

1 that it is acceptably safe for that use. So
2 that is a given. So this study can't be a
3 repetition of that. I mean, that would be
4 redundant.

5 So what do we need? From a
6 post-approval study, we need to be able to
7 refine the label, I would suggest, which means
8 to get a better point estimate of the safety
9 issues from observational data, which this
10 study can do the way it is designed. And I
11 would suggest it provides us with an attempt
12 to refine the algorithm for treatment that
13 would be based on the data that would be
14 collected.

15 One could consider a design that
16 would within the group that got the device
17 fairly prescriptive algorithms to be used,
18 more than one, to see whether one is different
19 from another, you know, fairly straightforward
20 and rigorously defined algorithms that would
21 respond to the issues that we are all raising
22 so that ultimately there is more information

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1 out there and the people who use the device
2 would be in a better position to use it.

3 I think the comparison of
4 hospitalizations that is specific aim three of
5 this, hypothesis three, the hypothesis that
6 there will be fewer hospitalizations, I find
7 that kind of silly. I mean, I don't know how
8 you can possibly interpret the data from an
9 observational study that has nested this and
10 case control for that. I find that one a
11 little difficult. That is interesting and
12 great, but that should have been taken care of
13 before approval, whether it works or not.

14 So I would suggest that one needs
15 to look at those two issues; that is, the two
16 issues that I think are most important in
17 refining the label, point estimate of safety
18 and the effectiveness algorithm of the
19 algorithms most effective.

20 Now, there are two other issues
21 that are specifically asked by the FDA in this
22 question: use of all-cause mortality versus

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1 heart failure mortality as a primary endpoint
2 for whatever. You know, to the extent that
3 you want that kind of information, I would
4 argue in favor of all-cause mortality.

5 And the reason I say that is that
6 the people who will be getting this device are
7 sick people, very sick people. I would have
8 no way of teasing out the heart failure
9 contribution to a death that is presumably
10 non-heart failure. I mean, I don't know.
11 Nobody does. So I think the conservative
12 approach is best; that is, looking at
13 all-cause mortality.

14 Moreover, I am making an
15 assumption here, but you asked about heart
16 failure deaths. Are you including sudden
17 deaths in people who have heart failure?
18 Because if not, then we have a real problem.
19 you know, half the people with heart failure
20 die suddenly, another reason to think in terms
21 of all-cause mortality.

22 And the second question is with

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1 regard to possible adverse events due to
2 inaccurate use of the Chronicle data. For
3 sure. You know, we would love to know about
4 that. I am not sure how you tease it out.
5 The data generally require some clinical
6 corroboration, I would think. I am not sure
7 how you tease out that except by testing
8 different algorithms within the population
9 that gets the device, which is why I suggest
10 that that is something that should be
11 considered in this post-approval study.

12 So those are my sort of general
13 thoughts on the post-approval study.

14 CHAIRPERSON MAISEL: Dr. Kato?

15 DR. KATO: In reflecting on that,
16 on the post-approval study, it reminds me of
17 the studiers trying to look at mortality and
18 survival in critical care settings because
19 this is essentially outpatient critical care
20 is what you are doing.

21 And one of the problems that you
22 are going to be faced with -- and, again, I

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1 don't know how to deal with this. I'm just
2 going to bring it up. From what I know of Dr.
3 Stevenson's team, not only when she was at
4 UCLA but also the Brigham and Women's, it is a
5 multi-disciplinary team with different people
6 with different expertise. And many times what
7 it comes down to in terms of overall survival
8 of patients and decrease in mortality may just
9 be better communication and better teamwork
10 among, you know, one time at one hospital
11 versus another.

12 And that's going to be one issue,
13 is going to be how to standardize. And I
14 guess this comes back to the algorithms to
15 some degree. On the other hand, it is also
16 management of the team, peer-to-peer
17 interactions, interactions among team members,
18 but how do you make that team function in
19 order to get that patient, you know, to have
20 the best clinical outcome?

21 I don't know how you are going to
22 do that, but that is going to be an

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1 interesting problem.

2 CHAIRPERSON MAISEL: So typically
3 the post-approval studies are designed to look
4 at a couple of common themes in device trials,
5 including rare safety events, which seems
6 pretty straightforward. You just need a
7 registry of patients who get the device and
8 quantify the number of events that occur in
9 real world experience; in other words, how
10 does a device perform outside a clinical trial
11 when it gets out to the community, which also
12 in my opinion could potentially be done in a
13 registry of consecutive patients in the
14 community compared to the clinical trial data,
15 which might give you some information.

16 In my mind, the question is, do we
17 need a control group for that registry data?
18 And what is the appropriate control group?
19 Dr. Borer?

20 DR. BORER: Yes. That is what I
21 was trying to get at earlier and didn't quite
22 get there. I am not sure what the non-device

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1 control group adds to this. I think what we
2 need is a consecutive patient registry that
3 allows, again, refinement of the point
4 estimates for safety for adversity and let
5 capacity, opportunity to look at different
6 ways of using the data so that we can figure
7 out what would be the best application of the
8 data to achieve the goal.

9 The control group, the non-device
10 control group at this point, if the device is
11 approved, then the non-device control group
12 doesn't tell us anything that we presumably
13 didn't know already.

14 CHAIRPERSON MAISEL: Dr. Domanski?

15 DR. DOMANSKI: Yes. Well, the
16 other thing is a non-device control group in
17 that setting might not really be ethical. I
18 mean, after all, you have now decided that
19 something is safe, effective, and ought to be
20 added to the therapy. And now you're denying
21 it. So I don't think that makes sense.

22 CHAIRPERSON MAISEL: Which leaves

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1 us with the only two options that the sponsor
2 selected, which are patients who refuse the
3 device or patients at a center that can't get
4 the device if we want a non-implant control
5 group.

6 Dr. Teerlink?

7 DR. TEERLINK: So I would actually
8 -- I agree with all of the comments so far.
9 And I would be in favor of an all-cause
10 hospitalization and cardiovascular mortality
11 plus device-related mortality as the
12 predominant endpoint that is followed for the
13 trial.

14 Once again, that is all-cause
15 hospitalizations, reason being, you know, we
16 don't know without an endpoint committee. It
17 is hard to decide what is a heart failure
18 hospitalization? What is a renal
19 hospitalization? Because they got too much
20 diuretics?

21 So all-cause hospitalizations
22 knowing that it is going to dilute out any

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1 potential big effects, but presumably if and
2 when this gets approved, we will be
3 comfortable that those big safety effects
4 aren't there, then also cardiovascular
5 mortality, which I think can be sorted out a
6 little easier; and then device-related
7 mortality just to allow for the patient who
8 gets, you know, the rare patient who gets,
9 floored sepsis from a lead problem and
10 decompensates and ends up dying of sepsis, but
11 it is really due to the device.

12 CHAIRPERSON MAISEL: So were these
13 endpoints in a registry or in a control group?

14 DR. TEERLINK: I don't think you
15 can have -- this is why, actually, I think
16 Jeff's idea of what would be nice, this would
17 be a great opportunity to look at how
18 different management strategies work. I don't
19 think we have a good control group, even
20 within that, because there are going to be so
21 many different approaches in terms of trying
22 to do clustered analysis. And it becomes a

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1 5,000-6,000-plus patient trial that is
2 uncontrolled.

3 So I think it is a great idea, but

4 --

5 CHAIRPERSON MAISEL: Dr. Somberg?

6 MEMBER SOMBERG: Well, I am going
7 to take a contrarian point of view here. And
8 the hypothetical we have is that the device
9 has been approved because it is safe and
10 effective in reducing hospitalization. And
11 then you are asking, what would we do as a
12 post-marketing study of import?

13 And I think the sponsor has
14 suggested a study that has to do with
15 mortality. And I agree with that because that
16 is the next question out of any I think
17 cardiologist's mind is, "Well, okay. It makes
18 you feel better, but does it make you live
19 longer?" And that is going to be a critical
20 issue.

21 Now, I would say the only way to
22 prove that is to have a control group. And I

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1 think it is more than ethnically valid to have
2 a control group as long as you offer them --
3 there are IRB ethical issues now -- but if you
4 tell the patient, "Look, we have a therapy
5 device and a change in drugs. We have a
6 therapy that can make you have less
7 hospitalizations. You may feel better. You
8 may go through a lot to do that, but you may
9 feel better. But we don't know how it affects
10 your mortality. We want to put the device in.

11 And then we want to randomize you. And we
12 may use the device and not the device. You
13 may suffer more hospitalizations, but you may
14 live longer."

15 And I think it is more than
16 ethical to do that. Otherwise you will never
17 get to that answer. So if you do all the
18 registries in the world, et cetera, don't have
19 a mortality endpoint and never ask the
20 mortality question and what you're telling is
21 "Don't approve this drug" until you have a
22 mortality thing because you only get half the

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1 answer for all eternity.

2 So I think you could approve a
3 drug based on hospitalizations,, but you have
4 to then have the willingness to do a mortality
5 trial versus a control. Otherwise you will
6 never answer that question.

7 CHAIRPERSON MAISEL: I think the
8 only way we are going to definitively answer
9 the mortality question is with a randomized
10 trial. We are not going to answer it in a
11 post-approval study. I think it is asking a
12 lot to study control patients, collect all
13 this data, and try to make a mortality
14 decision based on data that is going to be
15 inadequate.

16 MEMBER SOMBERG: Hold on. But
17 what happens if this study -- I mean, maybe
18 you are right. But if this study today,
19 hypothetical, had a p-value of .0025, meeting
20 the two pivotal study requirement of some
21 bizarre Neanderthal or something like that,
22 let's say it did that. It would be approved.

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1 And then you would say you could never answer
2 the -- I think you could do that. You could
3 do a mortality trial afterwards. And it is
4 possible.

5 Now, you could do a mortality
6 trial the sponsor said to people who refuse
7 this, you know, refuse. But that is not a
8 very good trial. But I think you can also
9 justify in many senses maybe 30 percent the
10 IRBs wouldn't want you to do it, but you use
11 my algorithm justification for that.

12 So I would think, especially with
13 devices, that you are never going to have it
14 all up front, feel better, live longer in this
15 area, but you are going to have a staged
16 approach. You are just going to have to face
17 that and be aggressive with the post-marketing
18 studies.

19 I'm sorry. I disagree with you,
20 Bill.

21 CHAIRPERSON MAISEL: I think the
22 post-approval mortality trials would need to

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1 be as Dr. Borer suggested. I mean, you could
2 compare all patients who got the device to two
3 different treatment algorithms or something
4 and look at a mortality difference. But I
5 don't see a way that a control group is going
6 to be adequate.

7 Dr. Domanski?

8 DR. DOMANSKI: Yes. You know, I
9 think it's fine to conceive a monstrously
10 large trial, which would certainly be an
11 interesting one. But I think to ask the
12 company to do that, to tell the company that
13 they have to do a post-approval trial when you
14 have got it approved for one indication and
15 now you want to study it further as a
16 post-approval thing, I don't think that is
17 reasonable.

18 CHAIRPERSON MAISEL: Dr. Normand?

19 MEMBER NORMAND: I know I left,
20 but I am back. And I did want to say that we
21 have; that is, the FDA and this panel, gotten
22 into trouble when there is no control group in

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1 the post-market setting.

2 And I think that people say, "It's
3 not ethical to do" this, that, and the other
4 thing. I have my disagreement with some of
5 those things in terms of whether that is
6 ethical or not.

7 But, regardless of that, I think
8 we do have a dilemma because when it comes
9 down the line and it is out for a while, we
10 will come back with some rates.

11 And someone is going to say,
12 "Well, are they too hard, too low?" And
13 suddenly the population has changed. The
14 practice has changed. And we are not going to
15 know.

16 So, although it may be difficult,
17 I would encourage everybody to think about
18 getting some sort of control group. You know,
19 it is not going to be perfect, but it is going
20 to be better than none.

21 And so I really, really think
22 saying that, you know, "It is not ethical" or

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1 "We can't do it" is I feel in my mind a
2 non-starter these days.

3 CHAIRPERSON MAISEL: Dr.
4 Zuckerman?

5 DR. ZUCKERMAN: Yes. For a panel
6 that didn't want to discuss this question,
7 there is a certain irony here.

8 (Laughter.)

9 DR. ZUCKERMAN: I think what the
10 FDA and sponsor need are just some general
11 guidelines. And you have given us some
12 guidelines regarding safety, just
13 generalizability to different, less
14 experienced sites.

15 And we come back to Sharon-Lise's
16 appropriate comment that, time and again, in
17 our post-market studies, we really do need a
18 control, however limited they may be.

19 Dr. Normand, the sponsor has
20 proposed a control, a realistic one, being
21 sites that are not going to be the first sites
22 to get a new technology. It is highly

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1 unlikely that the sites where the new
2 technology is available, patients there will
3 want to defer that technology.

4 Dr. Blackstone had some comments
5 about a control that is at a different
6 hospital being very problematic. Do you have
7 any practical suggestions?

8 MEMBER NORMAND: Well, you know,
9 certainly Dr. Blackstone is correct in terms
10 of it will be confounding in terms of we can't
11 separate the site effect or the teams effect.

12 But then that is again if it is either that
13 versus no control group, I would rather have
14 that. So is there anything in between that we
15 could use?

16 And so part of me thinks that I
17 really doubt based on my experience -- and I
18 think we all need to think about that in this
19 room -- that every single person in the site
20 where there is the available technology who is
21 eligible will actually take it. So I do think
22 you can find some controls within the current

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1 sites. And that has got to do with how the
2 information is presented.

3 So we could use the different
4 sites altogether. Sometimes, sometimes heart
5 failure practitioners practice at more than
6 one site. So we could try and see about sort
7 of how much team overlap there is between
8 sites.

9 But, again, Dr. Blackstone is
10 right. But it were me and it is either no
11 control or that, I will take that and at least
12 think of some confounders that one could
13 measure a priori to try and take out some of
14 the side effects so we could collect or one
15 could collect information about the experience
16 of the nurse, you know, more data perhaps to
17 try and eliminate that confounding by site,
18 such as experience of the nursing team, other
19 things about the patients.

20 CHAIRPERSON MAISEL: Dr. Normand,
21 would it be helpful if data were collected
22 starting now or soon before the device becomes

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1 available, whether or not it's approved, there
2 is going to be a delay and different sites
3 could start collecting data on the heart
4 failure patients at the sponsors, you know,
5 via the sponsor and that would be available to
6 compare post-implant?

7 MEMBER NORMAND: Yes.

8 CHAIRPERSON MAISEL: Okay. At
9 this point, we are going to move on. The last
10 question is to "Provide your overall
11 assessment of the risks and benefits of the
12 Chronicle Implantable Hemodynamic Monitor as
13 demonstrated in the pre-market approval
14 application." We are going to hold off on
15 that question. We will go around the table
16 after the vote and let people give their
17 answer to that question.

18 2ND OPEN PUBLIC HEARING

19 CHAIRPERSON MAISEL: So at this
20 point, we are going to move on to the second
21 open public hearing portion of the meeting.
22 Is there anyone in the audience who wishes to

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1 address the panel at this point before the
2 vote?

3 (No response.)

4 CHAIRPERSON MAISEL: Okay. So now
5 I am going to ask the panel, do you want to
6 take a short break now or go on? Yes. So a
7 15-minute break. We will reconvene for the
8 vote in 15 minutes.

9 (Whereupon, the foregoing matter
10 went off the record at 3:49 p.m. and went back
11 on the record at 4:05 p.m.)

12 CHAIRPERSON MAISEL: Okay. Good
13 afternoon. We will reconvene. What I would
14 like to do at this point is offer the FDA and
15 the sponsor a chance to make some final
16 remarks. And we'll start with the FDA. Dr.
17 Zuckerman or the rest of your absent FDA team,
18 do you have any comments to make?

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20 DR. ZUCKERMAN: Okay. On behalf
21 of the FDA team, I would like to say that we
22 don't have any further comments.

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1 (Laughter.)

2 CHAIRPERSON MAISEL: Thank you.

3 And now I would like to invite Medtronic to
4 make some final remarks.

5 DR. STEINHAUS: I started out by
6 saying "Good morning." Well, good afternoon.

7 It has surely been a long day. And I want to
8 let you know how much we at Medtronic really
9 do appreciate the efforts you have put into
10 reading the data, to looking carefully at our
11 application, and to your consideration. We
12 really do.

13 We have heard a lot of recent
14 discussion today. I am a realist. I
15 understand what you said. And certainly there
16 is nothing terribly surprising in what we have
17 heard.

18 And I understand how hard it is to
19 approve something which has not met its
20 primary endpoint, how difficult that is. I
21 guess I would only ask you to realize several
22 things.

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1 First of all, I want you to
2 realize how hard it is to do this work and how
3 much we have put into it after 15 years of
4 trials, of difficulty with leads, hermeticity,
5 trying to figure out, could we make a sensor
6 that is even going to be stable? Was it going
7 to be reliable? Would there be not enough
8 drift, all of those issues being raised?
9 Would it be compatible in the human being?

10 And there have been people who
11 have worked on this. I look at Tom Bennet.
12 And he had dark hair when we started this
13 years ago. So I do want you to appreciate
14 what has really gone into this, first of all.

15 Second of all, I also want you to
16 appreciate that this is a new era. And I
17 think Dr. Zuckerman really mentioned that
18 quite clearly. This is a new paradigm. It
19 may be transformational. And the problem with
20 it is the endpoints aren't entirely clear.

21 When we first started doing this,
22 no one had ever measured pressures inside the

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1 heart in an ambulatory patient. No one had
2 ever done that. What are the relevant
3 numbers? I mean, is it the PAED? Is it
4 supine at night because we're used to doing
5 that with patients in the hospital? Is it
6 arise with exercise? Is it a heart rate
7 increase with exercise? Is it a pressure
8 increase with exercise? Is it the dp/dt ? Is
9 it the delta? I mean, what are the relevant
10 features that we are going to need to look at
11 as we assess this therapy?

12 I would submit to you that it's at
13 some point a point we don't know. And we are
14 going to be learning. And I think we are
15 going to be learning for some time to come.

16 I think one of the ways of
17 learning is really to get this somehow in the
18 hands of physicians who can try to figure out
19 how best to use it because certainly we as a
20 company are not going to be able to do that
21 alone.

22 I also want you to remember that

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1 we made a commitment. And the commitment we
2 made to physicians was to provide a device
3 which would measure pressures inside the heart
4 and they would be reliable and they would be
5 stable and to help them manage patients. I
6 think we as a company have done that.

7 So I guess what I would just ask
8 you is, have we accomplished that goal? And
9 if it is, you know, I think we have
10 demonstrated some things today. I think we
11 have demonstrated that we have proven that the
12 measurements we can make, that they are
13 accurate, that they are reliable, and that
14 they are stable.

15 Number two, I think this is
16 intuitively clear to anyone who has ever
17 managed heart failure patients from the time
18 we go back to fellowship. You know, it's one
19 of those things. I grew up as a child of the
20 '60s. And I remember the statement -- I am
21 sure you will remember it as well, some of you
22 in the room -- that it doesn't take a

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1 weatherman to know which way the wind is
2 blowing.

3 And, in fact, Swan-Ganz catheters,
4 which were the gold standard, I would submit
5 to you no longer are the gold standard. I
6 would submit to you this device is the gold
7 standard.

8 And if you remember back to those
9 times of managing patients acutely in the
10 hospital when you were fellows, I would
11 suggest to you that no one had done a study to
12 demonstrate that Swan-Ganz catheters improved
13 outcome in these patients.

14 So I think that that is important
15 to realize. I think it is also important to
16 realize that we have demonstrated that the
17 pressures that we measure relate directly to
18 events. I think we have demonstrated that
19 effectively. And I think they certainly
20 relate to symptoms. I think that is also
21 intuitively obvious, but I think we have
22 demonstrated that as well. And, finally, I

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1 think we have demonstrated the device is safe.

2 So I would ask you -- one of the
3 problems we have got is if we designed an
4 imperfect study, which, no doubt, we did, I
5 hope you will realize or it's underpowered
6 because there were things out of our control
7 to understand or the randomization didn't work
8 or we got unlucky or whatever those reasons
9 are, I would ask you to appreciate that and to
10 think about it.

11 If you really do think there is
12 value here, I would like you to consider at
13 least some type of approval, even if it means
14 a change in labeling is necessary.

15 So beyond that, I would ask our
16 physicians, who really are the experts in this
17 field, I think, and also are so passionate
18 about this. I would really like to get a
19 couple of comments from them. And then we
20 will leave you.

21 Thank you very much for your
22 attention.

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1 DR. STEVENSON: As clinicians who
2 take care of heart failure patients, we
3 realized a long time ago that we needed a
4 diagnostic device to measure filling pressure
5 in patients at home, to help us adjust their
6 medications, to help treat their treatments,
7 to respond to and reassure them when they call
8 us.

9 The sponsor developed this device
10 that gives us this information and, as I
11 understand it, satisfied the FDA some years
12 ago on the diagnostic accuracy of this device.

13 We were then challenged for how
14 would it be used. So we came up with an
15 algorithm, the best we could at the time, for
16 how we would use the information. As the
17 panelists pointed out, there is no question
18 that this algorithm can be refined. It will
19 be refined forever as we see it in different
20 patients and different settings.

21 We were then further challenged to
22 make sure that this information wouldn't be

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1 used to over-treat patients, to over-diurese
2 patients to get us into trouble. And
3 certainly I think the data that we have seen
4 today suggests that there is no signal of risk
5 that patients are being over-treated using
6 this.

7 On the other hand, we have
8 demonstrated that it is decreasing filling
9 pressures. And I think there is a consistent
10 trend for hospitalizations. But we have
11 certainly helped to validate the physiologic
12 basis on which we developed this.

13 So we have the device that we
14 asked for. And we would like to be able to
15 use it. The guidelines have evolved during
16 the development of this project to the point
17 where it is now mandated that we assess volume
18 status and treat fluid status in patients with
19 heart failure. But 95 percent of the time,
20 patients are at home. And we don't know how
21 to do this there.

22 And the novel information, some of

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1 which you have seen today, actually tells us
2 that we're even worse than we thought at
3 trying to understand patient volume status at
4 home.

5 So I would say that we actually
6 stand in the same place that we stood in some
7 ways at the beginning of this development
8 program, which is we would like to see this
9 approved as a diagnostic device, not a
10 therapeutic device -- that involves a whole
11 heart failure program -- but a diagnostic
12 device that is approved for the indication of
13 monitoring filling pressures in the management
14 of patients with advanced heart failure.

15 DR. ABRAHAM: Well, I, too, would
16 like to thank everyone for their attention and
17 effort today and just make a few comments that
18 I hope will be a bit integrative from the
19 perspective of the investigators and the study
20 sponsor and perhaps summarize a bit of what I
21 have observed in the discussion today.

22 First of all, the discussion has

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1 been incredibly complex and I think
2 appropriately so. There are a number of
3 things that I think there has been general
4 agreement among all of us on.

5 One, there seems to be in general
6 enthusiasm for the concept that underlies this
7 device and enthusiasm for the device itself.
8 I almost get the impression that there are
9 some real cheerleaders out there that really
10 want to see this succeed. And so we end up
11 with a question regarding burden of proof.

12 I think the enthusiasm stems
13 largely from the biological plausibility of
14 this approach to managing heart failure and
15 the fact that the concepts seem to be
16 intuitively sound to all of us.

17 But, yet, there is angst among us
18 regarding a negative primary endpoint. And I
19 think that, in fact, has really become a
20 large, perhaps appropriate focus of the
21 discussion, but I think it's important to come
22 back to some of the themes that Drs. Steinhaus

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1 and Stevenson have already introduced in their
2 summaries and, in particular, the fact that
3 this is a diagnostic device.

4 I think, as you deliberate your
5 vote, we have got to really ask a serious
6 question regarding where the bar should be set
7 for the approval of a system or device like
8 this.

9 And in some ways, I think, based
10 on our selection of a primary endpoint in this
11 trial, we have created a bit of a monster here
12 because, in fact, much of this discussion has
13 focused on therapeutic implications, rather
14 than on diagnostic implications.

15 Though certainly this is a
16 diagnostic device that informs therapy, we
17 have shown that this device produces data and
18 that that data does prompt clinicians to make
19 changes in therapy, particularly in diuretics.

20 And, in fact, when that is done, one can
21 arrive at the correct or optimal filling
22 pressure or volume status in patients.

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1 The link that is missing in these
2 data is the link to outcomes based on the
3 negative outcomes of the primary endpoint for
4 this trial. So one question I would have you
5 consider is, where exactly one should the bar
6 be set? Is it sufficient to get all the way
7 to the correct pressure or are outcomes for a
8 diagnostic device really a necessary
9 requirement for approval?

10 I will also mention
11 parenthetically, as you all know, that when
12 one designs a clinical trial, you know, it is
13 always a bit of a roll of the dice. Even if
14 one looks at outcomes as being necessary in
15 this study, we chose as a group of
16 investigators in discussion with the FDA an
17 outcome that looked at all heart failure
18 hospitalizations, actually all heart failure
19 events, which went beyond heart failure
20 hospitalizations.

21 Those of you -- and I think most
22 of you are familiar with the literature on

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1 heart failure. The most common measure of
2 morbidity in heart failure clinical trials is,
3 in fact, heart failure hospitalizations,
4 harder events than these ED or urgent clinic
5 visits, and generally assessed using a time to
6 event analysis. And, in fact, in this study
7 had we chosen that to be our primary endpoint,
8 the outcomes for this trial would have been
9 positive.

10 So what I would suggest is that
11 when one looks at this as a monitoring or
12 diagnostic device and considers the totality
13 of the data available from phase one, phase
14 two and the COMPASS-HF trials, that there is,
15 in fact, reasonable assurance of safety.

16 I don't mean to minimize
17 hospitalizations or device-related
18 complications. Those are important. They
19 diminish with experience. But I do want to
20 point out that there were no device-related
21 deaths. And, in fact, regarding the
22 functionality of the system, there was no

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1 indication of adverse events related to
2 over-diuresis. In fact, dehydration events
3 occurred more frequently in the control arm,
4 rather than in the Chronicle arm of this
5 study.

6 I think we have also provided
7 reasonable assurance of effectiveness where
8 effectiveness is designed as providing data
9 that informs a clinical change in therapy and
10 arrives at a correct pressure.

11 So I think, at the present time,
12 as Lynne has demonstrated, there really is an
13 unmet need within the heart failure community
14 to find better ways to assess our patients.
15 And this is a diagnostic device that has shown
16 substantial benefit in doing so.

17 Thank you very much.

18 CHAIRPERSON MAISEL: Any other
19 comments from the sponsor at this point?

20 (No response.)

21 CHAIRPERSON MAISEL: No. I'll
22 give the FDA another opportunity. Anyone from

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1 the FDA want to comment?

2 DR. ZUCKERMAN: No thank you.

3 CHAIRPERSON MAISEL: Okay. Thank
4 you.

5 PANEL VOTE

6 CHAIRPERSON MAISEL: At this point
7 we are ready for the vote on the panel's
8 recommendation to the FDA for this PMA. Mr.
9 Swink will now read the panel recommendation
10 options for pre-market approval applications.

11 EXECUTIVE SECRETARY SWINK: "The
12 medical device amendments to the Federal Food,
13 Drug and Cosmetic Act, as amended by the Safe
14 Medical Devices Act of 1990, allows the Food
15 and Drug Administration to obtain a
16 recommendation from an expert advisory panel
17 on designated medical device pre-market
18 approval applications that are filed with the
19 agency.

20 "The PMA must stand on its own
21 merits. And a recommendation must be
22 supported by safety and effectiveness data in

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1 the application or by applicable publicly
2 available information.

3 "The definitions of safety,
4 effectiveness, and valid scientific evidence
5 are as follows. Safety is as defined in 21
6 CFR section 860.7(d)(1). 'There is reasonable
7 assurance that a device is safe when it can be
8 determined based upon valid scientific
9 evidence that the probable benefits to health
10 from use of the device for its intended uses
11 and conditions of use when accompanied by
12 adequate directions and warnings against
13 unsafe use outweigh any probable risk.'

14 "Effectiveness, as defined in 21
15 CFR section 860.7(e)(1), 'There is reasonable
16 assurance that a device is effective when it
17 can be determined based upon valid scientific
18 evidence that in a significant portion of the
19 target population, the use of the device for
20 its intended uses and conditions of use when
21 accompanied by adequate directions for use and
22 warnings against unsafe use will provide

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1 clinically significant results.'

2 "Valid scientific evidence, as
3 defined under 21 CFR section 860.7(c)(2),
4 'Valid scientific evidence is evidence from
5 well-controlled investigations, partially
6 controlled studies, studies in objective
7 trials without matched controls,
8 well-documented case histories conducted by
9 qualified experts, and reports of significant
10 human experience with a marketed device from
11 which it can fairly and responsibly be
12 concluded by qualified experts that there is
13 reasonable assurance of safety and
14 effectiveness of a device under its conditions
15 of use. Isolated case reports, random
16 experience, reports lacking sufficient details
17 to permit scientific evaluation, and
18 unsubstantiated opinions are not regarded as
19 valid scientific evidence to show safety or
20 effectiveness.'

21 "Your recommendation options for
22 the vote are as follows: Number one, approval

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1 if there are no conditions attached; number
2 two, approvable with conditions. The panel
3 may recommend that the PMA be found approvable
4 subject to specific conditions, such as
5 physician or patient education, labeling
6 changes, or a further analysis of existing
7 data. Prior to voting, all of the conditions
8 should be discussed by the panel.

9 "Three, not approvable. The panel
10 may recommend that the PMA is not approvable
11 if the data do not provide a reasonable
12 assurance that the device is safe or the data
13 do not provide a reasonable assurance that the
14 device is effective under the conditions of
15 use prescribed, recommended, or suggested in
16 the proposed labeling."

17 Thank you

18 CHAIRPERSON MAISEL: Are there any
19 questions from the panel about these voting
20 options before we entertain motions? Dr.
21 Domanski?

22 DR. DOMANSKI: Yes. I would like

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1 to just hear -- maybe it's again from the FDA
2 -- that measuring pressures per se is not an
3 approvable indication if that's true. I mean,
4 is that true? I would just like to have that
5 on the record because I think this device
6 measures pressures. You know, I am concerned
7 that it doesn't -- it clearly wasn't
8 demonstrated effective for its intended use.
9 So I would like to understand that, if I
10 might.

11 CHAIRPERSON MAISEL: I think it is
12 up to this panel to determine whether the
13 device is safe and effective and that we have
14 within our purview the option of changing its
15 intended use. And the FDA can comment if they
16 would like to clarify that.

17 DR. ZUCKERMAN: I would just
18 remind the panel that this is a chronic
19 implant with a known safety profile. The
20 requirement of this panel is to make a
21 decision to weigh benefits versus risks for a
22 chronic implant and to be sure that if the

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1 vote is positive, that there is shown clinical
2 utility.

3 CHAIRPERSON MAISEL: Any other
4 questions regarding the voting process? Dr.
5 Fleming?

6 DR. FLEMING: No, I do not have a
7 vote, but I have been on other panel settings
8 before. Do we have to vote on the questions
9 as listed? I think I would expand on --

10 CHAIRPERSON MAISEL: We are going
11 to vote first on approvable, approvable with
12 conditions, or not approvable. Then if it's
13 approvable with conditions, then we will
14 outline each of the conditions. We are not
15 going to be voting individually on the FDA
16 questions.

17 DR. FLEMING: I think what I mean
18 is, can you vote on a lesser -- as was
19 suggested earlier, for measuring pressures
20 only, as opposed to clinical efficacy.

21 CHAIRPERSON MAISEL: Yes. That
22 would come in under approvable with

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1 conditions.

2 DR. FLEMING: Good. So you can't

3 --

4 CHAIRPERSON MAISEL: So if someone
5 wanted to make a motion, then we could add
6 conditions about changing that and have
7 discussion about it. I am reminded that there
8 is a voting outline in your folder that some
9 of you have out that will help guide us
10 through this.

11 So at this point I would like to
12 entertain any motions from the panel:
13 approvable, approvable with conditions, or not
14 approvable. Is this a motion or is this a --
15 I am going to call on Dr. Teerlink because he
16 was one of the primary reviewers.

17 DR. TEERLINK: So I would like to
18 make a motion that it is not approvable.

19 CHAIRPERSON MAISEL: We have a
20 motion for not approvable and a second from
21 Dr. Somberg. Discussion regarding the
22 non-approvable? Any additional discussion?

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1 MEMBER SOMBERG: Dr. Maisel?

2 CHAIRPERSON MAISEL: Dr. Somberg?

3 MEMBER SOMBERG: I just want to
4 say in light of some discussion the last
5 couple of minutes, that I think it is very
6 important to obtain factual data on these
7 issues and that if we say, "Well, you know, in
8 our heart of hearts, we feel something," et
9 cetera, "and we have this opinion and all
10 that, that's the way medicine will be
11 practiced."

12 In my short career in this area, I
13 have seen too many certainties demonstrated
14 absolutely to be fallacies. So I would hope
15 that we could try to -- as the sponsor has
16 made a good effort to produce the data, I
17 think we should make a good effort to
18 adjudicate it and to honestly try to
19 encouraged future determinations. Therefore,
20 I feel one way that it may, may, have utility.

21 I must say it is not proven. And
22 to do otherwise is really to shortchange

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1 medicine in the future.

2 CHAIRPERSON MAISEL: Dr. Borer?

3 DR. BORER: I think John is right,
4 but I want to respond a little more
5 specifically to some of the very cogent and
6 important statements that were made by the
7 sponsors and their consultants.

8 And this was an outstanding
9 presentation. It's an extraordinary
10 development effort. And ultimately I think it
11 is going to be a step forward, a major step
12 forward. However, I would suggest that a
13 diagnostic test is appropriate for application
14 only if we know how to use it.

15 And I don't think we yet know how
16 to use this one. We may know in general, but
17 we don't know specifically, I think, which
18 means that gaining further knowledge is
19 research, which is very appropriate. I mean,
20 I think that is what must happen.

21 But research is by definition not
22 therapy. Research is seeking the appropriate

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1 answers, seeking new knowledge. So I don't
2 think that the fact that we can measure
3 pressures and that the pressures may be or are
4 likely to be useful in informing therapy in
5 the future when we figure out how to apply the
6 information is a valid basis for improving the
7 implantable device that will be in somebody
8 presumably forever.

9 So I think that by way of agreeing
10 with what has been said here, I just need to
11 make that point.

12 CHAIRPERSON MAISEL: Any other
13 comments on the not approvable motion before
14 we vote? Dr. Brinker? Yes?

15 DR. BRINKER: Well, I am going to
16 vote against non-approvable for the following
17 reason. I think that we do know something
18 about pressures and what they represent.

19 My issue would be that a condition
20 be made so that there is a very limited
21 patient population that might get this. But
22 there are clearly some patients who recur in

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1 the emergency room in repeated
2 hospitalizations where difficult diagnostic
3 situations in terms of whether they have heart
4 failure or in certain instances other disease,
5 whether they would benefit from a diuretic or
6 orthotherapy and in whom sometimes invasive
7 monitoring is afforded in the hospital.

8 So I think if we could be
9 selective enough -- and I'm sure the FDA and
10 the sponsor could work out a proper selected,
11 I would encourage that. I think pressures are
12 proven. The issue in this case is painting
13 with a broad brush a population who might
14 benefit from that knowledge.

15 And I agree that the evidence that
16 this is effective is not there. But of
17 specific patients who meet specific criteria,
18 the knowledge of intracardiac pressures can be
19 because of the uniqueness of this precludes
20 other options, other than invasive, repeat
21 invasive, procedures.

22 I would like to at least entertain

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1 the possibility that the FDA might work out a
2 very select population for whom this would
3 appropriate.

4 CHAIRPERSON MAISEL: Dr. Page?

5 MEMBER PAGE: I would like to
6 agree, Dr. Brinker, but as you say, there may
7 be a population that would benefit from this
8 remarkable technology

9 We just haven't seen that
10 demonstrated to us.

11 And in the setting where the
12 primary endpoint is not met and the secondary
13 endpoints really are not met and there are
14 issues, this is not a benign procedure. It is
15 not a major procedure such that it would
16 dissuade us from putting in a device that has
17 been proven to be effective in this
18 population. There is clearly a need of new
19 and innovative therapies. I could overcome
20 that. But we don't have the data to support
21 approval here.

22 And a further concern I have is

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1 once approved, where else would this be
2 generalized to? I think have the opportunity
3 I hope in the future to get data to support
4 approval. But right now I can't see it.

5 CHAIRPERSON MAISEL: Okay. It has
6 been moved second that the Medtronic PMA
7 application P050032 for the Chronicle
8 Implantable Hemodynamic Monitor System be
9 found not approvable. We are going to vote
10 now. As we go around the table, please state
11 your name for the record and for the
12 transcriptionist and then vote yes or no.

13 A vote of yes means you agree with
14 the notion that it's not approvable. A vote
15 of no means you disagree with the motion that
16 it's not approvable. I would like to start
17 with Dr. Domanski.

18 DR. DOMANSKI: Michael Domanski.

19 And I vote yes.

20 CHAIRPERSON MAISEL: Dr. Page?

21 MEMBER PAGE: Richard Page. Yes.

22 CHAIRPERSON MAISEL: Dr

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1 Blackstone?

2 DR. BLACKSTONE: Dr. Blackstone.

3 Yes.

4 CHAIRPERSON MAISEL: Dr. Teerlink?

5 DR. TEERLINK: Dr. John Teerlink.

6 Yes.

7 CHAIRPERSON MAISEL: John Somberg.

8 MEMBER SOMBERG: John Somberg.

9 Yes.

10 CHAIRPERSON MAISEL: Dr. Kato?

11 DR. KATO: Norman Kato. Yes.

12 CHAIRPERSON MAISEL: Dr. Normand?

13 MEMBER NORMAND: Sharon-Lise

14 Normand. Yes.

15 CHAIRPERSON MAISEL: Dr. Ewald?

16 DR. EWALD: Gregory Ewald. Yes.

17 CHAIRPERSON MAISEL: Dr. Brinker?

18 DR. BRINKER: Jeff Brinker. No.

19 CHAIRPERSON MAISEL: Dr. Borer?

20 DR. BORER: Jeffery Borer. Yes.

21 CHAIRPERSON MAISEL: Dr. Hauptman?

22 DR. HAUPTMAN: Paul Hauptman. No.

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1 CHAIRPERSON MAISEL: So it is the
2 recommendation of this panel to the FDA that
3 the Medtronic PMA application P050032 for the
4 Chronicle Implantable Hemodynamic Monitor
5 System be found not approvable. The motion
6 carried by a vote of nine to two.

7 At this point we are going to
8 around the table and ask each panel member to
9 explain why they voted the way they did. Dr.
10 Domanski?

11 DR. DOMANSKI: Well, I think it is
12 a remarkable device. And I can certainly
13 appreciate the business of being able to
14 monitor pressures, potentially being useful.
15 But in the end, at the very last, we persuaded
16 by Dr. Borer's argument that we really have no
17 shown that it is clinically efficacious for
18 anything. And I guess I am impressed that
19 this trial is quite as negative as it is. I
20 mean, there is just nothing there anyway, not
21 in the first primary endpoint, not in the
22 secondary endpoint, not anywhere.

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1 So I reluctantly vote yes but with
2 great reluctance.

3 CHAIRPERSON MAISEL: Dr. Page?

4 MEMBER PAGE: I agree. I have
5 great respect for the investigator and the
6 sponsor. And the presentation has been
7 outstanding. And your diligence I hope will
8 continue.

9 Nevertheless, despite the fact
10 that I would agree that it is intuitive that
11 it would work, if the signal is there, we
12 ought to have seen it or we need to see it
13 before we can approve.

14 And I do believe when this
15 technology reaches a point where it is
16 approvable and demonstrated to be effective,
17 when it is released, it is going to be used a
18 lot.

19 So this is the opportunity to make
20 sure that this technology is of satisfactory
21 effectiveness and safety before we approve it
22 and have it be used commercially.

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1 CHAIRPERSON MAISEL: Dr.
2 Blackstone?

3 DR. BLACKSTONE: I voted yes, but
4 I have the vague feeling that the fundamental
5 problem is the endpoints that are chosen. I
6 am impressed with the anecdotal information
7 that is given and the fact that it has
8 biologic plausibility.

9 I think that needs to be
10 translated into something that can be shown.
11 That's a clinical efficacy which hasn't been
12 shown here. And that is our task given the
13 data in hand, not given data that we don't
14 have.

15 CHAIRPERSON MAISEL: Dr. Teerlink?

16 DR. TEERLINK: So I voted yes for
17 the reasons that I have outlined during much
18 of this meeting. I think on the data that was
19 provided, recalling that this is a diagnostic
20 device that requires implantation results in
21 initial hospitalization or hospital visit,
22 occasionally results in rehospitalization for

1 device-related complications, does need to
2 demonstrate some kind of relative benefit to
3 those down sides. And while that down side is
4 relatively small, I saw no up side to
5 counterbalance that in the data that was
6 provided.

7 CHAIRPERSON MAISEL: Dr. Somberg?

8 MEMBER SOMBERG: I voted yes
9 primarily because I think there is a very
10 narrow window of opportunity to provide
11 adequate information for the use of
12 therapeutic devices. And I think it is
13 necessary to do that in randomized controlled
14 trials. And the data was insufficient at this
15 point. And I hope that the appropriate trials
16 are designed so the data will be sufficient to
17 make an appropriate determination.

18 But if we have approval creep, as
19 I would describe it, we will approve things
20 but much lesser by criteria. And we will
21 never get to the definitive results that are
22 critically needed for these patients.

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1 Thank you.

2 CHAIRPERSON MAISEL: Dr. Kato?

3 DR. KATO: I voted yes. I must
4 say that I share the sponsor's enthusiasm for
5 this device. I think that one of the facts
6 that have tempered my consideration of it is
7 the fact that Swan-Ganz catheters, which is a
8 right heart catheter, the device was acutely
9 used in cardiac surgery and critical care.
10 These Swan-Ganz catheters have not proven to
11 be at a survival benefit in any randomized
12 prospective study, at least that I am aware
13 of.

14 On the other hand, I think that I
15 would encourage the sponsor not to give up on
16 this topic. I think that there is going to be
17 some benefit. I think that the target market
18 is probably I would -- and this is just a
19 guess -- probably double or triple the number
20 that I think Dr. Stevenson talked about. And,
21 therefore, I would really like to have seen
22 some positive number, some evidence-based

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1 number that we could hang our hat on.

2 And I think, even with that, I
3 would have been swayed to vote another way.

4 CHAIRPERSON MAISEL: Dr. Normand?

5 MEMBER NORMAND: I voted yes
6 because of the lack of therapeutic efficacy
7 that was demonstrated in the study compared to
8 the safety issues that we saw.

9 CHAIRPERSON MAISEL: Dr. Ewald?

10 DR. EWALD: I voted yes
11 reluctantly. I think the technology is really
12 outstanding. And I think that as a heart
13 failure cardiologist, clearly knowing cardiac
14 filling pressures and probably something about
15 activity and clearly remotely monitoring that
16 is the way that things are going to move in
17 the future.

18 But I think without some clear-cut
19 evidence that it benefits the patient, it is
20 hard to tell a patient that we want to implant
21 this device without that.

22 CHAIRPERSON MAISEL: Dr. Brinker?

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1 DR. BRINKER: I voted no for the
2 reasons that I mentioned before. I would like
3 not to throw the baby out with the bathwater
4 at this point of time.

5 I believe that the FDA could come
6 up with a very limited applicability which
7 would not dissuade the sponsor from doing the
8 appropriate trial for the broad clinical
9 application.

10 But this is a diagnostic device.
11 I am convinced that it gives real data. The
12 utility of that data depends on how it is used
13 by the physician monitoring it, but I think
14 that it is as effective as invasive data and
15 that it should be available for select
16 patients.

17 CHAIRPERSON MAISEL: Dr. Borer?

18 DR. BORER: I voted yes because
19 this diagnostic tool is a lifelong implant
20 with certain known risks and others that may
21 be defined as it is tested further that
22 provides information that I think ultimately

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1 is going to be useful.

2 But in order to justify the risks,
3 I think we need to have some information that
4 tells us how to use it so that patients who
5 use this information can derive clinical
6 benefit. And while I believe that is going to
7 happen, I haven't seen the data that tell me
8 how to apply this information for clinical
9 benefit, for predictable clinical benefit.

10 I have to add something here, if I
11 may. We have heard a little bit from a number
12 of people today about historical precedents.
13 I would say forget it.

14 What we may have done 30 years ago
15 or 40 years ago or even 10 years ago is
16 interesting, but it isn't relevant today
17 because we have more knowledge today. We have
18 more tools today. And we have to make our
19 decisions based on today's standards.

20 And I believe, therefore, that we
21 need to hold this device, like any other
22 diagnostic test and certainly like any

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1 therapeutic, to current standards, which I
2 believe require that we have reasonable
3 instructions for use so that patients can
4 benefit.

5 And while intuitively I believe
6 that this technology is going to be proven to
7 be useful in this way and I hope that the
8 research with the device will go on, I don't
9 think we have reached that standard yet.

10 CHAIRPERSON MAISEL: Dr. Hauptman?

11 DR. HAUPTMAN: I reluctantly voted
12 no. And I say that because I think that it
13 would have been conceivable for very
14 restrictive language to be constructed that
15 would have allowed this device out on the
16 market, a very well-designed post-marketing
17 study as well, potentially could have been
18 designed. I would encourage the sponsor to
19 continue to develop the technology, but I
20 believe that the panel has spoken pretty
21 clearly.

22 And I think the opinions are quite

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1 clear. I had the luxury of being the last
2 person down the line to vote.

3 CHAIRPERSON MAISEL: Dr. Fleming,
4 do you have any comments you would like to
5 make following the vote?

6 DR. FLEMING: Well, I would have
7 been with the two no votes in the sense that I
8 think that the device has fantastic future
9 potential in terms of patient management and
10 treatment, actually. Personally I hate to see
11 it not available in some restrictive manner,
12 as elucidated here in the panel.

13 But I would encourage the sponsor
14 to continue work on it. I think it is an
15 exciting new technology and one that is going
16 to benefit many very sick people.

17 CHAIRPERSON MAISEL: Dr. Yaross,
18 do you have any comments?

19 MEMBER YAROSS: The only
20 additional comment that I would make is that,
21 you know, while the panel is correctly trying
22 to apply the standard of showing that the

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1 product has clinical utility during the debate
2 and the discussion, there were references to
3 trying to determine impact on mortality. And
4 it is not necessarily the responsibility of a
5 sponsor for every device to do that.

6 So I just encourage that the
7 sponsor continue to work on this device. They
8 have done phenomenal work. And hopefully they
9 can come back with something that will meet
10 the panel's expectations.

11 CHAIRPERSON MAISEL: Thank you.
12 Your points are well-taken.

13 At this point since the panel
14 voted to recommend that the PMA is not
15 approvable, our next and nearly final task is
16 to discuss what needs to happen in order for
17 this device to be approved based on the
18 information in front of us in thinking in a
19 least burdensome sort of way so that we
20 require the least amount of data necessary to
21 get the device approved in some way.

22 So I heard a lot of discussion

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1 regarding the device as a diagnostic, rather
2 than a therapeutic, tool. And that may be an
3 approach that is the quickest way to get it to
4 market. I don't know if people agree with
5 that. And if they do, what sort of additional
6 data would be necessary?

7 For example, if we were to say,
8 "The device measured pressures" without making
9 a statement regarding what it does for
10 patients, if we had additional data, would
11 that be acceptable or do we need the clinical
12 endpoint and additional randomized trials, et
13 cetera? Dr. Somberg?

14 MEMBER SOMBERG: Well, I think we
15 need additional data and we need a randomized
16 clinical trial. And one of the things I
17 wanted to say earlier was that I think it is a
18 fallacy in this type of study area, not just
19 with devices but all studies, make the power
20 calculation and assume that things will be
21 like they were in the past. Almost invariably
22 when you do a study, things change. And they

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1 usually change for the better.

2 And, you know, I'm not smart
3 enough. I will bet a lot of the heart failure
4 people here had an inclination that when they
5 called the patient once a week, they would
6 improve them or something. But I didn't know
7 that. But, I mean, it makes a lot of sense
8 now.

9 So you decreased your event rate
10 in the controls. And you powered the study on
11 one. And you had another event rate. So I
12 think the first thing to say, just generalized
13 and if there are any other sponsors listening
14 to other areas is to -- you know, don't be
15 cheated at the input because you get killed at
16 the output. And it is needed to do a larger
17 study a priori.

18 So I would do a larger study. I
19 would do something akin to this. I mean, we
20 can spend another three or four hours here
21 discussing, you know, all-cause
22 hospitalizations, heart failure

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1 hospitalizations, time to first
2 hospitalization.

3 There are a lot of endpoints.
4 There is a lot of possibility for fixed
5 endpoints. And there even is a possibility
6 for a mortality endpoint and hospitalization,
7 where it is probably driven by
8 hospitalization, but you might still get your
9 mortality.

10 And I think the reason, just as an
11 aside, why we talked about mortality is I
12 think the sponsor and the people in this area
13 of devices talk about mortality because that
14 is what their market really wants.

15 I would like to make people have
16 less hospitalizations, but if I knew it
17 actually improved their survival, that would
18 be a winner. Instead of maybe 200,000
19 implants the first year, you might have a
20 million implants the first year. And I see a
21 few smiles from the sponsor.

22 So I think it is certainly

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1 important to design a trial that both works to
2 their marketing advantage as well as the
3 efficacy advantage. And it may turn out that
4 this little snag -- and this is the sales
5 pitch, but this little snag in the approval
6 process may turn out to be a boon because you
7 may actually have a clearly demonstrated
8 device efficacy and with clear benefits, clear
9 superiority versus, you know, the safety
10 drawbacks, which would be minimal, and that
11 there will be a high entry into this area as
12 well.

13 So I think it may work out very
14 well to the sponsor and to the patients.

15 CHAIRPERSON MAISEL: So, Dr.
16 Somberg, rather than performing and creating a
17 completely new clinical protocol, how would
18 you feel if this sponsor continued with this
19 protocol, enrolled X number of patients, got
20 penalized for an interim analysis, and met
21 their primary endpoint?

22 MEMBER SOMBERG: Well, I think

1 they may should hire you, Dr. Maisel, to
2 consult as well. I think that that is a great
3 possibility. And I must tell you that I am
4 not the statistician on the Committee, if you
5 haven't realized that by now.

6 So I wouldn't say I knew the best
7 way to design that particular trial, but if
8 someone came back to me in six months and had
9 twice the number, and had a very positive
10 endpoint on this trial, I would a) not be
11 surprised. And b) I would be very supportive
12 of the jargon, although I do not usually
13 commit my vote in advance.

14 Is that what you are asking me,
15 Doctor?

16 CHAIRPERSON MAISEL: You answered.

17 Thank you.

18 Dr. Borer?

19 DR. BORER: Yes. I will get back
20 to your second question second, but I don't --
21 you asked the question whether it would be
22 good enough to show that this was a diagnostic

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1 tool. I think that has already been shown.
2 And I don't think it's good enough.

3 I think that it's necessary to
4 know how to use a diagnostic tool if you are
5 going to sell it to people and apply it for
6 clinical benefit and you have to show that you
7 know how to apply it for the clinical benefit.

8 You need instructions for use, which I think
9 is an FDA requirement.

10 This is a diagnostic tool. I
11 think it measures pressures accurately. I
12 think the pressures are physiologically and
13 pathophysiologically relevant. But it carries
14 risks with it.

15 This is an implantable device. A
16 lead is put in the right ventricle, carrying
17 the risk of cardiac perforation, vascular
18 perforation, infection. I mean, I can go on
19 through the whole list. In absolute terms,
20 those risks are relatively low, but I would
21 like to know that we predictably have a
22 benefit. So I don't think it's good enough

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1 just to show that this is a diagnostic tool.

2 I would echo, however, what Dr.
3 Yaross said. The sponsor didn't suggest that
4 information could be obtained that would
5 enable reduction in mortality somehow. And I
6 don't think that's an appropriate standard or
7 impediment to put in their path.

8 I think feeling better is
9 perfectly adequate if you know how to use
10 these data to make people feel better. And
11 reducing hospitalizations is a perfectly
12 adequate endpoint.

13 I think if one were going to
14 design additional data-gathering exercises --
15 and I won't say a new trial because you raised
16 another possibility that I will respond to in
17 a minute -- I would consider several issues.
18 Number one is taking the population more
19 effectively.

20 And Jeff Brinker raised the issue.

21 I mean, why not pick sicker patients or
22 circumscribe the population more completely

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1 than one did? So that it might be more
2 likely, so that you would have a greater
3 likelihood of events in the untreated
4 population. If the diagnostic tool medicated
5 interventions than work, you might be more
6 likely to see them.

7 Pick a better endpoint. Bill
8 Abraham suggested that. You know, the trial
9 designers added soft endpoints to harder
10 endpoints. As he pointed out, if they had
11 picked the harder endpoints, maybe we would be
12 talking just a little bit differently. Maybe
13 that is a good thing to do.

14 Power the trial a little bit
15 better, as John suggested. So I think there
16 are a number of design elements that can be
17 rethought if you think of the experience we
18 now had as a pilot experience.

19 Now, then you raised a very
20 interesting question. How about just
21 extending the trial? Well, I am suggesting
22 there are some other things that have to be

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1 changed within the trial to extend it. And I
2 don't know what kind of penalty a statistician
3 would say you have to take for that. So I
4 would defer to Dr. Normand and to others to
5 figure out how to deal with that.

6 If it can be done, that would be
7 an interesting option. I wonder if it would
8 save all that much in terms of population and
9 resources, but that is a question I can't
10 answer.

11 So I would think of those design
12 element changes and then consider the
13 extension if it is doable that you suggested.

14 CHAIRPERSON MAISEL: Dr. Normand?

15 MEMBER NORMAND: I guess I
16 disagree a little bit in terms of showing that
17 it is a good diagnostic tool. And the reason
18 why I am saying that is as follows.

19 To me part of the diagnostic tool
20 is how you use the information. I don't think
21 you can separate the two pieces. So that
22 although it may be very accurate and reliable

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1 at measuring the pressures, one would
2 typically think of assessing the accuracy of
3 the action based on the information. And so I
4 guess I sort of have a two-pronged thing.

5 If one wanted to think about
6 approving it for a diagnostic tool, maybe
7 there is information that has already been
8 collected. I know there are problems because
9 we have looked at some things already, but it
10 might be helpful to look at how much between
11 clinician or between research team variability
12 there is in getting the information from the
13 Chronicle device versus from the control
14 group. I mean, we need some of those types of
15 measures.

16 So I can't list all of the things,
17 but one suggestion is if we are going to say
18 this is a good diagnostic tool, I don't know
19 if there is already information collected that
20 can help inform us about some of the measures
21 that one would typically assess in terms of
22 good diagnostic tool.

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1 How much of the information was
2 acted on appropriately? How much between
3 research, clinician, team variability was
4 there? Is there more with the new tool
5 relative to regularly scheduled phone
6 contacts?

7 Those would be the types of things
8 one would usually assess in a diagnostic tool
9 that is chronically implanted, as opposed to,
10 you know, a simple diagnostic tool.

11 I will be quiet in a second. So
12 the next thing would be if you wanted to end
13 with a therapeutic, if you said, "Okay. Fine.

14 We are not going to go it as a diagnostic
15 tool. Let's go down to the -- you want to get
16 the therapeutic indication," then I do think
17 that we are even still -- you would have to
18 definitely collect more patients.

19 And if everybody still felt that
20 the endpoint was fine, I, frankly, have
21 nothing wrong with number of hospitalizations
22 and maybe adding in the hospitalizations that

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1 relate to the implant and all that kind of
2 stuff.

3 If you felt there were changes to
4 the implant, we're talking about a new study,
5 obviously. If we're talking about keeping
6 these same endpoints, then you could accrue
7 more patients. FDA could think about how to
8 penalize. It will be difficult, I think, in
9 challenging to penalize appropriately.

10 But the other thing I want to
11 strongly urge everybody is don't forget you
12 have to collect for this clustering. And you
13 haven't even taken that account in the first
14 trial.

15 So, again, to me it would be two
16 thoughts. If I am going to stay with the
17 diagnostic tool, there is additional
18 information that needs to be collected. In my
19 mind, maybe it has been collected already. I
20 don't know.

21 If you are going to go down to the
22 therapeutic end, if you are going to change

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1 endpoints, obviously we need a new trial
2 design, I don't feel that we have to change
3 the endpoints. So I would think about looking
4 at how much new patients we are going to have
5 to collect given the clustering issues and
6 other issues and whether or not it is so far
7 apart that you actually have to accrue new
8 people, treat it as a new design. I'm sorry.

9 CHAIRPERSON MAISEL: Dr. Domanski?

10 DR. DOMANSKI: Yes. I have
11 several comments. One is that hospitalization
12 actually is a reasonable soft but appropriate
13 endpoint. And I guess I have the sense that
14 this trial was really under power. I mean, to
15 start a trial, to start a clinical trial, with
16 80 percent power based on assumed event rate,
17 well, the secular trends being what they are,
18 gee, it is an invitation to having the problem
19 that you had.

20 But I do think that the endpoints
21 are appropriate. In fact, I am intrigued by
22 just how negative this really was. In fact,

1 if anything, that is a little bit bothersome.

2 You know, at some point you ought to be able
3 to show a utility to using these pressure
4 measurements.

5 I mean, it would be interesting if
6 you had -- maybe there is a hidden flaw
7 somewhere in the paradigm, not so much in the
8 actual measurement of the pressure, but maybe
9 there is something wrong with the paradigm.

10 Nature sort of always sides with
11 the hidden flaw. And maybe we don't
12 recognize. We all sort of assume intuitively,
13 including me, that this thing is wonderful and
14 it is going to work and you just need more
15 patients and the king needs more horses and
16 more men.

17 Maybe that is not it. Maybe there
18 really is something wrong. But I think
19 redoing this trial or maybe extending it -- I
20 would have thought that now that you have
21 unblinded everybody, you would be sort of
22 stuck starting a new trial. But I will defer

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1 to the statisticians about what is appropriate
2 there.

3 But I would add power to this one.

4 And if you can't show anything, then,
5 frankly, I think there is an underlying flaw.

6 CHAIRPERSON MAISEL: So we've
7 heard a lot of ideas. More specific patient
8 population might help increase the treatment
9 effects, different endpoints. Obviously there
10 are pros and cons. Longer would make it more
11 difficult to get a new study started.

12 I personally don't have a problem
13 with the endpoint that was selected. Heart
14 failure hospitalizations are used in many
15 heart failure trials, obviously more patients.

16 And I think we will leave it up to the
17 sponsor of the FDA to negotiate the way
18 forward.

19 And I think I can speak for the
20 panel when we say we would like to see this
21 product continue down the pipeline and
22 hopefully get out to patients in a relatively

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1 short time frame with some more data behind
2 it.

3 Dr. Borer?

4 DR. BORER: Yes. Bill, just one
5 comment. I agree with you that heart failure
6 hospitalizations is a perfectly adequate
7 endpoint. That wasn't the endpoint. And my
8 comment about soft and less soft endpoint was
9 Bill Abraham's comment.

10 In fact, the sponsor declared
11 hospital equivalents. And it's the equivalent
12 part that was the software endpoint. If they
13 did what you said, then I would be delighted
14 with that.

15 CHAIRPERSON MAISEL: You make a
16 good point.

17 Dr. Page?

18 MEMBER PAGE: I just wanted to
19 clarify, Bill. Have you closed the door on
20 this being evaluated further as a diagnostic
21 test? Because I personally could not approve
22 it as a diagnostic test. If there aren't

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1 outcomes to support the diagnostic test, then
2 I couldn't approve this extensive device that
3 has some risk.

4 CHAIRPERSON MAISEL: I mean, I
5 think we heard from most of the panel members
6 on that topic. And my sense of the panel was
7 that there are some people who feel
8 comfortable as a diagnostic test now.

9 There are some people who feel it
10 could be a diagnostic test but we need more
11 rigor. And most people feel that, even if it
12 were a good diagnostic test, that is not
13 enough and that we need the clinical utility.

14 MEMBER PAGE: Right.

15 CHAIRPERSON MAISEL: So at this
16 point I would like to ask if the sponsor has
17 any other comments they would like to make
18 before we close the meeting.

19 DR. STEINHAUS: Thank you.

20 CHAIRPERSON MAISEL: Dr.
21 Zuckerman, does the FDA have any other
22 comments that they would like to make?

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1 DR. ZUCKERMAN: Thank you for a
2 very rich and productive meeting today.

3 CHAIRPERSON MAISEL: Thank you
4 very much. At this point I would like to
5 close this meeting of the Circulatory System
6 Device Panel. And the panel has my thanks.

7 (Whereupon, the foregoing matter
8 was concluded at 4:59 p.m.)
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CERTIFICATE

This is to certify that the foregoing transcript
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Advisory Panel Meeting

Before: William H. Maisel

Date: March 1, 2007

Place: Gaithersburg, Maryland

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.



Eric Mollen