

1 because the bias is going to be tremendous on
2 who stays on what. And I don't think there's
3 any way to extract it if you don't randomize
4 it. Now I understand PROTECT has been
5 started. It seems a shame with that many
6 people going into a trial to not answer
7 another question. I don't know if it's
8 possible to have a factorial design to allow
9 for different prescribed therapies.

10 I mean here's an opportunity for
11 Medtronic to prove that they don't need a
12 prolonged course of therapy, but they're not
13 going to prove it by looking retroactively and
14 saying, well, this center only did 3 months
15 and this center only did 6 months, because,
16 you know, there are centers that do high risk
17 patients and centers that do low risk, and
18 that's not going to clean the issue up.

19 DR. ZUCKERMAN: Okay. I think
20 Medtronic, meaning Dr. LeNarz, wants to add a
21 few objective descriptions of the proposed
22 plan.

23 DR. LeNARZ: In an earlier
24 description, I indicated that the shortest

1 duration based on the instructions for use
2 outside the U.S. and the comparator would be 3
3 months, but we recognized with the steering
4 committee that the actual duration would be
5 based a lot on their own practice, the
6 selection of the patients, whether they were
7 stable or had pericardial infarction, because
8 this is the all comers type of patient
9 population.

10 So we recognize that the
11 physician's discretion is anywhere from 3
12 months to guidelines that would indicate up to
13 a year, also, taking into effect that there
14 are influences, as I mentioned, such as
15 reimbursement in certain countries. With
16 that, FDA has reviewed the OUS PROTECT study
17 and we withheld its enrollment until we were
18 aligned on the design and on the case report
19 forms and the ability to pool this data and
20 understand to your point exactly what the
21 physician's practice might be in any certain
22 region or with any particular patient.

23 And as indicated, knowing that you
24 have many factors here, one being the

1 physician's choice and the influence of the
2 patient and the patient's own adherence to
3 capture as much information as we can in this
4 8,800 patients across all comers and then be
5 able to take the information in the U.S. and
6 hopefully pool it and then analyze the
7 influence of antiplatelet therapy. Does that
8 help?

9 DR. LINCOFF: I mean it certainly
10 clarifies the issue, but it doesn't change --
11 it will a long way. I mean we all know
12 multigrade analyses, propensity analyses, all
13 different ways -- I mean I'm sitting next to a
14 statistician who can certainly comment on this
15 better than I can -- but I don't think you're
16 going to be able to definitively assess if you
17 need a prolonged course of therapy. I'm not
18 saying this -- it's an ongoing trial. I
19 recognize the difficulties in changing the
20 structure of it, but 8,000 patients are going
21 into a randomized trial already. It would be
22 nice to get more than one answer from such and
23 such a trial, if that was possible.

24 DR. LeNARZ: I think that's part of

1 it and offering this and not to debate or
2 belabor this, there was an extensive debate
3 about this issue with clinical trialists in
4 Europe and there was concern that, quite
5 frankly, we would confound the endpoint. The
6 endpoint of this study is late stent
7 thrombosis which we thought was the question
8 at hand, and the secondary points of interest
9 are death and MI. They're clinically
10 relevant.

11 But additional standard DES
12 endpoints will be captured there as an
13 independent CEC in DSMB. Dave DeMets is the
14 head of the DSMB and there are interim looks
15 at this data in a randomized study at 25, 50,
16 75 percent with the power to potentially stop
17 this if we see a signal for the strong -- for
18 the relevant clinical endpoints of death and
19 myocardial infarction.

20 But I think, Dr. Lincoff, the
21 concern was that with the geographies involved
22 and the issues that I mentioned, that trying
23 to identify the physician's own decision
24 making around the patients was still of value.

1 And the sample size for the study that you're
2 looking at is quite large.

3 DR. SOMBERG: Could I ask just two
4 detailed points here about -- it may help them
5 in the study.

6 CHAIR YANCY: Please.

7 DR. SOMBERG: If you could just for
8 a moment, the issue -- are you going to be
9 able to capture the duration of antiplatelet
10 therapy the person's on with a good degree of
11 assurity? And also, are you going to be able
12 to capture concomitant medications that they
13 may be on looking for possible drug
14 interactions? And those are two things that
15 you can add to this study now which would not,
16 you know, change in any way by improving the
17 case report form, a simple amendments to do
18 that.

19 And that would go a long -- so
20 those people who end up with very late stent
21 thrombosis, you can say they were on for 3
22 months, 6 months, a year. And those people
23 who had a problem, you would be able to say,
24 well, maybe they were on a medication that

1 prevented the activation of the pro drug,
2 clopidogrel. So you could get at some
3 important data by just increasing your ability
4 to grasp these issues.

5 DR. LeNARZ: Once again, we have
6 intensified the case report form, and
7 collection of information that is previously
8 outlined to look for interruptions, to also
9 understand the nature of those interruptions,
10 the duration and then the potential to go back
11 on dual antiplatelet therapy and the timing of
12 any of that. However, I think based on
13 zotarolimus and the lack of a CYP 3A4
14 interaction, we really were not trying to
15 confound the study to the point that you're
16 making here which, again, I think is unlikely.
17 But we could discuss that.

18 We are interested in this issue.
19 We're involved in a number of efforts outside
20 of PROTECT. I won't go through those today,
21 but one of those would be just the stent
22 thrombosis study which has been described at
23 the DES Panel, to be led by Greg Stone, which
24 has in that study the timing of the events and

1 also looking at their responsiveness to
2 clopidogrel.

3 So there's a lot of things
4 happening in this area of dual antiplatelets.
5 We're all anxious to hear about a new dual
6 antiplatelet, but that's another discussion as
7 well.

8 CHAIR YANCY: So let me just say
9 that I believe the sponsor understands the
10 sensitivities that the panel has about dual
11 antiplatelet therapy, the duration of therapy
12 and the necessity to capture this very
13 important information. Let's try to wrap
14 ourselves up now in addressing question six.
15 Can you just put up the schematic of the post-
16 approval study so that we can make a
17 definitive statement about that?

18 MS. HILLEBRENNER: And so this is a
19 good time if there are any objectives that you
20 feel need to be added to this registry or
21 modified or changed. This is where we want to
22 hear your suggestions. And to get back to Dr.
23 Naftel's original question, the sponsor will
24 be asked to report to us every 6 months on the

1 status and results of this study for the first
2 2 years and then annually after that. And
3 then that helps us make a determination how
4 this device is performing post market in
5 safety and efficacy in the real world
6 population, whether there should be labeling
7 changes or any other warnings that should be
8 issued by FDA if we see something unusual in
9 that data.

10 DR. NAFTEL: I don't remember where
11 I saw it recently, but somebody pulled
12 together post-market studies and said tons of
13 them never get finished and delay until they
14 get started. And I'm not sure if that's true
15 or not, but I'm -- that helped but I'm still
16 not positive what's their incentive to do this
17 rapidly and quickly, and again, I'm talking
18 about any company. I don't quite see where
19 the --

20 DR. ZUCKERMAN: Dr. Naftel, your
21 points are very valid, and that's why there's
22 been a critical change at the agency under Dr.
23 Schultz' leadership over the last few years to
24 beef up our post-approval studies and the

1 diligence with which the industry and FDA
2 undertake these studies. There are
3 appropriate regulatory actions that now would
4 be considered if a sponsor doesn't meet their
5 post-approval regulatory challenges.

6 But from our perspective right
7 here, what you're seeing is that we do have
8 adequate resources right now both at FDA in
9 the sponsor's ballpark to really design a
10 critical post-approval study. But what we're
11 still struggling with is what is the principal
12 question we have to have answered and what is
13 the optimal design for answering this
14 question. And if the panel can help you here
15 with that, that would be very good input.

16 CHAIR YANCY: Comments? Dr.
17 Yaross, I know I cut you off earlier and I'm
18 sorry.

19 DR. YAROSS: I was just going to
20 comment that I think FDA has framed it very
21 well in terms of what information is needed as
22 opposed to what information is nice to have.
23 I know a couple of times, people say, while
24 you're at it, it would be nice to do it, and

1 that's always of concern to industry.

2 CHAIR YANCY: So as we look at the
3 schematic before us, comments? Dr. Somberg?

4 DR. SOMBERG: I'm not sure why one
5 could not have a control group here of the
6 Driver stent and collect additional
7 information. And two is I think there was a
8 misunderstanding about what I was suggesting
9 of drug interaction. The concomitant
10 medications, for instance, the talk of statin
11 where there's literature going both ways,
12 pretty much against it now, things like that.
13 I'm not interested in zotarolimus. I'm
14 interested in clopidogrel and how it
15 interferes with 3A4, I believe, activation.
16 So those two things I would suggest adding to
17 that list over there.

18 DR. NAFTEL: Clyde, may I comment
19 then on the design a little bit?

20 CHAIR YANCY: Please. This is what
21 we need to address.

22 DR. NAFTEL: So thank you, Bram. I
23 understand better and I'm really pleased that
24 FDA has this sort of new look at post-market.

1 But this particular study, the way it's
2 designed, which I think is nice, you're
3 looking at the rate of thrombosis at yearly
4 intervals. And as I understand it, you're
5 making sure it's less than 1 percent per year.
6 So I agree with that. It gives you a
7 benchmark and -- that's you're calling that
8 acceptable and you need to be lower. So
9 that's good.

10 It was said in here that you might
11 want to adjust for multiple looks, multiple
12 tests and I would agree with that big time.

13 There are also plenty of methods
14 out there, parametric methods that will do
15 what I think you really want to do, and that
16 is you're trying to detect if there's an
17 upturn in this rate. You want to see if
18 things are falling apart or getting worse, so
19 there are plenty of reliable models out where
20 you can test for a constant hazard versus an
21 increasing hazard. So as far as the design, I
22 personally am pleased. I would just add to
23 the analysis to have methods that specifically
24 try to detect upturns.

1 DR. ZUCKERMAN: Okay. And those
2 are very useful comments, but Dr. Somberg
3 suggested that we need a concurrent control
4 here. You've just indicated that we can use
5 an OPC at appropriate time points or that 1
6 percent point estimate. What is the consensus
7 of the panel, because this is a big design
8 issue.

9 DR. SOMBERG: I just want to
10 clarify, it's not a randomized control because
11 people won't want to be randomized, but it's a
12 concomitant non-randomized control.

13 CHAIR YANCY: Dr. Lincoff?

14 DR. LINCOFF: I think a concomitant
15 randomized control would -- non-randomized
16 control would be hopelessly confounded by
17 factor -- I don't know what it would add. I
18 think the use of having objective performance
19 criteria is as effective as comparing to a
20 control that will probably be a low risk group
21 of patients anyhow because they'll be the only
22 ones the physicians aren't comfortable putting
23 in the drug-eluting stent. Regardless of what
24 the criteria would be, without randomization,

1 I'm not sure what you'd gain from it. You'd
2 just make it a more expensive study, more
3 difficult to do.

4 CHAIR YANCY: Do you think there is
5 sufficient available data to come up with an
6 OPC?

7 DR. LINCOFF: Well, we do have
8 long-term performance of bare-metal stents
9 that we followed for years, and we have, you
10 know, a feel for what these thrombosis rates -
11 - I think the 1 percent per year is a
12 reasonable real world rate for bare-metal
13 stents, so that would be a good performance
14 criteria for the drug-eluting.

15 CHAIR YANCY: So the OPC that you
16 would use for this trial would be one based on
17 bare metal stent and not another DES?

18 DR. LINCOFF: That's an interesting
19 question. I don't know if I'm allowed to
20 compare to other DES. I mean it certainly
21 would be a point of no concern if it fell
22 within a criteria for bare-metal stent. And I
23 guess if it was a higher level but one that
24 you thought was consistent with other drug-

1 eluting stents, then you'd have to try to
2 assess how good your data is for other drug-
3 eluting stents for which we do have some
4 registries forming. And I don't know, you
5 know, the status of those -- where you would
6 get a good OPC for that.

7 CHAIR YANCY: So if the OPC were
8 BMS, there would be no problem?

9 DR. LINCOFF: And if it conformed
10 to that or met that criteria.

11 CHAIR YANCY: Other comments about
12 design. One of the questions that we haven't
13 addressed is the definition. It just says,
14 generically stent thrombosis. Would it be the
15 per protocol definition used in the studies or
16 would we go with the ARC probable plus
17 definite. Dr. Hirshfeld?

18 DR. HIRSHFELD: I think for
19 consistency, ARC definite plus probable should
20 be the endpoint.

21 CHAIR YANCY: Dr. Morrison?

22 DR. MORRISON: I would agree with
23 that.

24 CHAIR YANCY: Okay. Dr.

1 Weinberger?

2 DR. WEINBERGER: I agree.

3 CHAIR YANCY: Okay.

4 DR. HOPKINS: And I agree as well.

5 CHAIR YANCY: And is the duration
6 of follow-up, 5 years, is that acceptable?

7 CHAIR YANCY: So what I'm hearing
8 the panel say is that we're comfortable with a
9 single-arm registry compared against an
10 objective performance criterion set probably
11 on the BMS data. Reasonable follow-up is
12 indicated. A definition of stent thrombosis
13 that's standardly used and the numbers of
14 patients appears to be reasonable,
15 particularly since, I think, that will be put
16 together with other data sets. There are
17 enough people expressing some approval. Does
18 that give you some guidance, Dr. Zuckerman?

19 DR. ZUCKERMAN: We're moving in the
20 right direction, but now I think we really
21 need to understand in more detail the design
22 of the Medtronic post-approval study, and I
23 would refer you to Medtronic slide 152. It's
24 important to appreciate that somehow Medtronic

1 is going to pool the on-label subset from
2 PROTECT with the on-label patients from the
3 U.S. 2000-patient post-approval study to come
4 up with their sample that they'll use for
5 hypothesis stent testing.

6 And Dr. Duggirala can supply more
7 details, but from your perspective, Dr.
8 Naftel, what do you have to say about that
9 design? There's a poolability question of an
10 OUS and U.S. trial? The strength of it is
11 that in addition to on-label patients, we also
12 see the off-label results.

13 DR. NAFTEL: As you know, I care
14 about poolability a lot. For sure I would
15 want to assess the poolability, but part of
16 the strength I think will be in the fact
17 there'll be a diverse population and a lot of
18 them will be off label. So I can imagine the
19 analyses will have to reflect that and we'll
20 want to look very carefully at subgroups, at
21 risk factors. So I personally am okay with
22 the pooling. I would hope there's be a really
23 definitive scientific analysis to see who the
24 high risk groups are.

1 And, you know, it may well be that
2 overall, your rate seems to be high, but once
3 you split it into on-label/off-label, the on-
4 label patients may be just fine. The off-
5 label may not. And that might be okay. So,
6 you know, I think it's complex and deserves a
7 really thoughtful, complete scientific
8 analysis.

9 And as far as your question, I'm
10 okay with combining, but I would want to check
11 the poolability.

12 CHAIR YANCY: Dr. Lincoff.

13 DR. LINCOFF: I have a question for
14 either Medtronic or -- this E-Five single-arm
15 registry, and I understand the enrollment is
16 complete, the plan is for 2-year follow-up,
17 but is there any way to fold that in and
18 extend to -- I mean that's 8,000 patients.
19 Can you pool that in as well? I just don't
20 understand --

21 DR. LeNARZ: There was a meeting in
22 January and there were a bunch of proposals
23 made by Medtronic to the FDA, and one of these
24 was to take a portion of the Endeavor V data.

1 I think that the fact that the FDA had not
2 seen this protocol and prior approved it, the
3 fact that it was a registry and was not a
4 randomized study such as PROTECT, and the fact
5 that the overall monitoring was at a low rate,
6 10 percent, that we came to an agreement that
7 we would stick with the protect study and
8 combine the data from both Outside the U.S.
9 and the U.S.

10 CHAIR YANCY: Just as a point of
11 clarification, what did you decide to do with
12 the other 90 percent?

13 DR. LeNARZ: Ninety percent of?

14 CHAIR YANCY: When you -- I saw
15 that you were only going to monitor 10
16 percent. I mean maybe monitor needs to be
17 defined.

18 DR. LeNARZ: In the PROTECT study,
19 we'll monitor the higher rate. We'll monitor
20 30-something percent. Dr. Yancy, your
21 question is why did we only monitor 10
22 percent?

23 CHAIR YANCY: Yes.

24 DR. LeNARZ: Well, I think it was

1 more or less the standard for an observational
2 type of environment at that time. And with a
3 move to electronic data capture and more
4 prompting through the electronic data system
5 for the study sites to enter data, you know,
6 we had -- we thought that this would suffice.
7 And I think we're learning that the fact that
8 the events that we're challenged now to
9 identify are so low, and that the follow-up
10 needs to be at a very high percentage, and the
11 monitoring of the data has to be at a much
12 higher level for us to have, and, you know,
13 confirm the integrity of these low events.

14 CHAIR YANCY: No. I would say that
15 and then some. I really agree with Dr.
16 Lincoff that this is a missed opportunity to
17 have that many patients in a data set and not
18 be able to access more of the information. So
19 I appreciate your answer.

20 DR. LeNARZ: I'll just throw this
21 on the student enrolled, you know, there was a
22 question about the commitment to enroll these
23 types of studies. We enrolled over close to
24 8,3000 patients in about 14 months. The 1-

1 year follow-up data will finish in November.
2 And we will then publish the data by Euro PCR
3 on Endeavor V. Now I think -- I'm a little
4 concerned that we're confusing Endeavor V and
5 PROTECT, Endeavor V was just a registry of
6 8,300 patients. It was initiated many months
7 ago.

8 CHAIR YANCY: No. That point's
9 very clear in my mind.

10 DR. LeNARZ: Okay. I'm sorry.

11 CHAIR YANCY: So I just wanted to
12 understand why you're monitoring so few
13 patients in Endeavor V, and you've answered
14 that question.

15 Do we need to comment any more on
16 the post-market study?

17 DR. ZUCKERMAN: Do you have any
18 other questions? It's been very helpful then.

19 CHAIR YANCY: Great. So we have a
20 critical part of the panel meeting still to
21 go. I appreciate everyone's patience. There
22 is one speaker who wishes to address the panel
23 for our second public open hearing. After
24 that, we'll take a very abbreviated break and

1 then come back for our final FDA and sponsor
2 summation comments and panel deliberations.

3 DR. MAISEL: Good afternoon. I
4 realize you've all had a long day, and I will
5 try to keep my comments as brief as possible.
6 My name is William Maisel. I'm from the
7 Cardiovascular Division at Beth Israel
8 Deaconess Medical Center and Harvard Medical
9 School.

10 In the interest of full disclosure,
11 I was previously a member of this panel, sat
12 on the TAXUS panel, chaired the drug-eluting
13 stent panel meeting in December, and have been
14 chair to the post-market device panel as well.
15 I have no industry ties and I think that's
16 about all I have in the way of disclosures.

17 What I'd like to do is provide a
18 little bit of perspective and talk about the
19 topic we've just been discussing which is
20 post-market surveillance. I'd like to provide
21 a little background on the post-market
22 surveillance of the currently approved drug-
23 eluting stents, including the strengths and
24 weaknesses of the DES post-market monitoring

1 so that we can maybe not be doomed to repeat
2 our mistakes and we can duplicate the
3 strengths of those monitoring programs.

4 I'd like to talk briefly about this
5 device's surveillance issues and make a couple
6 of specific recommendations for the
7 surveillance of this device. Well, Cordis was
8 approved on April 24th, 2003 and Boston
9 Scientific approximately 11 months later.

10 And contrary to popular belief, the
11 FDA got it right. They recognized the concern
12 about long-term outcomes and specifically
13 mentioned that it was, quote, unknown at this
14 time, at the time of approval. They asked for
15 5-year outcomes on original randomized patient
16 cohorts. They requested a 2,000 U.S. patient
17 registry to evaluate, quote, for the potential
18 for less frequent adverse events. Sounds very
19 familiar. And they asked for reports 3, 6, 12
20 and 18 months after device approval and
21 annually thereafter. Sounds very similar to
22 what we are talking about now.

23 Now this is data that was presented
24 last December from Cordis and it shows six

1 CYPHER stent registries, and the main U.S.
2 registry was this one which enrolled about
3 2,000 patients. There was an Outside of U.S.
4 registry that enrolled 15,000 patients. And
5 the main, in retrospect, mistake was that
6 follow-up was only at 12 months. And so there
7 was no follow-up after a year for these
8 registries.

9 And so 1-year registry follow-up
10 for the Outside of U.S. registry was published
11 in March of 2006 and it said, this analysis of
12 1-year data suggests a high degree of safety
13 for SES with the rate of stent thrombosis
14 similar to that observed in clinical trials.
15 And ironically, the very same month, the
16 question of late stent thrombosis or very late
17 stent thrombosis really took hold.

18 Now certainly there was data
19 presented the prior year at TCT in 2005, but
20 there was a presentation at the ACC in March
21 2006 that raised concern. It was the basket
22 weight study, and we don't have time to go
23 over it in detail, but it was the
24 cardiovascular death and non-fatal MI was

1 higher in the drug-eluting stent group than in
2 the bare-metal stent group.

3 And by September, at the ESC annual
4 meeting, there was concern that the meta
5 analysis showed that in randomized trials, the
6 death and Q-wave rate was higher in drug-
7 eluting stents. And patients and physicians
8 were bombarded with conflicting headlines.
9 Here's a press release.

10 "Safety and efficacy of drug-eluting stents
11 reaffirmed." New York Times --
12 "Cardiologists question the risk of using
13 drug-coated stents. The FDA says we currently
14 do not have the data allows us to characterize
15 the risk ."

16 All within about 10 days of each other.

17 And so when we look back, it's
18 interesting to look at where DES information
19 comes from and what it says. So on the left
20 are industry press releases for 2006 and 2007
21 from Boston Scientific and Cordis, and I've
22 categorized them as either positive, meeting
23 pro-DES equivocal, or negative. And we can
24 see there are 84 press releases or about 1

1 every 9 days for 2 years, saying that, for the
2 most part, drug-eluting stents are good.
3 There's no red in that circle.

4 The FDA, in the middle, issued 3
5 statements or press releases for patients, 1
6 announcing the panel meeting, 1 summarizing
7 the panel meeting and 1 other one that were
8 all, I call them equivocal. There wasn't --
9 wasn't saying the sky is falling, wasn't
10 saying they're great.

11 And the real truth probably lies
12 more over here in the medical journals. And I
13 just took JACC, and there are certainly many
14 other journals that published. There were 50
15 articles over this 2-year period, about a
16 third were negative, in equal amounts
17 equivocal or positive.

18 And so one of the messages I have
19 is I'm very concerned that whatever comes out
20 of this panel or whatever post-market studies
21 are requested, it's important that it reach
22 this right-hand side of this screen as quickly
23 as possible for peer review, because I think
24 that's what patients and physicians need in

1 order to manage their patients correctly. And
2 I think this part of the equation, while
3 certainly important and critical to the
4 approval process, I don't think is where
5 patients are getting most of their
6 information.

7 The other point I'd like to make
8 and everyone's well familiar with this slide,
9 the Swedish registry, are some of the
10 strengths and weaknesses of registry data.
11 This is a landmark analysis that shows no
12 difference at 6 months between bare-metal
13 stenting and drug-eluting stenting with an
14 increased mortality rate in the drug-eluting
15 stenting group. And this was also presented
16 at the panel meeting in December and published
17 in the New England Journal this spring.

18 Well, DES patients more often had
19 diabetes, hypertension, prior interventions,
20 worse coronary disease, worse renal failure.
21 They were sicker patients and this supposedly
22 adjusted for it, but it was not randomized.
23 And perhaps most importantly, it was subject
24 to physician bias. And so for me, the other

1 message is in any registry, the advantage of a
2 randomized trial, which is you don't know what
3 you don't know, but it's equal in both groups,
4 is lost. And so we need to study the
5 physician bias. We can't just study the
6 patients and stents. We need to understand
7 why physicians chose this stent in these
8 patients so that we can better compare them to
9 other groups.

10 And ironically, or maybe not so
11 ironically, in September of this year, just
12 six months after the publication in the New
13 England Journal, a re-analysis with more
14 patients and more update, longer follow-up
15 said that this registry showed no overall
16 increase in deaths with drug-eluting stents.
17 This very well could be the poster child for
18 registry studies in some statistical course.

19 So what has the history of post-
20 market surveillance with the drug-eluting
21 stent taught us? That the original post-market
22 surveillance plan for the approved DES was
23 reasonable, but it would have benefitted from
24 longer mandated follow-up, from a better

1 understanding of physician stent choices and
2 better and more timely public reporting of the
3 events.

4 And I won't belabor the post-
5 approval from the study's sponsor other than
6 to say that the PROTECT study is a randomized
7 study. They're taking part of treatment
8 group, combining it with a registry and
9 comparing it to a different control group of a
10 different randomized trial. It seems a little
11 bit like a statistical felony, but I will
12 defer to some of the other statisticians who
13 have studied this well.

14 I think the choice of a control
15 group for the U.S. study concerns me, the
16 control group for the U.S. study is to compare
17 it to the bare-metal stenting from the
18 randomized control trial, which is a little
19 bit like comparing apples and oranges.

20 And as a lesson, if we look at the
21 ARRIVE registry data which was for the TAXUS
22 registry, and simple is another way of saying
23 on-label, and compare it to the TAXUS studies
24 which were on-label, what you can see is that

1 they're not the same. And the registry data,
2 not surprisingly, in real world environments
3 had a higher mortality rate. It was not
4 statistically significant but a 1.2 percent
5 increase in absolute mortality, the stent
6 thrombosis rate was higher, although, again,
7 underpowered to detect a statistical
8 difference. So these patients are not the
9 same. You can't -- it's not easy to compare
10 them.

11 And so I think a better control
12 group would be a concurrent registry of non-
13 Endeavor stent patients, certainly recognizing
14 the shortcomings of that and highlighting
15 again that we have to ask about the physician
16 reasons for stent selection.

17 The final point I'd like to make is
18 that I find the acceptable very late stent
19 thrombosis rate too high. I've mentioned that
20 the major objective was for an upper 95
21 percent confidence interval for very late
22 stent thrombosis should be less than 1 percent
23 for each 12-month period beginning at 12
24 months. That means, if I could rephrase it,

1 that it would be acceptable to have a 4
2 percent very late stent thrombosis rate at 5
3 years. And if we play through some numbers of
4 what that means, if we have 6 million stent
5 implants, and we can imagine what the market
6 share for this device might be, we're looking
7 at close to or more than 1 million stents
8 implanted. And for a 0.5 percent risk, not a
9 1 percent risk but half that risk increase in
10 the drug-eluting stent group, we'd be talking
11 about thousands of patients. And if this risk
12 were 1 percent or 3 percent, we're talking
13 about tens of thousands of patients. I think
14 1 percent is too high. We need to get more
15 precise.

16 And so if we do a power calculation
17 for on-label comparison, and I put in some
18 numbers for very late stent thrombosis and
19 some number for drug-eluting stents, for on-
20 label sample size comparison, if we pick 0 and
21 0.5, we're at about 3,900, and this is
22 assuming equal numbers in both groups. That's
23 the total number. That's not in each group.
24 That's a total of 4,000 patients. Or if we

1 have .1 and .7, we're looking at 4,000
2 patients. And so if we assume a 40 percent
3 on-label sample size, that means 60 percent
4 will be off-label. We're looking at
5 considerably larger numbers.

6 Now before you get all bent out of
7 shape about numbers that are at 10,000, which
8 is basically what I would recommend for a
9 registry, the TAXUS registries involved over
10 7,000 patients. Cordis registries involved
11 over 20,000 patients. This is not
12 unprecedented. It's very doable and I think
13 the numbers that we ask for need to be higher.

14 The final comment, which I already
15 touched on, is there's been a delay in public
16 reporting of study findings. Medtronic
17 mentions that they'd like to blind the results
18 for three years although they will be
19 submitting data to the FDA. I think the
20 blinding is unnecessary and needlessly delays
21 public access. I think the annual reports
22 that are submitted to the FDA should be made
23 public at the time of submission to the FDA so
24 that the public can have access to this data.

1 would ask everyone to please have a seat so we
2 can do this. Thank you for having a seat so
3 we can resume the meeting.

4 I think the panel was highly
5 impacted by Dr. Maisel's presentation, and we
6 want to thank him for bringing that
7 information forward. In that context then,
8 we'd like to resume the meeting by accepting
9 final comments from the FDA and then final
10 comments from the sponsor, abbreviated in both
11 perspectives, please. And we'd ask the FDA to
12 start and specifically to help us understand
13 what you've gleaned from our very important
14 discussions about the post-marketing effort.

15 MS. BOAM: Thank you, Dr. Yancy.
16 We also would like to thank Dr. Maisel for his
17 very thoughtful comments and wanted to add
18 just a little bit of FDA's perspectives with
19 respect to the post-approval study proposal
20 from Medtronic in the context of FDA's
21 expectations.

22 One important item to note is that
23 the post-approval study that would be used to
24 meet FDA's objectives would not involve a

1 comparison of any of the endpoints to the
2 CYPHER stent. The comparison of the CYPHER
3 stent is in the context of the PROTECT study
4 which Medtronic is running for their own
5 purposes. Only some of the patients would be
6 pulled from the protect study for the purposes
7 of evaluation of U.S. post-approval
8 objectives.

9 Secondly, I wanted to mention that
10 the proposed comparison to bare-metal stents
11 would only be for patients who received the
12 Endeavor stent on label. So for patients who
13 received the Endeavor stent in accordance with
14 it's labeled indications, both in the U.S. and
15 those patients from the Endeavor arm of
16 PROTECT, a comparison of the rates of cardiac
17 death and MI would be made back to the rates
18 observed for the Driver stent in the Endeavor
19 II study. So this really will be to the
20 extent possible in a non-randomized setting,
21 an apples to apples comparison.

22 I also wanted to mention that the
23 blinding issue that was raised, Medtronic has
24 chosen to blind the comparison of Endeavor II,

1 CYPHER and the PROTECT study. However, that
2 would not impact FDA's ability to both review
3 the U.S. post-approval data and the Endeavor
4 patients from PROTECT that would be pooled as
5 part of the U.S. post-approval plan, nor would
6 it impact our ability to include those data in
7 regular labeling updates so that that
8 information would be made publicly available.

9 Finally, I wanted to address FDA's
10 recommendation for the study to evaluate stent
11 thrombosis rates at a rate of less than 1
12 percent in each 12-month period following the
13 first year after implantation. Our suggestion
14 of this 1 percent figure was in the context of
15 a performance goal for the purpose of looking
16 for safety signals with adequate precision
17 such as for a continuous or an increasing
18 hazard as was discussed earlier today. This 1
19 percent figure was not intended to be an
20 absolute level for acceptable safety upon
21 which FDA would make regulatory decisions plus
22 or minus in terms of labeling or the stent
23 being available on the market. Thank you.

24 CHAIR YANCY: Thank you. Are there

1 any other comments from the FDA referable to
2 anything that we've discussed today?

3 The sponsor now has an opportunity
4 to respond, comment or pass.

5 MR. SALMON: On behalf of
6 Medtronic, we just wanted to thank the panel
7 for their thoughtful preparation and
8 consideration of this device. We also wanted
9 to thank the review team from the FDA for a
10 very professional and interactive review, and
11 we look forward to continuing the discussions
12 with the Food and Drug Administration with
13 regard to these important questions on post-
14 market surveillance and labeling prior to the
15 availability of this product in the United
16 States for patients and physicians. Thank
17 you.

18 CHAIR YANCY: Thank you. We are
19 now ready to vote on the panel's
20 recommendation to the FDA for this pre-market
21 application. Mr. Swink will now read the
22 panel recommendation options for pre-market
23 approval applications. Mr. Swink.

24 MR. SWINK: I will first read the

1 appointment to temporary voting status for Dr.
2 Lincoff. Pursuant to the authority granted
3 under the Medical Devices Advisory Committee
4 Charter of the Center for Devices and
5 Radiological Health dated October 27, 1990 and
6 as amended on August 18, 2006, I appoint
7 Michael Lincoff, MD as a voting member of the
8 Circulatory System Devices Panel for the
9 duration of this meeting.

10 For the record, Dr. Lincoff serves
11 as a member of the Cardiovascular and Renal
12 Drugs Advisory Committee of the Center for
13 Drug Evaluation and Research. He is a special
14 government employee who has undergone the
15 customary conflict of interest review and has
16 reviewed the material that was considered at
17 this meeting. This was signed by Randall
18 Lutter, Ph.D, Deputy Commissioner for Policy
19 on September 24, 2007.

20 The Medical Device Amendments to
21 the federal Food, Drug and Cosmetic Act as
22 amended by the Safe Medical Devices Act of
23 1990 allows the Food and Drug Administration
24 to obtain a recommendation from an expert

1 advisory panel on designated medical device
2 pre-market approval applications that are
3 filed with the agency. The PMA must stand on
4 its own merits and your recommendation must be
5 supported by safety and effectiveness data in
6 the application or by applicable publicly
7 available information.

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

19 Effectiveness as defined in 21 CFR
20 Section 860.7(e)(1) -- "There is reasonable
21 assurance that a device is effective when it
22 can be determined based upon valid scientific
23 evidence that in a significant portion of the
24 target population, the use of the device for

1 its intended uses and conditions of use, when
2 accompanied by adequate directions for use and
3 warnings against unsafe use, will provide
4 clinically significant results."

5 Valid scientific evidence as
6 defined in 21 CFR Section 86.7(c)(2) "is
7 evidence from well-controlled investigations,
8 partially controlled studies, studies and
9 objective trials without match controls, well-
10 documented case histories conducted by
11 qualified experts and reports of significant
12 human experience with a marketed device from
13 which it can fairly and reasonable be
14 concluded by qualified experts that there is a
15 reasonable assurance of safety and
16 effectiveness of a device under its conditions
17 of use. Isolated case reports or random
18 experience reports lacking sufficient details
19 to permit scientific evaluation and
20 unsubstantiated opinions are not regarded as
21 valid scientific evidence to show safety or
22 effectiveness."

23 Your recommendation options for the
24 vote are as follows. Number one, approvable

1 if there are no conditions attached.

2 Number two is approvable with
3 conditions. The panel may recommend that the
4 PMA be found approvable subject to specific
5 conditions such as physician or patient
6 education, labeling changes or further
7 analysis of existing data. Prior to voting,
8 all of the conditions should be discussed by
9 the panel.

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

18 Following the voting, the Chair
19 will ask each panel member to present a brief
20 statement outlining the reasons for his or her
21 vote. Thank you.

22 CHAIR YANCY: Are there any
23 questions from the panel about these voting
24 options before I prompt us to take a vote.

1 Again, the choices are approval if there are
2 no conditions attached, approvable with
3 conditions if you feel that a condition needs
4 to be specified, or not approvable if you
5 believe the data do not meet reasonable
6 assurances of safety and efficacy.

7 There is a chart in your blue
8 folder that outlines the voting procedure so
9 that we can through this in an orderly manner.
10 Are there any questions? Dr. Hirshfeld?

11 DR. HIRSHFELD: Yes. I'd just like
12 to make sure that I know whether the
13 requirement for and the design of the post-
14 market studies is considered a condition or
15 whether that's independent of the approval
16 process.

17 CHAIR YANCY: It is considered a
18 condition. Other questions? Having said that
19 then, is there a motion for either approval,
20 approvable with conditions or not approvable
21 from the panel? Dr. Morrison?

22 DR. MORRISON: I'd move to vote for
23 approvable with conditions.

24 CHAIR YANCY: It has been moved.

1 Is there a second? There's a second from Dr.
2 Hopkins and Dr. Lincoff.

3 (Whereupon, Panel has moved and
4 seconded PMA as approvable with conditions.)

5 CHAIR YANCY: We will not discussed
6 the main motion briefly but will not vote
7 until we decide which conditions. But at this
8 point, we'll discuss this main motion. Is
9 there any discussion to approve with
10 conditions? Seeing no discussion, are there
11 conditions that we would like to put forward?
12 Dr. Somberg?

13 DR. SOMBERG: The -- it seems from
14 some of the panel members questioning of the
15 sponsor that there was much additional
16 information that's been locked given their
17 analysis system. And I would like to say that
18 while this panel will not have the opportunity
19 of seeing that, I think unlocking that data
20 and presenting it to the FDA would give a much
21 more robust safety signal, so I'd like to see
22 that as a condition for approval, and I think
23 that would satisfy some of my doubts that
24 there was an adequate database at this time.

1 CHAIR YANCY: So your condition
2 would be for continued access to data from
3 already completed trials, follow-up data?

4 DR. SOMBERG: Well, the word
5 continued is -- I know what you're -- you're
6 trying to put it into some language, and I
7 appreciate I didn't do a good job. But
8 specifically, Dr. Naftel, you mentioned that
9 you thought there was a considerable amount of
10 additional data there in the analysis but that
11 that was not brought forth, because there's
12 such a long 1-year period of locking that data
13 in.

14 So I would like to see the data
15 that has been completed that could provide
16 additional information on the very late stent
17 thrombosis safety signal, should be evaluated
18 by FDA as a final road to approval. Does that
19 help in working it?

20 DR. ZUCKERMAN: No, Dr. Somberg. I
21 want the panel to understand the following,
22 and the panel members can vote any way they
23 want to, but if they do vote approvable with
24 conditions, it's with the understanding that

1 as of today, October 10th, I believe, at 5:00
2 p.m., these are the data that support the
3 approval.

4 The agency and sponsor, of course,
5 will always continue to look at subsequent
6 data. And, in fact, in the DES arena, we have
7 made special efforts to make sure that its
8 timely updating of data reporting. But we
9 have to make our decision today based on the
10 data in your three volumes here.

11 DR. SOMBERG: Then I withdraw my --

12 CHAIR YANCY: So the motion is
13 withdrawn, so we're standing with a motion to
14 approve with conditions and we're waiting for
15 the first condition. Dr. Morrison?

16 DR. MORRISON: The first condition
17 I would propose is the details of the post-
18 marketing surveillance study be established.

19 CHAIR YANCY: So not only a post-
20 market study, but you'd want the condition to
21 be with the details -- just so I can be clear
22 on your condition.

23 DR. MORRISON: Well, at the very
24 least, I think we should establish what sample

1 size and what duration and what endpoints of
2 the post-marketing surveillance we expect,
3 because I think Dr. Maisel's plea was that
4 this is our best opportunity to make sure we
5 get it.

6 CHAIR YANCY: If we can permit
7 discussion on trying to craft an entire post-
8 market study at this moment, we just need to
9 appreciate the enormity of that. So the
10 question is -- and I'll do -- I'll follow your
11 motion -- but is the condition approvable with
12 a post-market study, or is it approvable with
13 a post-market study design?

14 DR. MORRISON: Well, I would like
15 some consensus that the proposal to take the
16 patients from the OUS PROTECT study and the
17 2,000 patients enrolled in this either do or
18 do not constitute an adequate sample size,
19 that 5-year duration is adequate and that the
20 primary endpoint is late stent thrombosis and
21 secondary endpoint is death and MI, and
22 perhaps any other data that people feel
23 strongly about, because if we don't specify
24 those things, I don't think we're helping

1 either the agency or industry to understand
2 what we would like so that we don't have to
3 come back and --

4 CHAIR YANCY: So we can --

5 DR. MORRISON: -- the way people
6 felt in December in 2006.

7 CHAIR YANCY: So that we can put
8 something in a context where it can be
9 seconded. The motion then is approvable with
10 condition. The condition being a post-market
11 study that combines a 2,000 patient cohort
12 with data from PROTECT and a longitudinal
13 follow-up that looks at late stent thrombosis.
14 Is that what you said?

15 DR. MORRISON: I'm happy to say
16 that as a starting point, but obviously --

17 CHAIR YANCY: And that's good --

18 DR. MORRISON: -- there are a lot
19 of people who are much better than I am
20 sitting here at the table and I would hope one
21 or more of them would provide some input.

22 CHAIR YANCY: So can we second or
23 can we --

24 DR. LINCOFF: I'll second.

1 CHAIR YANCY: Okay.

2 DR. LINCOFF: But -- so can we say
3 -- we've discussed that previously as question
4 6.

5 CHAIR YANCY: Right.

6 DR. LINCOFF: Can we say subject to
7 the design considerations that we discussed in
8 --

9 CHAIR YANCY: If you can be a
10 little bit more specific.

11 DR. LINCOFF: So a post-marketing
12 approval study be conducted of the structure
13 and duration with the objectives that we had
14 previously discussed in our answers to
15 question 6.

16 CHAIR YANCY: Yes.

17 DR. SOMBERG: I think, and correct
18 me if I'm wrong, Dr. Morrison, but I think
19 what the proposal of the motion was is that --
20 and I was influenced, too, by Dr. Maisel's
21 presentation who thought out some of my
22 feelings, and that was the size, the need for
23 a control, and some other considerations which
24 we can begin to elaborate.

1 But certain guideposts -- I know we
2 can't do a whole study, but I think not 2,000
3 but 5,000 patients looking at the endpoint,
4 the primary and secondary endpoint you clearly
5 defined right now, very late stent thrombosis,
6 death and MI, secondary endpoints, and needing
7 of a control group were things that I would
8 like to see in your motion if you would accept
9 my suggestions.

10 DR. MORRISON: I accept all of them
11 except for the control group. I would agree
12 with Dr. Maisel that it's problematic trying
13 to apply statistics to two registry groups at
14 the end of the day that have very different
15 selection biases going in.

16 DR. MORRISON: But I thought he
17 said that -- I took it -- well, I guess we --
18 everyone hears what they want to hear. I
19 heard there was a need for a control group,
20 but I won't argue with that. Thank you for
21 accepting those.

22 CHAIR YANCY: Dr. Lincoff?

23 DR. LINCOFF: I think Dr. Maisel
24 did say he thought there was a control, but I

1 continue to disagree with that for the reason
2 -- I think what I would second would not be a
3 control group but --

4 CHAIR YANCY: So let's see if we
5 can crystalize a motion that we can move
6 forward for a vote. So this is approval with
7 condition, the condition being a post-market
8 study that is of the size of at least 5,000
9 patients, has a primary endpoint of late stent
10 thrombosis and a second endpoint of death or
11 MI -- very late stent thrombosis by
12 definition, and is a single-arm registry using
13 objective performance criteria. Can we agree
14 on the high points? Has that motion been
15 second? Dr. Hirshfeld?

16 DR. HIRSHFELD: One other modifier
17 to that. I think that when FDA staff work
18 with the sponsor on the design of the study,
19 it should be assured that the data collection
20 methodology is very robust, because I think I
21 heard comments about a very small fraction of
22 the total of cases being monitored. And if
23 that's the case, I think the opportunity to
24 accurately capture all the events may be

1 relatively weak.

2 So I think if we're going to use
3 this as a means of characterizing what the
4 true stent thrombosis rate is and what the
5 baseline variables that predispose to stent
6 thrombosis are, we need to be certain that the
7 methodology for collecting the data is robust.

8 CHAIR YANCY: So what I've captured
9 on this motion vis-a -- I'm sorry --

10 DR. SOMBERG: There was one other
11 thing. The duration was 5 years I think the
12 recommendation.

13 CHAIR YANCY: Correct.

14 CHAIR YANCY: So what I've captured
15 for this motion, that it is approvable with
16 condition, and these will be the tenets of the
17 post-market study -- at least 5,000 patients,
18 single-arm registry using objective
19 performance criteria compared to bare-metal
20 stent, primary endpoint is very late stent
21 thrombosis, second endpoint death or MI with
22 rigorous data monitoring and at least 5-year
23 follow-up. Is there a second motion?

24 DR. HIRSHFELD: Second.

1 DR. SOMBERG: Second.

2 CHAIR YANCY: And is there a vote?
3 All in favor? Those opposed. So the first
4 condition passes.

5 (Whereupon, unanimous vote reached
6 in favor of motion for approvable with
7 aforementioned condition.)

8 CHAIR YANCY: Is there a motion for
9 another condition? This is approvable with
10 condition and we're looking for condition two.
11 Yes?

12 DR. SOMBERG: That there be
13 instituted a post-marketing study to evaluate
14 antiplatelet therapy duration.

15 CHAIR YANCY: Is there a second for
16 this motion? Without a second, the motion
17 dies. Is there another condition? Dr.
18 Hopkins?

19 DR. HIRSHFELD: I would move that
20 the label under indications restore the word
21 "single" prior to de novo as was indicated in
22 the studies.

23 CHAIR YANCY: Is there a second for
24 that motion?

1 UNIDENTIFIED SPEAKER: I'll second.

2 CHAIR YANCY: Discussion? All in favor
3 of the motion that's been put forward? Two in
4 favor. Those opposed? That motion does not
5 go forward. Is there another motion for
6 conditions for approvability with condition
7 for this PMA? Seeing no other motion -- yes?

8 DR. SOMBERG: I just don't want to
9 belabor this point, but can you -- can the
10 Chairman refresh my memory of what is going to
11 end up with the consideration with dual -- if
12 we approve this motion as it is now, what is
13 going to be the recommendation for dual
14 antiplatelet therapy? Are we going to accept
15 what the -- does this motion entail what the
16 company said was 3 months is recommended or
17 does it not? That's my concern. I'm not so
18 concerned about whether I have another study
19 or not, but I'd like to know what we are going
20 to end up recommending before I vote to
21 approve or disapprove.

22 CHAIR YANCY: To answer your
23 question, I would refer you to FDA question 3
24 which we deliberated earlier and came up with

1 a global statement that the language that the
2 sponsor put forward was not acceptable and
3 that prescribed in 6 months was not
4 acceptable, but rather that the use of dual
5 antiplatelet therapy as done in the trials be
6 indicated within the label and that in lower
7 risk, they be prompted to follow the
8 guideline. That's what we deliberated.

9 DR. SOMBERG: I remember the
10 discussion but those were sort of like
11 general, and now we're having a vote here.
12 I'm sort of procedurally lost is what I'm
13 telling you.

14 CHAIR YANCY: Well, no we put
15 forward a motion and it was rejected, so we're
16 procedurally sound.

17 DR. SOMBERG: No. I said, I, not -
18 - I'm not --

19 CHAIR YANCY: So Dr. Morrison?

20 DR. MORRISON: Well, I would
21 strongly second or be happy to propose that we
22 make an additional condition that the label
23 suggest 12 months of antiplatelet therapy so
24 that in other words, the approval is

1 conditional on that additional condition.

2 CHAIR YANCY: And so that's an
3 appropriate way to bring this forward and I
4 appreciate that. So you've heard another
5 motion is that the label have precise language
6 that prompts 12 months dual antiplatelet
7 therapy in patients not at high risk for
8 bleeding. Is that fair? Discussion?

9 DR. WEINBERGER: Can I just suggest
10 a modification on that? And that is to say
11 that we recommend that we follow the
12 guidelines of the appropriate societies,
13 because that will change with time. I don't
14 want to be locked into 12 months as further
15 data comes out. So the recommendation in the
16 IFU should be that guidelines established by
17 AHA/ACC would be appropriate for antiplatelet
18 therapy.

19 CHAIR YANCY: So please restate
20 your motion so we can seek a second?

21 DR. MORRISON: The condition for
22 approval includes the statement in the IFU
23 that recommended duration of dual antiplatelet
24 therapy follows appropriate guidelines and

1 which currently is 12 months.

2 CHAIR YANCY: So that is the
3 motion. Is there a second?

4 DR. LINCOFF: I do.

5 CHAIR YANCY: There is a second
6 discussion?

7 DR. LINCOFF: Yes. I don't want to
8 keep clarifying but to be even more specific,
9 I mean the guideline that the FDA presented
10 that is now being used for CYPHER and TAXUS
11 was very complete. Can we specifically say
12 that identical guideline that said that 3 and
13 6 months had been used in trials, there's some
14 evidence that more is better, up to 12 months
15 in patients who are not at high risk for
16 bleeding complications as per the ACC/AHA
17 guidelines.

18 CHAIR YANCY: Would you like to
19 modify your motion to reflect the language
20 that Dr. Lincoff just used?

21 DR. MORRISON: Absolutely.

22 DR. LINCOFF: And then I second.

23 CHAIR YANCY: So there is a second.
24 So Dr. Lincoff, will you restate the motion?

1 DR. LINCOFF: That the recommended
2 duration of antiplatelet therapy use the exact
3 language that the FDA changed on the basis of
4 the December 2006 meeting that we just saw.
5 Then the text of that can be provided.

6 CHAIR YANCY: So the condition is
7 is approval with condition, this condition
8 being the use of dual antiplatelet therapy per
9 prevailing language and consistent in patients
10 who are not at high risk with the stated
11 guidelines subject to change? Is there a
12 second for that?

13 DR. HOPKINS: Second.

14 CHAIR YANCY: All in favor? That
15 condition carries.

16 (Whereupon, motion passed on
17 approvable with condition referenced above.)

18 CHAIR YANCY: Are there other conditions
19 for this PMA before we take a final vote?
20 Seeing no other conditions put forward, the
21 vote will be the following. We will be voting
22 for approvable with conditions and the
23 conditions we've outlined are two-fold. The
24 first condition is approvable with a post-

1 marketing study that incorporates at least
2 5,000 patients in a single-arm design using
3 objective performance criteria based bare-
4 metal stent events; primary endpoint is very
5 late stent thrombosis; secondary endpoint is
6 death or MI, with a rigorous data monitoring
7 and at least 5 years of follow-up.

8 And the second condition is for
9 language reflecting the use of dual
10 antiplatelet therapy consistent with
11 prevailing FDA language that follows the
12 guidelines as stated by professional societies
13 prompting 12 months in those patients not at
14 high risk for bleeding subject to change. Are
15 we ready for the vote? Those in favor?
16 Actually, there's some language -- put your
17 hands down. There's something I have to read
18 to you.

19 (Laughter.)

20 CHAIR YANCY: This is a government
21 thing. It has been moved and seconded that
22 the Medtronic PMA Application P060033 for the
23 Endeavor Zotarolimus-Eluting Coronary Stent
24 System is found approved with the conditions

1 the panel has just voted on. We will now vote
2 on the main motion.

3 With a show of hands, please
4 indicate if you concur with the
5 recommendations that the above-named PMA be
6 found approvable with conditions. You'll have
7 to keep your hand up so we can call your name
8 out for the record.

9 Dr. Lincoff votes in favor, Dr.
10 Naftel, Dr. Hirshfeld, Dr. Lindenfeld, Dr.
11 Kato, Dr. Somberg, Dr. Weinberger, Dr.
12 Hopkins, Dr. Morrison. That vote is
13 unanimous.

14 It is the recommendation of the
15 panel to the FDA that the Medtronic PMA
16 Application P060033 for the Endeavor
17 Zotarolimus Drug-Eluting Coronary Stent System
18 is approved with the previously voted upon
19 conditions.

20 (Whereupon, unanimous vote PMA
21 P060033 is approvable with the conditions
22 panel has voted on above.)

23 CHAIR YANCY: I will now request
24 that each panel member state the reason for

1 his or her vote starting with Dr. Lincoff.

2 DR. LINCOFF: I believe there's
3 reasonable evidence of efficacy based upon the
4 Endeavor II trial and, to a lesser extent, on
5 the Endeavor IV trial and that the data for
6 safety with regard to stent thrombosis and
7 late stent thrombosis is appropriate given the
8 stage of development and reasonable level of
9 safety.

10 CHAIR YANCY: Dr. Naftel?

11 DR. NAFTEL: I believe that the
12 analyses that we've seen today have painted a
13 very clear picture, and it totally helped me
14 understand how the Endeavor compares to bare-
15 metal stent and to drug-eluting stent. All of
16 the results across the studies seemed
17 incredibly consistent, so that's why I voted.

18 But I would like take a second to
19 tell Medtronic that this little detail about
20 follow-up that we've discussed, it's not a
21 little detail, because what could happen --
22 first of all, I'm sure you understand what
23 you've told me -- that you stopped follow-up
24 at annual periods, so there was a whole hunk

1 of stuff.

2 So what could happen when you re-
3 look at the data a year from now, there could
4 be some deaths and some stent thromboses that
5 happened last April that you'll have to report
6 on, and I think it's going to be embarrassing.
7 So I think you made a mistake in that decision
8 in the way you cut the data. But it doesn't
9 negate any of the good stuff about the study.
10 But I would I rethink that as a company
11 policy. Thank you.

12 CHAIR YANCY: Dr. Hopkins has a
13 flight to catch, so we will proceed.

14 DR. HOPKINS: Thank you, Mr.
15 Chairman. I also agree that safety has been
16 well demonstrated with good study design to
17 demonstrate that. Efficacy is a more
18 complicated issue, but in the context of a
19 combined device biologic, this device has some
20 real pluses, and I think that time will tell
21 where it sorts out. But it certainly is in
22 the ballpark with everything that's available,
23 so effectiveness has been demonstrated to my
24 satisfaction as well. Thank you.

1 CHAIR YANCY: Thank you for your
2 help today. Dr. Hirshfeld?

3 DR. HIRSHFELD: I agree that safety
4 and efficacy has been demonstrated. I
5 personally went through an interesting
6 evolution as I studied the data, because my
7 initial bias was colored by the reduced
8 efficacy to inhibit neointimal growth compared
9 to the other marketed drug-eluting stents.
10 And so I was intrigued and somewhat surprised
11 to find that the efficacy appeared to be in
12 the same ballpark with the other drug-eluting
13 stent.

14 And I think in terms of how I'm
15 going to apply this to my own practice, I
16 think we all still need to do some serious
17 thinking about what the role of this stent is
18 going to be vis-a-vis the other stents that
19 are available, and so I think that awaits a
20 lot more data and experience.

21 CHAIR YANCY: Dr. Lindenfeld?

22 DR. LINDENFELD: I agree in that I
23 think that safety has been well shown and that
24 we have adequate post-marketing follow-up to

1 show safety in the long run and efficacy
2 compared to bare-metal stents has been shown.
3 And comparability to other drug-eluting
4 stents, I think I'm confident of at least the
5 early data.

6 CHAIR YANCY: Thank you. Dr. Kato?

7 DR. KATO: I voted for -- I still
8 have some reservations regarding the total
9 number of patients followed. I think as
10 demonstrated in Dr. Maisel's presentation, I
11 think the numbers, and particularly when we're
12 looking at very small frequency of adverse
13 events does require, you know, 5,000, 6,000,
14 10,000 patients to look at.

15 Fortunately, coronary disease is
16 not an orphan disease process. It's rampant
17 throughout the world. And so I am cautiously
18 optimistic that Medtronic and the FDA will
19 continue on this course of getting that data
20 so that we can increase our confidence as to
21 the use of this new product.

22 That said, I'm still a little bit
23 unsure where the product fits in the grand
24 scheme of drug-eluting stents, maybe better

1 than one, maybe equivalent to one, maybe a
2 little bit worse than another. And again, you
3 know, we just don't have the data to make any
4 other comment other than that. So I guess at
5 the end of the day, I hope that the sponsor
6 and the FDA will work diligently to do the
7 post-market surveillance study and get the
8 data out and distribute it as quickly as
9 possible.

10 CHAIR YANCY: First of all, Chair
11 would like to apologize to Dr. Somberg if any
12 of my most recent comments were ill placed on
13 Dr. Somberg.

14 DR. SOMBERG: I don't know what
15 you're apologizing for, but I think it's been
16 a fine meeting and there's no problems.
17 Absolutely. But let me say I voted
18 reluctantly approval of this product, not
19 because I think there is an inherent lack of
20 efficacy or safety signal or it's dangerous.
21 In fact, I think the sponsor should be
22 congratulated, I've sat on this panel for
23 three plus years here and have seen all sorts
24 of devices come with, really, much more meager

1 material, and this is robust and to be
2 congratulated. And I'm not saying that to
3 please you, but it's really bringing up the
4 device area to a level of regulatory
5 requirements that we should see in every area.

6 With that said, I'm just concerned
7 about a couple of things, and one is in the
8 efficacy area. Yes in this very careful
9 population, which I don't think you did by
10 design, but it worked out that we have a
11 little bit of neointimal hyperplasia than the
12 other two DES's and how that will play out
13 with more complex lesions in the real world, I
14 don't know. And this is going to be an
15 important thing to keep an eye on.

16 But what I was most concerned about
17 was that there, for very late stent
18 thrombosis, which is really the safety issue
19 with DES, that we just had 670 patients, I
20 felt, was insufficient. But with the
21 amendments to the approval that we are going
22 to get a robust post-marketing study, that
23 will be known and whether the regulatory
24 aspect ever has to turn on this drug or not I

1 don't think is nearly as important as the
2 marketplace will know what will be happening,
3 and that will be the most important check on
4 its inappropriate use.

5 I also would like to say that I
6 feel that the whole field of DES is not looked
7 at the dual antiplatelet therapy, and I don't
8 want to single out Medtronic here, but
9 certainly post-marketing studies in that area
10 are needed. Otherwise, we would go to class
11 labeling and that just means we don't know,
12 and I don't think with all the money and
13 effort you've put into, that we should end up
14 not knowing when there is a good hypothesis
15 here that this particular antiproliferative
16 agent may indeed prevent very late stent
17 thrombosis and not need as long antiplatelet
18 therapy, which in and of itself is a risk.
19 Sorry to have gone on too long.

20 CHAIR YANCY: Dr. Weinberger?

21 DR. WEINBERGER: I have to
22 reiterate the safety and efficacy issue
23 discussed by everyone else. I think that this
24 device has a real place in the DES universe,

1 and the place that it has based upon what I
2 know so far, and I'm sure there'll be future
3 data coming out, is that as of today, if a
4 patient can tolerate antiplatelet therapy out
5 as long as a year or two, I don't have a
6 strong reason to prefer this device.

7 But if I have a patient for whom
8 the risks or the likelihood of being able to
9 continue antithrombotic therapy is limited, I
10 think that this device looks to me like it's
11 probably going to have a clear cut role.
12 Clearly, it's better than BMS. Whether it's
13 as good as the other DES's, we'll find out.
14 And there's a smell in the data that you're
15 likely going to be able to get away with a
16 little less antiplatelet therapy, but without
17 the randomized trials, I think it's going to
18 be individual practitioners deciding to do
19 what they want to.

20 CHAIR YANCY: Dr. Domanski wasn't
21 able to vote today, but I'd like to have your
22 comments, please?

23 DR. DOMANSKI: I think that safety
24 and efficacy was reasonably demonstrated.

1 CHAIR YANCY: Thank you. Dr.
2 Morrison?

3 DR. MORRISON: Well, I'm impressed
4 since I have come to the FDA meetings that
5 the emphasis from the agency seems to first be
6 on safety, and my career as a physician is
7 almost diametrically opposite. It seems to me
8 it's our job as clinicians to decide that a
9 patient really is likely to benefit from re-
10 vascularization, and then really likely to
11 benefit from PCI before we get into any of
12 that and that any risk is too high in people
13 that really don't need it.

14 So it seems to me, from clinical
15 experience, the Driver is an excellent stent
16 and having further reduction as demonstrated
17 in Endeavor II of restenosis is really quite
18 important. I'm trying to quell the desire to
19 be excited about the very preliminary finding
20 that they're reduced, they appear to be
21 reduced early non-Q-MI's, that maybe the
22 endothelialization with this is over and we'll
23 finally have a product that achieves the
24 plateau phase we though we had with bare-metal

1 stent.

2 But for the time being, I really
3 also agree with Dr. Maisel that we're at a
4 threshold where the agency can really change
5 healthcare by encouraging, shall we say,
6 industry to obtain the kind of prospective
7 safety data that's been proposed here. So I
8 think this is potentially a very useful
9 product. I'm not nearly as concerned as I
10 thought I might be about the surrogate
11 endpoint outcomes in Endeavor III and IV. And
12 I think that if the prospective post-marketing
13 surveillance works the way we all hope it
14 will, that this could be a big win for
15 patients.

16 CHAIR YANCY: Thank you. Dr.
17 Zuckerman.

18 DR. ZUCKERMAN: Okay. I want to
19 thank the panel for an extremely good day of
20 work today. The agency benefitted greatly as
21 well as the sponsor by your remarks. Just in
22 reply to Dr. Morrison's statements, I think
23 it's evident even as we see better products
24 that your responsibility as a physician is

1 never replaced by an FDA approval.

2 On the other hand, we've heard from
3 the entire panel today that there is
4 definitely a need to better understand the
5 pharmacology involved with these products.
6 The agency, through its Critical Paths program
7 is very interested in working with sponsors on
8 either an individual basis or a cooperative
9 basis to get the proper clinical trials going
10 as quickly and as efficiently as possible.

11 And I hope that the sponsors as
12 well as the outstanding physicians here today
13 have really taken to heart the comments made
14 by this panel. And we would certainly, from
15 the agency's perspective, be very willing to
16 move forward on this important question.

17 CHAIR YANCY: Thank you. We're not
18 done yet. Ms. Rue, please, as our consumer
19 representative?

20 MS. RUE: Everything was answered
21 very well and I appreciate the opportunity.

22 CHAIR YANCY: Thank you. Dr.
23 Yaross?

24 DR. YAROSS: I'd also like to

1 congratulate the sponsor on their excellent
2 program and presentation today and also thank
3 the panel and FDA for a balanced and thorough
4 discussion of most of the issues that are of
5 importance to industry.

6 That said, I believe I'd be remiss
7 if I didn't caution the panel on over
8 extrapolating from today's discussion on U.S.
9 versus OUS data. From discussions with FDA,
10 you know, there are times when there are
11 discernible differences in pharmacology or
12 relevant demographics that may mandate U.S.
13 studies. But in general, there is no specific
14 requirement in the medical device law for U.S.
15 based trials and just wanted to caution the
16 panel in terms of that for the future. Thank
17 you.

18 CHAIR YANCY: Thank you. I too
19 want to thank the FDA for a very concise and
20 clear presentation and the sponsor especially
21 for all the work you've done to bring this
22 information forward. It was a pleasure to
23 listen to the deliberations, so thank you for
24 that.

1 The Chair would have voted with the
2 majority and I believe the right decision was
3 made to approve this with conditions. There
4 are three comments that I'd like to make and
5 the first comment is that the most intriguing
6 thing that I observed today was the data
7 demonstrating evidence of endothelialization
8 early. I think with the preexisting stent
9 platforms, DES platforms, significant concern
10 has been raised and, in fact, may prompt very
11 late stent thrombosis because of the delay in
12 the endothelialization. And even though we've
13 represented it today as a lesser sign of
14 adequacy for the DES stent, the Endeavor, it
15 might, in fact, over the long term be a
16 reasonable feature. And so due diligence with
17 the studies that have been outlined would be
18 very appropriate to see if that translates to
19 a reduction, the most important thing that has
20 galvanized all of our interest which is a very
21 late stent thrombosis.

22 The second thing is like Dr.
23 Somberg, I have a limited tenure with this
24 committee and I've yet to see a post-marketing

1 study come back to this panel in a way that it
2 was reasonably done and relatively
3 straightforward to interpret. A lot of effort
4 has been put into the design of this post-
5 marketing study and it is our expectation that
6 that will be followed through, because it's
7 the only way that the field can go forward and
8 that there can be any integrity in this
9 process.

10 And then lastly, I'd like to thank
11 the panel. This obviously was an important
12 issue. We've stayed a little bit longer than
13 designed, but everyone provided invaluable
14 contribution and tolerated me so my personal
15 thanks for that.

16 With that having been said, we're
17 adjourned. Thank you very much.

18 (Whereupon, at 5:53 p.m., the
19 foregoing matter was concluded.)

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