet take our break because we are interested in commentary from all engaged and involved individuals. We had the opportunity for an open public hearing this morning. We were not able to host someone at that point in time, but we do have a speaker now. So we will proceed with the second open public hearing of this meeting. There is a transcript for the comments you are about to hear that are at our site and you can follow along with the comments as it comes forward.

I'd like to welcome Peter Lurie to the podium. Thank you for your patience, sir. I know you wanted to go earlier, but I appreciate your indulgence.

DR. LURIE: Thank you very much. And I won't read all of this. I'll summarize the most important points.

I am Dr. Peter Lurie. I am a physician. I am with Public Citizen's Health Research Group. I have no conflicts of interest to declare. Public Citizen takes no money from either

government or any industry.

We believe that for an adhesion barrier to be approved, there should be a clinically significant improvement and, to quote the statute, "a reasonable assurance of safety." We don't think that either has been demonstrated in this case.

Let me start with efficacy. I would agree that the severity of the adhesions appear to have been reduced, if one believes the non-validated outcome measure that is used here.

And I also agree with the panel that there is no evidence that the incidence of adhesions has been reduced. But actually, if you look closely at the data, there is not evidence that the extent of those adhesions has been reduced either. The percentage of the operative surface area with grade zero adhesions had a mean of 2.9 percent versus 0.90 percent, p of 0.32. So I don't think that you're showing that the extent of adhesions is reduced either.

Now all of this assumes that one buys the adhesion scale, one that has never been used

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before in any other study except to develop this product. And so you know, I think we need to be very careful in that respect. And I think that makes me, at least, look more carefully at the data operative time, because the operative time are the closest thing that we have to any kind of clinical benefit or assessment of clinical benefit for this product.

As you have heard, the median times for operation were not different from one another, although that is true statistically, they were practically identical. And for reasons unclear to me, if one looks at slide 82 of the FDA's presentation, this was the slide that the FDA elected not to present, if you look at slide 82, you see that the data on the dissection times with the individual raw data are practically identical. And it makes me be rather uninterested in the post hoc statistical analysis by the sponsor from which they excluded certain patients post hoc, you know, almost at their whim, and then came up with a claim of a five percent reduction in operative time.

The plain fact is that the operative times are the same. And they are practically super-imposable if you look at the raw data.

I would also point out that the analysis of whether or not the operative time is greater or lower for the REPEL group, depending on whether or not severe adhesions are present, is really irrelevant, because as a patient, you don't know and nor does your surgeon whether or not you will have a severe adhesion. So all that matters is the basic, overall aggregate data, and those data are not statistically significantly different.

I also have not heard a power calculation for that, although we have heard many times that it's impossible. I daresay that seeing as though these are continuous outcome variables, in general, the statistical power is not so bad and better than for the categorical ones for which there is a claim for at least some of these to have sufficient statistical power.

Now, in fact, therefore, I think that there is no evidence of clinical benefit, and it's

interesting to remember that historically, there was a requirement for clinical benefit, at least in another area in an FDA draft guidance.

Back in 1999, the FDA had a draft guidance for abdominal and pelvic surgery. And they said "Optimally, endpoints should directly address clinical outcome measures . . . The most direct method of providing valid scientific evidence of effectiveness is to select an appropriate clinical endpoint(s) and design a study that may demonstrate a statistically significant and clinically meaningful effect on recognized adhesions-related morbidity."

Now, this didn't sit very well with the Adhesion Barrier Task Force, a group of manufacturers that included SyntheMed's predecessor company. They wrote in to complain about that. And not long after that, the final guidance was issued by the FDA in which the whole idea of clinical outcomes had been downgraded. The clinical outcomes associated with adhesions may be reasonably assessed by parameters which are more

immediately measurable and potentially less confounded they said.

So once we thought that clinical outcomes were important, somehow we don't anymore.

This study was not blinded. And we have heard an analysis by the FDA and Dr. Xu about a multi-variable analysis that took into account blinding, well, un-blinding. But that analysis dealt with a single surgeon who became un-blinded.

What I have not heard mentioned at all today is reference to page 51 of the company's summary of safety and effectiveness. Let me quote from it. Although REPEL-CV should be absorbed within 28 days, a category of pathological finding described in that document as "implanted test material or a fibrous capsule, or other abnormal tissue was observed in 30 percent of patients in REPEL-CV and two percent of patients in the control group at the second sternotomy." This study was un-blinded, dramatically so. And I can't understand why that point was not made and why the FDA did not offer that in response to somebody's

direct question about un-blinding.

The study was un-blinded and it was un-blinded in a way that most likely would result in an overestimation of the effectiveness of this product.

What about safety? Well, we've heard a lot about the data on safety. We've heard a lot about lack of power. The fact is, the best data that we have are the data that are before us. And they consistently show that things are going in the wrong direction.

If you look at death, things are going in the wrong direction. Mediastinal infection, wrong direction. Adverse events, possibly, probably, or definitely related to the study, wrong direction. They are not statistically significant, but those are the best data that we have.

We also made a calculation of the power for the mediastinitis, the point that FDA made. And we calculated on our little laptop that only allowed two-sided calculations of sample size, but you would have to have a relative risk of ten, in

order to show statistical significance, if you used as a comparison group the incidence of mediastinitis observed in the control group in the study and the usual beta equals 0.2 and then alpha equals 0.05 in a relative risk of 10. And the company itself says that they were only powered to detect a three-fold increase in mortality.

Now, the statute says "reasonable assurance of safety." The data show that we know that this product does not kill three times as many people as would be otherwise the case. And the data show that it does not increase mediastinitis ten-fold. Now, I'm glad for that, but a reasonable assurance of safety that is not.

Let me make one more historical point before closing. Hovering over this meeting but unmentioned is the case of Intergelz. Intergelz was a different product used in the pelvic region, not in the thorax, but in that study, the data were remarkably similar to this. No evidence of clinical benefit, reduction in adhesions, and a non-statistically significant trend towards an

increase in infection. The advisory committee turned it down. The company went to a dispute resolution panel, and eventually the FDA reversed itself.

Less than two years after the device was approved, the company removed the device from the market due to dozens of reports of post-operative pain requiring repeat surgery, foreign body reactions, and tissue adherence, including three deaths. This history should give one pause before approving an adhesion barrier with data as similar as they are here.

SyntheMed has simply failed to demonstrate that its product will have any important impact upon the public health. In order to do so, the patients receiving the device have to undergo re-sternotomy. But in fact, only a minority of patients will do so.

To have a public health benefit, it would have to reduce adhesions. The fact is, all it does is reduce the severity of adhesions on a non-validated endpoint and has no impact upon

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extent or incidences.

The adhesions would have to have clear clinical significance. In fact, there is no evidence of that. And the best measure of clinical significance that we have shows that there is no impact whatsoever.

Finally, the product would have to have an appropriate safety profile and that is not the case either.

For those reasons, we oppose approval of this device. Thank you.

CHAIR YANCY: Thank you, Dr. Lurie.

We are at a point now where we will break for the afternoon. Let me provide a few directives.

For the sponsor, again, thank you for your patience. During the break, there is an opportunity for you to craft a limited response to the discussion you have most recently heard.

For the panel's benefit, there will not be a Q and A following the sponsor's remarks. It will simply be a summation statement that we are to

incorporate in our deliberations.

FDA will have an opportunity to make a summation statement, should they wish, but it's not required.

Let me also bring to your attention that there is a flow chart in the folder at your spot and it allows you to understand the voting options. You might want to take a look at that before we come back. And after we have heard the summation statements, we will then vote according to this template.

Thank you everyone for your patience. We will reconvene in 15 minutes at 4:30.

(Whereupon, the meeting went off the record at 4:21 p.m. and went back on the record at 4:39 p.m.)

CHAIR YANCY: Again, I want to thank everyone for their patience. I know we've had some deliberative discussions today, but it's been all for the good.

To begin with, is there is any further comment from the FDA? Any points of clarification?

Any issue you wish to address?

DR. ZUCKERMAN: No, there isn't, Dr. Yancy.

CHAIR YANCY: Dr. Patel?

(No response.)

CHAIR YANCY: Thank you. Sponsor, if you can limit your comments to within ten minutes, that would be preferable.

DR. DiZEREGA: Well the sponsor would like to begin by thanking Dr. Yancy for moderating a very productive and informative meeting. I think it's been very good, certainly for us. We've learned a great deal and we've enjoyed all of your comments.

In order to bring those comments into a final focus, we have prepared just a single slide, that gives summation, after listening to your suggestions and recommendations and knowing what we do about our program.

The first thing that we would like to just clarify, because there was some discussion about this. This wasn't literally accurate.

Although there are adhesion prevention devices approved below the diaphragm, and that's a good term, there are in fact no FDA approved adhesion prevention products for use for cardiac adhesions to be used above the diaphragm. So this would be the first one, if in fact it is approved.

The second point is, we did a number of preclinical studies. Dr. Pines shared with you some of our more clear-cut ones, that led us on to be getting our clinical trials. But in all of our preclinical studies, we in fact found very good safety and effectiveness and all of these studies were performed in adults. We used typical dog models they used in cardiovascular surgical preclinical studies, as well as rabbits. And we found very good results in these populations.

The second point is that being the author of essentially a hundred adhesion prevention papers and having authored three books, etcetera, as well as my colleagues, it is our clear conviction that adhesion formation is independent of age. If we are able to reduce adhesions in one

age population, there is no extended data that we're aware of that would suggest those data in fact or not extrapolatable to a different age population.

In terms of what we've been doing to really deal with the problems that the panel has wrestled with today, this is something that we've been thinking about over ten years. During the process that we performed the four clinical trials that we have discussed with you, we have in fact engaged multiple experts, cardiovascular surgeons in the United States, around the world, pediatric, adult, as you might imagine. And in every instance, in every instance, it has become very clear and it was said many times today, Dr. Yancy, that there are no models to evaluate effectiveness in a randomized clinical trial in adult sternotomy patients.

In fact, had there been a model, had there been something that could have ethically been done in a randomized clinical trial format, that's what we would have done for all these obvious

reasons, as well as comparability of data to other situations. We would like to do a randomized clinical trial in adults. We just simply can't find a way to do it in an ethical environment that meets with any kind of clinical standard practices.

The clinical models that are available restrict us into a very narrow indication in pediatric patients. And that of course, is what you have been deliberating. Our study was done in the pediatric population. We absolutely believe that was the only study that could have been done.

And we believe that, based on the physiology and pathophysiology of mesothelial repair and adhesion formation, that in fact that data is indeed independent of age from a physiological point of view.

Our randomized perspective multi-center study involved in fact 142 patients that have been evaluated over this four year period of time. We believe that, in fact, supports reasonable safety and effectiveness in a population that is likely to undergo subsequent sternotomies in the future. In

a population that is likely to undergo subsequent sternotomies in the future, 142 patients with very similar results, as they have been collected over this period of time.

And as a result, we would like to recommend that the label approve REPEL-CV for patients who may undergo subsequent second sternotomies and that is, in fact, independent of age.

There are two very important points that come out of this. One, with that type of label, we in fact would be able to conduct a meaningful post-approval study. The very kind of study that you have been deliberating. With this type of label, we could do a post-approval study to get the kind of information that we would all like.

In addition, the label approving for patients who may undergo a subsequent second sternotomy independent of age, would also the clinical community to utilize the product on label in that are expected to undergo a subsequent sternotomy. We don't sue products off label on a

regular basis in our clinical practices. In fact, at USC, you just simply don't do that for lots of reasons. Things have clearly changed. We follow label restrictions. We believe, with 142 patients over this period of time, we have shown reasonable safety and effectiveness by restriction this based on age. In fact, those patients would be penalized or denied on-label use of what we think is a very important product and for which they have no alternative.

Now, I would like to thank Dr. Yancy for the time and the panel for their deliberations.

CHAIR YANCY: Thank you very much.

We're now ready to vote on the panel's recommendation to FDA for this PMA, pre-market application.

Mr. Swink will now read the panel recommendation options for pre-market approval applications. Mr. Swink.

MR. SWINK: The medical device amendments to the Federal Food Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of

1990 allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market approval applications that are filed with the agency.

The PMA must stand on its own merits. Any recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. The definitions of safety, effectiveness, and valid scientific evidence are as follows.

Safety, as defined in 21 C.F.R. Section 860.7(d)(1). There is reasonable assurance that a device is safe when it can be determined based upon valid scientific evidence that the probable benefits that health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use outweigh any probable risk.

Effectiveness as defined in 21 C.F.R. Section 860.7(e)(1). There is reasonable assurance that a device is effective when it can be

determined based upon scientific evidence that in a significant portion of a target population, the use of the device for its intended uses and conditions of use when accompanied by adequate directions for use and warnings against unsafe use will provide clinically significant results.

Valid scientific evidence, as defined in 21 C.F.R. Section 860.7(c)(2) is evidence from well controlled investigations, partially controlled studies, studies in objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and reasonably be concluded by qualified experts that there is a reasonable assurance of safety and effectiveness of a device under its conditions of use.

Isolated case reports, random experience reports lacking sufficient details for its scientific evaluation in unsubstantiated opinions are not regarded as valid scientific

evidence that shows safety or effectiveness.

Your recommendation options for the vote are as follows.

Number one, approval. This is in case there is no conditions attached.

Number two is approval with conditions. The panel may recommend that the PMA be found approval subject to specific conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of these conditions should be discussed by the panel.

Number three, not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance the device is safe or the data do not provide a reasonable assurance the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Thank you.

CHAIR YANCY: Are there any questions from the panel about these voting options before I

ask for a main vote on this PMA?

Again, I would call your attention to the flow chart that should be at your seat.

Yes?

DR. KATZ: For the conditions, you said to reevaluate existing data only, not to obtain new data?

MR. SWINK: Yes, if you require new data, then this cannot be approved.

CHAIR YANCY: Any other questions from the panel regarding the voting options? Again approval, approval with condition, or not approve.

DR. JEEVANANDAM: Are we voting exactly on the labeling as stated or as we discussed here?

CHAIR YANCY: The way that situation works, and I will invite clarification if I misspeak, we are voting on what is on the application, with the labeling language as submitted by the sponsor.

If there is a sense that the labeling language needs to be changed or altered, my understanding is that would be a condition. Is

that correct, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. So I think his question was, under which bin would that fall. That would be approvable with conditions.

CHAIR YANCY: Does that help?

DR. JEEVANANDAM: Yes.

CHAIR YANCY: Other questions from the panel about our charge and our options? Dr. Somberg.

DR. SOMBERG: Yes, Dr. Yancy, it's been my experience that there is usually a motion requested and that the motion sets the parameters where we're now going to go through this algorithm. Is that a new branch?

CHAIR YANCY: We haven't gone to the motion yet. We're just getting clarification on the procedure.

DR. SOMBERG: What I'm just asking is, if you entertain a motion, the motion, to answer Vall, if I may also, the point is that was raised, is the motion may set the parameters for the approval.

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CHAIR YANCY: And that is the next line item on our agenda, to request a motion. But this is just for points of clarification, but I appreciate the input.

If there are not any other questions of clarification of the process, then we are ready to entertain a motion. And the motion that we're looking for is for either approval of the PMA as we see it, approvable with conditions, or non-approvable.

Dr. Somberg.

DR. SOMBERG: Well I would like to move that we move to approve this PMA with the indication for patients who are expected to undergo a sternotomy, repeat sternotomy within 24 months.

CHAIR YANCY: So to be clear, and I'm going to have to modify what you said, just as a function of protocol. The motion on the table is approvable with conditions. We will address the conditions later but the motion on the table is approval with conditions.

DR. HOPKINS: Second.

CHAIR YANCY: That motion has been forwarded and now second. And we can discuss just that motion, not yet the conditions. Is there a discussion?

DR. HOPKINS: I'll start. I think that there was no evidence that the safety parameters were different between the two groups and that the primary endpoint of the study which was designed in association with the FDA's recommendations or suggestions, I should say, did show the primary endpoint to be efficacious. However, we have all discussed some of the limitations that we see within the study in terms of approvability. But I think it's approvable with conditions and would recommend that.

CHAIR YANCY: Is there further discussion on this motion? This is simply approvable with conditions, without enumerating the conditions.

Dr. Neaton.

DR. NEATON: I also support approval with conditions, but more restrictive than was

suggested. So, we have a study of 142 people with clear evidence of a surrogate, which you know, prior opinion would suggest that would have effect on clinical outcomes of interest that it doesn't and some questionable data about safety.

And so I think that expanded indication for this is not warranted and should only come after further studies are done.

CHAIR YANCY: Is there any further discussion? Because we're ready to take the conditions, if this is the case. Dr. Domanski.

DR. DOMANSKI: Yes, I guess this is a general comment. I think it's inappropriate to do it for all age groups when it's a sufficiently strong study in my view to be approvable with conditions, but not very broad ones.

CHAIR YANCY: Okay, so let's begin to take the conditions. So I need a motion for the first condition. And the way this process will work is that we will need to vote on each condition.

Yes, Dr. Somberg.

DR. SOMBERG: Just a very brief comment, and then the condition I would like to propose is in light of the discussion, I think we should also be cognizant of what approval would facilitate getting the data we need, realizing that studies in adults for efficacy and safety is going to be very, very, very difficult and was not initially proposed.

With that said, I propose that it be approved for patients over the condition that there be, I guess the condition is that there be an indication for repeat sternotomy within 24 months.

CHAIR YANCY: So the motion that has been made is this PMA is approvable with condition and the condition is for patients who have a likelihood of having a repeat sternotomy within --

DR. SOMBERG: I said 24 months.

CHAIR YANCY: Twenty-four months. Is there a second for that, approval with that condition and that time frame?

DR. KATZ: Second.

CHAIR YANCY: There is a second. We

will now vote on that condition, approvable with condition, with the motion and the condition as stated. Do I need to repeat the condition?

So the condition is to approvable with conditions and the condition is indicated for, and I want to be clear, did you intend to say all patients or are you specifically speaking just about the re-operation issue?

DR. SOMBERG: You said you wanted to talk about one condition at a time.

CHAIR YANCY: That's right. I just want to have your language clear.

DR. SOMBERG: Yes, it's repeat, the likelihood of repeat sternotomy in a period of 24 months, unless somebody has a good reason to restrict or expand that.

CHAIR YANCY: Okay, so the motion has been approvable with condition and the condition is patients who have a likelihood for repeat sternotomy within 24 months. We need to vote on this motion with condition.

Yes?

DR. BLACKSTONE: Could you clarify? Must we vote no if we think the two years is not appropriate or is it a discussion about that?

CHAIR YANCY: It is specifically with the language we have just outlined.

DR. BLACKSTONE: Okay.

DR. SOMBERG: If you're willing to modify it.

CHAIR YANCY: So at this point, we have to vote on this condition. We have to vote on this condition, now, Mike.

DR. DOMANSKI: Yes, I know. But I mean, and this discussion is a little bit of clarification. That condition, you know about the 24 months, but then we're going to go to other conditions. Is that right?

CHAIR YANCY: That is --

DR. DOMANSKI: Like restricting the age?

CHAIR YANCY: -- correct. That is correct.

So should I restate this once again?

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Are we clear? We are voting on approval with condition in patients who have a high likelihood of a repeat sternotomy within 24 months.

DR. PAGE: I'm sorry, Dr. Yancy. I'm still unclear. If I vote yes to this and there is a subsequent vote, another condition on an age limit and that's say voted down, does my vote then stand as if I had voted in favor of this as a stand-alone? Because in my mind, I cannot vote for this approval with this one condition. But I'm assuming that this condition is being added to the eventual motion where we approve with the conditions that we agree upon. Is that correct?

CHAIR YANCY: If the language we have just used is not acceptable, then you should vote accordingly.

So the clarification is that if you don't like one of these conditions, you can vote against the motion, but it doesn't affect the status of approvable with condition, we just have to go on to the next condition. Was that clarification?

DR. PAGE: I'm sorry, but I'm still unclear.

CHAIR YANCY: Okay. We are going to vote on approvable with condition. And the first condition is the context of the vote. It doesn't disqualify the original statement of approvable with condition. The first vote is specifically about condition number one. And condition number one is in patients with a high likelihood of repeat sternotomy within 24 months. If that language is unacceptable, you should vote accordingly. If it is acceptable, you should vote accordingly.

Dr. Zuckerman, did you have a comment?

DR. ZUCKERMAN: No. Perhaps again, it would be helpful if people just look at the flowchart. Dr. Yancy is following the flowchart.

CHAIR YANCY: All in favor of this motion, please raise your hand and condition to raise your hand so that we can call the names of those who vote in favor.

(Show of hands.)

CHAIR YANCY: Doctors Hopkins, Katz,

Zahka, Somberg, Weinberger vote in favor of this motion.

Those opposed?

(Show of hands.)

CHAIR YANCY: Doctors Hirshfeld, Domanski, Page, Neaton, and Blackstone vote against.

DR. JEEVANANDAM: Clyde can I -- I'm sorry. Maybe I'm confused. So we're voting right now to see --

CHAIR YANCY: Just on the condition.

DR. JEEVANANDAM: The condition of high probability of re-operation in two years?

CHAIR YANCY: In 24 months.

DR. JEEVANANDAM: In 24 months.

CHAIR YANCY: That's what we're voting on.

DR. JEEVANANDAM: And --

CHAIR YANCY: And if it's voted down --

DR. JEEVANANDAM: -- you will have another condition after that?

CHAIR YANCY: -- we can put another

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condition in, yes.

DR. JEEVANANDAM: Okay. I need to vote yes, then.

CHAIR YANCY: Okay, so I --

DR. JEEVANANDAM: I didn't vote at all. Sorry.

CHAIR YANCY: -- need to do this again. So, I'm going to make this very simple. This is the vote. Condition number one, high likelihood of re-operation within 24 months. Those in favor?

(Show of hands.)

CHAIR YANCY: Doctors Hopkins, Katz, Zahka, Jeevanandam, Somberg, Weinberger.

Those opposed?

(Show of hands.)

CHAIR YANCY: Neaton, Blackstone, Page, Domanski, and Hirshfeld.

DR. PAGE: And just so it's clear I'm voting against this approvability with this condition as a stand-alone.

CHAIR YANCY: Your vote is just on this condition.