DR. HAUPTMAN: Thanks, Bill.

I will just add to the chorus. I think it was an excellent presentation today and provocative data. I would like to get back in the trenches just for a minute and begin by asking again the question I asked earlier today about the non-heart failure cardiovascular hospitalizations and a clarification that when a patient had a lead revision, was that listed as a non-heart fail cardiovascular or a heart failure admission or hospitalization or event?

And, second, I wanted to understand whether or the degree to which patients may have crossed over to other device technologies, like CRT.

DR. ABRAHAM: Paul, the events that comprised the primary endpoint were either hypervolemic or hypovolemic dehydration events, did not include those rehospitalizations for device-related events.

And I'm sorry. The second

question?

DR. HAUPTMAN: CRT, ICD placements, and so forth in the group following randomization, which would presumably be a non-heart failure cardiovascular event.

DR. ABRAHAM: Yes. Let's go ahead and have -- do we have the device slide? Try to get you those exact numbers. As you saw in the baseline characteristics, there were in excess of 40 percent of patients that had existing devices.

Let's have this slide up, which I think -- show the slide, please -- which shows the concomitant devices by type implanted during the randomization period. So you see that there were a small number of devices that were implanted after enrollment in the trial.

Remember, the intention here was to try to have patients on a stable and optimal heart failure regimen before enrollment in the trial so optimization of ACE

inhibitor, beta blocker, use of a CRT for at least three months if a patient was indicated for a CRT, for example. So I think, as we would expect given those enrollment criteria, the number of concomitant devices subsequently implanted after randomization is relatively small.

DR. HAUPTMAN: Okay. Thanks.

This question may seem a bit dense at first, but I'll explain why I'm asking. Do you have any data about the time from, let's say, a phone call in either group to the subsequent admission or event?

And the reason why I ask that is I'm wondering whether to some degree we have an artifact of detection in the control group because a call, random or otherwise, that is made to a patient might not ordinarily have been made.

So while you might think that, "Well, this will mean that the clinician will be able to treat something if they hear about

it, it's also conceivable that they detect something that they otherwise would not have detected. And then that patient ends up with an ED visit or a hospitalization.

However, if the time between the phone call and the event is prolonged, then I don't think you can draw that conclusion.

DR. STEVENSON: We don't have that information, Paul, but I think this may be helpful to look at how urgent events were initiated and show this slide, please.

When we look at the two groups, in fact, what led to the urgent events was surprisingly similar in both groups in terms of the majority of the events were actually initiated by the patient and not by a clinician, either by a phone call or by clinic visits. So about 60 percent the patient came and said, "I need to be taken care of," rather than somebody called them.

DR. HAUPTMAN: Okay. That's very helpful. Thanks.

Just two brief comments, then, one I guess more about the labeling. I would suspect that this is a device that should not be put in someone who has new onset heart failure but has established heart failure. Otherwise you'll be in a position of finding a number of patients who have improved their rejection fractions no longer have heart failure.

Second is just a brief comment about the post-approval study. I am a little concerned about one part of the design. I guess it's in your pack on page 8-3. And that is that the centers not using Chronicle will have control group patients only. And the question is, why are you designing it in that way?

If you want a little more insight into long-term follow-up, real world use, and so forth, you would probably want a non-Chronicle center to start using it and seeing what kind of effects you get in a

hospital that doesn't have the clinical trials experience in COMPASS.

DR. STEINHAUS: We're certainly open to changes in that trial design, first of all, let me say. And I think it really is a question of numbers. I mean, you know, we're looking for 400 patients in each arm. And we assume that most of the Chronicle center patients will probably want to go into that trial, but we don't know that for sure.

So it's a good question. We don't really have a good answer for you other than we're open to consider changes in that design. We have a slide. We can put the slide up if you would like, but I don't think it is terribly helpful to your question.

DR. HAUPTMAN: I understand there can be crossover, but, of course, if a center decides not to cross over, then you're going to have potentially some effects that are related to the hospital. And that I think adds to the complexity of the statistical

analysis.

Thank you.

DR. BLACKSTONE: Not possible, Bob. In other words, if you have a systematic one institution does one thing and one thing the other, it is permanently confounded by institutional factors and never separable. So propensity scores won't help you.

CHAIRPERSON MAISEL: The panel has a question regarding the post-market study design. So we can all participate in that discussion a little later.

Paul, do you have any other questions?

DR. HAUPTMAN: I am set, Bill. Thanks.

CHAIRPERSON MAISEL: Okay. Dr. Fleming?

DR. FLEMING: First I also want to say what a very informative, excellent presentation this morning, made it simple for the lay person, like myself. Okay?

As a consumer rep, obviously my concerns lean more toward direct patient care and the benefit to the patient of anything related to a medical device. So I want to ask a couple of questions that may seem a little bit off of what we have been talking about here for the moment, but I think they do impact directly on the panelists' deliberations today.

One question I have for the sponsor is, where do you see this device going in the future? In other words, I can see, for example, that a device of this sort could be integrated, as Dr. Page referred to earlier, into a unit that does more than just one thing, one or two things, but, secondly, that it might be able to be paired with some sort of an infusion pump, for example.

I'm just raising this issue as of interest because a patient is going to look at this. And they are going to say, "Well, I am still having to go to the hospital just as

many times as I did before."

And that ties to my second question. I am wondering if you would mind for the panel's benefit and my own summarizing what you see as the benefits to patients, very simple, straightforward questions.

DR. STEINHAUS: Let me take the first question first. We are excited about this technology. We really are. In fact, those of you who know about Medtronic know that we have changed our name. We used to be Cardiac Rhythm Management for our division, and we now call ourselves Cardiac Rhythm Disease Management because we very much see this as the first in perhaps a sequence of other things we might be able to do to improve patient care.

If you think about it, we have been having the building blocks for that possibility for quite some time now. We have the system we call CareLink, which allows us to have remote access to the patient. We have

another system. Part of our telemetry is going to be the distance telemetry. So it takes compliance out of the picture.

Patients can have their values if they were values from the Chronicle or if they were from some other values from an ICD device or any other device you might have automatically sent to the secure Web site as well on a daily basis, if necessary, with alerts and all of that.

So we very much see as sensor development occurs, there has been a lot of work done in miniaturization of sensors. And we may be able to measure lots more things. How much of those will be valuable? We don't know at the present time, but we at least believe that some of them will be valuable.

After all, many of these patients that we deal with who have heart failure have a lot of other co-morbidities. They have diabetes. They have hypertension. They have obesity. They have hypercholesteremia, sleep

apnea. I mean, you can go down the list. In fact, it's really quite striking how many of them have these co-morbidities.

And if we can figure out more of a holistic approach so we can actually start managing the patients through these devices and improve their lives, we really think there is a huge advantage there.

And one of the things that you mentioned was, you know, perhaps delivering it through a drug pump. I mean, it might be that if we can have the appropriate sensor that can measure this and can measure cardiac output, you might have, for example, the machines adjusting themselves.

With CRT therapy, you might have VB timing or atrial ventricular timing adjusting itself in the machine or you might have a drug pump that's hooked up via telemetry to this machine. And it might give drug therapy at a certain time when the patient needs it or not.

This is all far out. I'm not saying we have this available right now. We're not asking FDA for approval of that right now. Let me make sure you understand that. But, I mean, it is true that that is sort of where we believe we are going. That is our vision for the future, and I think it is a really bright future. And I think it is going to be an interesting road getting there.

Your second question related to about the patient.

DR. STEVENSON: I am sorry. About the patient.

DR. STEINHAUS: Yes. I was going to go there.

(Laughter.)

DR. STEVENSON: I am sorry. As a heart failure doctor, I want to tell you what this is about. So you have just been hospitalized with heart failure. You were really short of breath. You were scared. And you don't ever want that to happen again.

And you come back to clinic. And I try to explain to you that it's because those filling pressures went up, that your lungs filled up with fluid and you got short of breath. And I explain to you that we are going to be adjusting your diuretics to try to keep those pressures low so this doesn't happen to you again and that I am going to be able to find out at home when we need to make those adjustments.

But one of the things that we haven't even discussed at all today because the control group has a device in and, in fact, the majority of patients thought it was being monitored, so they got the benefit of this, which normal patients wouldn't, is that when you don't feel well and you wake up in the morning and it's a bad day, you think, "Oh, what if it is happening again? What if it is coming back?" that you can transmit immediately and you call the nurse and you say, "Look, I don't feel well. I just

transmitted," and she can say, "No. It's okay. Your filling pressures are all right" or she can say, "They're up a little bit. Let's try increasing your diuretic."

And this degree of reassurance that this provides to patients is tremendous, but it's not something that we can show you in a study because our control patients have that as well. But that is a major thing as a patient that you would derive from this technology.

DR. FLEMING: Yes. That's what I was trying to get at. I see something that goes beyond the studies that is of benefit to the patient that is frightened. This is happening to them so frequently. And God knows the cost to the health care system of all this sort of thing. So I felt it very important to address that question.

CHAIRPERSON MAISEL: Dr. Yaross?

MEMBER YAROSS: Thank you.

I would like to comment on a

couple of things that I have heard in the discussion thus far today. And one had to do with the fact that here we have a device system and we're not looking purely at the device alone but the interaction with the center, the interaction with the physician or other health care professional.

And what I would comment on is I think that this is truly a factor of many, many medical devices and clearly is one of the ways that devices differ from pharmaceutical research and, you know, part of the difficulty inherent in doing randomized studies, complex device systems.

I think that the sponsor made a tremendous effort to design the study to try and address some of the complexities around blinding, but I think we have to recognize that clinician skill as a factor is true of many devices and is part of the real world of medical devices.

There has also been quite a bit of

discussion about whether the sponsor was unlucky in a number of factors. And I think that it's unrealistic to expect a perfect study, especially when something is first of a kind, and that sponsors tend to do the best that they can. In this case, compliance was exemplary. I can't recall the last study I saw with 99.6 or whatever percent compliance.

You know, to the extent luck or unluck comes into play, to the extent that a bad statistical break can account for differences in baseline characteristics, sponsors shouldn't be penalized for random occurrences. So I would just ask that the panel as deliberations continue think about those points.

CHAIRPERSON MAISEL: Thank you.

I just have a couple of quick questions. One is related to slide C-49, where you showed the correlation of the estimated pulmonary artery diastolic pressure and the correlation between the device, the

Chronicle, and the pulmonary artery catheter was not quite as good as systolic or diastolic pressure. In particular, there were some patients who have quite a significant difference between the two readings.

And I wonder if you might tell us what percentage of patients had more than a -- you know, pick a number -- ten-millimeter difference between the actual value from the PA catheter and the Chronicle device and what explanations you have when those differences do occur.

DR. ADAMSON: This is from Magalski and colleagues, who published this in the Journal of Cardiac Failure. And, remember, these are comparisons between a fluid-filled catheter and the high-fidelity sensor in the right ventricle. So the Swan-Ganz catheter was meticulously calibrated and the transducer was set meticulously, but, as has been already mentioned, there are some vagaries about the transmission of pressure in

a fluid-filled catheter system comparing to an instantaneous sensor.

The ePAD studies early on actually, if I could show you just the next slide up, were done with high-fidelity Malar catheters, rather than the fluid-filled catheter system, to validate that the pressure in the right ventricle at maximum dP/dt actually is equivalent to the pulmonary diastolic pressure.

And here you see a better correlation. And, in fact, here you see another study that is published that demonstrates an r2 value of 89 percent. And this is across multiple different type so interventions, rest, upright, valsalva, bike-exercised, dobutamine nitroglycerine. And you can see that in throughout those physiologic events, the correlation between high-fidelity measurements are very tight.

So a fair amount of that variability, I believe, came from the

measuring technique that we called the gold standard, which I think was probably not as gold as the sensor itself.

CHAIRPERSON MAISEL: Okay. Great. Thank you.

I was wondering if someone from the sponsor could comment on what I will term the biological plausibility of seeing New York Heart Association class III patients improving with the device and the observation that the class IV patients may do worse or we have observed that possibly that they do worse.

If we believe that to be true, how do we explain that observation from a biological perspective? And if we can explain it, should we be implanting the device in class III and then explaining it or not using the data when they get to class IV?

DR. ABRAHAM: You know, I am a little bit reluctant to draw any great conclusions on the data set in regard to the class IV subpopulation because it is

relatively small. So with that sort of caveat, you know, starting off here, you know, I do think we need to explore the question a bit more going forward and find out who the best patients are.

You know, one concept, for example, may be that there are some patients who, you know, are so ill and prone to decompensation that may be managing their filling pressure, you know, won't keep them out of the hospital. Part of it may relate to how we manage their filling pressure.

When this study was begun, we pretty much only had diuretic therapy. And, as you notice, we had a creatinine cutoff as high as 3.5 as an eligibility criteria. So some of these patients may be diuretic-resistant.

Nowadays maybe there are alternative ways to remove fluid in those patients, but I think that there are a lot of insights that we might gain that are more

hypothesis-generating about that class IV population than definitive.

DR. STEVENSON: I just want to address your question of the biologic plausibility of improvement in the class III patients. This is actually all patients, the slide I am going to show you right now.

Slide on, please. This data is not in your panel pack. Again, it's the first time that anyone will have seen it outside of our analysis. This is a very provocative set of data that really further supports the physiologic validity of this concept. And what we're looking at here is the difference between the right ventricle systolic pressure measured over time compared to baseline. We're looking at the changes in that.

In the Chronicle group, you can see that this pressure declines over time. This is six months at this point. In fact, this continues to decline over time. These patients are at a significantly lower volume

status by the end of the 12 months than they were at the beginning. This compares to the control group in which during the six months of the randomized time in which we did not have access to the hemodynamic information, they had no overall change in their filling pressures.

Once it was unblinded and we could see the filling pressures, we could begin intervention. And there was a trend by the end of that six months for them also to have what we might consider as a hemodynamic remodeling or a gradual return towards normalization of left ventricular filling pressures.

So I believe this gets to the biologic plausibility of why, in fact, we may see improvement in this population. And this improvement is something that is all patients over time, which is perhaps more relevant than just those patients who were hospitalized.

CHAIRPERSON MAISEL: Thank you.

Then I just have one question regarding a clarification. I was a little confused about which lead or leads are being asked for approval in the application. Are both leads, 4328(a) and (b), part of the application that we're reviewing today?

MR. MANDA: That's right. Both 4328(a) and 28(b), yes, they are.

CHAIRPERSON MAISEL: And the 4328(a) was the one that had the hermetic seal problem?

MR. MANDA: Yes. And then that subsequently was also changed as part of the manufacturing correction before the COMPASS-HF trial began. And so that is correct. 4328(a), the device version, was what was credited in COMPASS-HF.

CHAIRPERSON MAISEL: And so the corrected version is the (b) version or --

MR. MANDA: Both of these, the corrections that you are referring to with respect to the hermetic seal, that was already

incorporated before the beginning of the COMPASS-HF, which is 4328(a).

The 4328(a) and the (b) leads are essentially the same lead. We implemented a new class III through and essentially the lead body. The pressure sensing capsule, the basic functionality of the leads are identical. It's really to improve our manufacturability of the lead as well. And this has been part of the FDA's review as well. And their summary acknowledges that, too.

CHAIRPERSON MAISEL: If you needed one of the leads, which one would you have implanted in you?

MR. MANDA: 4328(b) or (a), either one.

(Laughter.)

CHAIRPERSON MAISEL: Good answer. And then I have one observation, which is, you know, when we look at the number of reduced hospital equivalents, it appeared that at 6 months, there was a reduction in 29

events in the Chronicle group among 124 implants.

And so just my quick math suggests that that means that there are 4 implants to this device to prevent one hospital equivalent in 6 months or another way of looking at it would be 124 hospitalizations to prevent 29 with a net negative of 90-something. So I am just trying to put a little balance onto the number of procedures versus the number of hospitalizations that we save.

So at this point I would like to move on to the FDA questions and give the panel to discuss or summarize some of the issues we have discussed at length already. So we will have opportunity to converse a little more.

So I would ask the FDA to put up question one, please. That's fine. I can read it. So question one is "Please provide your clinical and/or statistical interpretation of the results of the primary

effectiveness endpoint analysis in the entire study population."

And I think we can add question two to this at the same time, which is "Please provide your clinical and/or statistical interpretation of the results of the primary effectiveness endpoint analysis in the New York Heart Association class III patient population alone and in the New York Heart Association class IV patient alone."

So limiting our discussion to just effectiveness, we have heard a lot of conversation. Maybe, Dr. Teerlink, would you like to try to summarize both your feelings and the panel's, what you have heard from the panel regarding primary effectiveness for the device?

DR. TEERLINK: I don't necessarily feel comfortable, you know, kind of speaking for the rest of the panel, but I can summarize my opinions if you want me to discuss -- are you asking me to answer the questions now or

--

CHAIRPERSON MAISEL: Yes. We are just talking. We have had a lot of conversation. We have looked at a lot of data. And now it is time to discuss the hard questions. Is the device effective at doing what the sponsor claims it does?

DR. TEERLINK: And so I think I presented my personal approach to that, which is that we have initial studies that looked to see, can it successfully measure right ventricular pressures and the hemodynamics related to that? And I believe it does. The evidence supports that it can measure those pressures.

The more important question as defined by the label -- and for me when I look at it from what is important to a patient is, does it, in fact, impact and improve, reduce patient hospitalizations for worsening heart failure?

And I see no evidence for that in

any of the trial. You have the trial as it stands now cannot exclude a 25 percent in the hospitalizations. And I think we may be being prone to some wishful thinking here. We all wish to believe that the changes in hemodynamics directly correlate to our ability to reduce hospitalizations.

And it's a great hypothesis and one that I in my heart of hearts would love to believe in. Unfortunately, I don't believe that this trial has provided significant evidence or sufficient evidence for me to have that hypothesis verified.

There has not been a decrease in hospitalizations. And, in addition, we are asking every patient to undergo a procedure which then requires some patients to be rehospitalized for the device.

So if that is what you are looking for, that is my quick summary.

CHAIRPERSON MAISEL: Other thoughts? Dr. Brinker?

DR. BRINKER: So I am a little bit confused. I tend to believe what you are saying because it is true except that you are using the terms "hospitalizations" and "hospitalization equivalents" simultaneously, I think.

DR. TEERLINK: We can speak solely about hospitalizations as well. There is even less of a statistical power showing a change in hospitalizations.

DR. BRINKER: So I would like to see. I thought from the panel pack that there was a statistically significant difference in heart failure hospitalizations. No?

DR. TEERLINK: No.

CHAIRPERSON MAISEL: So I will remind the panel that the primary effectiveness was reduction in heart failure-related hospital equivalents.

Dr. Borer?

DR. BORER: I agree with John, but I would say it slightly differently. You

know, intuitively I think that this kind of approach probably works. However, what we need to do is determine whether the system is sufficiently effective so that it is acceptably safe for its intended use given what we know or what we can infer about safety.

What I think I know about the pathophysiology of heart failure is entirely consistent with what Dr. Stevenson said and other consultants the company said, which is that if you're going to pick a single parameter most closely associated with symptom development, it's PA pressure. There are others, but this is the one that is most closely associated.

And a device that allows me to interrogate this is really tantalizing and intuitively very attractive, but the question is, does the system, including the M.D. component, the physician component, using the current algorithm improve the symptom status

of patients with several heart failure? To this I have to say intuitively I believe it does, but I can't support my intuition with any rigor.

And, at best if I were going to say what I think, I would have to say I think that the improvement, as I see it right now, is only modest with the current algorithm and system.

And, most importantly, then, -- and, again, we are supposed to be talking about effectiveness, but you can't divorce the one from the other. Most importantly, though, I can't say that the effectiveness I intuitively am willing to believe renders acceptable the safety that I think I can infer.

CHAIRPERSON MAISEL: Other comments? Dr. Somberg?

MEMBER SOMBERG: I think I am not going to try to speak for the panel either, but it's my sort of feeling that there is a

general belief that this may work. And it's a very good study, and it's a very good hypothesis-generating study for future.

But as a pivotal study, you know, if you want to use the phase one, phase two, phase three clinical trial design, this may be an early phase two study. But as a pivotal study, I do not see statistically it did not meet its endpoint.

There is a lot of suggestive data. I wouldn't go so far as to say I have any belief that there will be 25 percent harm. I think that confidence interval is possible but very unlikely. But I think given the risk of an implantable device and given the number of patients that need this, it has to be shown definitively that this is an effective agent.

And it may be that the algorithms used, the interpretations could be fine-tuned to even further improve this to demonstrate that or the patients that you're studying may be more adroitly selected. But at this point

I think we do not have a statistical significance. And I think everyone would agree there.

And the clinical benefit is unproved, then. And, therefore, we really have to ask for another clinical trial to definitively determine this because this is not some sort of tangential unimportant question. And I think it is one of the core issues in CHF therapy, which is a large chunk of cardiology.

So I would hope that no one gets discouraged from my and other people's negative feeling, but at the same time, it would be a real reach to say this is clinically significant when we fail on statistical significance.

CHAIRPERSON MAISEL: Is there anyone on the panel who feels that effectiveness has been demonstrated? Dr. Zuckerman?

DR. ZUCKERMAN: I am not

responding to that question.

(Laughter.)

DR. ZUCKERMAN: I have a follow-up question to the --

CHAIRPERSON MAISEL: Okay. Just wait for one minute. So we're not taking a vote, but is there anyone who would like to make the case that effectiveness has been demonstrated, clinical effectiveness? Dr. Borer, effectiveness with regard to the primary endpoint?

DR. BORER: I guess I have a comment, rather than specifically saying that clinical effectiveness has been proven if you want to say clinical effectiveness is a beneficial response of patients.

I would like to say that this is a diagnostic test. And because this is an implantable device, it has a higher standard than other diagnostic tests. This device in itself is non-therapeutic.

So we could look at BNP levels and

other in vitro diagnostic tests. And if they give you some idea of reality -- and we know we have accepted that this gives you the same quantitative data, hemodynamic data, that invasive cardiac monitoring does with the Swan or other catheter.

So I think that this is effective in telling you what the pressure is. The issue, really, that we are stuck with is, number one, while it intuitively is obvious that if we knew the pressures, we would be doing something about it, it hasn't been proven in the study to the degree at which most of us would feel comfortable, I believe.

However, I believe it is problematic for me because I could say that in individual patients, I know that this value would be important. And if it were available, I would use it. And I am torn between that issue and the concept that maybe this trial didn't fetter out the best population and the best applicability.

But, again, this is a diagnostic test. And I have no doubt that this is a relatively safe diagnostic test and that it's effective as an invasive diagnostic test. And the real issue I would have is who should get it, rather than whether anyone should get it.

CHAIRPERSON MAISEL: Okay. I would also note that we are asked to comment on the clinical and statistical interpretation of the results of the primary effectiveness endpoint, which includes a reduction in heart failure regulated hospital equivalents.

Dr. Normand?

MEMBER NORMAND: I guess I am going to disagree with Dr. Brinker in the following aspect. If it is really viewed as a diagnostic instrument, I think we would be evaluating it on other criteria than those that you just proposed. We would be evaluating on not the accuracy as via a correlation coefficient, but we would be far more interested in the bid between clinician

variability in decisions and things such as that.

So I guess from my standpoint, as a lay person, I am not convinced at all of the diagnostic accuracy of the device because there is a whole section in CDRH that knows how to analyze and design studies that way. So I guess I disagree with you on that particular point.

So I just wanted to raise that issue because this is what I started to say earlier. If it really was going to be assessed as a diagnostic tool, I think we would have had a different design. If it was going to be evaluated based on its patient endpoint, then those people who do diagnostic tests know that there have to be a lot more patients.

CHAIRPERSON MAISEL: So with regard to Sharon's comments, how does the panel feel about the effectiveness of the device for measuring pressures that it

purports to measure? Does anyone have an issue with the device accurately measures the pressures based on the data that we saw, Sharon's comments notwithstanding? Dr. Somberg?

MEMBER SOMBERG: Well, I do not think this is as important as the comments I made earlier of the lack of statistical effectiveness and its true clinical effectiveness being in doubt. I was not convinced that this is measuring what it says it measures.

It may measure something that is useful. And it may turn out on the next randomized control trial that is designed differently highly statistically significantly, clinically benefit. But does it represent endiastolic pressure that is going to somehow be evaluated and treated and under all conditions.

And I think there are certain -- what should I say -- validations that could be

done in a cath lab situation of a catheter versus this device. So you didn't a fluid filled, and you had a gold standard.

You have different pressures. And, I mean, I could design these experiments. You can do then in vitro. You can do then in vivo. Then you would give two beta blockers. You could give ionotrophic agents, see it there is a dissociation or not.

So these types of things I did not see the evidence for. And I would say as a pharmacologist I would have demanded to validate my system if I was going back and validating the Walton Brody at a catheter.

But that may not be important. It may be more important to do a study and demonstrate clinical benefit. And I think you will find that in the end.

CHAIRPERSON MAISEL: Dr. Kato?

DR. KATO: I think one of the problems that we have faced as physiologists in cardiothoracic surgery in the whole idea of

pulmonary artery diastolic pressure.

The original studies that were done, actually, because the assumption behind this is that there is a Starling curve. And the Starling curve actually was developed using left ventricular endiastolic volume. And that is very difficult to measure.

So we then estimate it as left ventricular endiastolic pressure. Then we measure left atrial pressure. Well, that is difficult to measure. So then we measure pulmonary wedge pressure. Well, that's hard to do, too, with a certain risk. So what do we get? We have to use pulmonary artery diastolic pressure.

And, unfortunately, we can't even measure that here. We have to use this e-pulmonary diastolic pressure. So we're talking about a fourth or fifth order, maybe sixth order approximation of what the original observation was.

And that's where I also share Dr.

Somberg's concern, is that is what we are measuring the right measurement? And maybe part of the problem in this is maybe that isn't the right measurement that correlates with these heart failure symptoms and hospitalizations, et cetera, et cetera.

CHAIRPERSON MAISEL: Dr. Zuckerman, did you want to comment from before? Okay.

Dr. Domanski?

DR. DOMANSKI: Yes. You know, I am impressed that this thing really is measuring pressures that are relevant to the ones that we try to measure when we assess heart failure.

The problem, you know, almost from my point of view almost from what has been presented today is if the FDA is going to require clinical trials, then it would be hard to come up with one more negative on its primary endpoint. I mean, if this isn't negative, what is?

On the other hand, the device -- I am concerned that it is an artifact of the trial they did, rather than the device they developed. And I guess I am left wondering whether or not when you're looking at diagnostic devices a reasonable indication would be estimating these pressures without this particular endpoint being the most important thing.

I mean, I could see these pressures being useful diagnostically and this trial not being particularly well-designed to demonstrate its utility.

I understand we can't approve this. At least I don't think we can approve this thing to reduce hospitalizations with a trial that is negative. I mean, I don't know what to say, but I am concerned about letting this device go down when it might, in fact, be clinically useful for pressures.

CHAIRPERSON MAISEL: Dr. Page?

MEMBER PAGE: Just getting back to

your initial question and whether we thought the primary endpoint was reached, I think even the sponsor acknowledged it was not reached.

To answer your question number two, whether the class III and class IV distinctions are important, I consider those subgroup analyses without enough data to really say anything definitive. And for further research, I would still emphasize that class III and IV would likely be included in further studies.

But I don't think we can say that this helps one group and harms another group. I don't think there are enough data there. The primary endpoint wasn't reached.

CHAIRPERSON MAISEL: Dr. Borer?

DR. BORER: Yes. I would like to respond to two issues here. First is what pressures were measured. I believe, just as Dr. Domanski just said, that pressures were measured that are clinically useful.

It is not true that we are trying

to measure the left ventricular and diastolic pressure. What this device is intended to be used for is to enable reasonable management to reduce symptoms or prevent symptoms, actually, in people with congestive heart failure.

The operative pressure there is the pulmonary capillary pressure, not the left ventricular endiastolic pressure. It is what is the pressure that is pushing fluid out of the capillaries you have got to deal with. And, in fact, there are not five orders of measurement away from what they have got to measure. There may be one or two.

But in every situation of which we know from cath data, what they are measuring is a reasonable way to obtain the information they want. And you have five or six people who are sitting over there who are consultants to their company who can speak to this as well.

I think the pressures that are being measured are relevant and potentially

useful. The big issue is, can they be applied? Have they been applied in a way that would allow them to be useful in enabling the prevention of symptoms? And I think what you have heard from everybody is, well, we don't think that has been demonstrated. But it could. It could. Maybe a different study.

With regard to this question here, I would echo what Dr. Page said. But, again, I would like to sort of say it in a slightly different way just so it's in the record somewhere because I know this is all transcribed.

The functional class III data are consistent with my bias that the system was effective, even if only modestly so so far from the data we have. But we are now looking at a data subset of a small data set that itself didn't show a very consistent set of results. And the subset data also aren't highly consistent. You can substitute the word p-values if you like, but consistency is

what we are talking about.

They just tend to go the way we hope they would. And this must mean, it must mean, that another subgroup goes the other way. And one did. It was the functional class IV subgroup. Now maybe we can explain away the functional class IV data.

But now we are down to very small numbers. And I need to use a lot more intuition than I am comfortable using in potentially voting to approve a device that, as a result, will be available for general use in a large population.

So I am not very happy with subgrouping for the class III data, the same thing for the class IV data, which is exactly what Dr. Page said. And I think the numbers are just too small to draw firm conclusions on either functional class III or IV.

CHAIRPERSON MAISEL: Dr. Hauptman?

DR. HAUPTMAN: I would certainly concur with that review. Of course, heart

failure is much more complicated than just the filling pressure. And to some degree, we have to recognize that it is partly pathophysiologic and partly a surrogate for poor outcomes.

So, you know, a attractive an idea as it is that you can lower the filling pressures and your outcomes will be better, the fact is that if you look at all of the other endpoints, whether it is Minnesota living with heart failure questionnaire, a six-minute walk.

There really is no trajectory here that would allow us to say, "Well, the primary endpoint wasn't met, but everything else is pointed in a particular direction that gives us some comfort that the likelihood is that the way in which physicians are acting on this data is helping patients. So that is my concern.

There really is very little else to support this in terms of the secondary

data, which obviously is hypothesis-generating but certainly would be nice to have along for the ride.

CHAIRPERSON MAISEL: Dr. Normand? Anyone else have a comment on those? Dr. Zuckerman?

DR. ZUCKERMAN: One follow-up question to Drs. Borer and Teerlink. This was a randomized controlled trial with the reserved treatment effect being approximately 0.18 hospital equivalents. The sponsor has tried to indicate that a possible lack of more effectiveness may be secondary to the design of the trial, meaning that the control group received frequent communication in outstanding heart failure care. Did that argument impact on your calculations at all?

DR. BORER: Okay. I will. No. You know, if Cadillac care -- I'm sorry. I shouldn't use product names. If highest quality care was given to the people in the control group, that should be the standard of

care for patients with heart failure.

If, in fact, there isn't a meaningful difference between device-guided therapy and best therapy without device, then the device isn't worth putting in. We should just mandate or try to teach everyone or advertise that best quality care, conventional care should be given.

So no, it doesn't affect the way I think about it.

DR. TEERLINK: Well, I am going to so no, but. And the "but" here is that, first of all, it does present some challenges for clinical trial design. And when I was trying to think of how I would go about, you know, with the crystal ball, knowing what we know now, what would I do, one possibility, which nobody would like to do because it markedly increases the cost, the trial is let's find out.

So we do a three-arm study, where you have the one arm with the device, one arm

with the matching for the number of contacts, and then a third arm, where you say, "Okay. Let's see standard care."

And that way you can control for all three contributions to your treatment effect. And that would address the scientific question but make most sponsors miserable because now it's a much more complicated and expensive study.

So that would be possible. I think, though, that we don't -- and this is why I am -- contrary to how it may have come across, I am very conflicted on this inasmuch as I believe that this is very useful potentially.

And I am not sure that, you know, I would put Dr. Stevenson, Dr. Borer, Dr. Abraham, you know, this whole crew, Dr. Zile, up against any other heart failure specialist in the country and they will beat them.

You know, they will beat regular doctors. And the regular doctors and the

regular nurse practitioners, you know, the family practitioners, and the regular primary care doctors are the ones who are actually taking care of most of these patients.

So yes, it would be in a perfect world everybody would have the opportunity to be cared for by these outstanding heart failure physicians. But that is not how the real world works.

So in some ways, you know, this is not to take back what I said earlier. This trial does not provide effectiveness, any evidence of effectiveness.

But I'm not sure if these folks are the right comparator group. And so you may need to do actually more community-based trials and see how things work in that setting.

CHAIRPERSON MAISEL: So at this point I am going to try to summarize what we have heard regarding effectiveness. And I would say the following, that my sense of the

panel is that the most feel that the primary effectiveness endpoint of reduced heart failure-related equivalents has not been met. Many panel members feel that the device is effective at measuring pressures, although not all of us feel that way.

With regard to interpretation of New York Heart Association class III and IV, it sounds like most people feel that subgroup analysis of a primary effectiveness endpoint that didn't meet its endpoint is inappropriate, certainly provocative and hypothesis-generating but not enough to make any decisions on.

I would like to move on to question 3, which is "Please provide your clinical and/ statistical interpretation of the secondary endpoint results for the COMPASS-HF study."

Dr. Hauptman, you started talking about these. Maybe you can comment on your view of the secondary endpoints of this study

and what your view of the results is, which are most important to you and which might be used in future trials.

DR. HAUPTMAN: Well, I think some very relevant secondary endpoints were measured. There is a difference in Minnesota in the scoring, but it is modest. It does not reach the threshold that people generally use to say it's a clinically meaningful difference.

It would be obviously helpful to see some of these endpoints pointing in the direction of the device. And, unfortunately, at this point, they're not. Whether that is an issue of power, it may very well be. Whether it is an issue of the fact that, again, the control patients are taken care of so well can't be determined.

CHAIRPERSON MAISEL: Any other comments regarding the secondary endpoints? Dr. Somberg?

MEMBER SOMBERG: Well, just in

thinking of the future trial -- and I hope people are thinking of a future trial -- the secondary endpoint is certainly appropriate here. But I think, instead of mortality being a primary endpoint, I would think mortality would be a secondary endpoint because it is a stretch to go.

You know, hemodynamics in and of itself will affect all-cause mortality. But if you improve symptomatology at the expense of mortality, then you might have an issue.

So I think mortality is something to be considered as a secondary endpoint and sort of a consideration but not as your primary endpoint.

CHAIRPERSON MAISEL: Dr. Teerlink?

DR. TEERLINK: So I had already discussed the secondary effectiveness endpoints in terms of them not hitting significance. But I think for future trials, for this kind of study, particularly where we're trying to look at the combination of

causes and effects, days alive out of hospital is a very useful measure.

And the other thing to consider -- and this is something that has been reported by -- John Cleland is probably the main proponent of this, but a lot of us have also been very interested -- is the kind of clinical journey of the patient, where you get serial measures.

I would fully expect that if, in fact, this works the way we think it does, there would be on a day-to-day basis overall globally an improvement in the patient's well-being over the six-month period that would go in. And you would be able to show that with that kind of analysis. That would be another suggestion for a secondary/maybe a primary endpoint.

CHAIRPERSON MAISEL: Other secondary endpoint comments?

(No response.)

CHAIRPERSON MAISEL: So I think

that we generally feel that certainly if the primary effectiveness endpoint had been met, it would have been nice to see supporting information or if the primary effectiveness endpoint had been close. This is sort of a mixed bag. Some of them point in the right direction. Some of them are not particularly in one direction or the other.

Dr. Zuckerman, before I move on from effectiveness, do you have any other comments or questions for the panel about effectiveness?

DR. ZUCKERMAN: No.

CHAIRPERSON MAISEL: Okay.

DR. HAUPTMAN: Bill, sorry. I want to add one other thing. I was expecting more of a discussion about the analyses that the sponsor did. The whole issue of using baseline variables is covariance in the analysis.

CHAIRPERSON MAISEL: Discuss away.

DR. HAUPTMAN: Well, Sharon-Lise?

MEMBER NORMAND: I didn't raise it because I thought we were sort of concluding with that business, but there is a long discussion about doing that. We had information in our panel packs about that.

I can state my opinion in terms of the information that was provided. Certainly the information when you adjust for the covariates when you use something other than a linear regression model, the sponsors did not provide the right estimate. And what I mean by that is you have got to average over the covariate effects for patients.

So when one gives you an adjusted estimate from, let's say, survival analysis or a logistic regression, when you adjust for a covariate, that's not at the outcome. That's giving you an odds ratio. That's not tangible in terms of a causal effect. You need to take that down back to the probability level.

I know you are staring at me. You are starting to go down a bit. But let me

tell you what I mean by that.

DR. HAUPTMAN: It wouldn't be the first time.

MEMBER NORMAND: But I think the issue really is that the distribution of the covariates are such that the effect size differs. If I had a covariate distribution on my x-axis, the size of that effect differs when it's nonlinear. And most of these outcomes are nonlinear.

And so in general, the general feeling that I have and maybe most statisticians have is the randomization should take care of it. If it didn't take care of it, one is suspicious of how the randomization was conducted.

Clearly it could happen by chance and you could be unlucky. But if that is the case, most people would say you shouldn't have to adjust by covariates. And if you do adjust by covariates, a lot of people won't like that. And even if you do, they need to be on

the same scale as the observations. And the sponsors did not provide that to us.

And so the effect sizes that the sponsor showed us I ignored because they are not on the right scale.

CHAIRPERSON MAISEL: So, once again, I mean, the pre-specified analysis was performed and was presented, both by the sponsor and the FDA. I will make the observation that there were more p-values than patients presented in the packet as well.

So let's move on to safety, question 4, which is "Please provide your clinical and/or statistical interpretation of the results of the primary safety endpoint analyses."

So do people have safety concerns about the device? Dr. Borer?

DR. BORER: I think that the safety of the device is reasonable within the context of what you would expect of an implantable device. Is it reasonable relative

to benefit is our question. And, again, I have said what I think about that.

But I think that it is important here to point out that the sponsor met its pre-specified safety criteria. That is good. But they were arbitrary pre-specified safety criteria.

And in a small study with a relatively short observation period, some of the problems that we know historically can be associated with in-dwelling devices that Dr. Page alluded to earlier in sections, et cetera -- I mean, there are more -- that predictably will occur were not observed here. That doesn't mean they won't occur. It does mean that the upper bound of the confidence interval for those events is definable and probably relatively low, though we didn't see an estimate of that.

So my only point is that I don't think the adverse risks associated with this device have been completely defined. They

have been defined as well as they could be defined within the context of this trial. And that is what we have to balance against the effectiveness side.

But if further development is done -- and I, like everyone else, hope that there will be -- we need the larger data set to look at adversity.

I would like to make one additional point. I agree totally with John. This is an all-star team over here. You know, who would not want people like these to be taking care of your patients? Don't forget. The same thing is true with the device. Doctors still have to interpret the data. This is an all-star team at interpreting the data from the device, too.

So my original answer to you still stands. No.

CHAIRPERSON MAISEL: Dr. Zuckerman, would you like to comment on Dr. Borer's description of the arbitrary objective

performance criteria and maybe tell us about how the FDA arrives at such a number and agreement with a sponsor?

DR. BROCKMAN: Many of the device trials have safety endpoints analogous to this, system-related complication free rate. Others have major adverse events. Catheter ablation trials tend to be a little different, but all the implantable device trials use some subset of adverse events much like this generally compared against some objective performance criterion, either based on prior studies or based on published literature.

So while I wasn't part of the development of these particular endpoints, these are endpoints that are frequently used in implantable device trials.

CHAIRPERSON MAISEL: Thank you.

Dr. Page?

MEMBER PAGE: First of all, I would like to also comment that this is a dream team in terms of the consultants. And

it gives me pause when I hear them so genuinely favorably disposed toward this device when the Committee obviously has its reservations.

Along the issue of safety, I agree that the endpoints were met. And these would be reasonable endpoints if the results were blockbuster, but they're not.

And, in addition to that, the issues of dislodgement at five percent and entrapment, which has happened with one lead in my entire career and there are either one or two events here, give me pause, especially if it was a dream team of implanters. And once this goes from the initial investigators into others' hands using a timed lead, I think you can predict problems because, again, as I mentioned, a timed lead will not lodge necessarily where you want it to but can sometimes lodge where you don't want it to, such as in the valve apparatus. So I wonder whether in further iterations, an active

fixation lead would be made available.

And, finally, what came up through discussion more recently today is the battery life of three and a half years gives me concern in terms of the frequency of change-out.

And, as I mentioned, once a patient who has a device in -- I would hazard that most patients who would receive this device already would have a pacemaker or defibrillator in place.

And if you're doing repeated change-outs every time you go in and operate, you're running the risk of infection, one to two percent, even in good hands. And then you go down a road of extraction of not just this lead but the leads that are already in place. So I think that is an important safety issue as well.

CHAIRPERSON MAISEL: Dr. Teerlink?

DR. TEERLINK: Yes. So it did meet the safety endpoint. I was a little

concerned when I first saw that the sponsor felt that a 20 percent 6-month rate of system-related complications was acceptable.

Had it been close to that and we had other issues in terms of effectiveness to discuss, then that would have been raised. But in this case, it wasn't an issue.

I also think in terms of it's always a complication when we have a device for heart failure, what to do with the rehospitalizations for heart failure and the complications related to the device. Do the get counted against the primary endpoint? Do they get counted solely in the safety endpoint or do they get counted in both?

I think I showed the analysis. And I will publicly say that there was one flaw within the analysis that I didn't adjust for the number of patients in terms of the hospitalization. So the actual event rate was probably about half of what I presented.

Nonetheless, it's a considerable

number of events for hospitalized for device-related complications. And I think when you're putting in a device to help with heart failure hospitalizations, it's a heart failure device. Those events should count against a heart failure hospitalization. But then you also need to count them down here. And it would have been nice to have seen some of those analyses incorporated.

CHAIRPERSON MAISEL: Dr. Borer?

DR. BORER: Yes. I just want to ask a question. And it follows on something John said before about the fact that you preclude the use of MRI if the device is in place.

You know, this is sort of in the gray zone between safety and efficacy, I suppose, but in the label that was proposed -- we're not talking about the label here, but I picked it up reading the label -- in the section to be given to patients, it says that some precautionary measures have to be taken

if ultrasound studies are performed.

Now, I don't know what that means, but if it means that people shouldn't have echocardiograms done, that is going to be a problem in the current state of the art of taking care of patients. I am sure that is not what it meant.

But I would like for safety purposes a clarification if that is all right at this point of why there is a precaution in the use of ultrasound measures if this device is in place.

CHAIRPERSON MAISEL: My read of the technical manual was simply that the ultrasound had to be remote from the device by a certain distance. That would not preclude routine cardiac echocardiography from being performed. Is that an answer -- the sponsor is shaking their head yes, that that is accurate.

DR. BORER: Okay. Thank you.

CHAIRPERSON MAISEL: Any other

safety issues?

MEMBER SOMBERG: Bill, is there any reason that it has to be remote?

CHAIRPERSON MAISEL: I mean remote by a short distance. I mean that the probe needs to be --

MEMBER SOMBERG: No. I understand. But I mean just for my own edification, I mean, I am not an ultrasound engineer, but I could not see a reason. You know, a device is shielded. Why is that the case?

CHAIRPERSON MAISEL: Would the sponsor like to just respond to that question regarding ultrasound near the device or other energy sources?

MR. MANDA: Actually, we haven't really done any studies trying to determine the appropriate distance. What we do know is that, you know, the heat transducer will be replaced. Because this is also a pressure transducer, the general recommendation is not

to place the ultrasound probe right directly over the pressure sensing lead. But we don't have any data to show you right now as to the relative distances.

CHAIRPERSON MAISEL: Thank you.

Other safety comments or concerns?

(No response.)

CHAIRPERSON MAISEL: So at this point I think most of the panel feels that they have demonstrated safety. We obviously have some concerns about some rare events and ongoing issues that would need to be studied in a post-approval study if approved or studied further in an additional study if it's not approved.

Question five is to "Provide" our "clinical or statistical interpretation of the survival analysis." This gets back going backwards a little bit to effectiveness discussed in the panel pack. Specifically we were presented with six-month, one-year, I think even two-year follow-up at one point.

Dr. Blackstone, you seemed quite passionate about this issue. So maybe you can just summarize your thoughts again.

DR. BLACKSTONE: Yes. It's a non-issue. What you see in the panel pack is the patients were followed for up to six months. What is presented in panel pack are those few events that happen after six months.

So that you have very few patients followed up at six months. You have the classic Kaplan-Meier completion effect that everybody knows about. That stuff should be ignored. There is no question about that.

CHAIRPERSON MAISEL: So patients crossed over at six months. So I think we would have trouble interpreting --

DR. BLACKSTONE: Should be truncated is what I am saying. And it would pose no problem.

CHAIRPERSON MAISEL: Certainly with regard to primary effectiveness endpoint I think I agree and most of the panel would

agree. I think there is some value in looking at the curves and deciphering some other things, like Dr. Somberg was teasing out. But I think most of us feel once the crossover occurs, it's game over.

Now we move on to question six, which is the labeling, "The sponsor has proposed the following indications for use for this device, "The Chronicle Implantable Hemodynamic Monitor System I indicated for the chronic management of patients with moderate to advanced heart failure who are in New York Heart Association class III or IV to reduce hospitalizations for worsening heart failure in these patients. Please discuss whether the proposed indications for use adequately define the patient population studied an for which the device will be marketed.

"Please discuss whether the labeling accurately informs patients of the risks of the device.

"Please discuss whether there are

any other issues of safety or effectiveness not adequately covered in the labeling."

And I will comment we do always discuss labeling, whether or not the device is approved, because it helps the FDA and the sponsor.

So let's start with the indications for use. Anyone have any comments about the indications for use? Dr. Yaross?

MEMBER YAROSS: I think we have had a fair amount of discussion about potential other uses of this, in addition to what the sponsor had proposed. And perhaps if given the answers that I heard to questions 1 and 2, it might be appropriate to help the sponsor if you see indications in the current data set of efficacy for a different indication.

CHAIRPERSON MAISEL: Dr. Blackstone?

DR. BLACKSTONE: Yes. In a way, you would like to see the period after the IV.

If you listen to what these folks are saying, they are saying they believe there is efficacy when you are looking at individual patients. The trial wasn't designed for that kind of endpoint.

So that having the indication is something that we have clearly said hasn't been shown to be efficacious. I think that shouldn't be part of the labeling.

CHAIRPERSON MAISEL: Other comments?

DR. HAUPTMAN: Bill, if I can, I would just reiterate one point that perhaps the language should say "established heart failure of more than 6 or 12 months duration." And ideally indicate perhaps because there is no clinical trial data to support this at all that an inotrope-dependent patient or truly end stage patient would not benefit from the implantation of the device.

CHAIRPERSON MAISEL: So you have raised those points before, which are

obviously important, defining a more chronic heart failure population, not someone presenting with acute heart failure. Obviously these patients in the clinical trials needed to be on a stable medical regimen for at least three months but maybe teasing out exactly which population would be most appropriate for the device.

What other labeling comments? Dr. Teerlink?

DR. TEERLINK: Well, I think this is a general problem for the FDA. Overall as devices begin to move more and more into making therapeutic claims, like to reduce hospitalizations for worsening heart failure, we currently have the same therapeutic claim being made by some drugs and the same therapeutic claim being made by devices. Yet, we have markedly different standards of evidence for the two.

So you can basically get the same claim with very different standards of

evidence. And I think this presents a major problem. And it's a more general discussion. But I think that flag is raised any time the label includes such a therapeutic claim and I think leaves open interpretation what level of evidence is actually required and would be accepted by a committee or panel to define effectiveness in that setting.

CHAIRPERSON MAISEL: This panel has considered other heart failure devices before. We have approved devices that use the term "reduced first hospitalizations," terms like that. This may be an appropriate area for something like the Heart Failure Society or American Heart Association to take on and help standardize some of these definitions perhaps.

What other labeling issues? Dr. Normand?

MEMBER NORMAND: I'm sure this is -- I can't recall if this is done or not. I know that in the description of the

population, the population was I think a lot younger.

And so is there a place that says somewhere the characteristics of the trial that's enrolled in the population? It's not an indication per se, but I think it is important that when we look at this, we know that the trial population if it were to be approved was a much younger population than is typically seen in practice. Is that something that we can do, at least list the age ranges of the study?

CHAIRPERSON MAISEL: Dr. Somberg?

MEMBER SOMBERG: Dr. Normand, I would just say that it's asking a bit much for a trial to perfectly represent the universe that it is going to treat. And even with drugs, you see -- I mean, I remember a lot of the best studies in the early days were done in the VA system. And that is a very unrepresentative population of the general universe of heart failure.

I think we have to be careful. You know, certainly the study will be described someplace.

MEMBER NORMAND: That is all I am asking.

MEMBER SOMBERG: And, you know, there will be a publication. And there will be some data on that. But to say that because the mean age here was -- I don't know -- 50 and the mean age in heart failure is going to be 70 is a reason not to do this, if this had an adequately valid study with a good p-value, et cetera, I would be very happy to go ahead and apply this to the 89-year-old patient as well as the younger ones. So from a clinical standpoint, I don't think it's that critical.

I have another suggestion for us.

MEMBER NORMAND: If I could just --

MEMBER SOMBERG: Yes? Go ahead, Doctor.

MEMBER NORMAND: Because I know

how to disagree with you, but you are extrapolating way beyond the clinical data. And that is okay if you want to. And I would say we shouldn't repeat mistakes that we have made in the past if in the past that we extrapolated from the VA to the whole world.

Again, I am not saying that they have to write down everything. I am just hoping somewhere, not in an academic publication, but somewhere, it would be useful. And typically this is done that the trial population has described.

CHAIRPERSON MAISEL: Typically that is in the instructions for use where the study population is described where the indications and exclusion criteria for the study are included in the label. And I am sure that would be the case here.

Dr. Somberg, did you want to follow up?

MEMBER SOMBERG: I just wanted to mention the words "systolic" and "diastolic

heart failure." And I think that has to be looked at a little bit more carefully, properly discussed, and also maybe the times because there is going to have to be some recommendation of how often we have to look at this data. And it may differ between the two groups from some preliminary data here, but it's very preliminary. So these are just some things to consider but, again, not as critical as the overall efficacy endpoints.

CHAIRPERSON MAISEL: Dr. Brinker?

DR. BRINKER: It is difficult to suggest recommendations based on a study that we didn't feel was adequate in the first place. However, if one were to take these indications as a format for improving a study, I would focus on what heart failure specialists call frequent fliers; that is, require more than one hospitalization for heart failure within the time period that was selected. And they probably would get more bang for the buck per patient enrolled if that

were possible.

CHAIRPERSON MAISEL: Dr. Borer?

DR. BORER: Yes. Just sort of a note about labeling. And I want to pick up on what John Somberg said because I think he is right. And the implications of it are correct. That is that, you know, it is difficult to be very restrictive.

I think it is inappropriate to be very restrictive and very prescriptive in a label about an approvable therapeutic if we had an approvable therapeutic when there are so many questions that haven't been asked or answered.

This study was done in a population of patients with heart failure, most of whom were on multi-drug therapy. But not all of them were. Most of them were on all the drugs that we include in the current cocktail that's included in various guidelines, but not all of them were.

How do you tease out what the

device did for the ones who were and the ones who weren't? Well, the answer is, of course, we can't. And I think the reason that the label can't be so terribly prescriptive is that we don't know what to say.

So I think that the best one can do is to give a general recommendation of what we believe is true if we have an approvable therapeutic and then to provide as much information in the label about what is known or what was done to provide the information that maybe we know as we can.

I would be a little hesitant about putting in a lot of contraindications and whatever when we have so little information. I think that presumes knowledge that doesn't exist.

CHAIRPERSON MAISEL: Other labeling comments? Dr. Ewald?

DR. EWALD: I just wondered, too, if there should be some statement about utilizing this in the context of a heart

failure management program. I think Dr. Stevenson actually made that comment at one point, that -- you know, obviously implanting the device is not going to prevent the events. It's really what we do with the information.

And so I think trying to marry those two to some extent, that there is at least a baseline infrastructure that is set up to manage the patients is probably an important issue.

CHAIRPERSON MAISEL: Other comments?

(No response.)

CHAIRPERSON MAISEL: So let's move on to question 7, which is physician training. "The sponsor has provided a general overview of their plan for training physicians on the use of this device. Please comment on the adequacy of the training plan given the range of expertise of the physicians who may access the device and use the data in patient care." Now, the sponsor in their data pack did

include training description.

I don't know if anyone has any comments. My comment is mainly a point of clarification maybe. It wasn't clear to me that there was specific implant training provided. Certainly it included implanting physicians and heart failure physicians. And I'm sure the company would be more than happy to provide any appropriate implant training.

Dr. Page, what do you think would be appropriate implant training for physicians learning to implant this device?

MEMBER PAGE: Well, I think that technical expertise is probably managed by most people who are putting in pacemakers. I think there are nuances here that I'm sure the operators have learned and are beyond the description today but perhaps either some sort of proctoring but ideally we wouldn't mandate that but some sort of clear operator-to-operator educational materials in terms of the pitfalls, how to get this lead to

stick in the outflow track, how to avoid getting it trapped in the tricuspid apparatus.

But, again, I think, as was mentioned earlier, this is an early generation. I think the next lead, especially if it's incorporated in ICD, may have other things that need to be learned.

CHAIRPERSON MAISEL: Dr. Steinhaus, you have the unique position of having been a principal investigator and a Medtronic employee. How many implants do you think are required by a physician before they can implant it unproctored and without anyone there?

DR. STEINHAUS: First of all, let me say that we do plan to have physician training. It is a little different. And, really, the difference is the stylette doesn't extend all the way to the end. So what one has to do is essentially put a little bit larger curve in the stylette to get the thing to curve up toward the outflow tract and then

lodge it either in the outflow tract or actually mid-septum is also completely adequate in this situation. And I think basically it really doesn't take very long.

There is clearly a learning curve. If we look at dislodgements, you can see over time -- and we had a slide to show that -- that there is a little bit of a learning curve involved, which is not a surprise. But I think you get a physician who is used to putting in a number of leads like this. And I think five, ten leads is certainly adequate to learn how to do this.

CHAIRPERSON MAISEL: Okay. Thank you. Certainly it doesn't seem like there are any huge hurdles here with regard to physician training. Obviously training the ancillary staff based on the size we saw regarding who is actually caring for these patients is going to be probably the most critical component focusing on the heart failure, less so even the physicians than the nurse practitioners

and other support staff.

Dr. Somberg?

MEMBER SOMBERG: To follow up what he was saying, I think there needs to be some sort of prescribe algorithm for sensing or interpreting the information and then acting on it. It may not be the only one. Certainly you are not going to write it in.

But I would say whatever the group comes up with for anew evaluation and determination of efficacy, the way if that is effective, the way to actually get that to be effective in the general population is to have some simple, easy document for people to understand. And if it's what Dr. Stevenson mentioned about just changing diuretics, then that should be known because my first inclination is to modify a whole series of drugs.

And that might be the wrong approach. It may be -- so I think it has to be clear what to do because that is what the

host study interprets, is what you did on response to the information.

CHAIRPERSON MAISEL: Any other training comments? Dr. Hauptman?

DR. HAUPTMAN: Just a brief question. Since some of these patients, about 50 percent of the patients in the trial, had another device in, I didn't see in the reference manual any discussion about what happens to the device or what kind of programming is necessary after an internal defibrillation. That probably should be clarified unless I missed it.

CHAIRPERSON MAISEL: There was a recommendation for interrogation of the device following defibrillation.

DR. HAUPTMAN: I saw the external. I'm not sure if there is a difference between --

CHAIRPERSON MAISEL: I would think it should apply for both. Yes? We are being told by the sponsor yes.

Other physician training issues? Dr. Zuckerman?

DR. ZUCKERMAN: Can I ask Dr. Ewald to again expand upon his point? The real challenge here is with this type of transforming technology. How do you train the average physician to use this technology well?

The training program for interpretation of hemodynamic data -- I may be misreading it -- consists of a one-day program right now. If you were designing the program, what comments do you have to the sponsor? Is that enough? How do you get them to really understand this device?

DR. EWALD: Well, I guess my initial comment was to at least -- and I think the sponsor spoke to this earlier -- initially target places that are used to taking care of heart failure patients that are in the advanced stages.

And I think that, you know, certainly, you know, a day of training, you

know, may not be completely adequate. But I think if you already have a little bit of the infrastructure in place and the nursing support to do that, the physicians, then you will really I think be able to kind of show them how, you know, the data has been used in clinical trials, show them how you have applied the data in the real world to some extent, and give them scenarios, maybe for management.

I think it comes back, too, to kind of saying, you know, here is a prescription for how to manage various scenarios. I think that has come up a couple of times.

I think it is a useful consideration but not necessarily -- you know, we don't really want to go from a cookbook because I think some of the risks of over-diuresis and things we have talked about today potentially could be more concerning in that situation where we just have a

prescription to double the Lasix for a given pressure increase, those kinds of issues.

Does that answer your question?

DR. ZUCKERMAN: Partly. But realistically a great number of centers will potentially want to utilize this technology where structured heart failure programs aren't available. How are you going to train those physicians and nursing staff? What recommendations do you have?

DR. EWALD: Yes. Well, I think that has been a concern kind of all along, you know, through discussing this, that once it's approved or if it were approved, then it could be implanted. And if there's really no stipulation or no suggestion that there is the infrastructure in place, either advanced practice nursing or someone to really gather the data, respond to the data, stay in contact with patients, a lot of the things that we do in a heart failure management program, then I think the effectiveness is going to plummet

even further.

So I think that, you know, it has to be not only showing people how to use it but I think trying to show a program that once you start implanting the device, here are the features of a program that you really have to have in place to make this device work most effectively.

CHAIRPERSON MAISEL: Dr. Borer?

DR. BORER: Yes. I think one of the reasons that this is such a difficult question to answer is that the data don't exist to tell people how to use the results of this monitoring to best manage patients.

What is known in general is how the team that did the study did it. And that could be easily described within a day's training. I mean, it's not a complicated algorithm that they use. Whether it is right or not, I don't know.

In order to be able to read and interpret the implications of pressures,

presumably anyone who is a cardiologist went through a fellowship training program and was in a cath lab and should be able to understand the fundamentals. But the best way to apply the information once you have it isn't known yet. So how can you tell people how to do it?

I think what is going to probably happen if this were approvable at this point, which I don't think it should be, but if it were proved at this point, what we would have would be the algorithm that was used described as best that can be described from the relatively small set of patients in whom it was applied.

And then people will know that. And they will gain their own experience. And they will alter it if they think it needs to be altered. That is what is going to happen. How can anything else happen? Because we have no data.

CHAIRPERSON MAISEL: Dr. Page?

MEMBER PAGE: I would just like to

amplify on what has been said about the follow-up and the infrastructure. I think from what I am hearing, the implantation of the device is all too easy.

And to have the device placed without the infrastructure, without the training of the person who is going to manage the patient, the disconnect here is that the operator may not have any of the skills to manage heart failure.

And the heart failure expert may not have the skills to put in this device. But the person putting it in and billing for it is going to be a pacemaker-implanting cardiologist presumably or a surgeon.

So, one way or another, it should be really emphasized that it is not just putting in the device. This is a covenant between the cardiology establishment and the patient. Once this is in, you are exposing someone to a procedure with no value.

CHAIRPERSON MAISEL: It does speak

a little bit to training programs for electrophysiologists and heart failure doctors. And whether this gets approved today or a month from now or a year from now, it's coming.

And so both the heart failure training programs should start thinking about training heart failure doctors to implant these or similar devices. And electrophysiologists should be better trained in heart failure management, as should all cardiologists.

Dr. Normand?

MEMBER NORMAND: This is sort of what I was relating to when I was trying to say if this is assessing a diagnostic tool, then we would have had more information regarding the algorithm in place. So I'm sure people will correct me if I am wrong. Right now that information is obtained except not with this new device. And so the information that we are getting from the new device is

more continuous, more time points.

I am being gross about it. I mean, you could have a visit to the doctor and you get some of the information. But with the new device, then you have this curve that people were saying about the trends. You look at the trends. And that is going to be predictive of something.

Well, we haven't assessed that. We haven't assessed how predictive that is. You have done it retrospectively. But when you are teaching somebody to look at this information, presumably they know how to do it now, but they don't know how to do it now with much more data, where they may feel much more certain about how to react or not react.

And so I am just emphasizing the fact that I don't think we have the information because I, again, view this as a diagnostic tool that we did not assess as we would normally assess a diagnostic tool.

CHAIRPERSON MAISEL: Dr. Hauptman

and then Dr. Teerlink.

DR. HAUPTMAN: I would just try to summarize to Dr. Zuckerman. You called this a "transformative device." It sounds like we need transformative training and labeling, too, to accompany it.

CHAIRPERSON MAISEL: Dr. Teerlink?

DR. TEERLINK: So I would also emphasize that this doe require serial training. So I think you need kind of the introductory course and then the refresher buff-up. And I think this is something, an area where our nursing colleagues are so far in advance of us.

In terms of having studied, how do you actually teach people and physicians or nurses or patients how to do something? And so I would encourage sponsors to look at that literature, which is I think very under-utilized, actually, in these kinds of approaches?

But any kind of program should be

a serial program involving at least two different contacts with the care providers to assure kind of the initial preparation and then a follow-up.

CHAIRPERSON MAISEL: Okay. At this point I would like to move on to discussion of the post-approval study should the device be approved. "Discussion of the post-approval study is not meant to imply that the device will be approved, but, once again, this information helps both the sponsor and the FDA.

"Based on" our "review of the device, please comment as to the suitability of the proposed post-approval study and, if applicable, please discuss any other elements that should be included in the post-approval study." Dr. Somberg?

MEMBER SOMBERG: Can I make a suggestion that we amend this question to the effect that I don't think we should talk about a post-approval study if we're sort of, you

know, from one to five or one to six. We sort of haven't gone that direction. If the Dr. Zuckerman so pleases, we should talk about what we might recommend as a follow-up study that might optimize things.

CHAIRPERSON MAISEL: We had a discussion prior to the meeting about the best timing of this question. We decided we would discuss a post-approval study now. If the product is not approved, we will help the FDA and the sponsor answer the question of what needs to be done to get to the end line.

So right now we are going to discuss a post-approval study as designed. Dr. Normand?

MEMBER NORMAND: So I think that one thing that definitely has to happen is that the information here that is utilized is really clustered. And you definitely have to take that aspect into account in your study design.

And so that actually makes you

need to enroll more patients because you no longer have independent observation. So I don't think we can ignore the fact that this is a technology where the information by a group of people treated within the same institution or by the same physician or group of nurses is not independent. And that needs to be accounted for in the analyses. And so it would be incumbent upon the design of the study to include that.

That also relates to the fact that your endpoint, the analysis that was proposed originally used a negative binomial because you found over-dispersion. I would bet my life it's because of the clustering. There is more variance. And that is due to the fact that there is clustering. And normally that would have been something that you would have done at the beginning. So I recommend that.

The second thing is I think it is probably -- I don't know how my colleagues feel, but what is the right endpoint to be

measuring with this diagnostic tool. Is it really heart failure, reduction in heart failure equivalents? Is it successful use of the information?

Again, that is not something that I would know exactly the answer to, but certainly in these types of studies, one would want to know that: a) the information is being used appropriately. And to go down line to say that actually impacts heart failure hospitalizations might be too far from the intent of the device. So I raise that as a question in terms of an endpoint.

CHAIRPERSON MAISEL: Dr. Borer?

DR. BORER: Yes. A couple of thoughts. And I think that Sharon has raised a key issue here. This is a post-approval study, which presupposes that the FDA has determined that the device is effective for whatever the use is expected to be, which, as we have heard it, is to reduce heart failure hospitalizations or their equivalents, and