

1 dehydration thought to be due to the maintenance of a
2 medical therapy coupled with the beneficial effects
3 of the device resulting in an over-medication state,
4 if you will.

5 And I'm not going to argue that point at
6 all because that would be a good end point if such
7 occurred, but what I really want to make sure is that
8 one group or the other perhaps had a decreased
9 hospitalization rate because of medication change.

10 DR. SAXON: So patients did have an
11 outpatient follow-up, but it is true that in some
12 patients who have this well-described dramatic
13 dieresis improvement in blood pressure with the onset
14 of resynchronization therapy need to be followed
15 particularly if their medication is not adjusted and,
16 you know, it's very difficult to typically adjust it
17 or know how to adjust it. So I would state that,
18 yes, it is a possibility that a dramatic improvement
19 in the systolic response would cause a marked
20 dieresis that could potentially in some patients lead
21 to an event like that, but I would suggest that the
22 patients were tracked in such a way that that was

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1 probably a very rare occurrence.

2 DR. BRINKER: Just out of curiosity, are
3 you suggesting there should be a caution in the
4 labeling? Are you suggesting that --

5 DR. SAXON: No, I guess I'm responding to
6 your question, could you theoretically develop and I
7 would say, yes, you could. You could -- if you were,
8 for instance, requiring more diuretic dosage, you had
9 an improvement in your clinical condition --

10 DR. BRINKER: We don't have any evidence
11 of that.

12 DR. SAXON: -- there's no data that
13 indicates that that --

14 DR. BOEHMER: Just one piece of data, one
15 piece of data that we do have, we do have ACE
16 inhibitor and Beta Blocker doses over time. The ACE
17 inhibitor doses are in an Alaprol (phonetic)
18 equivalence. If you saw a substantial number of
19 patients with significant volume depletion you would
20 expect two things to occur to them. One is that they
21 would become hypotensive. The second is that they
22 would become asotemic, both reasons that clinicians

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1 will obviously respond by reduction in doses of ACE
2 inhibitors and this is over the 12 months of the
3 trial with every time point, including the one week
4 and one month time point and there's not even a blip.

5 DR. BRISTOW: And so with regard to the
6 Beta Blocker data, the majority of patients were on
7 Carvedilol. It's a lower set of curves. OPT
8 actually has a slightly higher average, daily
9 Carvedilol does throughout the trial. I don't know
10 if that's statistically significant. You can see the
11 absolute difference. And then a minority of patients
12 are on Metoprolol and these are very small numbers
13 as you get out there with OPT in particular, 17 at
14 the end, so there's no consistent change in Beta
15 Blocker dose and baseline Beta Blockers are exactly
16 the same.

17 DR. BRINKER: So what I might have
18 expected is a change if not a decrease in medical
19 therapy in the device group and increase in the drug
20 treatment group and maybe we're missing diuretic
21 therapy.

22 DR. BRISTOW: Well, the idea is there

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1 patients were maximally treated when they were
2 enrolled, background medical therapy. There was
3 nothing else for them to go on that had any proven
4 benefit in heart failure and they were on everything
5 at supposedly the target doses that they should be on
6 and so one answer is, there was no room to maneuver
7 it in an upward direction at least.

8 DR. BRINKER: My experience is there's
9 always room for Jell-O. There's almost always some
10 manipulation that can go on. Maybe that did go on in
11 terms of some diuretic or maybe even in the other
12 group in intravenous therapy.

13 DR. BRISTOW: Perhaps, but, you know,
14 these are chronic heart failure patients taken care
15 of by heart failure physicians, physicians with at
16 least an interest in heart failure and they were well
17 treated coming in and they were well treated
18 throughout the trial.

19 DR. BRINKER: This next question I have
20 is a little bit of a variation of the one I asked you
21 before. And after thinking about it, I might not
22 have asked you the complete question. That is, do

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1 you have difference in hospital burden maybe best
2 described in total days in the hospital in the two
3 different groups rather than admissions and durations
4 averaging?

5 DR. BRISTOW: Total days. Somebody grab
6 that data. I don't think we have it on backup but we
7 do have a text of it. I can tell you the hospital
8 duration of the two groups because I gave it to Dr.
9 Somberg earlier. So the average days in the hospital
10 which is what I gave him, 8.6 days on CRT-D and 10.9
11 on OPT, this is of the hospitalizations, the average
12 days in the hospital. Total number of days -- is
13 that normalized to size of the cohort? Well, that's
14 double so that doesn't mean anything. We don't have
15 the data normalized to the size of the cohort for
16 total number of days.

17 So the best thing I can give you is what
18 I just gave you, the duration of the hospital --

19 DR. BRINKER: Would you agree, however,
20 that a better indication hospitalization burden is
21 the total number of days rather than -- assuming
22 there's a meeting rather than --

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1 DR. BRISTOW: Yeah, I would agree with
2 that within the hospitalization measurement or the
3 hospitalization event by itself, the most sensitive
4 measure is probably the total number of days. One
5 could argue, it should be the total number of days
6 per patient, obviously which we just gave you. On
7 the other hand, remember you've always -- in a trial
8 like this where mortality is being effected by one --
9 by the treatment, you have the issue of competing
10 risk and so if you're an OPT patient and you're dying
11 with a higher incidence, you can't be hospitalized.
12 So that's always an issue in these hospitalization
13 data which in and of themselves or by themselves, I
14 think need to be taken with some caution.

15 DR. BRINKER: My final question is, how
16 many patients left the pharmacologic arm because they
17 developed criteria for a defibrillator. In other
18 words, how many people got a defibrillator alone?

19 DR. BRISTOW: Okay, not many but we'll
20 give you the real number.

21 DR. BRINKER: Two.

22 DR. BRISTOW: Something like that. Two,

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1 okay, yes. That's it.

2 DR. BRINKER: So interestingly, all the
3 other people left for presumably CRT-D.

4 DR. BRISTOW: Uh-huh, right.

5 DR. BRINKER: Okay, thank you.

6 DR. BRISTOW: There were CRTs as well.
7 We'll give you the actual number.

8 DR. BRINKER: That's close enough. I
9 don't want to burden you.

10 DR. BOEHMER: Well, interestingly, there
11 were a substantial number of patients in the OPT
12 group that were withdrawn and not implanted with
13 anything. As you can see here, the total number
14 withdrawn were 80. Thirty-one received CRT-P which
15 was the first device approved in the course of the
16 trial. Eleven received CRT-D and two received an
17 ICD, giving you a total of 44. About half the
18 patients withdrawn did not receive anything.

19 ACTING CHAIR LASKEY: Well, then where
20 did they go? Did they just die?

21 DR. BOEHMER: It's, I suppose, a common
22 circumstance in a clinical trial that the group not

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1 doing quite as well ends up either withdrawing or
2 stopping therapy at a higher rate, so those might be
3 explained in that regard. Not everyone was withdrawn
4 to receive the device. That's the important part.
5 It might be -- you know, in centers such as mine,
6 people travel a long distance to come see me and if
7 they ended up in a control group and the ride kept
8 getting longer and longer and the winters kept
9 getting smellier, they may not come the next time and
10 withdraw consent.

11 DR. BRISTOW: But to answer your
12 question, some were end pointed. We showed some data
13 about the number of end points we got out of the
14 withdrawn patients. Some were not end pointed and we
15 were able to follow them till December 1, 2002 and
16 others we could not ascertain, so it was sort of a
17 mixed bag in terms of what happened to them.

18 ACTING CHAIR LASKEY: Good. Thank you.
19 Dr. Normand.

20 DR. NORMAND: Okay, I have a few detail-
21 oriented questions and then some general questions.
22 And so the first question I have has got to do with -

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1 - and I know I'm going back to the beginning but
2 inclusion and exclusion criteria and I just am not
3 understanding something and it's probably pretty
4 obvious and that is I think people had to be
5 hospitalized for heart failure within the previous 12
6 months was an inclusion criteria.

7 DR. BRISTOW: Right.

8 DR. NORMAND: But then the exclusion
9 criteria said you couldn't be hospitalized in 30 days
10 prior to enrollment.

11 DR. BRISTOW: Right.

12 DR. NORMAND: So it's really within 11
13 months.

14 DR. BRISTOW: So the concept here is we
15 want the previous heart failure hospitalization
16 because that -- we know that that's associated with a
17 higher event rate mortality and subsequent heart
18 failure hospitalization, so that's the reason for
19 that. But we didn't want unstable patients. We
20 thought that would be a risk for device implantation.

21 DR. NORMAND: Okay. Now, I have a
22 question about the randomization by center. At one

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1 point there's a number of 128 centers and then it
2 goes down to 116 centers. The difference are centers
3 that never recruited anybody?

4 DR. BRISTOW: Yes, let me get some help
5 with that from someone, Dave or Fred or somebody, the
6 12 differential here. These are centers, I think,
7 that did not finish in -- as active centers, but let
8 me get confirmation of that. Sorry, with the slow
9 kinetics here. This is a question we had not
10 anticipated, as you can see.

11 DR. NORMAND: I might have a few more
12 about the centers, so keep the binder open.

13 DR. BRISTOW: We'll keep working on that.
14 Why don't we ask another question?

15 DR. NORMAND: Okay, the second question,
16 unfortunately is related to the centers and that is,
17 I believe in the FDA -- maybe the FDA can answer this
18 one, though. The FDA indicated that several of the
19 centers only randomized to one arm -- one of the
20 treatment, either just pharmacy or medical therapy or
21 not. I just want to understand why was that the
22 case. Is it the case that the centers only had a

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1 accrued one person?

2 DR. BRISTOW: Yeah. Yes, in some --
3 yeah, I think generally very small numbers of
4 patients and so the blocks that they had didn't allow
5 enrollment in the two groups. They didn't get to
6 those assignments.

7 DR. NORMAND: So it's 12 centers and four
8 centers, 16 centers in total. I just want to make
9 sure that indeed that's the reason. The numbers were
10 so small and hence, they couldn't be randomized.

11 DR. BRISTOW: Right.

12 DR. NORMAND: They were stuck in one
13 group.

14 DR. BRISTOW: Right.

15 DR. NORMAND: Okay, I didn't see any of
16 this data so --

17 DR. BRISTOW: Which is common -- which is
18 common in clinical trials to have these low
19 enrollment centers and that's what happens.

20 DR. NORMAND: Okay. I just wanted to go
21 a little bit over the blinding and the collecting --
22 do you have an answer?

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1 DR. FELDMAN: Yeah, 116 centers had an
2 OPT patient and so the others had a non-OPT patient,
3 either a CRT-D or a CRT-P.

4 DR. KRASNICKA: OPT plus CRT-D, 116
5 patients.

6 DR. NORMAND: Okay, and so the remainder
7 were on the other --

8 DR. FELDMAN: Were on the CRT-P, that's
9 what that is, okay.

10 DR. NORMAND: Okay. It's just nice to
11 know. I didn't know what happened with the data,
12 that's all. I have a question about blinding. This
13 relates to collecting data after the patients
14 withdrew from the study and I do want to echo the
15 comment that I think this is an extraordinarily good
16 thing that was done on behalf of the sponsor and that
17 is to collect data from patients that withdraw. The
18 intention to analysis is only unbiased under certain
19 conditions and when you have missing data, it's
20 biased. So I'm pleased that that was done.

21 However, I do have some questions
22 regarding how the data were collected given that

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1 there was no blinding, I think of certainly the
2 deficient participants and the --

3 DR. BRISTOW: Investigators and study
4 coordinators were unblinded. This is an unblinded
5 trial and that's one of the big factors, obviously,
6 creating this differential withdrawal.

7 DR. NORMAND: So, again, how were the --
8 so in terms of the CRF form, for example, when you're
9 going back to the patients that withdraw from the
10 study, obviously they knew which ones were in which
11 arm, and so I had heard a discussion a little bit
12 earlier, I don't remember who asked the question, but
13 it had to do with some hospitalizations and things
14 such as that. So that was the information that
15 somebody went into the medical record, collected that
16 information that was verified to say, indeed, they
17 didn't have a hospitalization.

18 DR. BRISTOW: Right, so again, the same
19 policies were followed. The patients that were
20 withdrawn and then data harvesting was accomplished,
21 there had to be source documentation. Every attempt
22 was made to get at the source of -- the verifiable

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1 source. All the data were assembled in a dossier for
2 each patient, reviewed by that adjudication
3 committee. The adjudication committee had sort of
4 pseudo-blinding as Dr. Carson talked about. Of
5 course, the coordinators and investigators were
6 unblinded but they had equipoise from the standpoint
7 of the trial presumably.

8 We had no idea which -- what was going to
9 happen in this trial and the idea was to go get all
10 the data in a very even-handed way.

11 DR. NORMAND: And I'm a little bit
12 surprised in the descriptive statistics, the base
13 link characteristics that there were no missing data.

14 It's -- I'm happy for you. I just wanted to make
15 sure that, indeed, was the case, that there were no -
16 - it was fully collected, that there wasn't a default
17 to note or anything, that that was --

18 DR. BRISTOW: Dr. DeMets, do you want to
19 comment on this or anyone? I guess we can apologize
20 for having too complete a data set, perhaps. I don't
21 know what to say about that.

22 DR. DeMETS: I don't have the data in

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1 front of me, but clearly -- I mean I wouldn't say
2 that every variable of a cast of thousands that were
3 collected, that they're all filled out completely but
4 for the key end points, key as in baseline variables,
5 I think that's correct. We had it all. So the
6 information in the baseline case report forms, we got
7 100 percent of them.

8 DR. NORMAND: It's all right. There's no
9 need to apologize. I was just trying to figure out
10 if that was --

11 DR. DeMETS: I understand. I mean, a
12 variable may not be, but the forms are there.

13 DR. NORMAND: I know. I'm going to start
14 with more questions regarding the hospitalization
15 again and the mortality analysis. And I think I'd
16 like to characterize my understanding of the FDA's
17 analysis and if I could, I'm going to give my
18 interpretation to the panel and I want the FDA to
19 correct me or say that's not really what you're
20 saying or that's what you're saying. So my
21 understanding is the following. That in terms of the
22 primary end point there is a concern that the

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1 assumptions for the Cox model are not met and what
2 that would imply seems to me would be that there was
3 a crossing of the curves and so that if you declared
4 that one therapy was better than another. That
5 wouldn't be true. It would be true on average but it
6 wouldn't be true at all points in time. Is that the
7 FDA's position? Yes.

8 Now, I realize you're -- you know, with
9 the data set it's very difficult to say it's clearly
10 violated or not clearly violated. I'm at the point
11 where I'm confused now because if it is violated,
12 then I don't believe the analysis at the end of the
13 day. I believe the average -- on average, it may
14 have been beneficial but -- so the question is really
15 for the FDA right now. In terms of if we agree that
16 the hazards do cross, then it's not proportional,
17 then I'm not sure what to conclude at the end of the
18 day. So somehow I feel it's really important to know
19 whether or not the assumptions were violated.

20 In your notes you're saying it may be
21 violated. Do you have any more information on that?

22 DR. KRASNICKA: Based on the hazard

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1 functions I think the hazard -- the proportional
2 assumption is not true. And when I look at -- I
3 tried to analyze this data from a different point of
4 view and I notice that this data has a lot of noise,
5 so it's difficult to analyze during a very short
6 time.

7 DR. NORMAND: I didn't hear the last
8 word. A lot of knots it sounded like.

9 DR. KRASNICKA: Noise.

10 DR. NORMAND: Noise, I thought --

11 DR. KRASNICKA: Noise.

12 DR. SOMBERG: What noise can there be?
13 They're deaths or they're not deaths? Are you saying
14 that they were reported one says death and one says
15 not a death?

16 DR. KRASNICKA: No. From -- when I
17 adjust for the baseline and I look what is going on
18 with treatment, with treatment estimation,
19 coefficients, I notice that it's changing sign from
20 minus to plus, so I don't believe that the
21 proportionality hazard assumption is true.

22 DR. NORMAND: So how do you feel about

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1 the Kaplan-Meier analysis then?

2 DR. KRASNICKA: Because of the important
3 assumption not for censoring, I have problem with
4 Kaplan-Meier.

5 DR. NORMAND: I'm wondering if perhaps,
6 Professor DeMets could say a few words about this as
7 well. Again, the reason why I'm struggling a little
8 bit about it is that for something where, you know,
9 the Log ranks an average and on average I'd like to
10 know sort of at what time -- over what time frame is
11 there a benefit if, indeed, there's a question about
12 things changing.

13 DR. DeMETS: Thank you. Well, let me try
14 to summarize some of these issues. As I tried to
15 point out this morning, let's examine the four --
16 three or four analyses. First of all, the Kaplan-
17 Meier makes no assumptions about proportionality.
18 It's totally parametric/non-parametric. It makes no
19 assumption about non-informative censoring. But the
20 way you address that and the only way I know to
21 address that is to get all the data and we tried very
22 hard to do that and I think came very close.

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1 So the Kaplan-Meier analysis is not in
2 question at all. Two, the log rank test which is
3 used to compare those two Kaplan-Meier curves also
4 makes no assumption about proportionality appendix.
5 Not from the very beginning did Mantel and Haenzel
6 develop that test. And again, it's documented in
7 here. So it's not a requirement. Yes, there's some
8 optimality principles if you have proportional
9 hazards.

10 As a footnote, I would say that the
11 Wilcoxin and the log rank test are members of the
12 same log rank family, just that the weight is
13 different, so whatever assumptions are true for one
14 are true for the other in terms of those kind of
15 assumptions. But at any rate, so as far as I'm
16 concerned, the log rank test is not in question,
17 again, with the issue of -- from the censoring which
18 we've addressed by getting all the data. Those two
19 statements are not my opinion, those are mathematical
20 facts.

21 Where we have some judgment here as to
22 whether or not the methods that purport from hazard

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1 Cox model fits and if you want to bring up backup
2 slide 71, say, which was shown with the shown failure
3 residuals. Now this is a complicated technical
4 matter, I recognize, for non-statistical colleagues,
5 but what's plotted there, the residuals, and their
6 confidence levels, you'll notice the dotted lines of
7 the confidence levels, that they, in fact, include
8 the linear straight line. So you cannot reject the
9 hypothesis that these fit. As a matter of fact,
10 that's what Dr. Lawrence did.

11 If you correlate the residuals with time,
12 you get, you know, P values that are not significant,
13 right? So it would be a tough argument to say -- to
14 reject that. You can say, well, of course, it's not
15 a perfectly straight line. But more important than
16 all of that is the reason you keep seeing the Cox
17 model used over and over again for the past 30 years,
18 it's a very robust method of analysis. You can
19 violate assumptions dramatically and it's still a
20 pretty trusted tool. That's why we keep using it in
21 trial and trial. But I would say that from my
22 opinion and from my colleagues at Wisconsin and Dr.

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1 Lawrence, is that these assumptions are not violated.

2

3 So the first analyses there's no
4 question. The third one, we could discuss that but I
5 don't, from my perspective and experience and my
6 colleagues, it's just not a statistical issue. Now,
7 the withdrawal issue is common to all of these
8 methods if you assume non-informing censoring. And I
9 was not happy when we got to the point of November of
10 2002 that we had this many withdrawals because you
11 know, it's hard to argue definitively when you have
12 that many.

13 So we went and tried to minimize that and
14 you've acknowledged that. So that's the solution for
15 that but that's common to all the issues. And you
16 try, very hard, of course, to get every observation.

17 We didn't quite make that but I think the important
18 part for me, to my satisfaction was on the CRT-D arm
19 and we wound up with four missing on the primary end
20 point and six, I think on the morality.

21 As a comment I would say, you know, when
22 we stopped the trial when it came to its termination

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1 point, at that point in time and with the updated
2 data, if you analyze the data censoring anybody at
3 withdrawal because you don't take into account any of
4 the withdrawal data, you still have a significant
5 result. Now, I don't like that analysis because I
6 argue that it doesn't take into account the
7 informative censoring, but if you looked at that, you
8 still have significance. And then one final point is
9 that if you look at the core rates that have been
10 listed, no, there's nothing significant but you could
11 say, well, maybe it's loaded somehow in one sense or
12 the other. So we typically do multi-variable
13 analysis and so in this case. The two risk factors
14 that stick with you in such analysis are New York
15 Allergy and the New York Heart Class.

16 In the presence of those and in the
17 presence of all the other cohorts, the treatment
18 effect is still significant and that's in your
19 packet. It would take me awhile to tell you exactly
20 which page but it's in there.

21 DR. NORMAND: No, I --

22 DR. DeMETS: So we've done, we think our

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1 standard conventional due diligence analysis to
2 address the issues that have been discussed
3 throughout the morning. Thank you.

4 DR. NORMAND: Thank you. I was wondering
5 if the sponsor could tell me what percent of
6 hospitalizations occur on the same calendar day or at
7 least CHF admissions, I mean admissions and
8 discharges, like a one-day hospitalization.

9 DR. CARSON: Yeah, you're talking about a
10 single calendar day change.

11 DR. NORMAND: No, I'm asking how many --
12 what -- does anybody know -- you could do all
13 hospitalizations or maybe you just want to do -- so
14 all hospitalizations for adults that a patient is
15 admitted and discharged on the same date, does
16 anybody know that number? You don't know it, because
17 you could find that number.

18 DR. BRISTOW: We did not track that
19 number. You had to have a calendar date change to
20 get a case report form to get adjudicated.

21 DR. NORMAND: I realize in your trial but
22 did you look anywhere else for that so we could

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1 ballpark sort of how many -- you don't have that --

2 DR. BRISTOW: I don't think we have any
3 information on that. Our personal experience, John
4 may want to weigh in, you know, it's not a very large
5 number, probably less than 10 percent but John you
6 might comment on that.

7 DR. BOEHMER: Yeah, as previously
8 mentioned, a hospital admission, at least just about
9 any payor is a hospital of at least 23 hours duration
10 and you can write admission orders. What you're
11 doing is observing a patient and historically, what
12 we try to do in clinical trials is distinguish ER
13 visits from hospitalizations from unanticipated
14 doctors' visits and that's where this evolution of
15 the 24-hour or greater than 23-hour definition came
16 from.

17 Less than 23 hours is, indeed, not a
18 hospitalization. You can write admission orders and
19 you get paid for an observation eventually, and it's
20 very confusing to then distinguish, well, was he
21 really admitted or was he just in the ER? Did he get
22 to a hospital bed or was he discharged before he was

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1 admitted? This was an observation, this was -- when
2 you're in the hospital for a full day, you were
3 admitted to the hospital and we took things that the
4 center said was an admission, everyone at the center
5 said was an admission and lasted over a calendar day,
6 which just about any payor, I believe, to pay for an
7 admission and I'm sure Medicare would say that that's
8 a hospitalization. So that was the evolution of it
9 and from a practical sense, you know, you could write
10 admit and discharge in the morning or in the
11 afternoon. You don't get paid for a hospitalization
12 and it's not the same thing. It's the same as an ER
13 visit and it becomes very confusing in a clinical
14 trial to distinguish those two.

15 We got everything that was a
16 hospitalization admission, a hospitalization of any
17 sort that lasted over a calendar day change.

18 DR. STEINBERG: If I may just add one
19 thing. We may have one piece of information that
20 addresses your question. I'm Jonathan Steinberg.
21 I'm one of the M & M committee members and am a
22 consultant for Guidant. The IV inotrope more than

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1 four hours was an end point that was often met in the
2 emergency room. Patients might come in and then go
3 home the same day. And so we did track that specific
4 end point in the trial and that was actually a very
5 small number of end points, in particular, a very
6 tiny fraction of the total hospitalization numbers.

7 DR. CARSON: If I can just make one more
8 comment to make you sorry you asked, but the --

9 DR. NORMAND: I am sorry I asked.

10 DR. CARSON: You're right. The only
11 trial that has ever had at least a statistic that I
12 could find out on this was the Overture trial. The
13 people running the Overture trial became concerned
14 because this issue arose during the hearing with the
15 Cardiorenal panel in 2001 on VALHeft. They looked at
16 all the data they collected that was one hospital day
17 or less and they found out for heart failure
18 hospitalizations at least, that was seven percent of
19 the total heart failure hospitalizations. But that
20 is one day or less. So therefore, whatever number
21 we're talking about I would think would have to be
22 considerably less than that.

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1 DR. NORMAND: And I guess I just wanted
2 to understand when the case report forms were
3 developed, the reason why I ask this, it's got to do
4 with the fact that you indicated that greater than
5 four hours was -- you know, there's a separate form
6 on the body of questions on the form for that, yet,
7 for defining a hospitalization, there was just a
8 date. It's the last question for me about this --
9 but when was that developed. Why wasn't a sort of
10 admit time and discharge -- because we do this all
11 the time in terms of -- so when was the case report
12 form, was that made in the absence of coordination
13 with --

14 DR. BRISTOW: Well, the case report form,
15 the C2R need to weigh in potentially on this but so
16 CRO, develop the case report forms, they were looked
17 at by everybody. I think this probably is something
18 that slipped through the cracks. Realizing though,
19 that even if you had it on there, you're not going to
20 get that filled in necessarily -- you're not going to
21 get it filled in until you do a lot of digging. The
22 coordinator -- this is not information that's readily

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1 available to the coordinator.

2 DR. NORMAND: I understand. So what
3 doesn't get filled in? I just didn't hear you.

4 DR. BRISTOW: The dates. The date of
5 admission might be but, you know, precise time of
6 discharge with an issue is 26 versus 23 hours and so
7 forth. I mean, that's going to be -- we're going to
8 have to go digging for that. It was not on the
9 original form. That's the issue. Somebody could
10 provide a little more color on that from the group.

11 DR. BOEHMER: This had to be filled out
12 under two circumstances. One is when the research
13 staff became aware that such an event did occur but
14 if the patient came in for the routine follow-up
15 visit every three months, they were asked if they
16 received intravenous medicines in the hospital over a
17 four hour period. It's a follow-up form, a regular
18 follow-up form, so along with, "Were you in the
19 hospital, did anything else bad happen to you", et
20 cetera, et cetera, et cetera, this was tracked.

21 DR. BRISTOW: So the real answer is that
22 the original case report forms had the dates, did not

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1 have the time.

2 DR. NORMAND: So it never had the times.

3 DR. BRISTOW: It never had the time and
4 that just -- and so, you know, that wouldn't be an
5 issue unless it's a matter of 23 versus 26 or
6 whatever and that just wasn't on there. And so they
7 couldn't -- basically, the adjudication committee
8 could not deal with this.

9 DR. NORMAND: If it's not there, you
10 can't make it up. Okay, thank you.

11 ACTING CHAIR LASKEY: Which is amazing,
12 because if we don't date and time our notes and
13 orders now, we go to prison. So I just find that
14 kind of ironic. I just had one question/way of
15 departing from this statistical discussion and moving
16 it more towards the clinical realm. While we
17 understand or we hope we understand that the log rank
18 analysis, Kaplan-Meier curves represents an overall
19 on average kind of measure of the difference of the
20 area under the curve, oncologists looked at this data
21 in another way which is just the difference in days
22 to first event.

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1 Can you -- I'm finding it hard to just
2 read the small print because the plots are so small,
3 but what is the median difference in days from first
4 event to your primary end point?

5 DR. DeMETS: I don't know if we have a
6 backup slide for that but I calculated it and for the
7 OPT arm it's 209 days and for the CRT-D device it's
8 269 or 270 days, something like that, 209 versus 269
9 or 270. Now, for mortality, you can't compute that
10 statistic because --

11 ACTING CHAIR LASKEY: No, right.

12 DR. DeMETS: Right, the primary as we've
13 presented it.

14 ACTING CHAIR LASKEY: Sixty day's
15 difference.

16 DR. DeMETS: Yes.

17 ACTING CHAIR LASKEY: For the average
18 patient.

19 DR. DeMETS: Right.

20 ACTING CHAIR LASKEY: Thank you. Dr.
21 Krucoff?

22 DR. KRUCOFF: I guess it's pretty clear

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1 that what we're wrestling with here is an ambiguous
2 data set from an experienced, obviously dedicated
3 group where it's raised a lot of concerns. And I
4 guess I break this out into three aspects of what
5 about the ambiguities in the data really matter
6 versus what don't, and hopefully, that will move us a
7 little bit toward a conclusion.

8 I think one level is just whether the
9 definition changes and the process changes that
10 occurred over the time line of this trial were driven
11 by quality concerns, which I think we've heard
12 expressed from the sponsor group pretty clearly. If
13 you find out, oops, we've got a case report form that
14 actually doesn't give us time of day and our primary
15 end point as defined by time of day, how can we get a
16 higher quality definition of that end point? We
17 don't perceive it as substantial. We think it could
18 be more active, more dependable. That, to me, is
19 sort of a steering process toward a higher quality
20 intention.

21 But the flip side of that is anywhere
22 that that opens the door to bias or to a shift or a

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1 change of definition of the primary end point along
2 the way, that makes the data actually less
3 interpretable or how much bias gets involved in the
4 data less interpretable, that's where we're at least
5 from my perspective, getting ready to tear our hair
6 out here because there really obviously is both.

7 So let me ask. I asked the sponsor and
8 Dr. Proestel from FDA if I could ask you, I guess one
9 of the things that I would like you guys to comment
10 on is are you all aware of any suggestion at any
11 point along the way that these definition changes
12 were actually driven by awareness of the data
13 enrolled to the point prior to that change as opposed
14 to changes in the landscape as we've heard discussed.

15 Are you all at any level aware of any communication
16 of actual data from the trial that might have overtly
17 influenced these definitions?

18 DR. PROESTEL: No.

19 DR. KRUCOFF: Okay, and I think we
20 already heard from the sponsor, the chain of
21 communications to my question earlier. I think the
22 other two levels then that I go to with ambiguous

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1 data is how much do the definition changes erode just
2 the certainty level as to how certain can we be the
3 conclusions are free of bias and likely to be
4 reflective of practice after a device is out in the
5 market versus how or whether or when any of the
6 changes of assumptions here actually change the
7 interpretation, change the conclusions?

8 So for instance, we've talked a lot about
9 the withdrawals. The one assumption that was
10 interesting to me because it appeared so frequently
11 in the panel pack that the withdrawals were because
12 the OPT patients were getting sick and needed a
13 device so they pulled out of the trial so they could
14 go get a device. The fascinating part to me is that
15 actually bias against the device. So let me come and
16 I have to thank Sharon-Lise for doing a lot of my
17 work and it's going to make my part much shorter, but
18 let me ask whether the reverse may actually be true
19 or whether there is any sense that patients in the
20 medical group who are healthier might have been
21 pulled out to go get a device.

22 So I think we've got the FDA's comments,

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1 so I'm going to ask the investigators or the sponsor
2 team, do you all have an impression as to what drove
3 the withdrawal and whether it was relative in any way
4 to the level of illness in the patient population in
5 the OPT group?

6 DR. BRISTOW: Yeah, I think we all think
7 it was linked to patients worsening with heart
8 failure and the investigator and the patient because
9 it's an unblinded trial lobbying for device
10 implantation. It certainly would not track in our
11 experience of doing well.

12 DR. BOEHMER: And we did look at the
13 baseline characteristics of the patients who withdrew
14 versus those who didn't and they were identical in
15 any way.

16 DR. BRISTOW: But that's baseline. It
17 doesn't speak to what's happening during the trial.

18 DR. KRUCOFF: Right, at the point they
19 withdrew -- we don't happen to have any data about
20 the level of illness or whether they had changed from
21 their baseline interval to --

22 DR. BRISTOW: No, we do not.

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1 DR. KRUCOFF: -- a three or a four or
2 anything like that at the time they actually
3 withdrew.

4 DR. BRISTOW: Not that I'm aware of.

5 DR. BOEHMER: As Dr. Bristow pointed out
6 this morning, the data in the preliminary analysis
7 before the patients who withdrew were obtained, was
8 qualitatively identical to the data set when it was
9 more complete.

10 DR. KRUCOFF: Okay, so then as far as I
11 can tell, most of the other concerns about
12 assumptions that might actually change the conclusion
13 from this set of data are work that hasn't been done,
14 which, you know, I can tell you from my perspective
15 this is something I'm really sorry to hear that from
16 both sides, from -- you know, you've clearly got the
17 fire power on the sponsor's side as FDA to address
18 some of these questions. If we have an enrollment
19 profile that has a higher instance of Class IV heart
20 failure and ischemic heart disease in the OPT
21 patients, where is the analysis that corrects for
22 that? Where is the analysis that we can look at

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1 that? If you have it that would be great.

2 DR. BRISTOW: We did -- Dr. DeMets just
3 mentioned that analysis.

4 DR. KRUCOFF: I mean, I've heard -- do
5 you actually have it here?

6 DR. BRISTOW: Yeah.

7 DR. KRUCOFF: Can we see it?

8 DR. BRISTOW: Sure. Can we get it up?
9 It's in the packet.

10 DR. KRUCOFF: I will apologize, I missed
11 that.

12 DR. BRISTOW: But the punch line is that,
13 Dave, you might want to give the real data, but --

14 DR. KRUCOFF: Okay, is it --

15 DR. BRISTOW: -- etiology and Class III
16 and IV made it through a unvaried analysis as did
17 treatment effect, and treatment effect survived the
18 multi-varied analysis with those factors in.

19 DR. KRUCOFF: For the primary end point
20 or for mortality?

21 DR. BRISTOW: Okay, it's green Tab 5-3,
22 sub-tab E, let's open it up.

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1 DR. KRUCOFF: I'm sorry, one more time,
2 green --

3 DR. BRISTOW: Sorry, that was a
4 misdirection, one second. All right, so go ahead and
5 say what it is.

6 MR. ECKLAND: It would be on green tab 5,
7 subtab 4, section B, page 4.

8 DR. KRUCOFF: Five, 4B?

9 DR. BRISTOW: Now, is this memory end
10 point or is this -- so that's the survival analysis.

11 DR. NORMAND: Table 6.

12 DR. BRISTOW: Table 6 is the survival
13 analysis and it's just as I said.

14 DR. KRUCOFF: I'm in 5.

15 DR. BRISTOW: So on multi-varied
16 analysis, we've got New York Heart Class, ischemic,
17 non-ischemic and treatment making it through
18 statistically significant.

19 DR. KRUCOFF: Okay, that's primary end
20 point. Was this done for mortality? Thank you. I
21 just overlooked that. I mean, to me these are
22 probably the most important things to -- if we have

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1 possible ranges of assumptions, there's more than
2 enough statistical power to begin to look at.

3 DR. BRISTOW: Yeah.

4 DR. KRUCOFF: Do these assumptions
5 actually change the interpretation of an outcome and
6 we have two ranges of outcome here. There's
7 mortality which I don't think anybody here has any
8 trouble with, and then there's the primary end point
9 which is trying to get the simple trial concept of
10 "all-cause" mortality and hospitalization and for
11 whatever purposes, quality or other, what's made it
12 not so simple is that the definition evolved over
13 time.

14 DR. BRISTOW: Yeah, exactly.

15 DR. KRUCOFF: And I think the key
16 question in my mind is, is that a fatal problem or is
17 it just sort of an annoying problem but there is, in
18 fact, enough information to separate out those two.

19 Let me shift, in fact, David, while
20 you're there, one of the things that I was also -- do
21 you want to take your book back -- led to is the
22 impact on the Kaplan-Meier curves which again, from -

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1 - in the slides I have quickest reference to from the
2 FDA presentation but on mortality, where around the
3 300-day range there's sort of the best separation and
4 then the curve sort of tail together again, and in
5 part, I think that's pretty clearly that there are
6 probably smaller numbers and where the slide that, in
7 their presentation, is eight pictures later or where
8 the confidence intervals between the treatment arms
9 begin to overlap and actually sort of bump into each
10 other a little earlier, do you all have a sense of
11 whether that's because of the lower numbers of
12 patients who are followed up to that level or because
13 there's really a difference in behavior and one of
14 the behaviors, of course, physiologically, we worry
15 about with anything that stimulates the ventricle in
16 heart failure is are you stimulating it for the good
17 or are you stimulating it as a setup to later
18 mortality. So can you --

19 DR. DeMETS: Let me comment on those two.
20 First, I pointed to the "all-cause" mortality
21 figure. You can tell by -- I mean, your eye always
22 seems to drift to the right but you can tell from

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1 those curves, that the side, the jumps, the steps, if
2 you will, on those Kaplan-Meier curves, what that
3 tells me and if you look at the tables which are
4 behind those graphs, that the number of patients at
5 risk that file out is small, so a single event will
6 make a major step. So you know, perhaps we should
7 stop graphing all of them but then that doesn't feel
8 comfortable either.

9 So we have to train ourselves to sort of,
10 you know, look at the entirety and not look at the
11 right-hand side. The log rank test, of course, and
12 any -- we had ranked statistic, tries to encompass
13 the entire survival curve and the differences there
14 and various tests, you know, will weigh things
15 differently. The log rank is a standard that one
16 would use almost always. The corollary to your
17 question is that because of the number of events and
18 the number of patients at risk declining with time as
19 it must in any stated entry real life trial. The
20 formula for the stated error of the Kaplan-Meier
21 curve guarantees that levels are going to get bigger
22 with time because there's less information. So

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1 that's kind of intuitive.

2 You know, the reason -- I mean, the
3 Kaplan-Meier paper was published in 1958 as the way
4 to analyze time to event but it was not satisfactory
5 because we were left with this point by point
6 comparison. So it's Y. Mantel in 1966 with Haenzel
7 proposed the log rank test and, you know, weeks,
8 later literally again proposed the Wilcoxin test is
9 because nobody was happy with this point by point
10 comparison.

11 Since then, we have advanced a field a
12 lot in terms of mathematics but not really much in
13 concept. We're still using weighted rank tests.
14 We've gotten fancier but what the weight should be et
15 cetera, et cetera. But you're absolutely right, that
16 is that the variability of the standard gets bigger
17 with time. It must be so unless you have all
18 patients in day one and follow them all till two
19 years. Then the variability would be much tighter,
20 but that's not the way clinical trials happen. So
21 that part just happens, but it is tempting. Our eye
22 just tracks that way but you have to remind yourself

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1 the number of events is small, the standard of error
2 is large and the best comparison that we know if in
3 fact, is the log rank test or weighted rank test in
4 general but the log rank test is the one that we all
5 are familiar with and use because of its properties.

6
7 DR. KRUCOFF: Thanks. So I mean, from my
8 perspective, one suggestion to the sponsor group that
9 would be helpful would be to do the one thing as was
10 done in the effort to get the data on patients who
11 were withdrawn to at least for mortality, to continue
12 to follow these folks so that at least the basis for
13 the data available might make clearer where the reach
14 of those boundaries actually lies since at this point
15 some of that is just plain going to be vague.

16 DR. BRISTOW: I might point out one
17 thing. In ultra-advanced heart failure the curves
18 usually come back together, i.e., rematch, i.e.
19 CONSENSUS I, i.e. a trial we just finished; good
20 treatment effect and then come back together. So you
21 don't -- you know, you delay things and so forth but
22 in a really sick population, ultimately curves are

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1 going to come together.

2 DR. KRUCOFF: Agree, everybody dies. On
3 the other hand, I think in a device which is driving
4 the ventricle, I think to at least adopt some sort of
5 follow-up point where we might actually see the whole
6 cohort at some sort of time would be a reassuring
7 piece of information.

8 DR. BRISTOW: Sure.

9 DR. KRUCOFF: Okay, the last thing that I
10 wanted to touch on is -- which to me is a very
11 critical piece that I am scratching my head over is,
12 what is the defibrillator really doing here, because
13 we already know that the biventricular
14 resynchronization therapy makes patients walk a
15 better six minutes, changes their heart failure
16 class, makes them feel better and if we go to the
17 litany of an outcomes end point from a patient's
18 perspective, is what do patients want as two-thirds
19 was said this morning, to live longer and to feel
20 better, the third part that we usually include is
21 and to avoid unpleasant experiences. So in putting
22 in a device, the shift here obviously, is from -- as

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1 was specifically mentioned right after lunch -- is to
2 a patient cohort in who a defibrillator might not
3 previously have been considered indicated.

4 Now, we're already all dealing with
5 particularly an ischemic low rejection faction.
6 Could you make a case that actually all these
7 patients already have an indication for a
8 defibrillator, in which case why do you need to drop
9 that from the indications for use if on a MADIT II
10 basis, you know, these patients all could be
11 considered to already deserve a defibrillator. You
12 don't need to fight this battle quite the same way.
13 But I really am concerned that a lot of the data --
14 and again, putting aside all the issues of what's a
15 hospitalization and what's a rehospitalization,
16 really imply in terms of counting toward the
17 hospitalizations from the patient's perspective.

18 To come back for a lead revision, to have
19 a three-hour procedure instead of a one-hour
20 procedure, from a patient's perspective, this is all
21 felling better and/or avoiding unpleasant
22 experiences. And what is the value of the

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1 defibrillator to me is the least discussed point of
2 the day and to me one of the most important issues.

3 DR. BRISTOW: Right. I think this is --
4 we have a reasonable answer to this. I don't know if
5 it's still accepted or not but basically the value is
6 you reduce sudden death and so you add that to the
7 pump failure death reduction and you get these
8 survival curves where you get an increment of
9 additional benefit which is now robust enough to be
10 statistically significant. And so this becomes, in
11 my mind, a discussion between the doctor and the
12 patient. How important it is to seek out an
13 additional survival benefit, vis-a-vis, a more
14 complicated device, vis-a-vis getting shocked once in
15 awhile maybe. These are all discussions that have to
16 occur.

17 If the only issue is quality of life,
18 you're absolutely right. The CRT-P device does all
19 of that.

20 DR. KRUCOFF: Well, we really don't know
21 whether just CRT therapy -- we do know CRT therapy
22 makes patients feel better. What we actually don't

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1 know at least from the approval-based data is whether
2 it makes them live longer.

3 DR. BRISTOW: Well, there's a survival
4 curve in CRT-P. It's not statistically significant
5 but it's a 24 percent reduction in "all-cause"
6 mortality.

7 DR. KRUCOFF: Right, and you know, for
8 better or for worse, this study design was really not
9 set up to address the question of incremental
10 benefits of --

11 DR. BRISTOW: Differences between the
12 devices, right.

13 DR. KRUCOFF: -- the defibrillator over
14 the biventricular resynchronization.

15 DR. BRISTOW: Right.

16 DR. KRUCOFF: So I guess my other
17 question is, can -- do you all have any data you can
18 share with us on the incremental morbidity procedure
19 duration time, technical complications associated
20 with the defibrillator platform --

21 DR. BRISTOW: Yes.

22 DR. KRUCOFF: -- because a lot of them

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1 have been put in or were put in in the initial stage
2 compared --

3 DR. BRISTOW: So here we are with --

4 DR. KRUCOFF: -- to just the CRT-P group,
5 just from a procedural morbidity component.

6 DR. SAXON: Yeah, so as I wait for that
7 data broken out that way, which I don't have
8 available, I would just say, as long as we're talking
9 patient scenarios, it's actually not an additional
10 three hours. You're putting in an RV lead anyway.
11 The morbidity potentially is in the defibrillation
12 test but, you know, that's a very controlled
13 situation and while it might be a difficult
14 discussion to have with a patient, you may have some
15 incremental morbidity or potentially mortality
16 associated with the device.

17 There's also nothing less tragic than
18 implanting a patient with a CRT-P device, having them
19 feel better, do more, only to have them die suddenly
20 at a time when their quality of life is for the first
21 time better. And one can always turn off the shock
22 piece of the device. If you encounter that unusual

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1 patient whose heart failure worsens, they get into
2 the spiral secondary VT events. But I would argue
3 that that can be discussed at multiple times after
4 the device is in. You can always disable that
5 therapy. You can't save that patient who had the
6 sudden death outside the hospital with the CRT-P
7 device.

8 DR. KRUCOFF: Okay, so standing back and
9 thinking about how we're really going to treat
10 patients if these data were taken as reasonable
11 assurance, let me just ask any of the clinicians in
12 the group, I mean, do you walk away from this study
13 with the feeling that actually Resynchronization
14 Therapy Pacing is in the future going to be
15 malpractice, that actually anyone who warrants -- who
16 has an EF that low, who has a QRS that wide that
17 basically what they warrant is a combination CRT-D?

18 DR. SAXON: I'll let everybody weigh in
19 but my tendency is certainly to reach for the CRT-D
20 device but these are individualized discussions with
21 patients according to the severity of their illness
22 and their strong preference and I don't think we can

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1 make blanket statements. I certainly don't think
2 it's malpractice.

3 DR. KRUCOFF: Can you tell me who you
4 would put a CRT-P in?

5 DR. SAXON: Sure.

6 DR. KRUCOFF: Can you give me an example?

7 DR. SAXON: Sure, there are some patients
8 who you have the discussion with and they don't want
9 -- they don't want a Class IV patient, for instance,
10 advanced. They don't want any issues related to --
11 they want to feel better alone and they don't want to
12 have the sudden death discussion or entertain the
13 thought of a shock. That's a minority in my
14 experience coming from the EP. Okay, maybe it's not
15 in others but to get to the adverse -- so I think
16 there are select patients, either from patient
17 preference, there are some very cachectic patients
18 who are 60 or 70 pounds, who you think twice about
19 even a subpectoral implant. That's again, a rare
20 event but that would be another instance.

21 So related to adverse events by type of
22 device, there don't appear to be a difference between

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1 Aes, whether they had a CRT-P or D.

2 DR. KRUCOFF: ARE complications or ARE
3 observation and complications?

4 DR. SAXON: ARE combined.

5 DR. KRUCOFF: Combined, how about
6 complications?

7 DR. SAXON: Sorry, no breakout according
8 to the device.

9 DR. KRUCOFF: No breakout. So --

10 DR. SAXON: Let me get back to that. I
11 do know what deaths occurred during the procedure and
12 there were certainly no deaths, procedural deaths due
13 to defibrillation testing. So I can tell you that.

14

15 DR. KRUCOFF: Yeah, but that's not --

16 DR. SAXON: That's not the answer but --

17 DR. KRUCOFF: Right, okay.

18 DR. BRISTOW: The implant success rate
19 was actually slightly higher in the CRT-D group.
20 It's not statistically significant. I think it was
21 91/87.

22 DR. KRUCOFF: All right, so my last

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1 question is, as clinicians, particularly those of you
2 who have actually put these in, what are you going to
3 tell a patient about their risk of a procedure when
4 you go through, by the time you have the failure to
5 implant of nine percent, the device safety-related,
6 the patient safety-related complications, the
7 reoperations, we're into about from my understanding
8 about a 75 to 80-percent likelihood of something
9 imperfect happening --

10 DR. WALDO: Don't forget about
11 inappropriate shocks for atrial arrhythmias.

12 DR. KRUCOFF: Okay, I'm going to be done
13 after this question, Al. I'm sure our chairman will
14 get to you. So what are you going to tell -- I mean,
15 if I put in 100 millimeters of stint in a coronary in
16 a patient, I'm going to tell them they have a much
17 higher likelihood that they're going to be back in
18 the cath lab than if I put in a 10 millimeter stint.

19 And that's a poor plumbing analogy but --

20 DR. SAXON: No, I understand.

21 DR. KRUCOFF: But what are you really
22 going to tell patients? What should be in the

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1 information a patient gets about the whole gambit of
2 misery whether from the procedure failing or the
3 device needing revision that invasive or a lead or
4 whatever?

5 DR. SAXON: Right. So what we tell these
6 symptomatic patients in need of a therapy that we've
7 shown to be beneficial and save lives is that, but I
8 also tell them and have told them as a procedure has
9 evolved to a much less -- to a much higher success
10 rate nationally than the 91 percent and as the tools
11 have improved and the hospitalization duration is
12 less, what I have historically told them and tell
13 them now is, this is the device. This is an
14 operation. You accept some up-front risk and you
15 have to, with your eyes open, accept that up-front
16 risk for the potential for the following benefit and
17 I outline what that symptomatic or mortality or
18 morbidity or whatever benefit is. And then I
19 quantify the risk according to the national data and
20 my own data of my own experience or my centers and
21 simply you know, do the informed consent process and
22 I can tell you that the majority of patients,

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1 particularly with this degree of disease severity,
2 opt for the up front risk.

3 DR. KRUCOFF: Thank you.

4 DR. STEINBERG: I'll just second that.
5 You tell them that they're likely to feel better
6 overall, likely to have fewer hospitalizations,
7 likely to have more energy and likely over time to
8 have potentially a lifesaving shock. And I think
9 most of the patients with sick heart failure
10 appreciate that and I think if you want to look at a
11 specific measure of whether they appreciate it or
12 not, you could look at a quality of life index which
13 takes into account the procedure, the
14 hospitalizations early on and the shocks that occur
15 over time and in trial after trial the patients opt
16 by quality of life measures to -- in preference of
17 having the device.

18 DR. KRUCOFF: Okay, so on an average,
19 informed consent discussion with an average sick
20 patient who would benefit long term from this
21 therapy, would you tell them they have a 70 percent
22 likelihood, an 80 percent likelihood of the procedure

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1 not going simply of having to come back of having
2 something else done? What would -- what number would
3 you tell them?

4 DR. STEINBERG: For a procedural revision
5 or reimplant or something like that?

6 DR. KRUCOFF: Or failure or a problem.

7 DR. STEINBERG: For a technical issue,
8 it's probably in the five to 10 percent range.

9 DR. KRUCOFF: It's nine percent failure
10 to implant, right?

11 DR. STEINBERG: In this procedure -- in
12 the study but the technique has evolved over time.
13 So the implant success rate is now higher. The need
14 for revision is now lower than it previously was.

15 DR. KRUCOFF: So and the total misery
16 rate you're saying is down around five percent?

17 DR. STEINBERG: The total misery index
18 has substantially decreased over time from the onset
19 of CRT implantation to the present day,
20 substantially.

21 ACTING CHAIR LASKEY: Okay, let's leave
22 the realm of imaginary numbers and let's finish with

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1 Dr. Somberg.

2 DR. SOMBERG: I thought we were
3 discussing politics with the misery index. Well, one
4 of the advantages of being at this end of the table,
5 besides getting a crimp in one's neck is most of the
6 questions have been answered. I think the most
7 cogent point that we have to consider is that we're
8 talking about a CRT-D implant without the same
9 indications as a defibrillator and I think what's
10 most critical there is the mortality data. And from
11 my estimation, the mortality data is a very clear
12 signal and I haven't seen anything that will dispute
13 the Kaplan-Meier curves that have been put up and the
14 quality of the data harvesting, I think is such that
15 I don't see any inconsistencies or problems with
16 that.

17 So I think the criteria for seeing that
18 the data is there to change the labeling is such but
19 we have to remember that was a secondary end point,
20 not the primary end point, but we're not here to
21 judge the study. The study quality -- and I
22 congratulate the investigators for initiating the

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1 study, that was very important of the sponsor to
2 obviously provide the resources to do that. I think
3 it's unfortunate that some of the -- not some the
4 hospitalization end point is clouded and that poses a
5 problem. And I don't think there's any way to get
6 around that.

7 There may be bias to introduce them, may
8 not have been bias, it's a little imprecise. But I
9 think with such a clear mortality signal and with
10 everything in the study being consistent, favoring
11 the CRT-D, I'm less concerned with that. I do think
12 the FDA reviewer is to be congratulated as well, and
13 I think there is an important concern here that are
14 we trading off a feel better reduced hospitalization,
15 which is the surrogate for that, with the risk of
16 implant and the bother of it? And I certainly think
17 it appropriate that the agreement was such that that
18 wasn't going to be counted, that being the
19 hospitalization, but I do think at some point in the
20 labeling that should be pointed out because maybe all
21 physicians are not going to spend their entire day
22 here and knowing all of the minutia -- minor points,

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1 how is that, minor points of the protocol. But they
2 should have that pointed out.

3 So I think from a patient's standpoint,
4 it's very important to know that when it looks at
5 total hospitalizations for everything, it is higher
6 in the implant group than the non-implant group and
7 no one can get around that. And that's an important
8 point to make.

9 But you know, going back to first
10 principles, you're dealing with patients and
11 patients, I think, fundamentally want to live longer
12 and hopefully feel better in that time and I do think
13 this device offers that. Thank you.

14 ACTING CHAIR LASKEY: Dr. Waldo, I know
15 you gave us your comments this morning but do you
16 have some additional?

17 DR. WALDO: Yeah, I do actually, if I
18 have the time, I would like to make a few comments.
19 First, I think we need to put some of this back in
20 perspective, because we really got involved with a
21 lot of statistics but understandably. I don't think
22 there was ever any doubt about the mortality.

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1 Everyone is agreed about that and if I read the
2 things correctly there are already indication for ICD
3 in terms of mortality from the MADIT II trial and
4 from other trials of overt ventricular arrhythmias,
5 not primary prevention.

6 The way I read this is that the
7 additional group that this would cover that is not
8 quite covered now and I think that's important to
9 confirm that, is that it ups the EF from 30 and made
10 it to 35 and it also includes non-ischemic
11 cardiomyopathies which if I understand it correctly,
12 don't yet have a primary prevention indicational
13 although the data would suggest that that might
14 change pretty soon. So I think that's really the
15 change that I see here.

16 It's kind of small really and in many
17 ways, I really think it's already out there, the
18 indications to do this sort of thing. I think the
19 second thing that is important and it's come out here
20 many times, that needs to be said, I think Dr. -- I
21 would support what Dr. Maisel said before, I mean,
22 this whole thing is driven by hospitalization as the

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1 primary end point and so the definition of
2 hospitalization becomes very, very important and
3 we've gone over that enough to know that
4 unfortunately it was not handled very well in my
5 judgment and I think I'm still not satisfied that I
6 understand this.

7 In fact, I pulled -- if you pull the New
8 England Journal article, it says, "The primary end
9 point was a composite of death from any cause or
10 hospitalization from any cause". That's what it
11 says. It's not -- I mean, that's very ambiguous in
12 terms of what I've learned today. I think the
13 definition that they're using is very sensible about
14 one day. I understand that but I think it's been
15 very, very confusing. So I think -- I also have to
16 say although I know we're not supposed to really but
17 I think this unfortunately is missing a big arm in
18 this study. That is just the -- just the device, an
19 ICD device with optimal therapy without IV pacing, I
20 mean, to me the first time I saw this, that was
21 obviously missing and I think it would have helped us
22 a great deal in this because -- but we'll never get

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1 that answer, so we're stuck with what we have. So I
2 think the impact of MADIT II is clear.

3 I think the impact of SCDHeFT is coming
4 along so a lot of this may be moot that we're all
5 talking about but I think that's one. The other
6 thing I think that's important that we haven't really
7 come to grips with -- come to terms with, we've come
8 to grips with but haven't come to terms with is the
9 difference between hospitalization for any cause and
10 hospitalization for heart failure and I think the
11 investigators would like to consider this principally
12 hospitalization for heart failure. That's fair
13 enough if they did it up front but they didn't and I
14 think that has been one of the major, major
15 confusions.

16 So I think where to come down is still a
17 problem for me. I mean, when I heard -- I only hear
18 voices and I don't always recognize the voice with
19 the name, so I'm not sure who was saying it all, but,
20 I mean, that thing that we'd all like to be true is
21 what was just said a little while ago, that patients
22 like to live longer. The ICD will do it and that

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1 they like to feel better and IV pacing will do it and
2 were that were true we would all jump up and down and
3 whistle Sweet Sue but I think one of the reasons
4 COMPANION was done is to date that's still a question
5 in the minds of many.

6 The IV pacing issue, per se, we don't
7 have to open up again. We all know how it helps some
8 patients enormously and others not at all. There's
9 still lots of issues, so I think we still have some
10 problems here and I think the biggest problem is we
11 know what we would like but have we seen the data to
12 support what we would like. What we'd like is an ICD
13 in patients and make patients feel better in the
14 category we've been discussing all day. Have these
15 data demonstrated that definitively and without any
16 questions, and I think we're still left with some
17 unanswered questions because of the way the study was
18 carried out.

19 I think basically, I think the data
20 really pointed to the fact that probably the
21 investigators have achieved what they're telling us
22 they have but I think it's very hard to say

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1 definitively and without question that that's what
2 happened and that's what's so unsatisfying about all
3 this in my judgment. I don't know if I've helped
4 anything or advanced anything with these few remarks,
5 but I still have a lot of problems and I wish I
6 didn't.

7 ACTING CHAIR LASKEY: Well, you'll have
8 the opportunity to express that shortly, Dr. Waldo,
9 so as we move closer to the vote, but thank you for
10 your thoughts. There's a gathering storm here at the
11 podium.

12 DR. BRISTOW: So one issue is what are we
13 going to be achieving with this additional expansion
14 of the indication? And I would direct your attention
15 to the sub-group analysis for mortality in the non-
16 ischemic cardiomyopic group which was 44 percent of
17 the population which would not currently be covered
18 with an ICD indication or CRT ICD indication. And
19 you can see the point estimate indicates a 50 percent
20 reduction in mortality with all the caveats around
21 sub-group analyses. It's not really statistically
22 different from the ischemic but you can see where

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1 that point estimate falls. The non-ischemic data,
2 indeed, we're very robust in this trial.

3 DR. BOEHMER: If I may add, as a heart
4 failure cardiologist, this is a world different from
5 MADIT II. MADIT II had a problem with worsening
6 heart failure hospitalization, a serious problem.
7 I'm not sure exactly why that was. This has been
8 expounded upon in many discussions. This did not --
9 in fact, this had quite the opposite, a profound
10 effect on reduction of heart failure hospitalization,
11 a profound effect on improvement in symptoms and
12 exercise capacity. So this is night and day from
13 MADIT II. There is absolutely no equivocation about
14 that.

15 Additionally, the end point was set as a
16 very challenging end point to take into account
17 computing risk. The definition was used consistently
18 throughout the population as adjudicated events.
19 This was applied to every event that was adjudicated.

20 So I would argue that as the definition stands,
21 those events are those events and that bar was really
22 high.

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1 If MADIT II had that as a primary end
2 point, there would be no MADIT II. It wouldn't have
3 made it. So this was a hard trial. It was
4 rigorously conducted. We got back and got the data
5 and the primary end point, I think is important and
6 it takes into account competing risk. Once those
7 devices were in, if they needed a lead revision, they
8 were counted as a primary end point. If they came
9 back with a shock, they were counted as a primary end
10 point. So that's taken into account.

11 DR. KRUCOFF: One of the things we're
12 stuck with, though, is that adjudication in this
13 trial simply could not be blinded. So understanding
14 that's nobody's fault.

15 DR. BOEHMER: As in any similar trial,
16 which is why -- which is why it was even more
17 important to take the most verifiable end point of
18 "all-cause" hospitalization and "not cause specific"
19 hospitalization as your primary end point. We
20 counted every hospitalization to the best of our
21 ability and that's exactly what we did, that's
22 exactly what you have. There is no equivocation

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1 about what that is. That is what that is.

2 DR. FELDMAN: If I could make one comment
3 in response to Dr. Waldo's comments; this is Art
4 Feldman by the way, so you know who's speaking. I
5 think he raised a very good point about the fact that
6 we've -- all day we've been showing "all-cause"
7 hospitalization and it would be relevant to look at
8 heart failure hospitalization. So I'd actually like
9 to show that to you. Okay, so this is the slide that
10 we've been showing all day. This is the primary end
11 point which is "all-cause" mortality and "all-cause"
12 hospitalization. You can see this risk reduction of
13 20 percent. Now, if you narrow it down, if you will,
14 to the next slide looking at now "all-cause"
15 mortality or cardiovascular hospitalization, you
16 would like to see the same trend and, in fact, if
17 this study was as exciting and as robust as we think
18 it is, you would actually like to see the risk
19 reduction get greater as you get more specific in the
20 end point. And, in fact, that's exactly what
21 happens.

22 Here the risk reduction is now 28 percent

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1 and then if we go to the next slide, these are all
2 secondary end points for this trial, prospectively
3 defined. This is "all-cause" mortality or heart
4 failure hospitalization and now you can see it's a
5 risk reduction of 40 percent. So this is very robust
6 data and this is totally consistent from end point to
7 end point to end point as we actually got more
8 specific. And so I think this is very supportive of
9 the question that Dr. Waldo was raising which is
10 that, if, in fact, this therapy is important, we
11 would like to see this kind of result on heart
12 failure hospitalizations and in fact, we do.

13 DR. WALDO: Art, if I may comment, I
14 mean, that's exactly my point. I have no doubt that
15 that's the way it is. My point about MADIT II is
16 that maybe I'm not quite right, but I thought that
17 there is now an indication from IV pacing and MADIT
18 II patients. I may be wrong about that, but that was
19 my point or if it's not here, it's around the corner,
20 that was in the report. And I think clearly MADIT
21 II, we realized being a MADIT II Investigator, we
22 didn't fully understand that heart failure problem

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1 until the light of some of these other --

2 DR. FELDMAN: Yeah, I'm not sure if
3 that's the case but I'm going to let one of your
4 colleagues like a physiologist answer that.

5 DR. SAXON: Dr. Waldo, this is Leslie
6 Saxon. The labeling for the MADIT II group does not
7 include an LV lead. There are two trials I'm aware
8 of that are in the planning stages to evaluate that
9 type of population with biodiverse IV but there's no
10 labeling -- there's no approved indication for MADIT
11 II IV. There is -- I think what you're thinking
12 about is, there is a CMS type coverage statement
13 related to a wide QRS group in MADIT II, just for the
14 coverage of the IR ICD but there's currently no
15 indication so, as I understand this group that we
16 studied in COMPANION, it's distinct without a whole
17 lot of overlap although some, but not a whole lot of
18 overlap with SCDHeFT or MADIT II. Some of these
19 patients would fall under those criteria but as
20 they're defined, you know, this is a much sicker
21 group with a heart failure hospitalization, all those
22 other characteristics we've talked about all day that

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1 are, you know, quite distinct.

2 DR. WALDO: No, but my point is, really
3 what's the indication to IV pacing now? I mean, the
4 indication of IV pacing now, isn't it not Class
5 III/IV heart failure with YQRS and EFS 35?

6 MR. DEVRIES: My name is Dale Devries.
7 I'm with Guidant corporation. I'm an employee/owner.

8 I would like to clear up one thing related to the
9 indication for Guidant's CRT-D devices. Guidant
10 existing indications for CRT-D include those patients
11 where indicated for an ICD. When we did the original
12 approval on the contact CD that came before panel
13 then subsequent information that we provided to the
14 FDA, that original approval was based -- did not
15 include MADIT II patients. However, subsequent to
16 that point in time, we worked with the FDA reviewing
17 the MADIT II information as well as the information
18 for CRT-D devices and actually our existing
19 indications today for CRT-D do include all patients
20 who are currently indicated for a Guidant ICD
21 product. So I think that can be verified by the FDA
22 if anybody is interested.

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1 DR. WALDO: Well, not to push a point
2 beyond reasonableness but what is the -- I'm asking
3 to clarify. What is the indication of simply IV
4 pacing?

5 DR. SAXON: This is Leslie Saxon again.
6 I'm sorry, Mr. Devries clarified that point. I was
7 incorrect. So the indications are as you've
8 described them. Symptomatic heart failure on maximum
9 medication, EF less than 35 percent and QRS
10 lengthening.

11 DR. WALDO: Okay, and my whole point is
12 that if you have those symptoms and you also have
13 MADIT II things, I would think that you -- do you not
14 then qualify for both IV pacing and an ICD?

15 DR. SAXON: So then I would bring up the
16 non-ischemic group again that Dr. Bristow referred
17 to. They would, in addition qualify.

18 DR. WALDO: Well, that's what I said
19 before, that this was the only group that would
20 really -- I mean, you increased -- what I said
21 before, you increased the EF by five percent in the
22 ischemic group and then you bring in the whole non-

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1 ischemic group and I -- you know, I think that group,
2 I'm suggesting from the SCDHeFT data, anyway I'm sure
3 that clearly has to be looked at for ICDs anyway and
4 if they meet the criteria for -- I think we're -- I'm
5 not -- this is not a point of contention in my
6 opinion. I just was trying to put this into some
7 perspective about where we are with things. I think
8 we're almost there anyway. I just wish that some of
9 the data here were -- I don't think contentious is
10 the word but statistically it's been -- we've spent
11 the whole day on statistics really. That's why I
12 tried to put it back in the clinical sense right now.

13

14 ACTING CHAIR LASKEY: No, Dr. Waldo, not
15 quite. We've wanted fairly far afield and I think
16 it's time to come back together again. So --

17 MS. WOOD: I would ask the sponsor to
18 take their seats, please.

19 ACTING CHAIR LASKEY: I'm going to
20 suggest simply a 10-minute break. Let's regroup at
21 4:00 o'clock and we will do the thing. So see you at
22 4:00.

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1 (A brief recess was taken.)

2 ACTING CHAIR LASKEY: Okay, in the home
3 stretch, folks, thank you very much. Moving onto Ms.
4 Wood reading the question and/or projecting them. Do
5 you want to just project them?

6 MS. WOOD: No.

7 ACTING CHAIR LASKEY: Okay.

8 MS. WOOD: Please comment on whether
9 modifications to the hospitalization definition
10 impact the interpretation of the primary end point.

11 ACTING CHAIR LASKEY: Okay, I'll do my
12 best to summarize the consensus or lack thereof of
13 today's panel discussion reminding everyone again,
14 that the primary end point here was the composite
15 "all-cause" mortality in hospitalization. The
16 modifications that we're referring to occurred on
17 several levels. I think the -- if I can summarize at
18 least the panel's conclusions with respect to the
19 modifications of the definition, is that the overall
20 feeling is that it probably did not impact adversely
21 on the primary end point efficacy determination. We
22 are certainly not happy with the lack of the total

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1 body of information potentially available that goes
2 with the term "hospitalization", but dealing with the
3 information that we currently have, I guess we're
4 coming down to the clinical interpretation of the
5 primary end point and that it was not adversely
6 effected.

7 You know, again, chime in to modify my
8 consensus statement.

9 DR. MAISEL: I disagree with that. I
10 think that the -- a number of the things that we
11 discussed including the changing definition, the
12 analysis of data prior to adjudication, the large
13 number of withdrawals despite an excellent effort to
14 account for those patients, I think does impact on
15 our interpretation of that end point.

16 DR. WALDO: Who was that, please?

17 DR. MAISEL: Bill Maisel.

18 DR. YANCY: This is Dr. Yancy and I take
19 the opposite perspective. I do not think that the
20 modification of the definition impacts importantly on
21 interpretation of the primary end point.

22 DR. NORMAND: This is Dr. Normand. I

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1 actually do think it impacts on the definition and
2 interpretation of the end point.

3 DR. SOMBERG: How are you going to reach
4 a compromise with those statements?

5 DR. KRUCOFF: So is the conclusion we're
6 divided?

7 DR. ZUCKERMAN: (Inaudible)

8 DR. WALDO: I can't hear you.

9 DR. ZUCKERMAN: This is Bram Zuckerman
10 from FDA and we're talking about question one and
11 there seems to be a difference of opinion which is
12 fine, that's why we're gathered here today. You
13 know, certainly some panel members feel that the
14 changes in hospitalization definition have impacted
15 their ability to make conclusions about the primary
16 end point, but is that in a qualitative way or is
17 that in an absolute quantitative way when we go back
18 to the analogy of looking at the Kaplan-Meier curves,
19 and certainly if you want to just use the log rank
20 test, you could conclude that the two curves are
21 different.

22 However, given some of the problems with

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1 the conduct of the trial, the precise estimate of how
2 much the curves differ may be in question. In this
3 circumstance, the panel members who've indicated that
4 they think there is an impact, are they referring to
5 a quantitative impact or even the qualitative
6 recognition that there is a difference between the
7 two curves?

8 DR. NORMAND: This is Dr. Normand. I
9 believe the analysis that we presented are correct.
10 My point of departure is what was included and
11 characterized as "all-cause" hospitalization. So
12 that's the problem that I am raising in terms of
13 what's counted as "all-cause" hospitalization. The
14 data that were presented, I believe the differences
15 that are there.

16 ACTING CHAIR LASKEY: We also heard from
17 both sides of the street that the log rank is a
18 fairly robust form of analysis and allows for
19 tremendous leeway. And that despite the limitation
20 of the data set, you were still able to demonstrate a
21 significant benefit. Now that does not excuse or
22 exonerate the changing definition or the lack of the

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1 complete data set, times and so forth, but it's a
2 terribly persuasive argument that despite these
3 limitations, you're still able to demonstrate a
4 benefit and I guess up here, it always comes down to
5 clinical versus statistical with all due respect to
6 our statistical colleagues. Dr. Somberg?

7 DR. SOMBERG: John Somberg. I would
8 suggest potentially wording the resolution or the
9 question which we vote on differently and that is
10 that there are substantial problems with the
11 hospitalization redefinitions. But even despite
12 these substantial problems, that the -- looking at
13 absolute mortality, looking at the other secondary
14 end points, and looking at combining re-volt with
15 hospitalization since all the results seem to be
16 going in the same direction and the mortality is the
17 most clinically meaningful, that the problems, which
18 are substantial with the hospitalization end point,
19 are still overcomeable and that the study still leads
20 to substantial clinical observation.

21 ACTING CHAIR LASKEY: Well, that helps us
22 with question number two, but we need to help the

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1 agency with question number one and I think somehow
2 we're going to have to -- we need to give them an
3 answer because this will go forth with additional
4 trials, I'm sure. Mitch.

5 DR. KRUCOFF: Well, it sounds like there
6 may be some variation, but if quantitative is really
7 being able to distinguish with some degree of
8 precision to what degree there is a reduction of an
9 end point and qualitative is just -- isn't really
10 better, then from my perspective, I think there's a
11 major problem in the former to feel precise that you
12 could tell a patient, "This is going to reduce your
13 likelihood of being back in the hospital in the next
14 180 days by X percent", I think these data would be
15 very difficult to feel certain about.

16 ACTING CHAIR LASKEY: That's not what
17 this question asks.

18 DR. KRUCOFF: Well, okay. I guess I'm
19 trying to respond to Dr. Zuckerman's question, which
20 I take it was a part of the interest in this
21 question. I just don't see the curves flipping or
22 that -- I don't see any evidence that suggests the

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1 conclusion that there's a real difference here would
2 go away.

3 DR. ZUCKERMAN: Dr. Laskey, I think
4 there's a little bit more to this question that we're
5 trying to tease out besides what's written on the
6 printed page. We've heard a difference of opinion
7 regarding the importance of the modifications to the
8 hospitalization definition and we're just trying to
9 tease out a little bit more what the real clinical
10 impact of that was as perhaps expressed by Dr.
11 Krucoff.

12 ACTING CHAIR LASKEY: Yeah, Jeff.

13 DR. BRINKER: I think that you're right,
14 that the wording of this question is devils into
15 details. I think most of us would agree, I hope,
16 that if you look at that question specifically, that
17 the modification -- modifications that occur are so
18 important, the issue is whether the original
19 definition of hospitalization was very good or
20 adequate to address the issue of that specific
21 indication at the very end. And I don't think the
22 modifications did anything to strengthen it or make

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1 it weaker, so that's an easy answer to that question.

2 I think the real problem will be are we satisfied
3 that hospitalizations, using that term as loosely as
4 it is defined, is -- was meaningfully -- clinically
5 meaningfully reduced in the device group of patients.

6 I think that -- and we'll have debate about that but
7 I still don't think that that will change our view
8 about the end point of this entire discussion. So
9 maybe we shouldn't get hung up on this and just go
10 ahead.

11 ACTING CHAIR LASKEY: Probably as a
12 practical matter, though, one thing that I struggle
13 with throughout the day is when these ongoing
14 modifications occur, are they strictly -- should they
15 be strictly considered amendments, or should they be
16 approached as protocol amendments? When this comes
17 up in the future, if it should, should there not be
18 officially protocol modifications and amendments and
19 so forth. Is that an appropriate way to get out of
20 trouble at this level?

21 DR. ZUCKERMAN: Yeah, I think the sponsor
22 and other sponsors are aware that the -- in the

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1 future, the FDA needs to be notified through the
2 five-day notice program or other mechanisms but you
3 know, the point is that we have the data as they are
4 right now today.

5 DR. SOMBERG: Why don't we just vote on
6 the motion as it stands?

7 ACTING CHAIR LASKEY: It's not a motion.

8 This is just a question. I guess maybe I should
9 rephrase the response now that I've heard the rest of
10 the opinions is, is that -- generically speaking, if
11 you modify your end point after the trial is
12 launched, that certainly impacts the interpretation
13 of the primary end point. However, what we've heard
14 today does not appear to be persuasive enough to
15 modify our clinical sense that the primary end point
16 has been met.

17 This is certainly not a prototype of how
18 to conduct a clinical trial, I think we're all
19 uncomfortable saying that.

20 MS. WOOD: Let's go to question two.
21 Please comment on the impact of modifications to the
22 hospitalization definition on the interpretation of

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1 the secondary end point and mortality.

2 ACTING CHAIR LASKEY: Well, Dr. Somberg,
3 you eluded or just mentioned it specifically, so if
4 you could just reiterate.

5 DR. SOMBERG: Well, to summarize, I don't
6 think it effected the primary end point of mortality,
7 I mean or the end point, the secondary end point of
8 mortality, which in my mind, is the primary -- of
9 primary importance.

10 ACTING CHAIR LASKEY: It seems to be what
11 the panel is most comfortable reaching consensus on
12 but realizing that looking at hospitalization as an
13 isolated end point, we would agree that because of
14 the competing risks, it's hard to strictly analyze
15 the hospitalization alone in that context.

16 DR. KRUCOFF: The only other caveat, I
17 think being that it -- while I agree, I think there's
18 agreement on mortality, where it's coming from,
19 whether it's from the resynchronization or the
20 defibrilator or both or how much, I think we don't
21 have a --

22 ACTING CHAIR LASKEY: Right, and we can't

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1 answer that and hopefully we will touch on this
2 again, because that relates to the key arm of this.

3 MS. WOOD: Number 3, are the data from
4 the COMPANION clinical trials sufficient to support
5 any expanded patient population for the sponsor's
6 CRT-D devices?

7 ACTING CHAIR LASKEY: Well, the expanded
8 patient population here refers to that from the CRT
9 precedent in addition to the life-saving aspects of
10 the defibrilator therapy in patients with EF's 35
11 percent or less, et cetera, et cetera, YQRS. I mean,
12 are we all pretty much in agreement that the
13 COMPANION provides data to this -- to answer this
14 question? I think that is what the patient
15 population was.

16 DR. SOMBERG: Yes.

17 DR. KATO: Yes.

18 ACTING CHAIR LASKEY: Thank you.
19 Anything you're uncomfortable with? All right,
20 Number four.

21 MS. WOOD: With respect to statements and
22 the indications for use regarding the primary end

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1 point, are the data from COMPANION sufficient to
2 support claims based upon the primary end point
3 results?

4 ACTING CHAIR LASKEY: Some of us think
5 so, some of us think not. We may need to resolve
6 this by who votes which way. I'm not sure in this
7 discussion we're going to answer that in greater
8 depth without just rehashing everything that we've
9 discussed. There is clearly a limited data set to
10 address the "all-cause" hospitalization part of this
11 and we don't know if we can go further than that.

12 MS. WOOD: Part B, of so, please comment
13 on whether the language of the proposed indications
14 for use statement adequately describes that end
15 point. In particular, please discuss whether the
16 terms "all-cause" hospitalization is appropriate.

17 ACTING CHAIR LASKEY: Well, we seem to be
18 asking the same question repeatedly and I hate to
19 sound monotonous but you'll get the same answer which
20 is there's clearly a division of opinion here.
21 Hopefully, you'll get a consensus by the end of -- I
22 know you'll get a consensus by the end of the day.

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1 DR. WALDO: But don't you think it would
2 help to put a definition in there. If they're just
3 going "all-cause" hospitalization?

4 ACTING CHAIR LASKEY: I'm not sure we can
5 put a definition in after the trial was over.

6 DR. WALDO: Oh, but the definition that
7 they used in the trial because, I mean, if it's the
8 COMPANION data that we're talking about, let's at
9 least use the specific definition for what "all-
10 cause" hospitalization means so there's no ambiguity.

11 DR. ZUCKERMAN: Yes, to help you, Dr.
12 Waldo, I would refer all the panel to Section 4, page
13 2 of Dr. Faris' review where the -- right after the
14 term "all-cause" hospitalization is listed, the
15 sponsor does have their current definition.

16 DR. WALDO: Okay, that's perfect then.

17 ACTING CHAIR LASKEY: We haven't heard
18 the word "perfect" yet today, so -- all right.
19 Everybody happy with that?

20 DR. WALDO: Definition has been so
21 important in what we're talking about all day.

22 ACTING CHAIR LASKEY: All right, well, it

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1 is specified in the protocol. Yeah.

2 MS. WOOD: Number five, with respect to
3 statements in the indications for use regarding the
4 secondary end point of mortality, are the results
5 from the COMPANION clinical trial sufficient to
6 support a mortality benefit claim for the sponsor's
7 CRT-D devices in the COMPANION population?

8 ACTING CHAIR LASKEY: I think the answer
9 here is a resounding yes.

10 DR. KATO: Yes.

11 MS. WOOD: Number six, please comment on
12 whether the CRT-D labeling should characterize the
13 total number of hospitalizations and length of time
14 patients spent in the hospital for the CRT-D and OPT
15 arms of the COMPANION trial.

16 ACTING CHAIR LASKEY: Well, we certainly
17 discussed that this morning, I guess. It's an
18 arduous amount of work to put this into the label and
19 whether it adds any meaningful information, let's
20 just hash that out. John.

21 DR. SOMBERG: I think what should be put
22 into the label is the implant hospitalizations as

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1 well. There should be some point where it is
2 understood that if one includes implant and implant
3 related hospitalizations, that "all-cause"
4 hospitalizations do equalize and that that shouldn't
5 be somehow hidden under the rug.

6 DR. WALDO: So then we lose a lot of the
7 impact of the primary end point.

8 DR. SOMBERG: That's exactly right. So
9 it's up to the physician to understand just what was
10 talked about all day here. That you take risk up
11 front and you trade that off for this surrogate steel
12 ventilator on which is a reduction in
13 hospitalizations but the trial was specifically
14 designed and agreed to that that wasn't going to be
15 taken into account but that is something that should
16 be noted to the patient because it's important for
17 the patient to know in the -- I'm sorry -- this has a
18 mind of its own, it keeps changing its height.

19 But just to very quickly summarize that,
20 I think it would be useful for the patient to know
21 and for the physician to be aware of that as well,
22 that the implant hospitalization impact on "all-

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1 cause" hospitalizations and that if it's not clearly
2 said someplace in the labeling would not -- will not
3 be known because I remember reading the COMPANION
4 study and never thought of that when I read the
5 COMPANION study and therefore, maybe I was an
6 uninformed person and I at least took the opportunity
7 to read that study.

8 DR. WALDO: Yeah, and again, I remind you
9 that the definition in the COMPANION study I read the
10 sentence, it doesn't -- it just says "all-cause"
11 hospitalization. It's terribly ambiguous really in
12 the end, although it's very -- what's spelled out
13 here is very clear and sensible, it's not clear --
14 it's not intuitively obvious when you read it from
15 the paper.

16 ACTING CHAIR LASKEY: That, of course, is
17 the answer to the next question but to stay with
18 where we are on Part A, which is whether the labeling
19 should characterize total number of hospitalizations
20 and length of time patients spend in the hospital, do
21 we agree to that, number one. Do we suggest that,
22 number two. Number three, if we do either one or

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1 two, it needs to be adjusted for the fact that there
2 are different numbers of patients in the two -- you
3 had twice as many patients in the device arm as you
4 did in the control arm. So that needs to be
5 normalized, if you will, but what's our advice to the
6 agency on changing the labeling to include total
7 number of hospitalizations and --

8 DR. WALDO: And maybe even add something
9 about competing risk because that point was very well
10 made also.

11 DR. YANCY: Warren, if I can speak to
12 this, I think so that even though I don't support the
13 persuasion, but just so that we can have some
14 internal consistency, if there are those on the panel
15 that are uncomfortable with the hospitalization data,
16 that I think it is certainly inconsistent to attempt
17 to quantitate it and put it in the label.

18 DR. NORMAND: Well, if I can make a
19 suggestion, I would quantitate it in the way that I
20 would have liked it at least defined and at the very
21 least, I would include Part B. So I don't advocate
22 putting total number of hospitalizations because of

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1 the adjustment that's necessary and I think that's a
2 little bit difficult to translate. But I do think
3 and I'm sorry, I can't separate A from B, but if I
4 didn't put -- I don't think it's necessary to put A,
5 but I would put B and I'd put B in, I want the
6 subsequent hospitalizations for the implants to be
7 put in there.

8 DR. ZUCKERMAN: And the way that I would
9 address that is that I would make it clear that there
10 is a requirement for implant hospitalization. So
11 something as simple as a phrase that says, "All-
12 cause" hospitalization apart from implant
13 hospitalization" would capture that.

14 DR. KRUCOFF: I would also vote for
15 really starting with what would you really want a
16 patient to know and that is, I think it was actually
17 stated quite well earlier, this is a procedure that
18 requires a hospitalization. There are risks to the
19 procedure that include you might have to come back
20 into the hospital at a later time and there are some
21 ball parks as to what the likelihood of those risks
22 are. That the benefit then that has accrued in this

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1 data is that there may be a change in your likelihood
2 of rehospitalization without knowing exactly how much
3 and that you may not die.

4 So I think in the same way you would talk
5 to a patient about it, I think putting some sort of
6 ballpark language and numbers together would be quite
7 reasonable.

8 DR. WALDO: Very well stated, may I
9 suggest.

10 DR. BRINKER: Well, Bram, maybe you can
11 help me. The indications are primarily to the
12 physician, is that not correct?

13 DR. ZUCKERMAN: That's correct.

14 DR. BRINKER: I mean, we're not writing a
15 patient pamphlet. We're writing something that the
16 physician can use as a guide to whether this device
17 is appropriate in his particular patient. And quite
18 frankly, I'm very unhappy with the way
19 hospitalization has turned out, the way it's being
20 configured. I think people go home, they may find a
21 more meaningful result to express but I'm not
22 absolutely positively sure that the way it's

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1 expressed right now in terms of single -- primary
2 hospitalization, the first one, is the best way of
3 determining whether a patient truly benefits from
4 this in terms of overall hospitalization over the
5 duration of his device.

6 I think it is, and I think if you look at
7 the data carefully, you can tease that out. I also
8 think that that would take away the issues about
9 readmission or pacemaker changes like remanipulation,
10 et cetera and would allow you to even include the
11 primary hospitalization for the device implant,
12 because I do think it will work out but I also think
13 that we're definitely convinced that the main issue
14 here, that is whether COMPANION patients should have
15 this device indicated is agreed to and the impact of
16 mortality is agreed to. I think we're really
17 focusing now, maybe too much time on wordsmithing the
18 benefits of the primary end point and how best that
19 can be expressed.

20 DR. ZUCKERMAN: All right, let me clarify
21 that. We're not here to wordsmith very sentence in
22 the label but we are -- the FDA and sponsor are

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1 looking for general guidelines, and I think the
2 general guidelines are the following. Dr. Waldo made
3 the statement that you know, in a New England Journal
4 article as well as in other available information,
5 information about the device implant's success rate,
6 complications, number of returns, isn't readily
7 available. We'd like to provide in a -- in our
8 clinical summary relevant data to the physician. I
9 think we saw, for example, a table that just lists
10 the implant data, which goes a little bit farther
11 than Dr. Yancy's statement and I'd like to have some
12 panel input on that but by the same token, we're by
13 no means asking that we're asking the panel at this
14 point to rewrite the primary end point to include in
15 the primary end point all those initial
16 hospitalizations.

17 We're just asking what supplemental table
18 would be helpful. It sounds like some more
19 information about the initial implant hospitalization
20 problems in perhaps tabular form simply stated could
21 be of help to physicians.

22 DR. KRUCOFF: Yeah, and Jeff, just to

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1 take one point, I'm not saying we should -- it should
2 be written like in a form of consent document, but I
3 think if we structured the information to the
4 physician so that it would be digestible in a way
5 that they could turn around and talk to a patient,
6 meaning like I think the syntax of how that
7 information is presented could be useful in the way
8 it's presented.

9 DR. BRINKER: All right.

10 DR. SOMBERG: You know what you were
11 saying, mentioning, I agree completely and I think
12 it's very important to realize that if we just -- if
13 we do recommend to the FDA to balance the
14 hospitalization data which has certain potential
15 flaws in it, with the observation that if you include
16 the initial implant hospitalization and all other
17 revisions, then the two are equal. We don't have
18 that balance, I don't think that would be picked up
19 by the average person who's going -- the physician,
20 not patient, the physician who is going to make use
21 of this and therefore, it's an important addition and
22 it's just as important as the mortality and just as

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1 important as the combined end point because it leaves
2 the whole label incomplete.

3 DR. BRINKER: Well, my only problem is
4 not the balancing act because I believe these other
5 pieces of information that we're talking about should
6 be somewhere in the labeling, not necessarily in the
7 indication portion. My problem is leaving in the
8 indication portion the statement that appears -- the
9 proposed statement that appears with regard to "all-
10 cause" hospitalization and "all-cause" mortality.
11 I'm not comfortable with that statement and balancing
12 it off by putting in the other pieces of information
13 about implant requirements and need for a replacement
14 and all this other business. While I think it's
15 important, I don't think that belongs in the
16 indication section.

17 I'd be happy with the second two things
18 in the indication section and leaving out the
19 hospitalization business or I would be happy if there
20 was some other review of the hospitalization to see
21 if it could be expressed in some other way. I'm
22 just unhappy about the way the hospitalization

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1 statement is read and what it's based on.

2 DR. ZUCKERMAN: I think we previously
3 answered the question from Dr. Waldo referring to
4 italicized text that defines hospitalization. And
5 I'm wondering if it's not possible to simply add
6 another bullet to said text that captures the query
7 and the concern about implants and revisits. I
8 really believe the issue of simplicity is where we
9 should target and I support what Bram just mentioned,
10 but I'm wondering if there's a simple way we can do
11 this so that it's not confusing.

12 ACTING CHAIR LASKEY: Well, probably the
13 simpleness way is just to have a separate table of
14 the events related -- surrounding the primary
15 implantation without basically coercing the sponsor
16 to redo the primary end point with the inclusion now
17 the penalty for getting the device, which I
18 personally think is unsupportable, to penalize that
19 arm. You can't get in that arm without having the
20 device, but I think it's certainly an appropriate
21 place in the labeling to indicate to all physicians,
22 whether they're implanting these or not, that there

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1 is an up-front risk as well as benefit with that
2 index procedure. That's one man's opinion.

3 DR. KATO: I think the one other issue
4 with the hospitalization question is that as was
5 identified earlier, you know, hospitalizations for,
6 you know, fixing the device, replacing the leads,
7 whatever, have gone down. And so to some degree the
8 hospitalizations that are going to occur with the
9 implantation of the device are going to be positioned
10 -- there's going to be certainly that component and
11 as a result, certainly that variability.

12 In some physician's hands, they may not
13 have hardly any hospitalizations and other ones may
14 have even perhaps double the rates of what we've seen
15 in the companion study. And along those lines of
16 being a surgeon, I think the hospitalization
17 definition is difficult enough and because of the
18 variability in the daily practice, I'm not even sure
19 a comment should be made, you know, one way or the
20 other about it. It's a device. A procedure is going
21 to be required and I think patients know that. I
22 think that's part of the informed consent discussion

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1 that takes place between a physician and a patient
2 but I think getting into that kind of writing that or
3 advising the FDA in terms of all the -- and the
4 sponsor in terms of an actual label, I think is going
5 to be very, very difficult.

6 DR. SOMBERG: The problem is when you
7 look at the data, it's very impressive towards
8 hospitalization reduction but when you add that in,
9 it reverses. So unless there's going to be some sort
10 of very dramatic change in user abilities, that's not
11 going -- so that balance has to be there. And I'm
12 just afraid if you mention -- if you just mention
13 "all-cause" hospitalization is markedly reduced and
14 we all know that the problem is with statistical
15 problems we have with hospitalization, you have to
16 mention a bullet point. And it could be a very
17 simple one. I don't know if it has to be a table
18 even, Warren, but just a statement that there is an
19 equalization of the two groups when that implant time
20 is included.

21 DR. MAISEL: Warren, can I suggest a
22 little wording potentially? That the Guidant CRT

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1 Defibrillators have demonstrated the following
2 outcomes in the indicated population specified above;
3 one, reduction in risk of "all-cause" mortality, two,
4 reduction of heart failure symptoms, three, reduction
5 in post-implant hospitalization rates and then in
6 parenthesis but not necessary a reduction in total
7 hospitalization rates.

8 DR. YANCY: You know, I'm going to be of
9 sort from here, but you know, we're talking about a
10 real world application now and when implanters and
11 clinicians are talking about hospitalizations and
12 someone with heart failure, it really is a given that
13 you've got to put the device in. So what everybody
14 wants to know about is what happens after the fact.

15 I think that part of what you said,
16 actually I agree with, but I think to massage this
17 further, this really obscures the information.

18 ACTING CHAIR LASKEY: I'd go further and
19 say to taint it is not helpful.

20 DR. BRINKER: Well, the only reason for
21 this is because there's a -- I mean, I feel at least
22 some discomfort with the calculation of

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1 hospitalization and I would like, actually if you
2 can't do anything better -- and it's a relatively
3 small point, I think. Like everybody said, this
4 device is going to be used for all the reasons that
5 people say. I would just not like to give my seal of
6 approval that this device decreases the need for
7 hospitalization based on the data that was presented
8 today. I agree it should be put in, in this
9 population. I just would withhold that, that's all.

10 ACTING CHAIR LASKEY: Put in for what
11 reason?

12 DR. BRINKER: For all the reasons that
13 have been expressed. I mean, number one, I don't
14 like the idea that we haven't incorporated all the
15 issues involved in the device hospitalization,
16 including rehospitalization for things like
17 reimplantation when the first implant is not
18 successful. The fact that one could, by the very
19 definition of time frame of hospitalization, have
20 come up with different results, we don't know that
21 because we don't have a track on that, but it's quite
22 possible that if we put -- included same day

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1 hospitalization, then lead revisions and all those
2 things would have shown up as hospitalizations. And
3 there's still some doubt whether the change in the
4 definition of time for hospitalization in some way
5 impact non-implant hospitalizations that may have
6 occurred. So because of all these things I just have
7 a little unsettled feeling about that particular end
8 point.

9 ACTING CHAIR LASKEY: Well, perhaps we
10 can help you along as we answer number seven.

11 DR. ZUCKERMAN: Okay, but Dr. Laskey, can
12 you -- we've heard a lot of opinions right now on
13 question six. Would you care to summarize? Is the
14 general spirit to put the data on implant
15 hospitalizations in the label? I think we've gotten
16 off on a tangent when we're talking about what
17 potential indications for use are. That's a separate
18 story here or would you summarize where we are for
19 six?

20 ACTING CHAIR LASKEY: Well, the IFU is a
21 separate issue although we seem to have achieved
22 consensus on that. That's distinct from whether the

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1 labeling should characterize the total number of
2 hospitalizations and length of time, et cetera, et
3 cetera. I think we're less in favor of that than
4 part B which is that, yes, information on device
5 implant, hospitalization and its sequelae, should be
6 included. I thought we were moving towards its
7 inclusion as a separate table in the label but not as
8 a mandate to revise the statistical analysis of the
9 primary end point. That information does belong in
10 the label but it should not be the undoing of the
11 primary. I think the primary end point has enough --
12 we have enough reservations and concerns about the
13 hospitalization piece that is going to be reflected,
14 I would suspect, in the labeling. But I think it's
15 helpful irrespective of that conversation, to
16 certainly separate out the risks of that primary
17 implantation procedure in the labeling. So to Part
18 B, I think we're more in agreement.

19 DR. KRUCOFF: One caveat that might be
20 useful would be to recognize that if this is a
21 patient population in whom CRT is indicated, that if
22 -- we didn't see it today but if data were made

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1 available that could differentiate what the CRT added
2 procedural would look like compared to what they
3 would receive a anyway, again, from a physician's
4 side, I think that would be helpful in talking to
5 patients. Is there a difference between putting in a
6 CRT defibrillator than just putting in a CFT,
7 recognizing you're going to need a procedure to have
8 this device put in at all.

9 ACTING CHAIR LASKEY: Well, again, we
10 weren't allowed --

11 DR. KRUCOFF: We didn't see that today.

12 ACTING CHAIR LASKEY: It's hard to
13 imagine in real life how this will be separated out.
14 People will view this all as a single entity but our
15 job today has been really delimited by the insistence
16 on just looking at the two arms.

17 DR. YANCY: But just to buffet the last
18 question, I'm not an implanter but once the CRT
19 platform is in, all the necessary hardware there to
20 facilitate the CRT-D application and so theoretically
21 if there are any risks they are incredibly small. So
22 I'm not sure if I would leave that as a lingering

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1 major concern.

2 MS. WOOD: Number seven, please comment
3 on whether the CRT-D labeling should present adverse
4 events for the CRT-D and OPT arms of the COMPANION
5 trial in a consolidated manner that would allow their
6 comparison.

7 ACTING CHAIR LASKEY: We just expressed
8 our unanimous desire to see these ARE's reflected as
9 a separate set of information within the -- within
10 the label. That includes both the index procedure as
11 well as any sequela.

12 DR. ZUCKERMAN: Okay, I think if we go to
13 Section 1-13 of the label, it's apparent what one
14 potential problem is in that all the CRT-D adverse
15 event information is first displayed. Then the OPT
16 information is displayed. So you don't have a side-
17 by -side comparison. We're talking more about some
18 of the side-by-side comparisons that would be
19 relevant here. This is on Section 3.1.

20 DR. KRUCOFF: I mean, one of the things,
21 I think we've pointed to pretty clearly is that
22 everything about having the device implanted is

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1 unique to having the device implanted compared to
2 medical therapy. I think but what to me is a real
3 world issue is that a large percent of the practice
4 in this patient population would now say medical
5 therapy once you've reached OPT, it's time for a
6 device. So how do you characterize that?

7 If this is came to the population who are
8 wide QRS, EF less than 30, and struggling on pretty
9 optimal medical therapy, then characterizing the risk
10 of putting the device in is not unique to this
11 platform other than the defibrillator component if
12 the defibrillator is not specifically indicated. And
13 we just -- we haven't seen any way of separating
14 those two sets of ARE's.

15 DR. YANCY: Warren, on this question I
16 would say no because I don't think it's clinically
17 relevant if that's what you're looking for because it
18 says on a side-by-side consolidated manner. It's
19 almost a nonsensical question.

20 DR. WALDO: But, you know, if you look at
21 the PDO, in Germany they do this all the time, I
22 don't see any harm in it and there might be some

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1 help.

2 DR. YANCY: Well, I think the CRT-D end
3 tables should be there. That's just a point of
4 information and that's perfectly appropriate but to
5 do it in a consolidated manner, it's -- they're not
6 equivalent comparisons.

7 ACTING CHAIR LASKEY: Now I'm not quite
8 sure what that means unless it's just the template is
9 in the PDR. Is that what you're referring to?

10 DR. ZUCKERMAN: Yeah.

11 ACTING CHAIR LASKEY: Or do you want to
12 see a pretty table?

13 DR. ZUCKERMAN: Usually -- look at all
14 the adverse events listed beginning on page 1-13. You
15 have the CRT-D events all listed. Then you have the
16 medical therapy events all listed. Should they be
17 side-by-side? Are they relevant comparisons for the
18 clinician to look at or is this the relevant format
19 to display them because of Dr. Krucoff's comments
20 that they really aren't equivalent therapies where in
21 your trial you are comparing these two therapies?

22 DR. KRUCOFF: I'm not sure if this is

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1 helpful or irritating, but to me the perfect table
2 would be to see CRT-P side-by-side with CRT-D. That
3 would be much more relevant, I think, in making a
4 current decision than compared to OPT.

5 DR. SOMBERG: It's a -- I must say it's a
6 relevant table. I mean, it's tantamount to the
7 placebo arm of a drug study. So you're saying what's
8 the frequency of something? What's -- you know, I'll
9 give an example. Sepsis, some people have said
10 sepsis should go up with a device implant. Some
11 people say, "Oh, no, it's -- in this day and age,
12 you'll never see it". Doctor looks here says, "Hey,
13 look, in the optimum medical therapy, the incidence
14 is zero and with device it's 6.5 percent". Then you
15 know you may have a sepsis problem in the best events
16 which is, you know, the investigators who took part
17 in the controlled trial, right? So I think it's
18 worth a comparison, but that probably should be done
19 in almost any study. Wherever you put any incidence,
20 if you have a controlled group, put that incidence in
21 too, so that people know whether that's just
22 happenstance or occurs by the intervention.

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1 ACTING CHAIR LASKEY: Well, maybe it's
2 something more than stylistic. I fail to really
3 understand the gist of this because comparisons lend
4 themselves to at least to those minds some
5 verification of what is the -- what is the
6 comparison, what is the nature of the association or
7 lack thereof? Are there differences? So it begs a
8 whole other series of questions. Are you prepared to
9 open that Pandora's box? You're just going to list
10 all this stuff and all this stuff and now what does
11 the clinician do without some attempt to compare this
12 list of -- it's here. I think an inquiring mind can
13 do with it -- it's not -- it's fully disclosed.

14 DR. SOMBERG: Well, if you put it side-
15 by-side, you can make a comparison.

16 ACTING CHAIR LASKEY: There is a lot to
17 put side-by-side here, though, that's the -- we need
18 to stratify what goes in and not to dumb this down,
19 but it needs some significant stratification, if you
20 will.

21 MR. MORTON: Dr. Laskey, I agree with you
22 that the point is not to capture everything that we

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1 could out of study but to put in this relatively
2 small document what information the physician needs
3 in order to decide whether to treat a patient with
4 the device.

5 DR. NORMAND: I'm confused about the
6 question. So is the question aesthetics? How you
7 display it or do we include it?

8 DR. YANCY: Aesthetics.

9 DR. NORMAND: I don't care what it looks
10 like, it should be included.

11 DR. ZUCKERMAN: Okay, the question refers
12 to how, if someone takes the time to read this
13 document, it will read in a way that it will be
14 useful and right now, there's not a side-by-side
15 comparison of events. There are pluses and minuses
16 to that sort of approach and we're just looking for a
17 general sense of feedback.

18 DR. SOMBERG: In drugs, isn't it
19 generally something that occurs in more than one
20 percent of frequency is something like that and you
21 do have a comparison. If you have comparative data,
22 you put the comparison to be made. Why should that

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1 be --

2 DR. ZUCKERMAN: That is correct.

3 ACTING CHAIR LASKEY: Yeah, I guess I'm
4 just going to the next level which is just looking at
5 numbers is not often helpful. You want to know if
6 they're actually different. So --

7 DR. KRUCOFF: The other thing, there is
8 in a small document the potential redundancy with
9 some of the earlier questions. If data on the risks
10 associated with the implantation of the device has
11 already appeared in the document, clearly stated,
12 then does the additional comparison of all of these
13 also actually redundantly characterized individual
14 line item comparisons add anything to the information
15 you're conveying to the physician or does it just
16 make a longer document? I just -- there's a
17 potential for a lot of redundant information that may
18 work reverse of giving information clearly.

19 DR. BRINKER: It's not going to make a
20 longer document if you put them side by side as
21 opposed to right after each other. I think that with
22 the exception of procedurally related factors, the

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1 implant procedure basically. The other thing we
2 would usually like to see adverse events and next to
3 each other seems reasonable.

4 ACTING CHAIR LASKEY: Eight.

5 MS. WOOD: Please comment on whether data
6 obtained from patients after withdrawals should be
7 used in any of the analyses described in the device
8 labeling.

9 DR. NORMAND: I'll say, yes, given the
10 description that the sponsor gave to us, that this
11 was done in a manner to where there was no systematic
12 difference between the collection of who was in what
13 arm. So actually, I view it as a good thing.

14 DR. KRUCOFF: I agree entirely. I think
15 compared to not having those data, that the work done
16 to go and get those data probably yields a lot more
17 important information, although it brings some
18 questions with it, but I totally agree that it's much
19 better than having all those blanks.

20 DR. KATO: I agree as well.

21 DR. YANCY: I agree, too.

22 ACTING CHAIR LASKEY: Are there any other

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1 areas you want us to elaborate on?

2 DR. ZUCKERMAN: No.

3 ACTING CHAIR LASKEY: Well, our schedule
4 has us breaking. I suggest we just surge forward
5 here and draw to a conclusion. Okay? So at that
6 point, I'd like to have -- at this point, I'd like to
7 have Geretta read the FDA -- wrong page, sorry.

8 Open public hearing portion. Anybody in
9 the audience who wishes to address the panel on
10 today's topic? If not, I'd like to close this
11 portion of the open public hearing and I inverted the
12 order here. I've already asked you if you had any
13 additional comments or questions before the vote, but
14 do you have additional comments or questions before
15 the vote?

16 DR. ZUCKERMAN: No.

17 ACTING CHAIR LASKEY: I'd like to ask the
18 sponsor if the company has any additional comments or
19 questions before the vote?

20 DR. DeMETS: No.

21 ACTING CHAIR LASKEY: Thank you. And at
22 this point, we can hear from industry and the

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1 consumer representative.

2 MS. MOORE: Well, I don't think there's
3 very much more that needs to be said. We've heard a
4 lot of discussion today and I'm reasonably sure if
5 the public were privy to this discussion today, there
6 would be more people who would be convinced that they
7 must adopt a heart healthy lifestyle. But it is
8 satisfying to know that there are devices available
9 that will alleviate or treat or improve the problem
10 of heart failure and I think it is extremely
11 important that the patient knows what the procedure
12 involves and also the risks and I think from
13 listening to your discussion today, I believe that
14 this will be the case.

15 ACTING CHAIR LASKEY: Thank you, Ms.
16 Moore. Mr. Morton?

17 MR. MORTON: Thank you, Ms. Moore. I
18 think we can all take pride in the fact that the
19 public is privy to what goes on here and we should
20 all be very proud of that. The FDA did a nice job
21 especially in the written summary and the sponsor did
22 a nice job in summarizing a lot of data.

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1 ACTING CHAIR LASKEY: All right. Thank
2 you. Geretta, if you could please read the voting
3 options.

4 MS. WOOD: The medical device amendments
5 to the Federal Food, Drug and Cosmetics Act as
6 amended by the Safe Medical Devices Act of 1990
7 allows the Food and Drug Administration to obtain a
8 recommendation from an expert advisory panel on
9 designated medical device premarket approval
10 applications, PMAs, that are filed with the agency.

11 The PMA must stand on its own merits and
12 your recommendation must be supported by safety and
13 effectiveness data in the application or by
14 applicable publicly available information. Safety is
15 defined in the Act as a reasonable assurance based on
16 valid scientific evidence that the probable benefits
17 to health under conditions of intended use outweigh
18 any probable risks. Effectiveness is defined as a
19 reasonable assurance that in a significant portion of
20 the population the use of the device for its intended
21 uses and conditions of use when labeled, will provide
22 clinically significant results.

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1 Your recommendation options for the vote
2 are as follows; approval if there are no attached
3 conditions. Approvable with conditions; that panel
4 may recommend that the PMA be found approvable
5 subject to specified conditions such as physician or
6 patient education, labeling changes, or a further
7 analysis of existing data. Prior to voting all of
8 the conditions should be discussed by the panel. Not
9 approvable, the panel may recommend that the PMA is
10 not approvable if the data do not provide a
11 reasonable assurance that the device is safe or if a
12 reasonable assurance has not been given, that the
13 device is effective under the conditions of use
14 prescribed recommended or suggested in the proposed
15 labeling.

16 Following the vote, the Chair will ask
17 each panel member to provide a brief statement
18 outlining the reasons for their vote.

19 ACTING CHAIR LASKEY: I'd like to ask
20 panel members for a motion on this PMA. Dr. Maisel?

21 DR. MAISEL: I would like to make a
22 motion that the PMA is approvable with conditions.

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1 ACTING CHAIR LASKEY: Is there a second?

2 DR. SOMBERG: I'll second.

3 ACTING CHAIR LASKEY: All right, I'd like
4 to have a condition for the PMA then. Bill?

5 DR. MAISEL: I would like to propose that
6 the indications for use statement be amended such
7 that the first bullet point, reduction in risk of
8 "all-cause" mortality that refers to "all-cause"
9 hospitalization is removed so that the statement will
10 read, "Guidant Resynchronization Therapy
11 defibrillators have demonstrated the following
12 outcomes in the indicated population specified about;
13 reduction in risk of "all-cause" mortality and
14 reduction of heart failure symptoms".

15 ACTING CHAIR LASKEY: Do we have a second
16 on this condition?

17 DR. BRINKER: I second it.

18 ACTING CHAIR LASKEY: Well, we need to
19 have some discussion.

20 DR. YANCY: I think that's the ultimate
21 penalty to the trial because that removes the --

22 MS. WOOD: Can you talk louder?

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1 DR. YANCY: I think that that is
2 tantamount to a penalty to the trial because I think
3 that removes one of the very most important issues
4 and so I'm uncomfortable with removing that from the
5 statement. That's not the way the trial was
6 designed. It's not consistent with the pre-specified
7 end point. I think we had captured a flavor of
8 identifying and qualifying hospitalization but I
9 can't accept removing it.

10 ACTING CHAIR LASKEY: Additional
11 discussion? Mitch?

12 DR. KRUCOFF: I basically have to agree
13 with Clyde, I think in spirit, but I do think what is
14 really present here amongst all of us pretty clearly
15 is the concern of the counter-balance of what is the
16 cost up front for the benefit ultimately and should
17 that be conveyed. So another option might be to
18 leave the primary end point as it was, in fact,
19 examined and reported as a reduction in mortality and
20 "all-cause" hospitalization. But to -- and I don't
21 have the wordsmithing in mind, but to include in that
22 wording above and beyond the morbidity associated

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1 with implantation of a permanent device or something
2 that sort of creates the reality factor that there
3 are two sides to this coin.

4 DR. SOMBERG: Well, I must say Bill's
5 motion and the reason I seconded it is I thought it
6 was not a penalty but it's the clear message of what
7 was shown and hospitalization is fuzzy. There are
8 some issues about it and to just gloss over that is,
9 I think, inappropriate. But no one is being
10 penalized here and in fact, I think that is a very
11 powerful indication. It is the most powerful and
12 what happens if we wanted to take out mortality and
13 just leave hospitalization. People would say, "Oh,
14 my goodness, I'm not sure but you're leaving --
15 mortality is the primary indication that this causes
16 the reduction in and is also a symptom mentioned
17 there". It's just the concept of hospitalizations is
18 clouded and why should we go ahead and increase
19 physician bewilderment as opposed to decrease it and
20 make it clear-cut that CRT-D reduces mortality and
21 improves symptoms.

22 ACTING CHAIR LASKEY: Well, this has been

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1 the theme of the day, so should we just vote on this
2 condition? Yes, I will restate the -- the motion, of
3 course, on the table is to approve the PMA with the
4 condition that the instructions for use be amended to
5 remove the claim of a benefit in "all-cause"
6 mortality and "all-cause" hospitalization and to just
7 refer to the benefit for mortality, "all-cause"
8 mortality, and the alleviation of symptoms. Is that
9 correct? Can we now vote? All in favor of --

10 DR. KRUCOFF: I'm sorry, Warren. Are we
11 voting on just the condition?

12 ACTING CHAIR LASKEY: Just the condition.

13 DR. KRUCOFF: Just the condition.

14 ACTING CHAIR LASKEY: Right. We've
15 finally got this straight. All in favor of that
16 language for the first condition raise hands?

17 DR. WALDO: Can I say "aye"?

18 ACTING CHAIR LASKEY: That's good. One,
19 two, three, Dr. Waldo and two, three, four, five, six
20 in favor. Against? Two against. So six to two.
21 May I have another condition for this PMA? Dr.
22 Krucoff?

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1 DR. KRUCOFF: I'd like to propose a
2 condition that at least mortality data be collected
3 for the entire available cohort out to three years.

4 DR. YANCY: The purpose being?

5 DR. KRUCOFF: To appreciate some of the
6 concerns about the low numbers at the end of those
7 Kaplan-Meier curves and whether their boundaries
8 actually cross or not, just to complete that data.

9 DR. YANCY: So we just voted to make
10 mortality the lead indication but now we have anxiety
11 about mortality.

12 DR. KRUCOFF: I wouldn't quite go that
13 far. I think, you know, we have a very reasonable
14 explanation, I think, that it's really the range of
15 follow-up and just the numbers. We've got patients
16 who have already been enrolled, who already have the
17 device in. Where completing mortality, I don't see
18 as overly burdensome, but it would be nice to know if
19 those confidence intervals, when you really finish
20 the data actually behave as you would -- as I would
21 expect them to based on the earlier observations.

22 DR. SOMBERG: Can I ask a point of

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1 information?

2 ACTING CHAIR LASKEY: Yeah. We're a
3 little ahead of ourselves. Can I just have a second
4 for this condition? Anybody second Mitch's
5 condition? Before we have the discussion, we need to
6 have --

7 DR. SOMBERG: I just wanted a point of
8 information which technically takes precedence but
9 whatever you want, Warren. I just wanted to ask if
10 I may, is that being done already by the sponsor to
11 continue with --

12 ACTING CHAIR LASKEY: If I don't get a
13 second for the motion, some derrick comes and removes
14 me from this spot. Do I have a second, gentlemen,
15 ladies? I guess we're not going to discuss it.
16 Okay, for that condition.

17 DR. YANCY: Is the floor open for another
18 condition?

19 ACTING CHAIR LASKEY: The floor is now
20 open for another condition, yes.

21 DR. YANCY: So I think another condition
22 should be a separate statement that describes the

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1 hospitalization experience consisting with clinical
2 trial results with the appropriate qualifiers and
3 statements of concern.

4 DR. NORMAND: I didn't understand your
5 suggestion.

6 DR. YANCY: A separate statement that
7 describes the hospitalization experience in the
8 clinical trial with the appropriate provisos that
9 capture our concerns about the change in definition.

10 ACTING CHAIR LASKEY: Second on Clyde's
11 condition?

12 DR. MAISEL: I second.

13 ACTING CHAIR LASKEY: Can we just
14 clarify? You mean a section on hospitalization
15 separate from the indications or as part of the
16 indications?

17 DR. YANCY: Preferably as part of the
18 indications but since we've just voted that away, so
19 this will be a separate statement.

20 ACTING CHAIR LASKEY: This will be a
21 condition for approval, second condition of approval
22 to be exact, as Clyde has stated it, so some

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1 discussion? I think it's a great idea.

2 DR. BRINKER: Yeah, I agree. I think it
3 is a good idea. I think it should not an indication,
4 just emphasized and it might also invite further look
5 at some of the things that were brought up in
6 question 6A about the number of hospitalizations and
7 the duration of hospitalization which I personally
8 would like to see.

9 ACTING CHAIR LASKEY: Appropriately
10 displayed, adjusted for differences in patient
11 numbers and so forth, right. That goes without
12 saying.

13 DR. SOMBERG: You said adjusted for --

14 ACTING CHAIR LASKEY: Well, twice as many
15 -- I mean, we keep going around it, so just asking
16 for numbers of hospitalizations or event rates, when
17 there's twice as many people --

18 DR. SOMBERG: Sure.

19 ACTING CHAIR LASKEY: -- in the one arm,
20 so let's get the language out there.

21 DR. KATO: So this is just going to be a
22 narrative, not within the indication section,

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1 correct.

2 ACTING CHAIR LASKEY: This is not within
3 the label or the indications for use. This is just
4 our list of conditions for approval of this PMA.

5 DR. KATO: Okay.

6 ACTING CHAIR LASKEY: So this has to go
7 somewhere. Okay, a third condition?

8 DR. MAISEL: Did we vote on that one?

9 DR. ZUCKERMAN: Okay, before we vote on
10 the second condition, Dr. Laskey, can you and Dr.
11 Normand just further describe what you envision --
12 you envision in the clinical trial section, a
13 discussion of the hospitalization information, the
14 pros and the cons that occurred in this trial. Would
15 you also, Dr. Normand, include any statistics with
16 that or how detailed would you comment on the Kaplan-
17 Meier curves for hospitalization and the primary end
18 point?

19 DR. NORMAND: Well, I think the issue is
20 that with the caveat, with the hospitalization
21 measured in the way it was just described, I think
22 it's a little -- I wouldn't want to break it out.

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1 I'm not sure what P values I'd want to put in. I
2 think I probably would like to think a little bit
3 more about it just because of what's included and
4 what's not going to be included. I think we're still
5 not clear on that.

6 ACTING CHAIR LASKEY: The problem is, and
7 we know where Dr. Yancy is coming from here, the
8 problem is going to be to assign statistics to this
9 information when we've been speaking all day to the
10 competing risk aspect, that they may not be
11 meaningful or interpretable. But clearly this
12 information belongs in there.

13 DR. YANCY: There is one specific way to
14 capture that, Bram, because since we've made it
15 appropriate to take secondary end points and put them
16 in some position of importance, let's use the heart
17 failure hospitalization data for which there should
18 be very little argument. Heart failure related
19 hospitalization, the data do exist. We've seen it
20 today and they are consistent with a clinically
21 important question when one utilizes these devices.

22 DR. SOMBERG: But you -- I would think

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1 you would want to put the "all-cause" hospitalization
2 data in. You would want to also put the heart
3 failure data in. And you would just want to put a
4 caveat that there are some problems with the
5 hospitalization considerations; A, statistically.
6 You don't have to go into detail, but in changing the
7 definition. That introduces some uncertainty. And
8 B, of the procedural hospitalizations may be of
9 consideration as well. But I think those are just
10 concerns that should be put in some place, but they
11 don't have to have equal weight and one does not have
12 to go into a complete discussion of what we did today
13 on the panel, because it will have no weight then.

14 DR. WALDO: I agree, and also something
15 about competing risks again ought to be a part of
16 that.

17 DR. KRUCOFF: An unblinded adjudication,
18 you know, ultimately heart failure hospitalizations
19 are an unblinded -- a relatively unblinded
20 adjudication.

21 ACTING CHAIR LASKEY: Well, it can be
22 stated as such, but I think it belongs in there. I

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1 would agree with this condition but starting with
2 "all-cause" and then drilling down, if you will.

3 DR. YANCY: I think something akin to
4 what Dr. Feldman presented would be a correct way to
5 display it, "all-cause", cardiovascular, heart
6 failure related. If we are going to capture it, that
7 would be the right way to do it.

8 ACTING CHAIR LASKEY: And let's not
9 forget the information on the index procedure for
10 device implantation is capture elsewhere. We've
11 asked for that to be put elsewhere in the label.

12 DR. YANCY: That's correct.

13 ACTING CHAIR LASKEY: So now may we vote
14 on this condition? All in favor of a supporting
15 separate statement regarding the hospitalization data
16 with the appropriate caveats. All in favor of that.

17 DR. WALDO: Aye.

18 ACTING CHAIR LASKEY: It's unanimous.
19 Thank you. Is there a third condition?

20 DR. SOMBERG: I have a question. You
21 said that we asked for the hospitalization but was
22 that placed -- that was in our questions. The

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1 hospitalization data in terms of the end deaths
2 hospitalization, et cetera, should that be a
3 condition as well or is that going to be included,
4 Warren?

5 ACTING CHAIR LASKEY: Well, the
6 information surrounding the implantation is to be
7 included in the label -- in the IFU. This is a
8 separate statement that we are assigning to the vote
9 as a condition of approval, so we'd like to see this
10 placed somewhere, but it's not going to have the same
11 position that the other information would have. That
12 has its own table, its box.

13 Third condition?

14 DR. WALDO: Warren, can I just make a
15 general point at this moment? I think there's
16 another big implication we haven't said. I'm not
17 sure that this should stand on its own merits, but
18 this is really stealing a march on the SCDHeFT
19 implications and I think that's a very important part
20 of how we think about this, too. I think someone
21 just ought to say that.

22 ACTING CHAIR LASKEY: You know, we want

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1 to consider just the data that we have at hand in our
2 panel pack today. We need to make a decision based
3 on these data, Dr. Waldo.

4 DR. WALDO: No, I appreciate that fully
5 and that's why I said that first, but I mean, the
6 implications are clear and they should be understood
7 by us. In effect, that will happen but this clearly
8 should stand on its own merits. There's no question
9 about it. I just wanted to emphasize the real
10 implications for this.

11 ACTING CHAIR LASKEY: Understood. If
12 there are no other motions for additional conditions,
13 we are going to vote. Are there any other motions
14 for conditions? No? So I'd like to restate the
15 motion and the conditions and then ask for a vote.
16 The motion on the table is to approve the PMA with
17 the following conditions. Number one, that we
18 approve under the condition -- the first condition
19 that the IFU be amended to remove the language
20 referring to the "all-cause" hospitalization and
21 simply refer to the benefit regarding "all-cause"
22 mortality and improvement in symptoms. The second

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1 condition applied to the motion being that there is a
2 separate statement regarding the hospitalization
3 information along with the appropriate explanatory
4 language and the caveats to be applied to that data.

5

6 So, will all those voting members in
7 favor of approval with these conditions raise their
8 hand? One, two, three, four, five, six, seven --

9 DR. WALDO: Aye.

10 ACTING CHAIR LASKEY: -- eight, thank
11 you. Unanimously approved. So eight to zero for the
12 motion to approve. We need to just simply go around
13 the table and state your reasons for why you voted as
14 you did. Dr. Kato?

15 DR. KATO: Well, I think the -- I think
16 again, the hospitalization issue was debatable. Many
17 of the areas, I think, were ill-defined. I think
18 that the target of showing the CRT-D can reduce
19 mortality and reduce heart failure symptoms is a very
20 powerful statement and I think that's what patients
21 are going to be looking for, so that's why I voted
22 the way I did.

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1 DR. YANCY: I voted in favor with
2 reluctance, because I'm concerned that we have --
3 this is strong language, but I think we've
4 bastardized a clinical trial because this was not a
5 trial where the primary end point was mortality
6 alone; yet our label is suggesting such. And I think
7 that that is academically inconsistent and something
8 about which we should have some angst. I think we
9 also have a question of clinical relevance here
10 because the hospitalization burden is substantial and
11 as we said earlier, hospitalizations in this context
12 are not all equal. Those hospitalizations that carry
13 the greatest merit are, in fact, substantially
14 impacted by this methodology.

15 But nevertheless, I applaud the panel for
16 making a vote to bring more patients to this platform
17 in hopes that it will change outcomes and improve
18 heart failure overall.

19 DR. MAISEL: I think the sponsor should
20 be commended for conducting an extremely important
21 trial for bringing these devices to a sick population
22 in need of both mortality and symptomatic improvement

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1 and I'm glad that we were able to do that today.

2 DR. BRINKER: I echo those thoughts. I
3 have no angst about the way we handled this. I think
4 that I would have much more problem if I -- approving
5 the original language given the uncertainties of the
6 definitions. I think they can be worked out. I
7 think that the paper that was published and the
8 reality of the practice habits of many physicians
9 have already established but I think that the imprint
10 of the panel should be based on what they feel is
11 unequivocal scientifically justifiable and I didn't
12 find that for hospitalization end point in the study.

13 DR. NORMAND: I also would have no angst.
14 I approved it with the conditions for the reasons
15 that were echoed by my colleague to my right. I do
16 feel that the definition of "all-cause"
17 hospitalization means something to someone like me
18 who could be a patient and when someone says "all-
19 cause" hospitalization that actually means something
20 in terms of how it is typically defined from the
21 patient's viewpoint. And I believe that the way it
22 was defined and measured in this study did not

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1 reflect what patients are going to think it is and
2 hence, that's the reason I voted with the condition.

3 DR. KRUCOFF: I voted the way I did for
4 very similar reasons. I think ultimately the
5 hospitalization issue remains unresolvably ambiguous
6 based on what's available today while the reduction
7 of heart failure symptoms and mortality does not.
8 Again, I personally, probably would have preferred
9 the label to be slightly different but I think in the
10 spirit of the panel, the most important thing in my
11 opinion was to bring this device forward. This has
12 been a huge effort by a lot of very dedicated people
13 in a very sick population and in a terrain that's
14 moving and changing and that we ended up with some
15 ambiguities. In a key point like hospitalizations is
16 part of the real world of doing clinical trials but I
17 think it's been a very thoughtful day and I think at
18 the end of the day, the important thing is to bring
19 the device forward and then let doctors and the
20 practice of medicine kind of take it from there.

21 DR. SOMBERG: I voted for the motion
22 because I thought this was a very important study. I

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1 think the mortality end point was important and I
2 think there was still some problems with the "all-
3 cause" hospitalizations and that this is a balanced
4 motion taking all those considerations into account,
5 not penalizing the sponsor, but most importantly
6 advocating its use for the indicated patient
7 population.

8 ACTING CHAIR LASKEY: Ms. Moore, any
9 additional comments?

10 DR. WALDO: This is Al Waldo, do I get --
11 I think, you know, one of the few advantages of being
12 at home is I could use the dictionary to look up
13 equipoise which was used so often. And I think we
14 did this is a state of equipoise which it means, as
15 the Webster Dictionary said, the state of equilibrium
16 counterbalance. I think we did this with balance and
17 care. I think it was a very important day. I think
18 we also have to remember that perfect is the enemy of
19 good. I think this was a good study. It was far
20 from perfect and I think we went over pretty
21 carefully the imperfections and I think our final
22 recommendations with the help of the panel put

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1 together some very good recommendations and I thing
2 we had a fruitful day and I'm glad I was a part of
3 it.

4 ACTING CHAIR LASKEY: Al, thank you very
5 much. And for my part, I hope never to hear the term
6 "equipoise" again. This concludes the report and
7 recommendations of the panel on PMA, P010012,
8 Supplement 26 from Guidant, and I too, add my
9 gratitude and thanks for excellent presentations from
10 the sponsor and the agency. Thank you, thank you,
11 all. Thank you, colleagues.

12 (Whereupon, at 5:24 p.m. the above
13 entitled matter concluded.)