1 the patients at times with the device in and
2 with the data available failed, and I'm
3 interested -- failed to prevent a
4 hospitalization.
5 I would be very interested in
6 knowing the failure mode. I mean, why did it
7 fail, just from a clinical point? It seems
8 like it was kind of all there, and once in a
9 while it fails, and I'm just curious about
10 why.
11 DR. STEVENSON: Well, certainly,
12 what we are hoping to get is an early warning
13 system, which is never going to be perfect.
14 IN the hospitalizations that did occur in the
15 patients in the Chronicle group, if we look
16 back, the pressure rises were in fact much
17 more rapid, so a much quicker decompensation.
18 Interestingly, the pressure
19 elevation at the time of an event in the
20 Chronicle group was less than at the time of
21 an event in the control group. So
22 interestingly, it happened faster and overall

1 was not quite as severe when it led to an
2 event in those groups, but certainly, we are
3 not going to be able to identify them all.
4 There are things that can happen relatively
5 quickly.
6 DR. DOMANSKI: Thank you.
7 CHAIRPERSON MAISEL: Dr. Hauptman.
8 DR. HAUPTMAN: Maybe I will take
9 advantage of Dr. Stevenson's expertise here.
10 I have a three-part question here.
11 the first is the whole definition
12 of optivolemia presupposes that you have a
13 clinician who can tell noninvasively when a
14 patient is in reasonable clinical condition,
15 and yet the argument here is that after that
16 determination of optivolemia, the clinician is
17 not as good and needs to use the device.
18 I wonder if you could address that
19 reasoning.
20 Second, if the emphasis here is to
21 increase, or it seems to increase diuretic
22 use, I wonder if you or Dr. Bourge could

1 comment on concerns in the heart failure
2 community about perhaps overuse of diuretics
3 in general and the downside.
4 Finally, in light of the ESCAPE
5 trial data, how do we look at -- So we have
6 data on the acute setting hemodynamic
7 monitoring, and now we have it more
8 chronically. Is it possible the two results
9 from ESCAPE and from COMPASS are actually
10 overlapping?
11 DR. STEVENSON: I think your first
12 questioning is a really interesting one. Can
13 I have the slide on? In terms of optivolemia,
14 when we started this we had this preconception
15 that, in fact, it was going to be different
16 for every patient and that we would have to be
17 adjusting this a lot.
18 As it happened, when we looked at
19 where people ended up, you can see that 89
20 percent ended up with their optimal e-PAD
21 defined as 12 + -4. So there wasn't a lot of
22 variation from patient to patient in terms of

1 what seemed to be optivolemic in terms of
2 where during that first month of monitoring we
3 decided that they were best.
4 So in fact, it was pretty much
5 what you would predict for this range.
6 In terms of the diuretic question
7 -- I'm sorry, I'm not sure I understood your
8 second question.
9 DR. HAUPTMAN: Sure. The question
10 is: It seems that the number one change that
11 was made in reaction to readings was, in fact,
12 manipulation of diuretics, both up and down,
13 but predominantly up.
14 Are there any concerns about the
15 long term impact of increasing diuretic dosing
16 in the heart failure patient?
17 DR. STEVENSON: Basically, I think
18 we all have concern that diuretics may be part
19 of the problem. There is no evidence that
20 they actually ended up on more diuretics on a
21 chronic basis. Many of the interventions that
22 were made for diuretics were one-time changes

1 only. About a third of the diuretic changes
2 were a one-time change.
3 As we all know, we increase
4 diuretics briefly to get fluid back down, and
5 then you go back down to the baseline. So
6 many of these were not changes in the
7 maintenance diuretic doses but brief changes
8 that we could monitor, and we have extensive
9 data, which I won't go into unless you want to
10 see it, of how effectively we intervened when
11 the pressure went up and how the next time the
12 pressure had gone back down again.
13 So in fact, it is doing what we
14 want for that.
15 DR. HAUPTMAN: It might be
16 interesting to see the overall exposure to
17 diuretics during the six months, if the
18 sponsor could perhaps provide that. Where did
19 the patients begin in terms of dose, and where
20 did they end up at the end of the trial?
21 DR. STEVENSON: I don't have that
22 at the moment. From looking through a fair

1 amount of the data, my impression is that it
2 is really not that much different over the
3 time. It is more a question of changes during
4 the six months than a systematic change in the
5 maintenance dose.
6 If I can see slide number 17,
7 please. The ESCAPE trial was an NHLBI
8 sponsored trial looking at patients in the
9 hospital with heart failure to see if their
10 outcome was improved when you managed them in
11 the hospital with a catheter that measured
12 these filling pressures.
13 As many of you know, in fact, the
14 six month outcome wasn't different between the
15 two groups, and we think we understand partly
16 why.
17 This is looking at the ESCAPE
18 trial, percent of patients who had clinical
19 congestion or high filling pressures at
20 hospital admission. We were successfully able
21 to treat them all with or without the catheter
22 in the hospital, and by the time of discharge

1 most of them appeared to be free from
2 congestion. But the reason we think that any
3 benefit of monitoring may not have been
4 visible over time is that by one month after
5 discharge -- and this is an incredibly well
6 monitored group of patients -- we already had
7 22 percent of patients who again showed
8 evidence of congestion once they left the
9 hospital.
10 So the way we have interpreted the
11 ESCAPE trial is that monitoring them during
12 the hospitalization doesn't have much long
13 term effect, because in fact we don't know
14 what we are doing once they went home. Hence,
15 we feel that it is very helpful to have
16 ongoing information about what the filling
17 pressures are in the outpatient setting,
18 because they spend most of their time at home.
19 DR. HAUPTMAN: Thank you.
20 CHAIRPERSON MAISEL: Dr. Kato.
21 DR. KATO: One thing I was
22 intrigued with about this device -- and again,

1 I want to echo some comments by my colleagues
2 here that, you know, from a research
3 perspective I think this is really intriguing,
4 and I think that there is still a lot of
5 questions that need to be answered.
6 I guess one question I have is did
7 you ever have any thought to utilizing this
8 device as that early warning system, not so
9 much for the doctor but more for the patient?
10 That is, let's say their e-PAD went up. You
11 know, how about a -- and this device is going
12 to be talking over the Internet anyway. How
13 about some type of signal back to them as an
14 e-mail, some type of computerized voice mail
15 to a cellphone or something like that, that
16 says, gee, maybe you ought to titrate up your
17 diuretics?
18 On the other hand, as we saw in
19 the presentation, this seems to be an
20 expensive device just to measure salted
21 popcorn intake, where clearly the patient
22 knows he is taking increased salt load. Does

1 he really need to have a device like this to
2 say, gee, maybe I ought to take some more
3 diuretics, because I'm going to be fluid
4 overloaded at this point?
5 DR. ABRAHAM: Thank you very much
6 for the question. My name is Bill Abraham. I
7 am a consultant to Medtronic, also an
8 investigator in the Phase II and COMPASS-HF
9 trials. I have no other financial interest in
10 the company.
11 Certainly, I think the possibility
12 that you raise is an intriguing one and
13 something that we would look forward to
14 exploring more in the future.
15 Because of the newness of
16 implantable hemodynamic monitoring
17 technologies, I think in these initial studies
18 we felt that it was important to have the
19 physician clearly in charge of prescribing
20 therapy on the basis of knowledge of
21 implantable hemodynamics.
22 In fact, what I envision in the

1 future is really a partnership between
2 patients and their caregivers in managing
3 their heart failure using these types of
4 devices.
5 You know, the salted popcorn
6 example is an interesting one, because one of
7 the things we've found with experience with
8 our own patients in these trials is that they
9 are able in many ways to perhaps better their
10 lifestyles with a collaborative knowledge of
11 these types of data. It may allow them to
12 actually splurge, have the popcorn, take the
13 extra diuretic, come back to an optivolemic
14 state, and in some ways have a bit more
15 freedom in terms of their lifestyle without as
16 much guesswork as we tend to have.
17 You are correct. It is an
18 expensive device. It is more expensive than a
19 scale, but I think one of the other things we
20 have learned from this experience that daily
21 weights are much less helpful than what we
22 believed they were in the past.

1 CHAIRPERSON MAISEL: Dr. Normand.

2 DR. NORMAND: Yes. I have a
3 question that has baffled me from the
4 beginning when I was reading this particular
5 trial.

6 That is the following. Dr. Kato
7 has alluded to it in terms of the following.
8 This device, it seems to me, is providing
9 information to the physician, and the
10 physician is using that information in a
11 number of ways.

12 IN that regard, the unit of
13 analysis here really is the physician, what
14 the physician is doing with that information
15 for patients. So in some sense, you don't
16 have an effectiveness finding at all. But I
17 think I would argue about the generalizability
18 of this altogether in the design of your
19 study.

20 By that, I mean the following.
21 This also has implications for the post-market
22 study. The information -- You are really

1 testing what the physician is doing, although
2 you are estimating the outcome on the patient.
3 So there is -- Everybody wants to
4 ignore clustering anyhow, but this is a study
5 in which you really need to take account of
6 the physician. So even with that in mind,
7 that means that your intervals are going to
8 need to get wider.
9 So it seems to me that the design
10 really should be one of looking at the
11 physician as the unit of analysis, even though
12 if you want to have the endpoint being the
13 patient, that's fine. But without question,
14 at least in my mind, this analysis is clearly
15 a nested design in which you have to account
16 for that.
17 I'll make one more comment and
18 maybe Dr. Stevenson is going to respond to
19 that. But it also seems to me that, when you
20 actually do this -- that is, account for the
21 fact that you have surgeons -- not surgeons,
22 I'm sorry -- physicians involved in this,

1 there has been some implications or hypothesis
2 generations of why the baseline rate in the
3 control group is high.
4 You know, one explanation has
5 been, well, the fact of the protocol. Well,
6 the other explanation could be the physicians
7 that you have involved in your study. So the
8 practical generalizations from the study are
9 completely questionable to me, because of
10 course, the physicians weren't randomly
11 selected.
12 DR. STEVENSON: If I could have
13 the slide on, please.
14 These are very key questions about
15 how we are going to take care of a huge volume
16 of patients with a small number of people who
17 have expertise, and this is a challenge we
18 face in many ways.
19 Part of what we hope is that this
20 technology and this type of information will
21 actually help translate the art of people who
22 do this as a career into something that can be

1 done in other offices.

2 If we look at who is actually
3 reviewing the data of this, it is not
4 primarily the physicians. It is the health
5 care professionals, the nurse practitioners
6 and the nurses who work in the heart failure
7 management setting, and this is a slide
8 demonstrating who actually is looking at the
9 data when it comes in.

10 A small fraction is actually
11 reviewed primarily by the M.D.s. The idea is
12 that when an alteration is detected by the
13 person who first reviews the data, that that
14 is then reviewed with the physician in what is
15 really quite a time effective way, taking very
16 few minutes, and then the nurse makes the
17 intervention.

18 So what we are hoping is that the
19 physician is not, in fact, the primary person
20 who is making all these decisions, but who is
21 in fact just reviewing information on a
22 relatively small number of events in order to

1 intervene on those.

2 DR. NORMAND: Just to follow up on

3 that, Lynne, are the same nurses looking at

4 all the patients, the control and Chronicle

5 patients?

6 DR. STEVENSON: Yes.

7 DR. NORMAND: So it's the same

8 person that is reading the information -- or

9 getting the information?

10 DR. STEVENSON: Well, it's the

11 same person for a given patient.

12 DR. NORMAND: Okay, but --

13 DR. STEVENSON: And some of the

14 patients will be controls, some will be

15 Chronicle, but the same nurse is responsible

16 for both sets of patients. In the individual

17 patient, it may not be the same nurse, but

18 it's the same team of nurses who take care of

19 both the control and the Chronicle patients.

20 CHAIRPERSON MAISEL: Dr. Brinker.

21 DR. BRINKER: I would like to get

22 back to some more practical issues involved

1 with recording of pressures.

2 Although I think you made a point

3 that patients with pulmonary hypertension due

4 to non-cardiac causes probably shouldn't be

5 enrolled in such a form of observational care,

6 if you will, about half the patients enrolled

7 in this study had some sort of pulmonary

8 disease, COPD, emphysema or asthma, and almost

9 half had sleep disorder which might be due to

10 obstructive sleep apnea.

11 All of these things which

12 episodically could cause an elevation in

13 diastolic pressure, pulmonary artery diastolic

14 pressure estimated.

15 So how careful does one have to be

16 in selecting patients with these disorders,

17 and did, in fact, any of these -- Were there,

18 in fact, problems in dissociating elevations

19 in e-PAD between primary lung and primary

20 heart?

21 DR. BOURGE: I don't believe the

22 rate of lung disease was as high as you

1 indicated. This is going from memory. But we
2 tried to exclude on the opinion of the
3 investigator patients with significant
4 pulmonary disease.
5 They could have had a history of
6 it, but it was not significant. That would
7 have been exclusion from the protocol.
8 What we did see in this study was
9 a correlation between pulmonary artery
10 pressure and pulmonary end-diastolic pressure,
11 which has been well described by Drazner and
12 others, where in general with heart failure
13 the pulmonary systolic pressure is about twice
14 the wedge pressure. So it is about twice the
15 pulmonary end-diastolic pressure, and that
16 correlate was seen in this study also, which
17 has been well described in prior studies.
18 Indeed, we also have data -- in
19 fact, we have a sub-study ongoing now -- on
20 the use of this device, and have diagnosed
21 sleep apnea with this device. What you see is
22 not only an increase in the systolic right

1 ventricular pressure but also diastolic
2 pressure on an episodic fashion, clearly
3 demonstrable with sleep apnea.
4 When we look at changing the
5 information -- that is why it is very
6 important to see the trends that we see. We
7 are not just seeing intermittent snapshots of
8 information. We are looking at trends which
9 change over time, and with time we have
10 learned to interpret those trends and apply it
11 to the individual patient.
12 Does that answer your question?
13 DR. BRINKER: I think it does, but
14 in patients who have heart failure, for
15 instance, who are ambulatory and at night
16 mobilize fluid, one might see an elevation in
17 their pressures as well. So the question is
18 how do you go about distinguishing this?
19 DR. BOURGE: Indeed, we did, and
20 that is why we have. We look at what we call
21 nightly minimums, the pressures when they are
22 not moving usually between midnight and 4:00

1 a.m. where most patients are not moving
2 anywhere, where we can see, because we have an
3 activity sensor, whether they indeed were
4 moving or getting around at that time.
5 So we have been able to, we think
6 -- and we have a sub-study looking at that --
7 pick up those who have sleep apnea. In fact,
8 we have some patient examples.
9 I'm not supposed to give
10 anecdotes, but I will just tell you, we have
11 seen patients who have had marked rises in
12 mainly nighttime pressures with volume
13 overload, because they do redistribute at
14 night. In those same patients BNP remained
15 stable, no change whatsoever, because they
16 stood up in the day, pressures cooled in their
17 legs, diabetics primarily.
18 So again, as alluded to earlier,
19 this is a wonderful tool to look at the
20 pathophysiology of heart failure. It allows
21 us to look at the pressure and, therefore, the
22 volume status in patients on an individualized

1 basis, and does take an individualized
2 approach.
3 As you saw, most of the readings
4 are done by nurses and NPs. Some are done by
5 physicians. Twelve percent overall were done
6 by physicians, and it tended to be those that
7 required more intensive scrutiny in terms of
8 figuring out what is going on.
9 DR. BRINKER: Thank you. Can I
10 just follow up that for one quick --
11 CHAIRPERSON MAISEL: I would like
12 to give other people a chance to speak. Dr.
13 Somberg.
14 DR. SOMBERG: One comment and one
15 question to the manufacturer.
16 My comment is -- and I was going
17 to save it for later, but it was brought in
18 discussion now -- is when I looked at the
19 Panel pack, I immediately saw that it is not
20 just a device. It is a device plus an
21 algorithm, and when the FDA does consider
22 approval of this or in the future some future

1 device, I submit that you have to really have
2 a very detailed therapeutic algorithm in this
3 case.
4 It is not putting the device in
5 and training the physician how to put it in or
6 even how to read it, etcetera, but it is what
7 the interventions are, because if it is
8 beneficial, it's what they did, these
9 physicians; and if it is not beneficial, it
10 may be that there is another algorithm that
11 would add benefit or more benefit to it, and
12 it may not just be the device is sensing the
13 information.
14 So it is really an information
15 source, and how do you deal with that is a
16 very complex series of questions because,
17 clearly, not everybody is going to be in an
18 academic center who is involved in great
19 detail in the heart failure area. It's going
20 to be used by a spectrum of people. They may
21 use it better. They may use it worse. But
22 it's going to be a real issue.

1 Now for my question. The
2 information side of it -- it is based on a
3 pressure assessment that is turned into some
4 sort of surrogate for end-diastolic volume.
5 Do the therapies affect that in
6 some way? You have a very homogeneous and,
7 once again, aggressively treated group,
8 appropriately treated on beta blockers,
9 etcetera. But if the patients who weren't on
10 beta blockers, if the patients were given more
11 intimate and inotropic therapy, would that
12 dissociate this surrogate from end-diastolic
13 volume? Has that been looked at?
14 You wouldn't need a large number
15 of patients, but you would need a controlled
16 trial with small numbers of patients on beta
17 blockers, off beta blockers, etcetera.
18 DR. STEVENSON: I want to
19 apologize. I may have misled you on this. We
20 are measuring pressure, which is what is
21 transduced. From that, we are making
22 inferences in that, as pressure goes up, the

1 overall circulating body volume in general is
2 going up in these patients. We are not making
3 any calculations on volume.
4 We are just saying, when the
5 pressure goes up in a heart failure patient,
6 the most common reason is that the overall
7 circulating volume has gone up.
8 DR. SOMBERG: And what I'm saying
9 is, yes, I understand that, but you are
10 assuming that the device at that point in the
11 EKG or what have you is giving you something
12 that will somehow give a reflection of volume.
13 it's a pressure measurement, but you get a
14 reflection of volume.
15 I am saying that association may
16 be true at certain instances, but with an
17 inotrope or a beta blocker, is that true or
18 not? Can there be a dissociation? In other
19 words, the pressure may go up or the rate of
20 rise of the pressure and, therefore, the
21 total, what the machine sees, maybe
22 dissociated from this volume surrogate in your

1 head that you are making the adjustments on.

2 So let's say, if you were a

3 physician and you were taking care of patients

4 mostly who were treated by more intermittent

5 diatropes, would that change the information

6 base? Where you are a physician who didn't

7 use beta blockers in their heart failure

8 practice more frequently, would that change or

9 this surrogate consistent over a host of

10 pharmacologic baseline therapies?

11 DR. STEVENSON: The association of

12 symptoms of heart failure and deterioration of

13 heart failure with elevated filling pressures

14 in heart failure is very consistent,

15 regardless of the intervention that we are

16 making.

17 So we are not really measuring a

18 surrogate for anything. The pressure is the

19 pressure, and that is what is related with the

20 symptoms.

21 Certainly, in terms of the overall

22 cardiac volume, that may be changing with

1 different things, but we are making
2 assumptions about the circulating volume, and
3 that seems to be very reliably on a clinical
4 basis associated with the pressure
5 measurements, regardless.
6 There is one comment with regard
7 to intermittent inotropic therapy. I don't
8 want to upset the people from the FDA who are
9 in the audience, because intermittent
10 inotropic therapy is not approved at all,
11 should not be used for patients with heart
12 failure. So, hopefully, none of us know any
13 of that. Thank you.
14 CHAIRPERSON MAISEL: Thank you.
15 Dr. Ewald.
16 DR. EWALD: I just wanted to
17 expand for a minute on, I think, the same
18 theme about how you really feel that this
19 technology will kind of translate to a more
20 general heart failure population.
21 Obviously, the data we have
22 reviewed today is using this device in a

1 fairly selected group of heart failure, and
2 some of the transplant centers, who have, we
3 assume, the infrastructure to review this data
4 on a regular basis and perform these changes.
5 I guess one of the issues is that
6 kind of who then do you see as the target
7 user, and especially in a system where there
8 may be an implanter who is completely removed
9 or different from the heart failure management
10 team?
11 I think one of the key points that
12 I see in that regard is that you supplied some
13 data about follow-up in the post-randomized
14 period, and the number of reviews of the data
15 went down from 5.7 to 2.2, even in this
16 carefully selected, involved population of
17 physicians and nurses.
18 What are we going to see in a
19 general heart failure population, if this were
20 approved?
21 DR. ABRAHAM: Yes. Greg, I think
22 that is a terrific question. First of all, I

1 would expect in terms of the patient
2 population that it would be similar to that
3 studied in the COMPASS-HF trial. I think that
4 trial really sets the boundaries currently for
5 patient selection for a Chronicle device.
6 Where will we start? I think it
7 will start where most new diagnostic or
8 therapies start in the heart failure arena.
9 It is going to start with patients with more
10 advanced disease and in specialized centers.
11 As a matter of fact -- and I think
12 that the sponsor can speak to this as well --
13 the plan is to really roll this out, if there
14 is a favorable decision for approval,
15 initially to additional heart failure centers
16 as people gain more experience and can mentor
17 other centers to begin to roll it out to the
18 general cardiology community.
19 So I think that there really is a
20 sort of rationale stepwise approach to rolling
21 this out that will help assure additional care
22 and safety as this goes out into the

1 community.

2 CHAIRPERSON MAISEL: Thank you.

3 Dr. Stevenson, do you have a comment?

4 DR. STEVENSON: I wanted to add to

5 that one as well. One of the things we need

6 to recognize is that we are really in a

7 revolution of quality of care, not just for

8 heart failure but for many chronic illnesses,

9 which is really going to change the way that

10 we approach these diseases into something

11 where we are held to a much higher standard.

12 It is currently a recommendation

13 that all patients with advanced heart failure,

14 which is usually defined as a heart failure

15 hospitalization and persistent symptoms, be

16 followed in a heart failure management

17 program, which is defined by the

18 infrastructure that we are talking about here.

19 So I think, after the first phase

20 of the rollout, it is pretty clear that this

21 would roll out into heart failure management

22 programs, and the number of those is going to

1 have to increase.

2 CHAIRPERSON MAISEL: Thank you.

3 In a moment we are going to break for lunch.

4 I just have a couple of quick announcements.

5 Number one is take any personal

6 belongings you may want, because this room

7 wills be secured during lunch, and you will

8 not be able to get back in here.

9 Number two is simply to remind the

10 Panel that all discussions regarding this PMA

11 will happen in this room in public and that

12 you should not be discussing it at lunch.

13 We will reconvene in one hour.

14 (Whereupon, the foregoing matter

15 went off the record at 11:49 a.m.)

16

17

18

19

20

21

22

1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (12:52 p.m.)

3 PANEL DELIBERATIONS AND FDA QUESTIONS

4 CHAIRPERSON MAISEL: Good

5 afternoon. What I would like to do at this

6 point is resume the panel discussion. And I

7 would like to give each member of the panel a

8 few minutes to make any points that they want

9 to make, question the sponsor or the FDA.

10 And so we will just go around the

11 table. We will be skipping over the primary

12 reviewers this time around the table. And

13 then after we have that, we will have a little

14 more discussion and then go into the FDA

15 questions.

16 So why don't we start with Dr.

17 Domanski? And if each panel member could

18 confine their comments to about five minutes,

19 that would be great.

20 DR. DOMANSKI: You know, this is

21 really, really an intriguing device. And I've

22 already said what I have to say about the

1 engineering, which is marvelous.

2 I guess, though, I would like the

3 sponsor, I would like Medtronic, to answer a

4 couple of questions. The first one is if you

5 were -- you know, I would like to have your

6 view of why it is that you think that the

7 trial that you have done really proves that

8 this thing is effective to reduce

9 hospitalizations because, much as I'm

10 enthusiastic about the thing, I have to say

11 that, you know, it's a pretty negative-looking

12 trial. I mean overall. So I would like your

13 rationale because I would like you to give me

14 some ammunition.

15 And number two is I wonder in

16 looking at this population whether, really,

17 the right population was selected. I just

18 wonder whether or not the population that's

19 more likely to benefit would be the ones who

20 have been in and out of the hospital and it's

21 just hard to keep them out.

22 So I would be very interested and

1 intrigued by your thoughts about those two
2 things.
3 DR. ABRAHAM: Mike, as always,
4 questions that are really right on.
5 You know, I think that there are
6 data in this trial. And certainly when one
7 looks at the totality of the data across phase
8 one, phase two in the COMPASS-HF study, that
9 really does support approval of the device,
10 demonstrating reasonable assurance for safety
11 and efficacy. And I think that relates to the
12 fact that the root cause of worsening heart
13 failure and what we tried to measure in this
14 study were episodes of decompensation
15 resulting in hospitalization or
16 hospitalization equivalents, but there are
17 lots of other episodes of worsening heart
18 failure that occur on an outpatient basis.
19 So the root cause of worsening
20 heart failure is an increase in left
21 ventricular filling pressure. And I think we
22 have demonstrated very nicely throughout the

1 development program for this device that one
2 can use these data and treat elevated or
3 depressed filling pressures.
4 I mean, part of this comes back to
5 an earlier comment from Dr. Normand that says
6 that, you know, really, part of what we should
7 be measuring here is how does this diagnostic
8 device, not a therapeutic device, diagnostic
9 device, affect the clinician?
10 And, in fact, you saw very nice
11 data earlier to show the clinicians respond
12 appropriately. If pressures are high, they
13 increase the diuretic. And they lower those
14 pressures. If pressures are low, they may
15 withhold a lower dose of diuretic and allow
16 those pressures to come back into an optimal
17 volemic range again.
18 So I think when you put the whole
19 story together along with its sort of
20 biological plausibility in the data that's
21 been presented, there really is a fairly
22 consistent story here that can be made.

1 DR. DOMANSKI: And the population?

2 DR. ABRAHAM: Yes. In terms of

3 the population, you know, I think there is a

4 sweet spot here that we're still

5 understanding. Certainly there are probably

6 patients that are too sick and perhaps at this

7 point in time based on currently available

8 data patients that are too well.

9 You know, most of the data if you

10 really dig deeply into it -- and the data are

11 available in your panel pack -- a very small

12 number of outlying patients substantially skew

13 this data set. There's no question about

14 that.

15 Whether you look at the class IV

16 population, where 3 patients accounted for 16

17 hospitalizations in the Chronicle arm or

18 whether you look at those outlier patients

19 that had a cumulative total of greater than 30

20 days of heart failure hospitalization during

21 the 6-month period of time, there is a small

22 number of outlier patients who now, in

1 retrospect, one might think aren't good
2 candidates for this particular approach to
3 monitoring or managing patients.
4 In addition to that, you know that
5 certain things happen in the context of
6 clinical trials that are simply flukes. For
7 example, one of our patients is one of those
8 outlying patients. The patient had class IV
9 heart failure. He was pretty ill. He got
10 hospitalized, and a decision was made to put
11 an LVAD in. And the patient then stayed in
12 the hospital for 124 days because of the LVAD,
13 not because of the Chronicle device. So those
14 are the types of challenges you encounter in
15 trials like this.
16 DR. DOMANSKI: Okay. Thanks very
17 much.
18 CHAIRPERSON MAISEL: Dr. Page?
19 MEMBER PAGE: I'm going to reserve
20 my general comments for when we go around
21 through the questions, but I had a couple of
22 particular questions that might be best

1 answered by the physicians who have been
2 involved in the implantation.
3 I appreciate the comment about
4 real estate, again putting in implantable
5 devices and taking them out. There are only
6 two shoulders. I'm wondering, in the patients
7 who have these and have pacemakers, are they
8 put on the same side or are you using both
9 shoulders?
10 And, secondly, what kind of
11 interaction do you anticipate potentially with
12 the two devices? This is reminiscent of when
13 defibrillators first came out and we had
14 endocardial defibrillators and pacemakers.
15 And the cross-talk was really quite
16 challenging.
17 And, addition to that, patients
18 who were enrolled in this trial I believe only
19 had Medtronic devices. Am I correct there?
20 DR. LOVE: Correct.
21 MEMBER PAGE: And how does that
22 apply to the other patients out there with a

1 different device? And then I have one other
2 follow-up question.
3 DR. LOVE: Let me answer several
4 things. First, I think you are right on with
5 regards to this is not a new concept.
6 Patients with the original ICDs also got
7 separate pacemakers. And then we had ICDs
8 with pacemakers. Then they got dual chamber
9 pacemakers. And then they had ICDs and
10 biventricular pacemakers. So we have done
11 this many times.
12 As it turns out, in total, there
13 were 53 percent of these patients at some
14 point had concomitant devices. And there were
15 no issues with device-device interaction.
16 Generally one device is put on one side, one
17 on the other side.
18 There were two exceptions to that,
19 where two patients had the devices on the same
20 side. They were able to communicate
21 independently with those. Even being the same
22 manufacturer's device on the same telemetry,

1 wavelength, et cetera, they were able to
2 separate those out, interrogate one, program
3 them separately.
4 But as far as the labeling goes,
5 in the teaching, we are asking people to place
6 them on opposite sides to minimize any risk of
7 telemetry communication issues. The study was
8 designed to exclude patients that had other
9 manufacturers' devices. And that decision was
10 made I think simply to minimize any risk to
11 the patients with regards to having two
12 different telemetry schemes, et cetera.
13 So that hypothesis has not been
14 tested, but we have in the past had the
15 patients with device A from manufacturer A and
16 a different device from manufacturer B. And
17 we have not seen any issues with those because
18 they really do communicate differently.
19 With regards to the real estate
20 issue -- and I think that is an important
21 issue because I see patients with multiple
22 devices and leads and things of that nature --

1 this is really a non-issue. We upgrade people
2 all of the time. We are able to extract leads
3 and place new leads in if necessary, even if
4 totally occluded vessels.
5 The real estate issue, really,
6 it's an interesting concept, but it really is
7 not going to affect patients with regards to
8 having a diagnostic monitoring device like
9 this.
10 MEMBER PAGE: I understand. The
11 only exception would be if there's an
12 infection and you've got two shoulders
13 involved. Then you're out of shoulders.
14 DR. LOVE: You're out of
15 shoulders.
16 MEMBER PAGE: And I don't imagine
17 the sponsor needs to comment on this, but I
18 would envision if this technology went
19 forward, that a system that would include both
20 the diagnostic and the therapeutic operations
21 of pacing, diventricular pacing,
22 defibrillation, and hemodynamic monitoring

1 would be something that is aspired to. Could
2 you comment on that?
3 DR. LOVE: Yes. Actually, the
4 chronicle ICD study is underway right now.
5 MEMBER PAGE: You're ahead of me.
6 And the final question I have -- and I'm not
7 sure whether physicians or maybe the sponsors
8 could comment on their projections. And that
9 is Dr. Stevenson commented on one of the
10 advantages of this being the large volume of
11 patients who might be eligible for this. And
12 I've heard heart failure described as an
13 epidemic.
14 If this were to be approved -- and
15 I understand that there will be a step-wise
16 release and experience developed. But if this
17 were approved, how many patients would be
18 anticipated to be candidates for this device
19 now?
20 DR. STEVENSON: No one really
21 wants to answer this question. It's very
22 difficult to estimate exactly how many people

1 have what severity of heart failure.

2 Certainly those patients who are

3 class scores that are close to terminal, we

4 wouldn't want this device. We would be

5 looking at hospice and other things.

6 And certainly the patient who is

7 class I, II who hasn't been hospitalized who

8 is doing well in their current therapy, we

9 wouldn't anticipate this device for them.

10 So, you know, we're looking --

11 there are two populations. One is the low EF

12 population. And the other, which is a

13 population that has absolutely no documented

14 therapy right now, is the preserved EF

15 population.

16 So, you know, I would say that if

17 you talk about the number of patients, it's

18 probably, I would say, maybe in the range of

19 400,000 patients. However, the issue is that

20 we feel very strongly that this is part of

21 appropriate heart failure management.

22 And the percentage of patients

1 currently who have a heart failure management
2 program to report to is a small fraction of
3 that, probably five percent of those patients.
4 And certainly this device needs to be
5 implemented in the context of a heart failure
6 management program with all the appropriate
7 infrastructure.
8 MEMBER PAGE: Thank you.
9 CHAIRPERSON MAISEL: Dr.
10 Blackstone?
11 DR. BLACKSTONE: I have two major
12 and different kinds of concerns. One is that
13 this device, as we have said this morning, is
14 coupled with a therapeutic strategy. There is
15 one place in the panel material in which you
16 mention a formal method to look at these
17 trends for this early warning.
18 You mention, for example, if there
19 is any way that you have looked at how to
20 formalize a protocol so that it becomes a
21 repeatable protocol? As part of that
22 protocol, you are mentioning this estimated

1 PAD, the estimated PAD you showed in your
2 early studies has both the narrowest range and
3 the widest scatter. And, yet, you also have
4 said that the nurses who are looking at these
5 probably do look at all sorts of things,
6 including the patient activity and this sort
7 of thing.
8 But how can we be sure that there
9 is a formal way of handling this information?
10 And what steps have you made?
11 DR. ADAMSON: Those are very good
12 observations. And I appreciate the question.
13 First of all, I think what my experience has
14 been as well as other investigators is that
15 observing hemodynamic information is much like
16 other diagnostic tests that we perform, such
17 as electrocardiograms.
18 And the learning curve is
19 measurable, but once one becomes accustomed to
20 seeing the displays, the changes that occur
21 outside optivolemic range are much easier to
22 recognize and become similar to the way we

1 would read an electrocardiogram. This is a
2 new intervention and new data sets.
3 DR. BLACKSTONE: Interestingly,
4 that's not data you have provided us. In
5 other words, you have showed what happens over
6 the weeks ahead before you're hospitalized in
7 a group that didn't have this device, but we
8 don't have similar data that says in the
9 patients in whom you have known this
10 information, what do those trends look like?
11 DR. ABRAHAM: Well, first of all,
12 if I could have a slide up, I would like to
13 take a bit of time, if you don't mind, to
14 demonstrate how the interaction between a
15 clinician and the information occurs because
16 it is important to recognize how the pressure
17 changes are identified by the user.
18 What you see here is an actual
19 screen print of the Web site, which
20 demonstrates a previous transmission, which
21 you see the date there, and then the current
22 transmission, which is the one being reviewed.

1 First of all, data that are
2 outside the preset limits or the optivolemic
3 range are highlighted so that individuals will
4 be able to identify changes in pressures that
5 fall outside the predetermined optivolemic
6 range. That is how the typical first shot of
7 the pressures was encountered by the
8 clinician.
9 These numbers actually represent
10 the nighttime minimum with zero activity
11 numbers, which we have demonstrated to be the
12 highest correlate to the measurements that
13 would be done in a cath lab, for example. So
14 these are numbers that we are most comfortable
15 with.
16 Let me just go to one more slide,
17 slide number PA-26, please, 26. Once, then,
18 the quick look summary is assessed, then the
19 user is able to interrogate a long-term trend
20 analysis to see changes that occur over time.
21 In order to more objectively
22 quantify changes over time and possibly

1 associate those with outcomes, we developed a
2 computer-based algorithm that analyzed these
3 changes over time, incorporating both
4 variability, duration, and magnitude of
5 changes over an optivolemic range.
6 If I could have PA-120? The
7 performance of that algorithm demonstrated was
8 used, actually, in the control group, in which
9 the outcomes were not determined by knowing
10 the hemodynamics, in the performance of this
11 found that 82 percent of hypervolemic events
12 that qualified as an adjudicated heart failure
13 equivalent were captured by a detectable
14 change in pressures. And only 18 percent of
15 events occurred without a detectable change in
16 the pressures prior to the heart failure
17 event.
18 So in the panel pack, you see a
19 detection algorithm which was determined by a
20 computer-based scanning of the pressures.
21 This was a retrospective evaluation but did
22 discover a significant change in pressures

1 prior to an event.

2 Lynne?

3 DR. STEVENSON: I just wanted to

4 get to your other question, which is, what

5 happens to pressures in the Chronicle group

6 before and after intervention? And I would

7 emphasize this is not in the panel pack we're

8 giving you. This is in answer to your

9 request. And also this is data that has never

10 before been seen anywhere because we never

11 knew, in fact, what happened when we made

12 these interventions.

13 If I can have the slide on,

14 please? What you see in the blue bars are the

15 changes in pressures before the increase in

16 diuretics in the Chronicle arm. What you see

17 in the orange bars are the decreases in

18 pressures after we made the changes in

19 diuretics.

20 And if I can have the next slide,

21 39? This is different. Now what you see are

22 these changes in the Chronicle group and in

1 the control group, both for increase in
2 diuretics on the left and decrease in
3 diuretics on the right.
4 And what you can see first on the
5 left is that, in fact, we are responding to
6 larger increases in pressure. In these cases,
7 when we look at the control group, it's not
8 clear, in fact, what the triggers for those
9 interventions are. And we had a more complete
10 response in the increase group.
11 The decrease group is particularly
12 interesting, I think, if we look at what
13 happens when we decrease the diuretics in
14 response to a pressure fall.
15 In the Chronicle group, we had the
16 appropriate increase in pressures after that.
17 However, in the control group, when the
18 diuretics were changed, in fact, what you see
19 is an overshoot where patients returned to a
20 filling pressure that was higher than the one
21 that we would have been aiming at.
22 Again I would emphasize this is

1 not in the panel pack. We will be happy to
2 provide it to you. But this provides further
3 validation of the physiologic concept that we
4 have the information on the pressures, we make
5 the intervention, and we achieve the desired
6 result.
7 CHAIRPERSON MAISEL: Thank you.
8 Let me let Dr. Blackstone continue with his
9 questioning.
10 DR. BLACKSTONE: Okay. The second
11 question relates to the emphasis that is being
12 placed on the post hoc analyses, the
13 multi-variable analyses. The justification
14 for those given in the packet were, first,
15 because you believe that there were some
16 imbalances of some strong predictors of
17 outcome. And there's evidence in the
18 literature that that is a good thing to do.
19 But I am a little surprised,
20 therefore, if you thought there were some
21 imbalances that you didn't use things like
22 propensity scores as something to aid in

1 trying to adjust for those.

2 The second thing is that you

3 confirmed this morning what I suspected and

4 what you actually said. And that is that you

5 have analyzed only the very first heart

6 failure event. And so I am curious as to why

7 you have done that because I am presuming that

8 you have all the armamentarium to look

9 multi-variably at all the events or if you

10 thought that you needed to look at individual

11 ones, that modulated renewal processes. And

12 so what I'm curious is when you did that, what

13 did you find that then forced you to look at

14 only the first event, which probably was the

15 most significant.

16 DR. BOURGE: Well, we have

17 actually done it all, all that she described.

18 It is not in the panel packs. And I will be

19 glad to share that with you separately.

20 Slide on, please. When you looked

21 at our subgroup analysis, again, the first

22 thing that clued us in to possibly something

1 different in the sicker patients was this
2 imbalance that we saw between class III and
3 class IVs, where in the class IIIs, there was
4 a lower event rate in Chronicle versus
5 control, but it seemed to be the opposite in
6 New York Heart Association class IV patients.
7 So we wish to clinically as clinicians
8 investigate why could that be.
9 When we went forward with an
10 analysis -- and I'll show you now on the next
11 slide, the difference graphically the event
12 rate per month was higher in the Chronicle
13 group versus the control group. Even if you
14 look at it, again, as we have said earlier,
15 there were 3 patients with 16 events. It
16 seemed to get worse in these patients. So was
17 there something magic about class IV, a
18 dynamic change?
19 As we know, in New York Heart
20 Association classes dynamic, one day they may
21 be class IV. Then three days later, they may
22 be class III. So what we did was, next slide,

1 we looked at certain imbalances at baseline,
2 just looking at the class IV patients. And
3 what we saw was, for example, there was a
4 difference in six-minute walk tests between
5 the patients randomized in the Chronicle group
6 versus the control group and the class IV
7 patients.
8 We also saw another index of
9 severity of heart failure. The creatinine was
10 higher in the Chronicle group versus the
11 control group. So as we went forward, we
12 tried to then expand that analysis because we
13 didn't think the differential effect between
14 class III and IV patients was due to baseline
15 characteristics. We thought it could be to
16 other more objective, not just baseline
17 characteristics, but could be more due to
18 other objective findings that are attributable
19 and could explain the degree of illnesses. So
20 we had a hypothesis that the clinical
21 characteristics would have a strong
22 correlation to the outcome.

1 In looking at that, we did do, as
2 you saw in your panel packet , a
3 multi-variable methodology, which we thought,
4 slide on, was appropriate when imbalances
5 existed between the two study groups, as Dr.
6 Blackstone said.
7 We also thought there were strong
8 associations between certain baseline clinical
9 characteristics and the measured outcome. We
10 did, next slide, a univariate analysis looking
11 at these baseline characteristics specifically
12 to look for their predictive relationship with
13 outcome, both with negative binomial
14 parametric hazard analysis and Cox regression.
15 We did a multi-variable analysis.
16 And we looked at covariates that were
17 predictive of outcome. We're into the
18 multi-variable analysis. And, again, this is
19 in your panel pack. In this analysis, we
20 found that if you adjust for those baseline
21 characteristics, there was a difference.
22 Next slide, please. In fact,

1 although it did not come out significant, you
2 see the p-value improves to .11 when you
3 adjust for those baseline characteristics.
4 In this negative binomial
5 regression analysis, the primary endpoint is
6 cumulative events. So it is applied to
7 multiple events. And, in addition to this,
8 again, not shown to you, we did do a
9 multi-variable parametric hazard analysis
10 using the methods of Dr. Blackstone, which was
11 totally consistent with this.
12 CHAIRPERSON MAISEL: Okay. Thank
13 you for your comments.
14 At this point, we are going to
15 move on to Dr. Somberg's questions.
16 MEMBER SOMBERG: Well, following
17 forward from this morning, I had asked about
18 the difference between class III and class IV
19 in terms of the 6 to 12-month period. Did
20 those differences persist? Because we all
21 know that while there may be imbalances, it's
22 very hard to correct for them. And that's why

1 we do randomized trials.

2 Maybe the trial wasn't large

3 enough. Maybe you just, unfortunately, had

4 that. But did anyone look at the -- did that

5 difference persist between benefit and

6 non-benefit?

7 DR. BOURGE: Slide on, please.

8 Again, as alluded to earlier, after six

9 months, when we are talking about events, the

10 Clinical Events Committee did not look at and

11 differentiate heart failure events. So we go

12 back to investigator-adjudicated events,

13 which, by the way, when we correlated that

14 with the Clinical Events Committee, the

15 correlation was over 90 percent. There was

16 excellent agreement between the Clinical

17 Events Committee and the investigator's

18 determination of what was a heart

19 failure-related event.

20 If we look at class III patients,

21 as you see something very similar to the

22 overall group, we see an event rate lower in

1 the class III patients compared to control in
2 the randomized period. After the randomized
3 period, 6 to 12 months, we see the control
4 rate.
5 And at this point, we are able to
6 look at the pressures and act on it. And we
7 see a drop in the control rate events to,
8 again investigator-adjudicated with the
9 caveats we said before, something very similar
10 to the overall Chronicle events.
11 Next slide. When we go to class
12 IV, we see very similar things. Although
13 there is not a difference, we didn't see any
14 worsening certainly of the events between zero
15 to 6 months and 6 to 12 months. Again, these
16 were investigator-adjudicated. And there was
17 excellent correlation between that and the
18 Clinical Events Committee.
19 Does that answer your question,
20 Dr. Somberg?
21 MEMBER SOMBERG: Well, I
22 understand what you are saying after 6 to 12

1 months, but between zero and 6 months, in
2 terms of events, I was under the impression
3 that there were more events in the class IV
4 patients due to the imbalance. Now you are
5 saying they were equal here in these two
6 slides?
7 DR. BOURGE: These were
8 investigated. It is not exactly the same
9 thing. Before I showed you the Clinical
10 Events Committee, which overall had a 90
11 percent correlation, but the event rates were
12 low because of the small number of patients in
13 the class IV patients.
14 MEMBER SOMBERG: Well, to answer
15 your question, I see your points, but I was
16 just comparing different fruits. So I don't
17 see how. I mean, you are saying that "We have
18 a problem, you know, a basis was on the
19 Clinical Events Committee. We had a problem
20 in class IV. It was due to an imbalance."
21 I said one way that would make me
22 feel a little more comfortable would be to

1 look at that in 6 to 12 months, and then we're
2 going to another thing where it doesn't show
3 that problem up front, which may be due to
4 bias. We have always qualified that.
5 So I don't think it resolves the
6 issue at all.
7 MR. MANDA: Actually, Dr. Somberg,
8 indeed you raise a good question. I'm sorry.
9 I think Dr. Bourge was referring to a
10 different. This was not the result of
11 adjudication being the problem here at all.
12 What you're looking at here is
13 actually their data. This data actually
14 includes a subset of the patients that were
15 the overall class IV patients if you recall in
16 the original slide that Dr. Bourge presented,
17 we had 40 patients in class IV. Not all of
18 them lived and/or made it into the second
19 six-month period.
20 So this is using only 28 of those
21 patients who actually made it to the second
22 6-month period. As you can imagine with these

1 sick patients, some of them died during the
2 first six months. So this is just a subset of
3 the patients who actually had data time
4 points.
5 The adjudication had no
6 introduction to the bias. In fact, the
7 concordance was over 95 percent between the
8 investigator and clinical investigative
9 adjudication.
10 MEMBER SOMBERG: Well, that's
11 helpful, but, of course, the reason that the
12 patients didn't continue on may have been that
13 the intervention that was chosen based on
14 hemodynamic data was deleterious to the
15 patients and that's why they're not in that
16 cohort. So there is an adverse possibility.
17 MR. MANDA: That is a very
18 important question. And I would like to
19 address it. I am going to invite probably Dr.
20 Stevenson to address that question as well.
21 We do have some information to clarify. That
22 is a very important topic.

1 DR. STEVENSON: Once again, now if
2 we look at the class II and IV -- slide on,
3 please -- these are the overall events divided
4 up into class III and IV. These are the
5 hypervolemic events.
6 CHAIRPERSON MAISEL: Can I
7 interrupt for a second?
8 DR. STEVENSON: Yes.
9 CHAIRPERSON MAISEL: Can we try to
10 answer Dr. Somberg's question?
11 DR. STEVENSON: Yes.
12 CHAIRPERSON MAISEL: Because he
13 asked about what happened to the class IV
14 patients who were not shown on that paired
15 slide. I think there were about six in the
16 device group that disappeared from the
17 analysis you just showed. So did those
18 patients die or were they lost to follow-up?
19 What happened to those patients? Could we
20 address Dr. Somberg's question, please?
21 DR. STEVENSON: Well, actually --
22 okay. Next slide, please. This is the class

1 IV patients and what happened to them. I'm
2 sorry. I don't have the mortality data for
3 that.
4 I was actually trying to answer
5 his question of, did we do something that, in
6 fact, worsened their outcome? So can you give
7 me the slide for the adverse events in the
8 class IV?
9 Next slide. The slide would be --
10 CHAIRPERSON MAISEL: The number of
11 patients don't add up. And we're just trying
12 to understand what happened to those patients
13 that aren't on that paired slide.
14 DR. STEVENSON: Okay.
15 MR. MANDA: So I will just clarify
16 the numbers. There were a total of 40
17 patients in class IV that were randomized.
18 DR. STEVENSON: Slide on. I am
19 going to let you do this.
20 MR. MANDA: Okay. No problem. So
21 this was of the 40 patients, 12 patients died
22 in the study. There were eight in the

1 randomized Chronicle group and 4 in the
2 control group. And this was the Clinical
3 Events Committee adjudicated classification of
4 death.
5 And so these 12 patients could not
6 contribute to the pair analysis we saw
7 previously, which is 28 patients. So 40 minus
8 12 is 28. So we have to have some data, at
9 least in the second six months.
10 CHAIRPERSON MAISEL: Okay. That's
11 fantastic. Thank you.
12 Dr. Somberg, did you have any
13 other question for this sponsor?
14 DR. STEVENSON: Next slide,
15 please. Next slide.
16 CHAIRPERSON MAISEL: Dr.
17 Stevenson, just excuse me for one second. Dr.
18 Somberg, did you have any other questions for
19 the sponsor?
20 MEMBER SOMBERG: Well, I had other
21 observations, but if it's okay with you, Dr.
22 Maisel, I am willing to -- if she wants to add

1 another thing to my questions, --

2 CHAIRPERSON MAISEL: Okay.

3 MEMBER SOMBERG: -- I am more than

4 happy. I don't anticipate exactly what

5 question I asked to elicit your response, but

6 I am interested in your response.

7 DR. STEVENSON: I was answering to

8 what I thought was your concern that something

9 that we had done based on the hemodynamic

10 monitoring might, in fact, have been bad for

11 the class IV patients. And the only thing

12 conceivably that we would have done might have

13 been to over-diurese the patients because we

14 knew the filling pressures.

15 And what we are looking at here

16 for the class III patients and for the class

17 IV patients is all those events that we could

18 in any way have attributed perhaps to

19 over-diuresis: renal insufficiency,

20 hypokalemia, hyponatremia, hypotension, volume

21 depletion, dehydration.

22 Just to demonstrate, there is no

1 increase in those events in either the class
2 IV or in the class III in anything we could
3 attribute to overaggressive therapy based on
4 hemodynamic monitoring in either class.
5 MEMBER SOMBERG: By the way, I was
6 not implying that you intentionally, but
7 sometimes we try our best and we still do bad
8 things.
9 I have another question to the
10 sponsor. And I'll preface it by my thoughts
11 are that for a drug, which in some ways is
12 easier to take away than a device of this
13 nature, we ask for two pivotal studies in
14 RTCs. It seems that this was a very small
15 trial.
16 We are looking at a limited
17 predominantly hospitalization endpoint. And I
18 just wondered why with the potential
19 adversities that we have it was not the
20 intention to look at a more than one
21 randomized trial or one large one that would
22 really have the power to look at two different

1 questions in this because it seems as though
2 we're asking less of a device in this serious
3 field of heart failure than we do for a drug
4 therapy in this serious field of heart
5 failure. And that concerns me.
6 DR. ABRAHAM: No. I would like to
7 address that question. And I know that you
8 referred it specifically to the sponsor. But
9 if you feel that it is appropriate, I think it
10 would be worth asking the FDA to comment as
11 well.
12 I have substantial experiences in
13 investigator and device trials. And those
14 trials of these sorts of devices tend to be
15 sized about the size of this study. And when
16 we started off this trial, we thought that
17 this was prospectively adequately powered to
18 reach an endpoint based on the assumptions
19 that were made and presented to you earlier.
20 CHAIRPERSON MAISEL: Dr.
21 Zuckerman, would you like to comment?
22 DR. ZUCKERMAN: I thought that Dr.

1 Borer in his opening comments explicitly
2 indicated in a practical clinical definition
3 what this advisory panel is trying to look
4 for, a reasonable assurance of safety and
5 effectiveness that provides indications of
6 clinical utility. This advisory panel knows
7 that there are specifically different
8 regulations for devices, as opposed to drugs.
9 There is no requirement that two
10 trials be performed. The only requirement is
11 that with a given data set we are confident
12 that we can meet the reasonable benchmark as
13 practically defined by Dr. Borer.
14 The only comment I would have is
15 that every heart failure trial by definition
16 should not have a sample size of 300 patients
17 or 3,000 patients. One needs to design the
18 trial to answer the appropriate questions.
19 CHAIRPERSON MAISEL: Thank you.
20 At this point we will move on to
21 Dr. Kato.
22 DR. KATO: Thank you.

1 I have two questions for the
2 sponsor, one question for the FDA. Let me go
3 for the sponsor first. I noticed -- and this
4 is from a practical perspective. I read
5 someplace -- I just can't find it anymore, but
6 the battery life is anticipated to be about --
7 it was about three and a half years or
8 something like that, which seems to be a
9 little low compared to a standard DDD
10 pacemaker. It looks about the same size.
11 And I would assume also that --
12 and I would think, actually, that the market
13 is probably going to be a lot bigger than
14 this, than maybe 400,000, probably closer to a
15 million based on -- and that's just a guess,
16 too.
17 But is there any attempt by the
18 sponsor to improve this device so that we're
19 not changing these things out every -- let's
20 say you get approved. But you're not changing
21 this thing out every three and a half years
22 because then you're just going to have --

1 you're just creating this whole business of
2 device change-outs.
3 DR. STEINHAUS: Sure, first of
4 all, I think you have to realize this is our
5 first shot. I mean, if you go back through
6 the history of devices, I go back to the time
7 when we were implanting ICDs that had to go in
8 the belly. It took three and a half hours to
9 put in. I mean, we are all well-aware of
10 that. We expect significant improvements over
11 the course of time again. This is our first
12 attempt at it.
13 It does take more energy. I mean,
14 if you think about it, if you are measuring
15 all the time and you are measuring these
16 changes all of the time, it takes a little bit
17 more circuit energy to run this than it would
18 a regular pacemaker, which accounts for the
19 difference.
20 DR. KATO: The second question
21 comes back down to the inclusion and exclusion
22 criteria of the study. One of the problems

1 that we have as clinicians out in the field is
2 there are a lot of assumptions, I think, that
3 go into when these devices should really be
4 used. And obviously you're trying to choose
5 relatively optimal conditions.
6 People out in the field I think
7 have to -- you know, again, they are dealing
8 with a patient in front of them, not with a
9 protocol. And so there is this constant
10 struggle about when should these devices be
11 used.
12 And, as has been mentioned before,
13 this isn't like a device that's going to be
14 put in and then taken out. And it's not like
15 a drug where you can stop it or once it goes
16 in, even if it was put in for the wrong
17 reason, chances are somebody is going to have
18 to keep replacing this thing every, you know,
19 three and a half -- I will give you five
20 years. And there is a potential that a
21 patient could maybe require three or four of
22 these in a lifetime.

1 So I would like to hear a little
2 bit more about, you know, inclusion and
3 exclusion criteria that you can narrow this
4 down to give us this real tight group of
5 patients where there is going to be some
6 benefit because, at least from what we have
7 seen so far, using this criteria didn't give
8 you the numbers that you wanted to see.
9 DR. STEINHAUS: Right. Well,
10 first of all, I think we have tried to explain
11 why we think the numbers turned out the way
12 they did. You know, to some degree, I think
13 we were, I think you mentioned, unlucky in the
14 sense of under-powering the study for a number
15 of reasons and also in the sense of having the
16 randomization not work as well as
17 randomizations usually work. So I think that
18 is one issue that we would say right off the
19 bat.
20 Again, I think you have to realize
21 this is going to be a learning process. This
22 is just like the early days of defibrillators,

1 where we didn't know. We didn't know exactly
2 who would benefit all the time. We didn't
3 know exactly, you know, how to put them in.
4 They changed rapidly over the course of time.
5 So I would expect that to happen.
6 We get it. We get it that this is
7 a new, you know, management strategy for
8 patients. And it's going to take a
9 significant learning curve. So when we roll
10 this out, we are going to initially roll it
11 out to, really, the high-volume heart failure
12 centers, where they have the infrastructure to
13 be able to deal with this.
14 We hope when we learn from that
15 group with peer-to-peer interactions and all
16 of that, that we will really be able to hone
17 down the patients who truly, truly will
18 benefit and those who might not benefit quite
19 so much. So I think that is part of our
20 learning experience in this whole plan.
21 DR. KATO: Thank you.
22 And, finally, one question for the

1 FDA. The FDA gave us a condition at the end
2 of their presentation that if this device was
3 approved, that the FDA would require some type
4 of post-market surveillance study. Whether
5 it's sponsor-funded or however it's funded is
6 unknown.
7 We have been told this time and
8 time again that, you know, over the past four
9 years that I have participated in this
10 committee, this panel that there would be a
11 post-market surveillance study of this device
12 or that device. And then, all of a sudden, we
13 hear, "Well, maybe there's no funding." I
14 guess the compliance with post-market
15 surveillance studies has been, shall we say,
16 less than optimal.
17 What assurances can you give us
18 that this will not fall into the proverbial
19 black hole of bureaucracy and not be done?
20 DR. ZUCKERMAN: Well, I will try
21 to give you those assurances right now. And I
22 am sure that the commissioner and our center

1 director, Dr. Daniel Schultz, would underline
2 the points that I am going to make more
3 eloquently.
4 Certainly in the area of chronic
5 device implants, I think it has become obvious
6 to all stakeholders, meaning the industry,
7 clinicians, and the FDA, that the need to
8 follow devices through the total product life
9 cycle; i.e., the need for appropriate
10 post-market surveillance, is a critical one.
11 It has been an important part of our program
12 over the last few years. And I would stand by
13 the fact that we have made tremendous strike
14 in part of the program.
15 As you know, our last panel
16 meeting was the DES panel meeting where
17 because we had the appropriate post-market
18 data sets, we were able to quickly analyze an
19 important public health dilemma. That is the
20 way we do work at the agency right now.
21 There has been a fundamental shift
22 over the last few years. And I would have no

1 hesitation to believe that if the advisory
2 panel went in a certain direction, that the
3 commitment to do a post-market trial is part
4 and parcel. That's the way the device center
5 does work right now.
6 CHAIRPERSON MAISEL: I would add
7 two comments. One is we have been given the
8 task of assessing this with the PMA
9 application that is in front of us and not on
10 any hypothetical post-market data.
11 And number two is we have been
12 presented no evidence that Medtronic has done
13 anything other than have a good history of
14 doing things. So we shouldn't necessarily
15 hold them liable or responsible for others'
16 shortcomings.
17 Dr. Normand?
18 MEMBER NORMAND: Yes. I have one
19 question for the sponsor and one for the FDA.
20 I didn't have a chance to thank the sponsors
21 for a very nice presentation and a really nice
22 design, by the way. The crossover was a

1 really nice idea.

2 I wanted to get more of a sense of

3 the endpoints in terms of heart-related

4 equivalents. And let tell you I'll just be

5 right up front that I am about this.

6 I wouldn't care from my

7 perspective if it's heart failure-related or

8 not. And if I'm getting information and my

9 physician or nurse or whoever tells me to go

10 to the hospital or tells me to go somewhere

11 and someone says, "Well, guess what. That

12 really wasn't related to your heart failure.

13 So it's not going to be counted" I think that

14 is fundamentally wrong.

15 But I don't know how information

16 was counted in terms of the decision of

17 counting a heart failure-related event.

18 And I'll say one more thing. I

19 think you can probably understand where I am

20 going with this. So somebody could have come

21 in thinking it was a heart failure-related

22 event, but on discharge, it really wasn't a

1 heart failure event. And I still say that
2 should account against them because the
3 patient had to go somewhere, use his or her
4 time.
5 So that is the gestalt of my
6 question. Could somebody tell me (a) how
7 those events were adjudicated, why were
8 adjudicated in that manner?
9 DR. ABRAHAM: Yes. I actually was
10 a non-voting liaison to the Clinical Events
11 Committee form the steering committee. The
12 Clinical Events Committee was completely
13 independent of the investigator group and
14 involvement with the study.
15 So the events were independently
16 adjudicated by an independent clinical events
17 review committee that had access to source
18 documentation from the hospitalization but did
19 not have access to the hemodynamic data. And
20 so that is critically important.
21 Their adjudication it was
22 suggested, (a) were not biased by knowledge of

1 study assignment or by access to hemodynamic
2 data. So these were adjudicated on the basis
3 of clinically available information the way we
4 adjudicate cost-specific hospitalization in
5 other heart failure trials.
6 So that was the methodology used
7 --
8 MEMBER NORMAND: Okay. Just to be
9 clear, I am not asking whether -- I am sure it
10 was independent and all that kind of stuff.
11 DR. ABRAHAM: Correct.
12 MEMBER NORMAND: My question is
13 really about the choice of the endpoint.
14 DR. ABRAHAM: Coming to that. So
15 then you had to say for a device that measures
16 pressure and that will allow us to make
17 interventions based on pressure, what can we
18 realistically expect to impact in a heart
19 failure patient?
20 Do we think that we can reduce
21 events related to non-cardiovascular causes of
22 hospitalization or either non-heart

1 failure-related causes of hospitalization?
2 And we thought not.
3 I mean, we really thought based on
4 our understanding of the mechanism of this
5 management strategy that what we would most
6 significantly be able to impact was heart
7 failure events and not non-heart failure
8 events.
9 MEMBER NORMAND: Thank you. But
10 you can see where my point is, correct? And
11 that is the following. I am not meaning this
12 whatsoever as an exaggeration, but what
13 happens if the people who are interpreting the
14 information -- because, remember, we are
15 assessing how the management of the
16 information is implemented -- that they just
17 get this newfangled device. They're getting
18 misinformation. And, oh, my God, maybe they
19 should do something.
20 So, in fact, it could cause
21 utilization, but the utilization is not
22 related to heart failure at all. And so

1 that's not counted. So I just wanted to get a
2 --
3 DR. ABRAHAM: Yes. You know, we
4 could put this slide up. You know, we didn't
5 see that. So this slide looks at health care
6 utilization. So it looks at all hospital
7 equivalents, heart failure, hospitalizations,
8 which is the second from the right pair of
9 bars. But then you see all-cause
10 cardiovascular and also non-cardiovascular
11 hospitalization equivalents listed here as
12 well.
13 What you see is that there was no
14 increase in non-cardiovascular hospital
15 equivalents. There was the trend towards the
16 decrease in heart failure hospitalization
17 equivalents, which largely drove the trend
18 towards a decease in cardiovascular and all
19 cause --
20 MEMBER NORMAND: That is perfect.
21 Thank you.
22 DR. ABRAHAM: Okay?

1 MEMBER NORMAND: Thank you. That
2 is what I was looking for, that type of
3 information.
4 I have one last question. That is
5 to the FDA. It really relates to your
6 thinking about, everybody's thinking about,
7 the design. And I had mentioned this earlier,
8 but I really wanted to get the FDA's response
9 to this.
10 Sort of again, I said I do this
11 more as an encouragement, though not
12 technically speaking a true encouragement
13 design but almost like an encouragement
14 design. And that is a study in which
15 information is given. It's like a diagnostic
16 tool.
17 And typically, for those of you
18 who know about these types of studies, you
19 don't evaluate the patient endpoint. You
20 evaluate how the information is utilized.
21 So, on one hand, I feel like it is
22 tough that the sponsor picked this endpoint

1 because in other studies, when we look at
2 this, we know that for those trials, you put
3 in 2,000 patients because it is difficult to
4 show the endpoint. On the other hand, if you
5 are looking at if the information is managed
6 appropriately, you can use a smaller sample
7 size.
8 So I would like to get the FDA's
9 thought on this. Do you want us to think
10 about the endpoint? Should we be thinking
11 about the management of the information? How
12 do we look at this?
13 As you can tell, I am frustrated
14 by this in terms of it seems to be entirely
15 the wrong design, but it's done. And I could
16 say you are unlucky again, but I wouldn't want
17 to repeat myself. But I just want to get a
18 sense of that from the FDA.
19 DR. ZUCKERMAN: Let me try to
20 answer it in a general sense, Dr. Normand,
21 because, actually, I think the question would
22 be more appropriately addressed by the heart

1 failure experts around the advisory panel.

2 Again, I would go back to kind of

3 first principles as defined in a clinical

4 context by Dr. Borer. At the end of the day,

5 we want to have a reasonable assurance of

6 safety and effectiveness for an individual

7 patient such that we believe that certain

8 device provides appropriate clinical utility

9 in appropriate risk-benefit fashion.

10 The sponsor has designed a trial

11 where they have tried to do that. And I think

12 the bulk of the discussion needs to center on

13 the trial that has been successfully completed

14 by the sponsor. And whether they have

15 achieved at the end of the day an appropriate

16 risk-benefit profile for the average patient

17 treated with this device, if other heart

18 failure experts want to comment on your

19 interesting question as to whether there are

20 other ways to extrapolate clinical utility

21 with this type of device, I would look for

22 some comment from the advisory panel.

1 MEMBER NORMAND: I didn't mean to
2 raise an interesting question just to chat
3 about it. I was really trying to figure out
4 -- well, first of all, I think people probably
5 know what I am thinking. There is no evidence
6 of clinical benefit.
7 And so now we need to figure out
8 to weigh those two together in terms of risks
9 and benefits. And I am just sitting here
10 struggling with, well, we know we have to
11 measure this information. It is recommended
12 to measure the information that this device is
13 measuring. And it's vacuous in terms of I
14 think some of the data that we have.
15 So I wasn't trying to be
16 provocative or interesting. I was really
17 struggling with the idea of the whole design
18 of what really one should answer with this
19 question. That's all.
20 CHAIRPERSON MAISEL: Dr. Ewald?
21 DR. EWALD: I have a quick
22 device-related question and then a couple of

1 questions about the study. Number one, there
2 were some lead failures initially and then a
3 modification made. And I think there was a
4 comment made that it was 100 percent
5 effectiveness of the lead, at least through
6 the six-month predetermined follow-up period.
7 Have there ever been any failures
8 in the lead in the totality of the follow-up,
9 the pressure sensor?
10 MR. GERMANSON: My name is Jack
11 Germanson, a Medtronic employee and a
12 shareholder.
13 Great question. We are happy to
14 say there are no failures of the lead in the
15 subsequent follow-up, which is over 300
16 patients and about greater than 4,000 months
17 of experience.
18 DR. EWALD: I guess I want to make
19 a couple of comments. One is I find it
20 interesting. We have kind of been going back
21 and forth about class III, class IV question.
22 And in the FDA presentation, the

1 events are broken down both for the class III
2 subgroup and the class IV subgroup. And I
3 think, interestingly, in the class IV
4 patients, ones that we assume are the sickest
5 patients, both in the Chronicle group but also
6 specially no ER visits, there were no urgent
7 visits to clinic, and really no short
8 hospitalization stays.
9 I guess I am just kind of
10 wondering and some experience of having taken
11 care of some of these patients in the trial,
12 if you could speak to why. Are these people
13 just so sick that they're just assumed, you
14 know, when things are going bad, they just get
15 admitted because if you look at those class
16 III patients, in the control arm, there were
17 11 ED visits. and 3 urgent visits to clinic.
18 But in the class IV patients, there were none
19 of those events.
20 DR. BOURGE: Slide on, please.
21 This is the class IV looking at the
22 hospitalizations, emergency department visits,

1 and urgent clinic visits. In general, the
2 class IV patients showed up in the emergency
3 department for all evaluation or they call and
4 said, I'm on my way," So that is exactly what
5 happened.
6 Remember, if the patient came to
7 the emergency room and was admitted, it counts
8 as a hospitalization, not as an emergency
9 department visit.
10 DR. EWALD: Right, right.
11 DR. BOURGE: The emergency
12 department visit would only be if they got IV
13 therapy and ended up going home.
14 DR. EWALD: Right.
15 DR. BOURGE: The urgent clinic
16 visits, let me make you understand. Some of
17 the clinics involved, such as UABs, we have
18 heart failure clinic every day. So we tell
19 patients, "Don't go to the ED. If it's
20 between 7:00 A.M. and 6:00 P.M." -- actually,
21 they come either to our clinic or they come to
22 -- we have an outpatient clinic in our heart

1 transplant unit. And they come there, rather
2 than going down and wait in line in our
3 football-sized emergency department. We treat
4 them right there so they will avoid the lines
5 in the emergency department.
6 So that's why we included urgent
7 clinic visits. To our surprise, there weren't
8 very many in either group. Does that answer
9 your question?
10 DR. EWALD: Yes. That's what I
11 assumed, that they just probably got admitted
12 to the hospital and counted it as
13 hospitalizations.
14 DR. BOURGE: Right.
15 DR. EWALD: I think I want to just
16 go back one more time to I think a question
17 that I asked earlier. I think that you have
18 shown us some data about how the trend in
19 pressure goes up before a hospitalization
20 event. Those absolute changes in pressure are
21 fairly small in RV pressure on the order of
22 three or four millimes of mercury.

1 And so I think that that really
2 speaks to the fact that the trend is a very
3 important tool to have if you look at the
4 graphs that you provided us in terms of the
5 trend in pressure going up for a two to
6 three-week period before a hospitalization.
7 I want to get back to kind of then
8 extrapolating this into the real world in that
9 even within this trial, in the post-randomized
10 follow-up period, the number of interrogations
11 by the caregiver, whether it be the physician
12 or nurse practitioner, went down from 5.7 to
13 2.2 when everybody could actually look at the
14 data and manage patients with the -- and these
15 are centers that were invested in using this
16 technology because they're in your study.
17 So I guess my question is, is this
18 really going to hamper the effectiveness of
19 this device, in fact, if we put this out for
20 everybody to use, if it's only being looked at
21 once or twice a month?
22 DR. ZILE: My name is Michael

1 Zile. I'm a consultant for Medtronic. And I
2 receive research support, but I have no
3 financial interest. And I am an investigator
4 in the trial.
5 I wonder if we could show the plot
6 that you were talking about to get us started
7 here. And this is ZI-8, please. Put this
8 slide up, please.
9 This plot actually shows -- and it
10 actually breaks the patients down into those
11 with a heart failure and a decreased ejection
12 fraction, which is the top line in blue and a
13 heart failure and normal ejection fraction.
14 So this is systolic heart failure
15 on top and diastolic heart failure on bottom.
16 Just to show you that across all kinds of
17 heart failure, these trends are the same.
18 So if you look, let's just look at
19 the middle panel because it's easiest to see.
20 You can see that -- and this is RV and
21 diastolic pressure. You can see that these
22 trends go up over time. The important thing

1 is that there is time to see this. In all of
2 these patients sometimes more than a two-week
3 period of teem to be able to identify these
4 patients.
5 Now, you made the point about post
6 the six-month randomization period and that
7 the observations went down from five to two.
8 The transmissions of the data stayed once a
9 week. It was the contact with the patients
10 that went from five to two. So the
11 transmission of the data stayed constant. And
12 the way this would be applied to a patient
13 population is that would be true.
14 And it shows the utility of the
15 device because it means that, rather than
16 having to call the patient once a week, you
17 would have to call the patient only when you
18 see a sustainable increase in this trend.
19 Now, one of the points that has
20 been made is that the control group was a
21 highly intervened control group in the sense
22 of the contact. But I think it's important to

1 put that in context of what we do in the real
2 world and how this could be used.
3 So in the real world, we don't
4 call the patients once a week. And we
5 wouldn't like to call the patients once a
6 week. We would like to call the patients only
7 when necessary. And it's the utility of
8 knowing these pressures and knowing
9 specifically the trends of these pressures
10 which would allow you, as we have seen in the
11 post-six-month, non-randomized follow-up that
12 the clinicians taking care of the patients
13 naturally decrease their contact with the
14 patients to less than half of what it was
15 before.
16 The point of this slide, however,
17 is to show you that there is plenty of time to
18 identify this increase in pressure prior to a
19 hospital event or a heart failure event. And
20 it also shows you that these pressures go up
21 well in advance of symptoms sufficient to put
22 the patient in the hospital.

1 And the third point that this
2 makes is how well that the therapy applied to
3 these patients works and that you can follow
4 immediately the success of your care.
5 A lot of times, even in the
6 hospital, we are unsure. Are we doing enough?
7 Did we diurese them enough? And we are all
8 left with that question. Sometimes we look at
9 BNPs following diuresis and hospitalization.
10 And we are all concerned because the BNPs are
11 maintained at 1,200.
12 But this device would allow you to
13 understand that you return filling pressures
14 exactly back to their pre-symptomatic and
15 pre-event levels and give you that safety
16 margin to knock over diuresis patients, even
17 used in the hospital.
18 DR. EWALD: Thank you.
19 CHAIRPERSON MAISEL: Sure?
20 MEMBER SOMBERG: You say there is
21 more than enough time, but, you know, if you
22 are not looking at it all of the time, you

1 know, you said not even once a week for the
2 diastolic. How many days is that? It's less
3 than seven days for that sort of increment, as
4 opposed to the long increment there? And is
5 there a difference between the two?
6 DR. ZILE: Let me amplify your
7 question because that is a very insightful
8 question. If we go to this slide? Put that
9 up, please. Again, we chose the middle
10 parameter just because it is easier to see and
11 the changes are a little bit more dramatic.
12 If you look at the time line here
13 and suggest that approximately a ten-day
14 period of time might be present in the
15 diastolic heart failure group, where it might
16 be a little bit longer in the systolic heart
17 failure group, you point out a very important
18 point of the care of patients with diastolic
19 heart failure.
20 And you point out that it is
21 possible that in selected patients, either
22 because of their frequency of admission to the

1 hospital or their underlying heart failure
2 cause, it might be that these kinds of
3 patients would be selected for more frequent
4 downloads to the physician's office.
5 But knowing his trend in an
6 individual patient, you would never know that
7 that is really what you needed to do. So with
8 this device in place and with this experience,
9 you would then understand how to individualize
10 care to your patient depending on the kind of
11 slopes that your patient might have.
12 I'm sorry. Did that answer your
13 question?
14 CHAIRPERSON MAISEL: Yes. That
15 was excellent. Thank you.
16 Dr. Brinker?
17 DR. BRINKER: Just a few
18 questions, as everybody else has. It is
19 suggested in the panel pack that this device
20 can do a lot more things that you really
21 expressed in the data. Amongst these are the
22 measurement of temperature and heart rate.

1 Now, other people have tried use temperature
2 for a variety of things, including pacing
3 rate, with plus/minus results and a general
4 consensus that following temperature over a
5 long time is a problem.
6 And I am taking it for granted
7 that you have no designs on your temperature
8 monitoring aspect or if you do, none of it is
9 going to be in this iteration if this is
10 approved.
11 So you can answer that after I ask
12 you this question. On the other hand, heart
13 rate becomes an intriguing issue. And you
14 have beat-to-beat heart rate monitoring. And
15 then theoretically you could detect a
16 significant tachyarrhythmia or a significant
17 bradyarrhythmia.
18 Now, this gets to the other point.
19 Let's assume that you can do that. My
20 understanding from what you have said is that
21 the physician or the heart failure management
22 team goes on the internet to download this

1 information.

2 So it is conceivable that the
3 patient uploads his information on a Monday,
4 it is processed, I assume, almost immediately.
5 You can tell us how long it takes to process
6 that download and put it on the internet. But
7 if it is not looked at until the end of the
8 week, somebody could miss something

9 Now, maybe subtle increases in
10 diastolic pressure may not be so fine an issue
11 except in certain circumstances. But if I
12 knew, for instance, that you could detect
13 severe brachycardia or severe tachycardia, I
14 might want to know that sooner than a week.
15 And one issue here is, is there any way for
16 you to be more proactive in alerting
17 physicians when you find something out of the
18 norm or our affiliate management team.

19 DR. ADAMSON: Excellent questions.
20 And if I could have a slide on, I could
21 illustrate what this device can see when, for
22 example, a patient has a tachyarrythmia as

1 demonstrated by the heart rate plot on the
2 upper part of this panel.
3 This information is displayed on
4 the quick look summary, the first slide or the
5 first screen that comes up on the interaction
6 between the clinician and the internet
7 network.
8 Certainly there are now in
9 development triggers and notification systems
10 that will be applicable for this type of
11 information, not only based on changes that
12 can possibly be detected by pressure changes
13 but certainly in this iteration, there is --
14 and what was used in the COMPASS-FH trial
15 found when the data was interrogated by the
16 clinician.
17 So it is a useful parameter. It
18 certainly measures that. Other iterations
19 down the line may include heart rate
20 variability and other derived measurements
21 from that. But we have the ability to
22 diagnose tachy and bradyarrhythmias and in the

1 future, notification systems for important
2 events, such as what is being developed with
3 defibrillators as well as resynchronization
4 devices.
5 In terms of temperature, I will
6 refer to the Medtronic personnel.
7 DR. STEINHAUS: Yes. The
8 temperature basically was put in there as a
9 pressure measurement. It kind of came for
10 free. And we actually have temperature in
11 there. It is a valid measurement and can be
12 used. Occasionally I guess pneumonia has been
13 picked up in the past. Things like that have
14 been picked up with the temperature.
15 DR. BRINKER: One final question.
16 When you look at all of the medication
17 changes during the randomized period, almost
18 half of them were non-diuretic changes. So
19 that while -- and this is referring to figure
20 18 on page 693 of the panel pack. And while
21 there a couple of, ACE and beta blocker and
22 vasodilator, uses, a little less than half of

1 that is some undefined cardiovascular drug.

2 So I wonder if people aren't using

3 this more than for just diuretic and if so,

4 what are they using it for?

5 DR. STEVENSON: Can I have the

6 slide on, please? We are still looking for

7 the figure that you are exactly referring to.

8 This just summarizes the drug changes in the

9 two groups, the Chronicle and control, during

10 the course of the trial. And certainly the

11 majority of the changes, as we would

12 anticipate, are in diuretics.

13 However, volume status actually

14 dictates how we adjust a number of other

15 medications. For instance, I would not start

16 or up-titrate a beta blocker in somebody whose

17 filling pressures were high. Similarly,

18 someone whose filling pressures are relatively

19 on the low side, that's not the time I would

20 up-titrate an ACE inhibitor.

21 So certainly there are many of the

22 recommended medications that are influenced by

1 volume status. And we would expect them to be
2 influenced by this but not very often compared
3 to the diuretics.
4 DR. BRINKER: So I am still
5 confused. Half of these cardiovascular drug
6 changes were not diuretics, from four to two,
7 right? There are two changes per patient
8 month for diuretics and four for
9 cardiovascular drugs.
10 DR. STEVENSON: We also would
11 count potassium supplementation. Other
12 cardiovascular drugs are going to include
13 statins and --
14 DR. BRINKER: But these aren't
15 made on the basis of --
16 DR. STEVENSON: No. But most of
17 these are going to be diuretics and potassium
18 replacements that are related to heart
19 failure.
20 DR. BRINKER: Okay.
21 CHAIRPERSON MAISEL: Thank you.
22 Dr. Hauptman?