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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGIC HEALTH

CIRCULATORY SYSTEM DEVICES ADVISORY PANEL MEETING
CLINICAL TRIAL REQUIREMENTS
FOR FUTURE EVALUATION OF CORONARY STENTS

Monday, December 7, 1998

8:00 a.m.

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1 P R O C E E D I N G S

2 **Call to Order**

3 DR. CURTIS: I would like to go ahead and call
4 this meeting to order.

5 This meeting of the Circulatory System Devices
6 Panel is going to be discussing recommendations for clinical
7 trial requirements for future approval of coronary stents.

8 The first order of business will be the reading of
9 the conflict of interest statement by Dr. Stuhlmuller.

10 **Conflict of Interest Statement**

11 DR. STUHLMULLER: The conflict of interest
12 statement. The following announcement addresses conflict of
13 interest issues associated with this meeting and is made a
14 part of the record to preclude even the appearance of an
15 impropriety.

16 To determine if any conflict existed, the Agency
17 reviewed the submitted agenda for this meeting and all
18 financial interests reported by the committee participants.
19 The conflict of interest statutes prohibit special
20 government employees from participating in matters that
21 could affect their or their employer's financial interests.
22 However, the Agency has determined that participation of
23 certain members and consultants, the need for whose services
24 outweighs the potential conflict of interest involved, is in
25 the best interests of the government.

1 Therefore, waivers have been granted for Drs.
2 Brinker, Fitzgerald, Oesterle, and Vetovec for their
3 interest in firms that could potentially be affected by the
4 panel's recommendations.

5 Copies of these waivers may be obtained from the
6 Agency's Freedom of Information Office, Room 12A-15 of the
7 Parklawn Building.

8 We would like to note for the record that the
9 Agency took into consideration other matters regarding Drs.
10 Fitzgerald, Oesterle, Vetovec, and Curtis. Each of these
11 panelists reported interest in firms at issue, but in
12 matters that are not concluded or related to today's agenda.
13 for today's session. The Agency has determined, therefore,
14 that they may participate fully in all discussions.

15 The Agency would also like to note for the record
16 that Dr. Warren Laskey, who is a guest today, has identified
17 himself as having an interest in one of the firms at issue.

18 In the event that the discussions involve any
19 other products or firms not already on the agenda for which
20 an FDA participant has a financial interest, the participant
21 should excuse him or herself from such involvement and the
22 exclusion will be noted for the record.

23 With respect to all other participants, we ask in
24 the interest of fairness that all persons making statements
25 or presentations disclose any current or previous financial

1 involvement with any firm whose products they may wish to
2 comment upon.

3 **Old and New Business**

4 DR. CURTIS: There is no old business that needs
5 to be addressed this morning, so we will move on to the new
6 business. I would just like to let you all know, for anyone
7 who does not, that the order of the speakers for the open
8 public hearing is on the agenda that is available out at the
9 table, so that the speakers know what order they are going
10 in.

11 The next thing I would like to do is have everyone
12 go around the table and introduce themselves. We are
13 missing a few people here, but for everybody else who is
14 here, I would like to go ahead.

15 Dr. Fitzgerald.

16 DR. FITZGERALD: Peter Fitzgerald, Stanford
17 University.

18 DR. TRACY: Cynthia Tracy, Georgetown University.

19 DR. DOMANSKI: Mike Domanski, NHLBI.

20 DR. BRINKER: Jeff Brinker, Johns Hopkins.

21 DR. CURTIS: Anne Curtis, University of Florida.

22 I am an electrophysiologist there.

23 DR. STUHMULLER: John Stuhlmuller, FDA.

24 For the record, I need to note that our industry
25 rep and consumer rep are unable to attend at the last

1 minute, and replacements were not found.

2 DR. BAILEY: Kent Bailey, Mayo Clinic,
3 Biostatistics.

4 DR. VETROVEC: George Vetrovec, Medical College of
5 Virginia, Virginia Commonwealth University.

6 DR. LASKEY: Warren Laskey, University of
7 Maryland.

8 DR. CURTIS: We will move on now to the FDA
9 Introduction.

10 **FDA Introduction**

11 DR. BURLINGTON: Hi. I am Bruce Burlington. I am
12 the Center Director here at the Center for Devices, and I am
13 here to say welcome.

14 [Slide.]

15 I appreciate the help of the slides here.

16 [Slide.]

17 As they were set up by the team, we have for today
18 a mission, and that is to facilitate the development and
19 evaluation of stent technology in the United States, and we
20 have goals under that mission. We are very bureaucratically
21 organized, so we try and have missions and we try and have
22 goals in order to facilitate our understanding of what we
23 are about today.

24 [Slide.]

25 Goal No. 1 is to adaptively evolve preclinical

1 requirements and clinical trial designs for stents and
2 related equipment as appropriate to the changing clinical
3 knowledge base.

4 Well, I looked at this and I realized that the
5 people who put this slide together were really trying to
6 tell us something, and was trying to figure out exactly what
7 it meant, and I realized that one of the things that had
8 happened is probably a lot of you are aware that Vice
9 President Gore has a program in which he wants those of us
10 in the Federal Government to simplify the language we are
11 using and put everything in plain English.

12 So, we went down and talked to people in that
13 program, and in putting together these slides, we chose all
14 the things they had rejected.

15 What I think this really means is we know a lot
16 more about stents, we know a lot more about the good they
17 do, and we know a lot more about design, and we think that
18 all that knowledge means that we can look at future stents
19 differently than we did at the beginning, and we are here to
20 try and figure that out.

21 [Slide.]

22 Goal No. 2. To develop, by example, a viable
23 approach to acquiring and using input from the panel,
24 industry and investigators for establishing appropriate
25 clinical data requirements.

1 Okay. That one, what does it mean? I think it
2 means we are going to be here, and we are going to ask you
3 guys to help us figure out what we should be looking for in
4 the development of the next generation of stents, and that
5 we are going to then use this as a model, so that when we
6 look at other products where we begin to acquire a large
7 knowledge base, that we can use that in a rational way to
8 move forward with subsequent generations of products.

9 If I get this wrong, Dan, you are supposed to tell
10 me.

11 [Slide.]

12 A paradigm for device development, so far blank,
13 but it is supposed to fill in here. Good science. Of
14 course, we want to do it right, and we want to good science,
15 not only for its own sake and the value it brings to the
16 public, but also because we have a statutory requirement to
17 use evidence-based decisionmaking in market authorizations.
18 That evidence can't just be any type of evidence, it has to
19 be evidence based on valid science, and we have a statutory
20 obligation to consider the least burdensome study.

21 We are not actually mandated to say it has to be
22 strictly the least burdensome possible study, but we need to
23 be thinking about the requirements and what it costs
24 industry and what it costs the public to develop the
25 information that supports a marketing authorization, and we

1 are supposed to be considering how to do that with reduced
2 effort.

3 [Slide.]

4 We would like you to give us your best guidance
5 and be creative. This is in some ways hard. It is always
6 difficult to be creative, and we don't want you to be
7 reluctant to think outside the box. One of our jobs at FDA
8 is to take your creativity, look at the regulations, look at
9 the law, and say how far can we move within that.

10 So, we are not asking you to be the expert
11 interpreters of the Food, Drug, and Cosmetic Act. We have
12 got teams of lawyers downtown that will help us with that.
13 We are asking you for good, creative science, and then we
14 will try and see how closely we can fit that to the
15 requirements of the statute.

16 [Slide.]

17 As I just said, thank you. We are going to
18 carefully consider the suggestions you come up with, and as
19 I said before, we have a lot of areas across the device
20 program where we are in a similar situation, where we have a
21 well-developed body of information on an existing set of
22 products, and we need to figure how to move forward in
23 subsequent generations of products, and we are going to use
24 this discussion as a model for that

25 [Slide.]

1 Today's topics. Am I supposed to turn this over
2 at this point, Dan? Here she is. Thank you.

3 DR. ALPERT: Good morning. I am Susan Alpert. I
4 direct the Office of Device Evaluation. I would like to add
5 my welcome to all of you.

6 As was already pointed out, this is a rather
7 unusual meeting for us. It will not function strictly the
8 way we usually do it when we discuss data within a given
9 PMA, so you can all take a deep breath, sit back, relax, pay
10 attention to the conversations and participate with us in
11 discussing how to move forward with a very important area in
12 cardiovascular device development, and as Dr. Burlington
13 pointed out, in helping us develop a model for moving
14 forward in other areas.

15 What I would like to do for about two minutes is
16 provide some very specific context for today's discussion.

17 [Slide.]

18 Historically -- and you probably know this history
19 as well as I do, and some of you even better -- the first
20 stent was approved in 1994. It was randomized against
21 angioplasty. We then moved in '96 to an environment where
22 we could utilize previously approved stents as a control for
23 new investigational stent models.

24 We worked that out through discussion with an
25 advisory panel and a development of good clinical trials

1 practices to design those equivalence trials.

2 Between June of '97 and September of '98, eight
3 stents have moved into the marketplace here in the United
4 States. We recognize, however, that there are other stents
5 available in other countries that have not moved into this
6 marketplace, but we have eight currently approved stents,
7 and now we are at the stage of looking at the information
8 available to us about stents in general, seeing how we can
9 apply that to future development for new models in the U.S.

10 [Slide.]

11 There are, however, some regulatory issues. We
12 are precluded from utilizing proprietary information as we
13 go forward in this process, and PMA data is, in fact,
14 proprietary. We protect the data that has been developed by
15 -- whether it is developed by individual investigators, and
16 those are protected by copyright, as you know, when they are
17 published, and we are required to protect the data in PMAs.

18 Each Premarket Approval application therefore must
19 stand on its own independent assessment of the device in
20 front of us with some caveats that I am going to talk about.

21 [Slide.]

22 This is a reminder that PMA data includes the
23 information that we put into labeling and to summaries of
24 safety and effectiveness data. We make that data available
25 known publicly, so that all of you can understand the basis

1 upon which we have approved new products entering the
2 marketplace, but our publication of labeling or the labeling
3 that is distributed with the product in our publication of
4 summaries does not make that data, the data from within the
5 PMA, available to other manufacturers to use either in their
6 PMAs or as a control for their studies.

7 That has been hard concept for many people to
8 handle, that although it is known, it is not available. It
9 is not available for FDA to use, for other sponsors, and it
10 is not available to other sponsors to use themselves.

11 The FDA Modernization Act of 1997 provided several
12 options for us. One is that earlier than FDAMA, there was a
13 provision that had allowed us to access information once we
14 had four approvals of a kind.

15 The four-of-a-kind rule was never really
16 accessible. We had great difficulty in interpreting that
17 rule and in writing guidance that would allow us access to
18 information from proprietary submissions.

19 The four-of-a-kind was replaced in FDAMA by six-
20 year rule, giving FDA permission to utilize data from within
21 proprietary submissions six years after the approval, and
22 that included our use for streamlining data requirements for
23 future submissions, as well as for classification actions,
24 but we don't have access until that data is six year post-
25 approval.

1 [Slide.]

2 We also recently published guidance on how one may
3 utilize published literature, data that is available in the
4 public domain, studies that have been peer reviewed and made
5 available.

6 We published a guidance regarding how those could
7 be used to obtain new claims for already approved products
8 in a supplement guidance, and that guidance also explains
9 how one can utilize published information in any submission
10 to the Food and Drug Administration.

11 In addition, we are allowed to rely on expert
12 opinion, on recommendations from a panel such as yourselves,
13 recommendations brought to us by professional societies, and
14 information that is provided to us by manufacturers that is
15 made public, and that is what I would like to finish my
16 talk, talking about, and that is what kinds of data are
17 available to us.

18 [Slide.]

19 I already mentioned that publications and peer-
20 reviewed literature are available to sponsors and submitting
21 to us, and are available to us, to you, the panel, and to we
22 in the FDA to utilize as background information for the
23 actions we take.

24 In addition, the owners, the holders of
25 proprietary data can make that data available, and there are

1 several ways in which data from within a submission can be
2 made available. One is by providing that data in what we
3 call a master file, and then providing written authority to
4 us to access that data for another specific submission.

5 So, let's say Company A has developed data they
6 want to allow Company B to utilize that data. They may
7 supply the data in a master file and write us a letter
8 saying Dear FDA, you may use our data for Company B in a
9 given submission.

10 That also allows for individual investigators to
11 provide access to data that they hold as proprietary, and
12 provide access to specific companies under that same
13 mechanism by providing it to us in a master file and giving
14 us authorization to utilize that information on a case-by-
15 case, PMA-by-PMA, or supplement-by-supplement basis.

16 There are alternative methods of sharing, and that
17 really speaks to the issue that a company may make its data
18 publicly available either through publication or by, in peer
19 review literature, by providing it to us and saying this
20 data may be put into the public domain, and therefore
21 allowing everyone access, not just FDA, but other companies
22 access to that information.

23 [Slide.]

24 With that as a background and some idea of the
25 kinds of information that are accessible for this

1 discussion, and the kinds of the detailed information that
2 is not accessible for this discussion, I am going to turn
3 the podium over to the experts in the specific areas, and we
4 are going to hear about engineering and the clinical studies
5 to follow.

6 MR. OKTAY: Good morning. I am Semih Oktay. I am
7 a mechanical engineer, and I am one of the primary reviewers
8 for stents in the Interventional Cardiology Devices Branch.

9 [Slide.]

10 I am here today to introduce to you the current
11 bench testing requirements recommended in FDA's May 1994
12 guidance document for intravascular stents.

13 Current guidelines for bench testing of stents
14 follow a characterization-based approach and are grouped in
15 three categories including specification conformance, stent
16 integrity, and stent/catheter system testing.

17 [Slide.]

18 The specification conformance testing focuses on
19 the materials used to manufacture the stent. Specifically,
20 it involves the material composition analysis, the
21 material's resistance to corrosion analysis, and it
22 identifies the mechanical properties of the stent material,
23 such as the yield strength, the elastic limit, and percent
24 elongation.

25 [Slide.]

1 The second category of bench tests concentrates on
2 the stent integrity and the dimensional analysis. For
3 example, one of the important factors considered in the
4 stent design is radial strength. That is the capacity of
5 the stent structure to support circumferential loads
6 pressure. The radial strength test therefore determines the
7 changes in stent diameter as a functional circumferential
8 pressure.

9 The stent recoil test for balloon expandable
10 stents in general characterizes the amount of elastic recoil
11 following the initial stent expansion.

12 The stent expansion test, on the other hand,
13 consists of examination of expanded stents for crack
14 initiation during deployment.

15 In addition, the stent's fatigue resistance is
16 determined by the fatigue testing. Fatigue is defined as
17 the deterioration of a material under repeated cycles of
18 stress and strain resulting in fracture. This test was
19 deemed necessary since a stent structure subjected to
20 dynamic loads, such as cyclic blood pressure, will likely
21 fail at lower stress levels than when the same loads are
22 applied statically.

23 The other tests under the stent integrity category
24 are dimensional in nature, and include characterization of
25 the percent free area, uniformity of the extended stent,

1 expanded stent, and dimensional verification of the stent.

2 Lastly, MRI compatibility of the metallic stents
3 is also tested.

4 [Slide.]

5 Several stent/catheter system tests are required
6 to demonstrate that the delivery catheter can safely and
7 reliably deliver the stent, and that the stent is not
8 adversely affected by the delivery catheter.

9 For example, the maximum pressure test will assure
10 that the delivery catheter will not experience balloon,
11 shaft and seal failures at or below the maximum recommended
12 pressure required to expand the stent to its labeled
13 diameter.

14 The crossing profile test will determine the
15 delivery profile of the stent in the context of its clinical
16 use.

17 Finally, other stent/catheter system tests include
18 stent crimping, balloon deflatability, and withdrawal tests.

19 Next, my colleague, Ms. Donna Buckley, will
20 discuss engineering issues related to the standard coronary
21 stent.

22 Thank you.

23 MS. BUCKLEY: Good morning. As Semih mentioned,
24 my name is Donna Buckley. I am also a mechanical engineer
25 in the Interventional Cardiology Devices Branch.

1 [Slide.]

2 I would like to take a few moments this morning to
3 discuss preclinical issues in the context of clinical trial
4 designs. To date, the gold standard used for assessing the
5 clinical performance of coronary stents has been a
6 randomized controlled clinical trial using a one-to-one
7 randomization scheme.

8 Although FDA believes that the standard RCT design
9 is still necessary for novel stent designs and new
10 indications, alternative trial designs may be appropriate
11 for "standard" coronary stents in light of the existing
12 clinical data.

13 If this approach is conceptually feasible,
14 defining a standard coronary stent becomes an important
15 task. If one were to attempt to define a standard stent
16 based on engineering characteristics alone, several issues
17 would need to be addressed.

18 [Slide.]

19 First, the clinically relevant design and
20 performance characteristics of the stent need to be
21 identified. Second, standardized tests would need to be
22 developed to allow for a comparison of the clinically
23 relevant characteristics between new stents and stents for
24 which clinical data has been obtained.

25 Third, pass/fail criteria would need to be

1 established for each performance characteristic.

2 [Slide.]

3 Identifying those engineering characteristics that
4 are the most strongly correlated with clinical outcome is
5 the first and perhaps most important task. These
6 characteristics may be broken down based on the stent's
7 material, basic design, method of deployment, dimensional
8 characteristics, and performance characteristics.

9 The types of stents for which there is the most
10 clinical data are the balloon-expandable, stainless steel,
11 slotted tube, and wire mesh designs. For this reason, these
12 designs are perhaps the best designs to form a basis for our
13 definition. Other characteristics, such as stent diameter
14 and length, radial strength, recoil, and percent free area
15 may also be used to quality the definition.

16 Considerations need to also be made whether other
17 materials, such as nitinol, other designs, such as coils, or
18 other methods of deployment, such as self-expansion, should
19 be included in the definition.

20 [Slide.]

21 Once the essential design and performance
22 characteristics have been identified, the performance
23 characteristics will need to be evaluated on the bench.
24 Currently, there are no standardized test methods,
25 therefore, a direct comparison between stents is not

1 possible.

2 For example, we currently request that each
3 sponsor evaluate the radial strength of the stent. However,
4 we do not recommend any particular method for doing so.
5 Therefore, we see different methods used by different
6 sponsors.

7 One sponsor may evaluate the pressure required to
8 cause complete stent collapse. Another sponsor may evaluate
9 the pressure required to cause a 5 percent reduction in
10 diameter. Another sponsor may use another technique, and so
11 on.

12 Therefore, given the differences in testing
13 techniques and equipment, comparisons cannot be made between
14 stents. To allow for comparisons, standardized tests would
15 need to be developed and implemented.

16 [Slide.]

17 The next step is to establish pass/fail criteria
18 for each performance test. Perhaps the starting point would
19 be to assess the performance characteristics of currently
20 marketed stents using standardized test methods.

21 The results of these tests may then be used to
22 provide a range of values for which a maximum and minimum
23 could be specified. A new stent could then be considered
24 standard if it performs within a prespecified range.

25 An alternative approach may be to consider a new

1 stent standard if it falls above or below a maximum or
2 minimum value. Again, using radial strength as an example,
3 if a new stent had a radial strength that was slightly
4 higher than the radial strengths of other marketed stents,
5 should it still be considered standard?

6 Should we use clinical judgment to accept a higher
7 radial strength, and only require that the stent's radial
8 strength be higher than a minimum value? If so, how do we
9 consider the reduction in longitudinal flexibility that is
10 oftentimes associated with an increase in radial strength?

11 These questions and others would need to be
12 addressed if engineering characteristics alone are used to
13 define a standard coronary stent.

14 [Slide.]

15 To summarize, if only engineering characteristics
16 are used to define a standard coronary stent, then, we need
17 to identify clinically relevant performance characteristics,
18 standardize the in-vitro test methods and specify pass/fail
19 criteria for each test. Otherwise, we would need to take an
20 alternative approach where we would include clinical
21 performance characteristics in the definition.

22 I would like now to turn over the discussion to
23 Dr. Zuckerman, who will be addressing the clinical issues.

24 DR. ZUCKERMAN: I am Bram Zuckerman, medical
25 officer for the Food and Drug Administration.

1 [Slide.]

2 We are going to switch gears and consider clinical
3 issues. We have two key questions: what have we learned
4 from the present stent clinical trials, and where should the
5 Agency be going?

6 Perhaps in answering the latter question, it may
7 be useful to consider two scenarios. One is where can the
8 Agency go with a comprehensive stent database, and what are
9 the options without such a database in-house.

10 [Slide.]

11 Where is the Agency right now? As Dr. Alpert
12 indicated, for a new stent, the Agency is requiring a
13 randomized equivalence design. The patient population
14 primarily consists of patients with large-vessel, de novo
15 lesions. The manufacturers have the option of adding
16 adjunctive arms for abrupt and for an enclosure saphenous
17 vein graft and restenotic lesions.

18 Our primary endpoint has been a clinical endpoint
19 measured at a minimum of six months. It is either target
20 lesion revascularization or some variation thereof, such as
21 major adverse cardiac events or MACE, which also includes
22 death and nonfatal myocardial infarction.

23 Key to this primary endpoint has been independent
24 clinical adjudication of events. Angiographic data is
25 primarily looked upon as supporting data.

1 [Slide.]

2 For the new stent coronary trials, the acute
3 endpoints listed on the top half of the slide have also been
4 utilized as supporting data. However, at this juncture, we
5 are seeing a lot of minor to moderate variations of FDA-
6 approved stent designs.

7 For this scenario, the Agency will consider some
8 combination of acute endpoints. Hence, one of the questions
9 for this panel is when do we make the distinction between a
10 moderate variation on an improved stent design versus new
11 stent.

12 [Slide.]

13 What does the current literature suggest? Well,
14 the current literature suggests, for the FDA-approved
15 standard stent indications, an equivalence of stent design.
16 Using current procedural technique and antithrombotic
17 regimens, there are high acute and chronic success rates.

18 We are seeing low adverse event rates, and
19 moreover, in the foreseeable future, significant changes in
20 these rates are unlikely.

21 [Slide.]

22 Hence, where should the Agency be moving at this
23 point in time? Without comprehensive stent database,
24 perhaps at one end the Agency should continue as it has been
25 doing. Alternatively, as you will hear in the next

1 presentation from Greg Campbell and from your own opinions,
2 you may suggest to the Agency to develop several different
3 creative design and analysis options.

4 [Slide.]

5 If the Agency does have access to a stent
6 database, the Agency may be more flexible in terms of
7 offering different design and analysis options. This could
8 lead to fewer patients and shorter development times. The
9 potential public health impact of this approach should not
10 be underestimated.

11 DR. CAMPBELL: I am Greg Campbell.

12 [Slide.]

13 I want to talk about design options, in
14 particular, notions of changing the sample size. One could
15 do that by considering fewer controls with the same number
16 of subjects in the new stent arm. One could also abandon
17 completely the concurrent control arm, as one might do in
18 OPCs, operating performance characteristics.

19 There are potential problems associated with this,
20 problems of bias. The historical control that one would use
21 might be outdated or become outdated. Then, there are
22 questions about the scientific validity, and this could
23 perhaps put a company that would go down this route at
24 potential jeopardy.

25 One could also think about reducing the number of

1 patients in the treatment arm, and really, all three of
2 these approaches, or at least the top and the bottom, allow
3 you to consider situations where you might change the
4 randomization ratio. Instead of the current one-to-one
5 randomization, one could easily imagine changing it to two-
6 to-one or three-to-one without much change in sample size.

7 [Slide.]

8 There are other design options. One could
9 consider continuously monitoring the trial or consider
10 resizing the trial partway through, and for either or both
11 of these, one would find a Data Safety Monitoring Board
12 particularly helpful.

13 One could also consider using some kind of
14 surrogate measure instead of the primary endpoint of target
15 lesion revascularization rate or six-month MACE rate. One
16 could choose some surrogate for this primary endpoint. A
17 caveat might be that the surrogate may or may not work. One
18 would want to validate that surrogate. If validated, one
19 could use the surrogate to decrease the premarket burden and
20 shift to the postmarket the primary endpoint.

21 [Slide.]

22 If one considers a fixed sample size that were to
23 be established, there would be the need to still answer
24 important questions relating to power and sample size, in
25 particular for the Type 1 error protection alpha that one

1 would specify, how powerful would the design be in terms of
2 detection a clinically meaningful delta.

3 There are also issues associated with sample size
4 that relate to the notion that if one were making a
5 superiority claim, one might have a different burden, a
6 different sample size than for an equivalence claim.

7 The other issue relates to that, I suppose, is the
8 least burdensome designs, is there at least one single least
9 burdensome design for all companies, is the situation that
10 one size fits all applicable to everyone?

11 As mentioned earlier, if there are new indications
12 that may be a completely different matter, and the above
13 comments may not apply, it might be very difficult to come
14 up with an easy comparator.

15 [Slide.]

16 Let me present some notion of knowledge
17 acquisition in particular. Suppose you had complete prior
18 information. In that situation, you wouldn't need any data,
19 the data wouldn't change at all your prior engineering
20 understanding.

21 At the other end of the spectrum, you may not have
22 any prior information, and when we are confronted with new
23 products, that is certainly the case. One starts knowing
24 absolutely nothing. There is no prior information that
25 could help.

1 In the case of stents, I think we are at a
2 situation where we might well make the case that we are
3 somewhere in between, and in that case, what we need to do
4 is consider the value of the prior information with the
5 notion that the physical action of how stents work may now
6 be well understood, and that the action is essentially a
7 local action and unlike drug modification, not a systemic
8 one.

9 [Slide.]

10 That being the case, let me consider some analysis
11 options that you could use for prior information. The
12 reason for that is that there is now a growing body of
13 publicly available knowledge on stents, and as Dr. Alpert
14 had mentioned, a company could use its own proprietary data
15 or share in some sense data from another company. In the
16 past, trials have stood on their own.

17 [Slide.]

18 Let's consider now possible statistical
19 approaches. One approach is metaanalysis. Metaanalysis
20 comes in two flavors. You could imagine using summary data
21 from published studies or you could imagine using patient
22 level data, which in the statistical parlance is called
23 overviews.

24 One of the problems with metaanalysis is that it
25 tends to make conclusions about broad classes. If the data

1 comes from many different stents, then, the conclusion is
2 about all stents, and not about the particular stent of
3 interest.

4 If one had lots of data from different studies on
5 the same stent, then, metaanalysis would be quite
6 appropriate, and we do see, in the Agency, submissions based
7 on metaanalysis.

8 Another approach is a Bayesian approach. In the
9 Bayesian approach, the advantage is that one has the ability
10 to focus on the particular stent, and not just the class of
11 all stents. One approach would be to use what are called
12 quantitatively based or objective techniques, such as
13 hierarchical Bayesian modeling.

14 Hierarchical Bayesian modeling would gain strength
15 from a quantitative prior, but in the process of doing that,
16 it would gain strength when warranted. That is to say if
17 the current data reflected very much the experience of the
18 prior information, then, it would gain strength from it,
19 usually not accepting it completely, so there would be some
20 down weighting which would occur.

21 If one decided not to downweight it, that is
22 called exchangeability. That would be accepting in toto all
23 of the weight of evidence of the prior information. That
24 has inherent dangers associated with it.

25 There are also dangers associated with using a

1 subjective approach, which is to say relying only on expert
2 opinion in the formation of the prior information. I will
3 come back to that later.

4 In both approaches, namely, the metaanalysis
5 approach and the Bayesian approach, evaluation of the
6 quality of the prior information is absolutely crucial.
7 This is not just a statistical exercise. It relies on good
8 clinical experience, the notion of being able to look at a
9 study and decide is it well designed, well analyzed, is the
10 population similar or exactly the one of interest.

11 [Slide.]

12 Intuitive appeals of a Bayesian approach is that
13 it is a scientifically valid way of combining previous
14 information with the current data. You take the prior
15 information, you add to it your current data, and you get
16 what is called a posterior distribution from which you make
17 decisions.

18 It is a common sense framework in that it
19 automatically adjusts to changing levels of evidence.
20 Furthermore, it allows you to continually and constantly
21 update the information in the current experiment into what
22 you have so far.

23 With more experience, you get greater weight in
24 the prior, and the other thing is that the prior of the last
25 experiment becomes the posterior distribution for the next

1 one.

2 [Slide.]

3 What is the advantage of this? Potentially, you
4 could have a payoff of smaller and/or shorter trials. In
5 particular for stents, note that this approach is not a
6 substitute for good science, it is, in fact, good science
7 itself. You need to identify the prior information
8 beforehand and decide how to weight it.

9 It is still necessary to do good clinical trials.
10 You still need to worry about things like randomization,
11 blinding, bias, precision, and so on, and you do need to
12 plan ahead of time.

13 [Slide.]

14 Gaining strength in a Bayesian hierarchical model
15 or in a discount likelihood model, you gain strength from
16 the prior information and decrease the size of the current
17 trial in one or both of the arms.

18 You could use prior information for the control
19 arm, for which there is usually lots of data, and probably
20 dramatically decrease the size of that arm. You could also
21 imagine having other information, for example, trials done
22 in Europe in the new stent arm that would reduce the size in
23 that arm, as well.

24 The amount of strength that you gain depends on
25 the size of the prior information, as well as how close that

1 prior information is to what turns out to be the data from
2 the current trial.

3 [Slide.]

4 One of the nice things about this approach is the
5 notion of fairness. That it does is it automatically
6 guarantees a level playing field in the following sense.
7 Suppose you have two companies that have exactly the same
8 prior information, but they have differently performing
9 products.

10 In a hierarchical Bayesian model, the burden would
11 be different for those two companies. Correspondingly, if
12 two companies had essentially the same stent in terms of
13 performance, but had different prior information, maybe
14 because one company had done lots of other stent trials
15 beforehand, then, the burden would be different on those
16 two, as well, and there would be an advantage to the company
17 that did, in fact, have that prior experience.

18 As new data become available, there would be no
19 need to continually update what would be a potentially new
20 rule of how many patients one would need. It would
21 automatically be done. It regulates itself.

22 The burden, of course, is on the companies to come
23 up with the studies that they would use as part of their
24 evidence for prior information.

25 What are drawbacks? Drawbacks would include that

1 people may not be well prepared or eager to use a Bayesian
2 approach. It has something of a data analytic burden as
3 opposed to a burden in terms of clinical trial subjects.

4 If one were to use a subjective approach, it could
5 be problematic. It could be problematic because there might
6 not be agreement about the value of that subjective
7 information. The Agency could not use that subjective
8 information internally, because that might be based on
9 evidence that they have got even inadvertently from PMA data
10 that is not in the public domain.

11 The other problem I suppose is that sizing the
12 trial is somewhat more difficult.

13 [Slide.]

14 In conclusion, I think these are exciting
15 opportunities for changes in stent design and analysis, but
16 there is no substitute for good clinical studies. The
17 validity of the scientific evidence is absolutely crucial,
18 and we welcome your input.

19 So, with that, I will turn it over to Dan Spyker.

20 DR. SPYKER: Thanks, Greg.

21 [Slide.]

22 My goals are modest today. I just want to remind
23 you that the second section in your panel pack is what we
24 call a labeling template. Our goals here are really simply
25 not to have everybody fit exactly the same labeling, but a

1 great deal of time and energy goes in, as you all know, even
2 outside the panel to develop labeling which says what we
3 think is appropriate in terms of instructions for use,
4 indications, contraindications, and so forth.

5 So, we have some fairly sweeping changes in terms
6 of moving some of the detailed information to a later part
7 of the label, and we really decimated, some might say, the
8 warnings and precautions in the interest of having a few
9 that are most important, and many of the other warnings and
10 precautions that you have seen in previous labels have been
11 moved into Section 7 label.

12 [Slide.]

13 I only want to mention a couple of specific things
14 that we would like to call your attention to when we do come
15 to this discussion, which I am going to put off until we
16 have heard from the rest of our colleagues, but give some
17 thought at that time to how we should change indications as
18 we get subsequent data.

19 The indication now says we don't know what happens
20 to the permanent implants beyond six months, so how do you
21 think that wording should be changed, and what kind of
22 comparator would be appropriate for long-term follow-up
23 data. Stress and Benestent did continue to follow their
24 PTCA patients, but that is not typically the case of the
25 others.

1 [Slide.]

2 You have seen some of the folks there. As you can
3 imagine, a lot of folks have put a lot of energy into this
4 over the last few years, and will continue to do so, so
5 these are names that I wanted to leave you with.

6 We would like to go on to hear from our colleagues
7 in the professional societies and manufacturers.

8 DR. ALPERT: As we move to that, let me just sum
9 up what you have heard so far. What we have put on the
10 table is a desire to look at alternative mechanisms to study
11 and bring forward new stents.

12 One approach was to raise the question as to
13 whether engineering and bench testing with possibly some
14 animal testing was sufficient, whether we needed to add
15 objective performance criteria that could be developed based
16 on currently publicly available data that we could then
17 together develop into these objective performance criteria
18 as a threshold, so we would have engineering information and
19 clinical information with thresholds. Anything meeting that
20 threshold might be considered a standard stent and might be
21 able to move to the market.

22 We have also proposed that another alternative
23 would be to utilize a Bayesian model that Greg described, a
24 mechanism where we use some available information and add
25 the new, the current information from the current trial, and

1 develop a larger database for that specific stent, but by
2 combining previously known information either from the same
3 stent or something closely related, and then grow the data
4 stent by stent that way, or to continue our mechanism of
5 using the randomized control trial with some modifications
6 using either the current or alternative surrogate endpoints
7 and changing the ratios that we use in our randomizations to
8 try to develop the information in a more efficient manner,
9 but not lose any of the quality and any of the depth of
10 scientific information that we have about the trials.
11 That is what we have on the table and, as Dan pointed out,
12 now we will hear from the manufacturers of these products.

13 DR. CURTIS: We are now going to move on to the
14 open public hearing.

15 Open Public Hearing

16 DR. CURTIS: Each speaker is permitted ten
17 minutes. The first speaker we are going to have is Dr.
18 Richard Kuntz from Harvard University.

19 DR. KUNTZ: Good morning.

20 [Slide.]

21 Thank you for allowing me to give my perspective
22 from a coronary interventionalist and a clinical trialist on
23 evaluation of new coronary stents. I am going to focus on
24 the OPCs and I think my colleague, Jeff Popma, is going to
25 talk about surrogate endpoints.

1 I will cover these issues very quickly,
2 engineering, patient-lesion characteristics, endpoints,
3 controls, methods of comparisons and a multiple approach for
4 stent approval.

5 [Slide.]

6 We have heard about the engineering assessment. I
7 think that is going to play critically into the clinical
8 assessment which I am going to focus on; that is, I think a
9 first pass of any new stent should be evaluated by the
10 engineers in their efforts to develop a complicated possible
11 differential equation to understand whether stents are close
12 to those approved or different and that will have bearing on
13 how we determine what to do next.

14 [Slide.]

15 The other is understanding the difference in
16 patient-lesion characteristics. If we look at the late-term
17 risks in stent trials that have been done so far, we have
18 the real world here which has these kinds of characteristics
19 with increasing patient risk and lesion risk but we have
20 only studied stents in this area here which is the kind of
21 vanilla subset of stent-versus-stent trials.

22 If we were to compare it to cars, a race car, a
23 Ferrari, versus a Fairlane, using the same thing, we would
24 find, in fact, that if you looked the differences in
25 performance versus challenges such as driving with the kids

1 or a dog or your spouse, or driving on the Autobahn or a
2 racetrack, most likely this area here, which would be
3 parallel parking in a school zone would perform the same
4 between the Ferrari and the Fairlane.

5 Not until you get out in this area here do you see
6 significant differences in the role of comparison. A stent
7 analogy has not been tested yet.

8 [Slide.]

9 What we see is a lot of differences in the panel
10 pack that you have among all the different stents and their
11 performances, both in binary angiographic restenosis rate
12 and target-vessel revascularization even with this small
13 zone.

14 But we also have to acknowledge that those
15 differences were slightly different among the same stent for
16 binary restenosis--that is, the Palmaz-Schatz stent arm of
17 each of those trials--and clinical restenosis, too. I would
18 state that possibly this is due to differences in those
19 lesion and patient characteristics that make up those
20 differences in part and, in part, due to difference in the
21 stents.

22 We can see that there may have been larger
23 differences among the stents compared to the differences
24 seen with the Palmaz-Schatz in and of itself, but these
25 differences represent the play of chance and also

1 differences in the lesion characteristics which need
2 adjustment for true direct comparison.

3 Thus, direct comparison between trials, I think,
4 is quite impossible.

5 [Slide.]

6 We also know that lesion and patient
7 characteristics such as long lesions and small vessels
8 probably are not ready for these rapid pathways because we
9 don't even know if these are good to be treated with stents;
10 that is, are stents the optimal therapy for small vessels or
11 long lesions. We don't know.

12 [Slide.]

13 Endpoints are important to understand. There has
14 been a change in our understanding of endpoints. We know
15 that clinical restenosis is not best measured at six months
16 but rather measured at one year. The data that you are
17 looking at is six-month data. It is not the right answer
18 for clinical restenosis.

19 We have seen this in multiple trials. In this
20 trial of STARS, a 2,000-patient randomized trial, the true
21 clinical restenosis rate is not realized until one year.

22 [Slide.]

23 Why does that happen? Because, although the
24 biological restenosis that we are aware of happens within
25 six months, the clinical manifestation of that takes much

at

1 longer and that is because it has to go through clinical
2 signs and symptoms. The provider has to become aware. The
3 revascularization has to be scheduled.

4 If you are doing a study in Europe, that is going
5 to take up to a year. Finally, the revascularization has to
6 occur. So, when measuring clinical restenosis, we have to
7 look at the long-term, one-year, endpoint and not the six-
8 month.

9 [Slide.]

10 We also know that clinical and angiographic
11 restenosis are measured differently. This slide I won't go
12 into because I think Dr. Popma will follow this up in more
13 detail, but, basically, binary restenosis measured
14 clinically has much less power than the continuous MLD
15 measurements of angiographic endpoints.

16 So the idea to use angiographic endpoints to
17 measure clinical restenosis as a surrogate is very important
18 because of a tremendous amount of statistical power. These
19 are sample sizes required for very similar comparisons of
20 treatment effect and differences in standard deviation on
21 the continuous measure.

22 [Slide.]

23 What about controls?

24 [Slide.]

25 We have heard that randomized controls and

1 concurrent controls can be used, as are used now in the
2 equivalency trials, that the concurrent controls can be
3 derived from another trial such as a randomized trial
4 compared to a registry of abrupt and threatened closure or
5 vein graft or one can use multivariable matching; that is,
6 matching in the 1990's level using high-speed computers and
7 multivariable-- and, finally, historical controls addressed
8 by Dr. Campbell regarding literature and the OPC dataset
9 which I will go into a little bit more.

10 [Slide.]

11 I want to focus mainly on the methods of
12 comparison here. We can see, as the base case of our event
13 rates that we are looking at--that is, there used to be a
14 40 percent restenosis rate of angioplasty and now we are
15 looking at 10 or 12 percent restenosis rate with stents--
16 required a direct superiority comparison to go up
17 significantly in sample size.

18 Therefore, to look for 25 percent treatment
19 effects when we have base cases of 10 to 15 percent failure
20 is not feasible anymore because of the large sample sizes
21 required.

22 [Slide.]

23 That is when we got into the idea of the
24 equivalency trials.

25 [Slide.]

1 The equivalency trial issue here is that we
2 compare a new different statistic; that is, we are assuming,
3 under the null hypothesis, that the new treatment is worse
4 and, if we reject the null hypothesis, the conclusion is
5 that the treatment is better or the same.

6 What is important is understanding this thing
7 called the delta which is how much zone are we going to
8 give--that is, hitting the mark--how far a distance can one
9 treatment be from another in order to preserve the alpha
10 error so that we can make those comparisons.

11 [Slide.]

12 One of the problems is understanding what that
13 delta is. In the classical, scientific literature, that
14 delta is a 10 percent treatment effect. The standard
15 clinical approach is actually 20 percent. We have been
16 looking at trials at 30 percent for the FDA and 40 percent
17 is much more impractical.

18 If we want to get down to this level here, this is
19 practical for looking at mortal events, like TPA versus
20 streptokinase. This is more practical, I think, for looking
21 at restenosis events which is not that critical. This is
22 where we stand. This gives us, currently, sample sizes of
23 around 500 to 800 patients.

24 [Slide.]

25 The other way to look at measurement of outcomes

1 is to do a multivariate model of restenosis in which we take
2 the entire pooled dataset and experience so far at the FDA
3 and put all of the variables in a model and predict the
4 actual restenosis rate for any given registry.

5 Therefore, we can calculate an exact expected rate
6 and look at the difference between observed and expected and
7 that can be the measure of whether a stent gets approved or
8 not. But it does require collaboration among companies to
9 allow this to occur.

10 [Slide.]

11 We do know that when we pool data from our CDAC
12 population, we can predict stent thrombosis quite
13 accurately. This is from 6,000 patients where the average
14 thrombosis rate is 0.7 percent. We can come up with a
15 fairly decent predictor's model to look at what the expected
16 should be.

17 But, again, this is a very cursory predictor's
18 model. We should end up with one much more detailed for
19 stent approval.

20 [Slide.]

21 We can also do the same for clinical predictors of
22 restenosis. These are the variables; post-treatment lumen
23 diameter, stent length, diabetes mellitus, and for
24 angiographic as well. These can be highly powerful. These
25 are all derived from about 6,000 patients and the current

1 stent-versus-stent trials.

2 This one, the angiographic, is from about
3 1,400 patients with mandatory angiographic follow up.

4 [Slide.]

5 We can then construct tables, much more elaborate
6 than this, in which we stratify, say, diabetics and non-
7 diabetics by lesion length and give an algorithm and table
8 of the predicted restenosis rates for any given
9 classification of patient stented.

10 Although it is difficult to see, the range of
11 rates goes from as high as 46 percent for long lesions in
12 diabetics with small vessels to as low as 6 percent in non-
13 diabetics with short lesions.

14 [Slide.]

15 Finally, if we look at Bayes, Bayes is a very
16 technical and classical technique to look at evaluation of
17 testing and also of outcomes. This is the first statistics
18 before Fisher developed a frequentist approach. The idea is
19 that if you take a prior odds, or a prior distribution, and
20 add to it a likelihood ratio, you come up with the posterior
21 probability that is updated and the data continues to get
22 stronger without any penalty towards multiple comparison.

23 [Slide.]

24 If we were to take a stent, prior distribution,
25 with an average restenosis rate of 26 percent and add to

1 that another 150 patients, we have a narrowing of the
2 probability distribution on an equal weight so that, if we
3 want to look at the probability that that stent will ever
4 have any greater than some threshold--say, 33 percent
5 restenosis, something that we are worried about--we can
6 actually calculate the absolute, direct probabilities from a
7 Bayesian approach which is stronger than frequentist.

8 As we increase this prior distribution, we can
9 make those probability statements with more certainty.

10 [Slide.]

11 On the other hand, if we were to add to the prior
12 distribution a new dataset with a slightly worse outcome,
13 depending on how comfortable we feel, we can borrow from
14 that prior distribution and we end up with a distribution
15 which is still weighted just a little bit towards the prior
16 so that the posterior distribution still has some direct
17 measure of the threshold.

18 In this case, if we add a 150-patient new registry
19 of the restenosis rate at 33 percent and we are concerned
20 about a 33 rate being bad, if we add it to a prior whose
21 average was 26 percent, we still have less than a 5 percent
22 probability that the restenosis rate is greater than
23 33 percent when we do the posterior distribution.

24 Again, it depends on our subjective weighting of
25 how that is added and these are issues that we can to today

1 with registries on top of randomized trials.

2 [Slide.]

3 The multiple approach for stent approval, then,
4 can go like this.

5 [Slide.]

6 This is difficult to read and I apologize for
7 this, but let me just walk you through this. It is in the
8 handout. If we have a stent with minimal deviation from
9 approved stainless-steel tubes--that is, ones that are
10 approved--we can use possibly a 30-day endpoint to approve a
11 stent. That is a proposal from me as a clinical trialist.

12 The idea there is we feel very strongly that, if
13 the engineers tell us that this is a very, very common,
14 well-studied, stent, we can clinically predict the
15 restenosis rates by looking at the 30-day events; that is,
16 both the MACE and also the acute angiographic endpoints.

17 [Slide.]

18 If, in fact, we have a moderate deviation from an
19 approved stainless-steel stent, again directed from the
20 engineers, then we would rely on a more robust endpoint if
21 it is a performance such as a six-month angiographic
22 endpoint, one that is powerful but still doesn't require
23 clinical follow up.

24 That, in and of itself, will depend on the
25 correlation between the angiogram and the clinical outcome.

1 We can do this both with a frequentist approach and a
2 Bayesian approach, as I showed earlier.

3 [Slide.]

4 Finally, if, in fact, we have either a stent that
5 is a severe deviation from those approved or the patient
6 population is quite different, then we will have to rely on
7 the frequentist approach which is a randomized equivalency
8 trial or a randomized superiority trial depending on the
9 patient-population issues.

10 [Slide.]

11 So, in conclusion, new second-generation stents
12 have generally been evaluated in restricted-lesion subsets
13 that may have not tested their full application and clinical
14 benefit. That is an evaluation of the current equivalency
15 trials.

16 Within the stent-versus-stent studies, there is a
17 range of patient and lesion-complexity factors that affect
18 the estimate of late-term success. This makes direct
19 comparison between studies possibly inaccurate and I think
20 it is difficult to compare those without taking into account
21 those differences in lesion subsets.

22 Adjustments for comparison, especially through a
23 formal pooled dataset for meta-analysis and multivariable
24 modeling would be necessary for a fair comparison.

25 [Slide.]

1 For most newer stents, a rapid pathway for
2 approval will be possible through objective performance
3 criteria and new evaluation methodologies. OPCs may be
4 derived from the community pooled or company-specific
5 datasets, depending on the level of comfort that the
6 companies have of sharing data.

7 Finally, for extension of stent applications to
8 the real-world arena, many lesion and patient subsets such
9 as long lesions and small vessels still need comparison with
10 non-stent techniques.

11 Thanks for your time.

12 DR. CURTIS: The next speaker is Dr. Jeffery Popma
13 from Harvard.

14 DR. POPMA: Thank you, Madame Chairman.

15 [Slide.]

16 I want to thank the panel for the opportunity to
17 speak on what I think is an important subject which is
18 whether or not the follow-up angiogram or the acute
19 angiogram can be used as a surrogate for clinical
20 restenosis.

21 [Slide.]

22 Thus far, we have been fortunate to be involved
23 in, now, ten stent-versus-stent studies. Virtually all of
24 these studies have been using the Johnson & Johnson tubular
25 slotted stent as the control group and I will show you some

1 data that we have obtained in the core laboratory with
2 respect to this data, itself.

3 [Slide.]

4 What are the definitions for a surrogate endpoint?
5 I would like to say that these are taken from a lecture that
6 Dr. Callahan did in October of 1995. A surrogate endpoint
7 used in a clinical trial is a laboratory measurement or
8 physical sign used as a substitute for a more meaningful
9 endpoint that directly measures how a patient feels,
10 functions or survives.

11 [Slide.]

12 The first criteria, as proposed by the FDA, was
13 the use of a surrogate endpoint may be motivated by studies
14 in which clinical endpoints may not be feasible because of
15 higher cost or difficulty in obtaining the measurements.

16 [Slide.]

17 What are our current outcomes that we can expect
18 in randomized clinical trials using stents? This is data
19 from the STARS study and the Cruise substudy which was an
20 intravascular ultrasound-guided substudy. We can expect,
21 now, in most stent-versus-stent studies that the target-
22 lesion revascularization rate, which is the surrogate
23 endpoint that we will be discussing, is as low as 6 percent
24 using IVUS guidance and as high as 11 percent using
25 angiography-guided stent implantation.

1 As Dr. Kuntz has displayed, this is relatively
2 consistent amongst the clinical trials.

3 [Slide.]

4 What does this mean for sample size calculations?
5 If we consider that the control group has a 10 percent
6 target-vessel-revascularization rate and we hope to find a
7 treatment effect of 30 percent, this will require, in a
8 randomized clinical trial, over 2,800 patients.

9 [Slide.]

10 What about the use of the follow-up minimal lumen
11 diameter as an alternative? For most of our stent-versus-
12 PTCA studies and new-device efficacy studies, the difference
13 between the follow-up groups has averaged about
14 0.2 millimeters with a standard deviation of 0.7 millimeters
15 which means, if we use this for the broad confines to prove
16 equivalency or, alternatively, efficacy, that 480 patients,
17 rather than 2,500 patients, would be needed to show
18 differences between the two groups.

19 [Slide.]

20 The second criteria is that a surrogate endpoint
21 must have biologic plausibility that demonstrates a
22 consistent mechanism of action. The techniques that we use
23 in our angiographic core laboratory--we use the CMS system,
24 but these are illustrative examples of the ARTREK and CAAS
25 systems. Suffice it to say, all of these angiographic

1 systems have shown an accuracy of 0.04 millimeters and a
2 reproducibility of under 0.1 millimeter for assessing
3 immediate and late long-term results.

4 [Slide.]

5 When we look at some representative samples of the
6 randomized clinical trials which have been presented in
7 abstract form in the Johnson & Johnson stent or control
8 limb, we see that there is a remarkable consistency amongst
9 reference vessel sizes ranging from 2.97 to 3.03 with the
10 post-treatment lumen diameter ranging as low as 2.73 to as
11 high as 2.79.

12 I am excluding the GRII study because that
13 actually was done in a little bit larger vessels. But all
14 of these follow-up post-treatment lumen diameters
15 immediately after the procedure are ranging with six-
16 hundredths of a millimeter difference.

17 The post-procedure percent diameter stenosis
18 ranges from 8 percent to 10 percent, or 2 percent
19 difference, in well over 700 patients treated in these
20 stent-versus-stent studies, so, a remarkable consistency
21 with the recruit result.

22 [Slide.]

23 I think each of these studies has demonstrated
24 that the final post-treatment lumen diameter is one of the
25 most, if not the most, important predictor of the follow-up

1 result.

2 In our experience, when I was in Washington at the
3 Washington Hospital Center, we also found that, in
4 generalized clinical practice, the final percent diameter
5 stenosis was also an important multivariate predictor of
6 outcome, of late outcome.

7 [Slide.]

8 With respect to late results, what can we expect
9 from the follow-up percent stenosis in the test limbs, in
10 the Johnson & Johnson limbs? The follow-up mean percent
11 diameter stenosis ranged from 34 percent to 37 percent.
12 This is a very, very tight confidence interval for the
13 follow-up percent stenoses. And I think this does have
14 biologic plausibility.

15 [Slide.]

16 Now, the surrogate clinical endpoint in clinical
17 trials should show a treatment effect and a disease effect
18 that correlate with other devices. I think this panel has
19 heard before that there is an angiographic and clinical
20 discordance, a discordance between clinical findings and
21 angiographic findings in clinical trials.

22 [Slide.]

23 The following slide will summarize 7,000 patients,
24 nearly 7,000 patients, in randomized trials comparing the
25 ability of the angiogram and the concordance with the

1 follow-up target-lesion revascularization rates.

2 In this four-quadrant graph, in the upper right-
3 hand panel, are those events which have concordance with
4 lower clinical events and lower follow-up percent diameter
5 stenoses. The lower left-hand panel illustrates those
6 patients that have a worse outcome, both by clinical events
7 and by follow-up angiograms.

8 What you will see is an absence of clinical trials
9 in any of the quadrants that show discordance between the
10 angiogram and the clinical findings. I think this, in over
11 7,000 patients, displays that, in fact, there is a tight
12 concordance between the angiogram and the clinical finding.

13 [Slide.]

14 Finally, the acceptability of a surrogate endpoint
15 for device approval is based on strong evidence that the
16 surrogate endpoint is likely to predict clinical events.

17 [Slide.]

18 Now, the clinical events that we are proposing the
19 angiogram be used for is not the composite of MACE which is
20 a composite of death, myocardial infarction or any
21 revascularization but, instead, target-lesion
22 revascularization, which is an ischemia-driven renarrowing
23 at the treatment site that causes either a positive exercise
24 test or recurrent symptoms that is associated with a focal
25 stenosis requiring intervention.

1 [Slide.]

2 When we use this definition, data obtained from
3 the BOAT trial--but similar sorts of curves are available
4 for all the stent-versus-stent trials--the ROC curve in the
5 upper-right panel demonstrating the correlation between
6 clinically driven target-vessel revascularization and the
7 follow-up minimal lumen diameter and percent diameter
8 stenosis is extremely tight, and extremely good correlation.

9 As we move to any target-lesion revascularization,
10 clinically indicated or not, the ROC curve is less robust.
11 As we add in things like follow-up angina and positive
12 functional studies, which can clearly be caused by disease
13 progression at other sites and often are, then the
14 correlation is not as robust.

15 I think what we have from the available data, what
16 we know from clinical trials now averaging almost
17 10,000 patients, that, without question, we have, from the
18 angiographic data available now, substantial clinical and
19 angiographic evidence to suggest that angiography can be
20 used as a surrogate to target revascularization, both
21 acutely and at late follow up in coronary-intervention
22 trials.

23 Thank you for your attention.

24 DR. CURTIS: The next speaker is Dr. John
25 Hirshfeld representing the American College of Cardiology.

1 DR. HIRSHFELD: Thank you. I am really privileged
2 to have the opportunity to present the College's position to
3 the panel this morning. I would like to emphasize that most
4 of the points that I am going to make are points that are
5 well known and have been made in other presentations.

6 But I would like to just give the College the
7 opportunity to weigh in on these issues to manifest its
8 point of view to FDA. The College, as you know, has a
9 primary mission of being interested in fostering optimal
10 patient care. Toward this end, the College, for well over a
11 year, now, has had a task force on the coronary-stent issue
12 which was convened by our current president, Spencer King.

13 The concern about this was to work with FDA to
14 maximize the availability of these new and improved stent
15 designs without compromising the mission of being certain
16 that this devices are safe and effective when they are
17 released.

18 I think it is just worth backing up a little bit
19 to reiterate the fact that stenting is, arguably, the most
20 significant development in interventional cardiology of this
21 decade. One statistic which I think emphasizes this is
22 that, if one looks at compiled data of complication rates of
23 coronary-interventional procedures from the early to mid
24 '90's, the emergency bypass-surgery rate was generally
25 between 3 and 4 percent of all coronary-interventional

1 procedures.

2 The NHLBI Dynamic Registry, which was just
3 reported at the AHA meetings in November, reported an
4 emergency bypass-surgery rate of 0.4 percent, a really
5 stunning improvement and, I think, a testimony, in many
6 respects, to the impact that stenting has had.

7 The College has also known that the progress in
8 stent design has been rapid and dramatic and it is a tribute
9 to the creativity of the companies which have done this. We
10 are anxious to have these devices available to practitioners
11 provided that they are available in a fashion in which their
12 safety and efficacy is assured.

13 I would like to take a couple of moments to just
14 lay out the College's position on both the premarket
15 approval process and on the postmarket surveillance issue.

16 With respect to the premarket approval process, I
17 think the College takes a very strong position that we
18 advocate the development of standards for engineering-
19 performance testing. As we all know, the ASTM in working
20 with FDA and with industry to try to develop standardized
21 techniques. The College certainly endorses that. I will
22 assure us of quality products and it will also simplify the
23 FDA's job in evaluating premarket applications.

24 Similarly, the College would like to see FDA,
25 insofar as is rigorously possible, move away from the

1 randomized clinical-trial design and toward more registry
2 trials in an effort to streamline its ability to determine
3 whether new stent designs are safe and effective and can be
4 released to the marketplace.

5 You just heard some very elegant discussions about
6 these trial designs and the issue of the endpoints which
7 they should include.

8 Finally, I think it would be very important to
9 emphasize that ACC is very interested in expanded activity
10 in the postmarket surveillance issue. This is for several
11 reasons. The first is that it seems clear now that many of
12 the issues that may come up with respect to defects in
13 either performance or design of new devices are still going
14 to be rather rare events. They are going to require
15 substantial statistical power to detect that.

16 The randomized clinical trials which Rick Kuntz
17 laid quite nicely in which the Fairlane and the Ferrari
18 perform equivalently well will not detect these and,
19 therefore, it is really essential that a rigorous and
20 effective means of good postmarket surveillance exist.

21 I should add that the College is seriously
22 examining internally whether or not there is a role that it
23 can play to collaborate with FDA on the facilitation of the
24 type of data-gathering of what goes on in the real-world
25 clinical practice.

1 With respect to real-world clinical practice,
2 again, as Rick demonstrated, a tremendous number of stent
3 implants are implanted currently in what would be considered
4 to be off-label applications. Not only does FDA have
5 relatively little information as to whether or not these
6 stents perform properly in off-label applications, but we,
7 as clinicians, also don't really know what we are doing
8 because, in addition to there not being clinical-trial data
9 in these situations, there are no data that really guide us
10 in the use of this.

11 So we are currently really forced to operate based
12 totally on our intuition as to whether or not we think a
13 device will perform well in a given situation.

14 We think that it is probably unworkable to perform
15 randomized clinical trials to examine all of these off-label
16 and unusual applications. Therefore, we feel, once again,
17 that the good postmarket surveillance and good registry
18 information may very well be the way to give us the insight
19 on this.

20 Finally, I would just like to add that the College
21 is anxious to use its resources to collaborate with FDA to
22 try to facilitate this sort of data-gathering if at all
23 possible.

24 Thank you.

25 DR. CURTIS: The next speaker is Dr. Katherine

1 Detre from the NACI Registry.

2 DR. DETRE: Good morning. First of all, I would
3 like to say that--

4 DR. CURTIS: If I could just interrupt one second,
5 I should have been asking everybody if they had any
6 financial conflicts or interests in the companies involved
7 here. If you could just state whether or not you do.

8 DR. KUNTZ: No.

9 DR. POPMA: No.

10 DR. HIRSHFELD: No.

11 DR. CURTIS: That was Drs. Kuntz, Popma and
12 Hirshfeld all said no.

13 If you could go ahead and state yours.

14 DR. DETRE: No. In fact, we have been at the
15 University of Pittsburgh. We have been at the business of
16 evaluating coronary interventional approaches since Gruntzig
17 started his first case. It was always, always, funded by
18 the NHLBI. Apart from small clinical trials, they have
19 never been funded by industry, unfortunately.

20 I want to say that what I am going to show are the
21 slides not from the NACI Registry which was our new approach
22 to coronary intervention. The history of all these
23 registries is that we started collecting consecutive cases
24 from all the centers who were willing to enroll consecutive
25 patients and collect uniform standardized data from all

1 their patients and follow them.

2 [Slide.]

3 This slide is from the bypass angioplasty
4 revascularization intervention trial which was, as probably
5 most of you know, a comparison of the five-year clinical
6 outcomes, survival and myocardial infarction, in patients
7 who had multivessel coronary disease, who were all de novo--
8 they didn't have a revascularization before--and they needed
9 revascularization because severe coronary symptoms, usually
10 unstable angina, necessitated it.

11 Along with the clinical trial where we compared
12 percutaneous transluminal angiography, so it was just the
13 balloon--we specified in that trial that they couldn't use
14 any new devices. Parallel with the randomized trial, we did
15 surveys at each of the participating centers.

16 This slide shows the surveys between 1990 and
17 1996. The purple bars are the balloon only. The slide
18 shows that, over the six years, particularly from 1993 to
19 1996, the use of balloon-only angioplasty really was
20 drastically reduced. The blue is the balloon new device,
21 which was increased.

22 One of the criticisms you have if you do these
23 studies, whether they are randomized trials or registries,
24 by the time you publish the one-year results, people say,
25 "Well, we are not using that device anymore." So what can

1 you do to keep current with the new device approvals and
2 uses so that your scientific work is not rejected on the
3 basis that it is outdated by the time you are ready to
4 publish.

5 [Slide.]

6 So what devices? We then designed the Dynamic
7 Registry to try to answer the questions what designs are
8 currently used, are the designs safe and effective, what
9 types of patients and lesions benefit from each device.

10 As you know, at the NHLBI, you always must be
11 interested in how the women and minority patients fare. In
12 this case, it is a very important question because women
13 have smaller arteries and they are known to fare differently
14 in the past.

15 Has the population of patients suitable for these
16 of procedures expanded? That is a very interesting point.
17 We are saying the new devices allow you to do different
18 kinds of patients than the previous devices. Then how can
19 you do randomized studies comparing, let's say, PTCA with
20 stents, if PTCA is used for different indications than
21 stents.

22 So there are a lot of interesting questions when
23 you want to discuss evaluation of new devices.

24 [Slide.]

25 The goals of the Dynamic Registry which was funded

1 a year and a half ago is to build on the success of the
2 earlier registries between 1981 and 1994. What is the
3 strength of all our work is that we take consecutive cases
4 and we have all kinds of things built in, controls built in,
5 to be sure that consecutive cases are entered.

6 We assess the device use over time. We publish,
7 now, quickly and we function cost-effectively, I think.

8 [Slide.]

9 This Dynamic Registry was approved by the NHLBI
10 for five years. We had funding for 6,000 patients. We are
11 using the same participating hospitals that have been
12 participating in all the previous PTCA registries. When we
13 took a survey, these fifteen hospitals, on the average, the
14 case load was 1,200 per month.

15 Even small centers are represented. Some of our
16 sites have twenty cases a month, others 200. So we have a
17 decent representation. Women were 25 percent of the case
18 load and minorities 10 percent.

19 [Slide.]

20 The design issues; over five years, we thought
21 that we can keep abreast with new development if we do waves
22 instead of continuous. This is also a cost-effective way to
23 do it. We had three waves of 2,000 patients. We worry
24 about the underrepresentation of low-volume sites so we have
25 a cap of 200 cases so that the sites that finish early must

1 stop after 200 cases.

2 After 1,500 white males are entered, we oversample
3 the women and minorities. In other words, in each wave when
4 1,5000 white males are recruited, we stop recruiting white
5 males and we go on to other minorities.

6 [Slide.]

7 This is the time line. In the first six months,
8 we recruit the first wave. Then, six months later, from
9 twelve to eighteen months, we evaluate the one-year outcome
10 of the first-wave patients and then, between 18 and 24
11 months, we recruit the second wave.

12 Six months later, we begin the one-year follow up
13 so that after now, when we are now at the point that we are
14 looking at the one-year results of the first wave, from here
15 on, we will be able to publish early results, one-year
16 results and, pretty soon, we are going to be able to publish
17 the second-wave baseline results and the procedural
18 outcomes.

19 So we can constantly compare what is new in device
20 use, what is new in the--as Jeff Popma said, in the
21 angiographic characteristics of the lesions that are treated
22 or the patients that are treated. This way we get sort of
23 like a moving picture of interventional cardiology in these
24 centers who participate in our study.

25 [Slide.]

1 The first wave was recruited between July, '97 and
2 November, '97, consecutive patients. Between November and
3 February, we completed the non-white patients. We were able
4 to present five abstracts. We are going to show seven in
5 March.

6 The second wave, as I said, is starting in a
7 couple of months.

8 [Slide.]

9 These are some of the results. Balloon is almost
10 always used. It is not that it is updated. It is just that
11 new devices are added to the balloon. So balloon and stent
12 was used in 60 percent, balloon only in 25 percent or 26
13 percent. Another 7 percent had balloon and stents plus
14 rollerbladers and only 5 percent balloon and rollerladers
15 and other is lasers, basically.

16 [Slide.]

17 I just want to show you some of the examples of
18 what we can do. We have one site in Canada which is
19 Montreal. If you look in the U.S. during this first wave,
20 38 percent of the stents were Palmaz-Schatz followed by Cook
21 whereas, in Canada, NIR and ACS Multilink and they
22 practically didn't use any Palmaz-Schatz.

23 We also had one site in the Czech Republic, in
24 Prague. They used something called AVE Microstent and NIR.
25 There is a sort of spread, but the prevalent uses are

1 different by different countries, I'm sure.

2 [Slide.]

3 So the average age is now 63. 36 percent were
4 women. 16 percent were non-white. It is interesting that
5 28 percent of the procedures are repeat procedures, either
6 previous angioplasty or bypass surgery. Multivessel disease
7 was 58 percent and 19 percent was revascularization for
8 acute MI which is probably going to change in the second
9 wave.

10 [Slide.]

11 The number of attempted lesions--it is
12 interesting; in 70 percent, they only attempted one lesion
13 in the procedure, and 25 percent two, three or four. Rarely
14 IIb/IIIa was used in 23 percent. The angiographic success
15 was a spectacular 96 percent.

16 [Slide.]

17 This is just to show that still most of the
18 procedures occur in the LAD. RCA is second, circumflex.
19 Grafts and left main is quite rare. It is almost 1 percent.

20 [Slide.]

21 Prediameter stenosis, on the average on all the
22 lesions, was 84 percent and the final diameter stenosis is
23 12 percent. Abrupt closure is 2 percent and that is quite
24 low. This is on a lesion level. On a patient level, the
25 mortality was 1.6 and the MI was 2.9. Q-wave MI was less

1 than half a percent.

2 I agree with the speaker before, bypass surgery is
3 very rare, 1.4 and this includes emergency and elective.

4 There is MI. There is Q-wave MI, very low.

5 [Slide.]

6 I don't know if you want to see some of the
7 presentations from the AHA. I think I have finished my ten
8 minutes. Maybe just the topics which compared to the PTCA
9 Registry, when you compare 1985 to ten years later, there
10 are many differences, some of them in the direction that you
11 wouldn't expect.

12 For example, the age, obviously, is older, more
13 women, because we have enriched the sample. A quarter of
14 the patients, now, are diabetics. MI intervention went from
15 10 percent to 22.

16 Now, this is very interesting. Multivessel
17 attempt went from 21 percent ten years ago to 9 percent. So
18 when we talk about the big success, it is partly because the
19 approach to treatment is different and probably the patients

20 are somewhat different.

1 Cardiology Research Foundation. Please state you if have
2 any financial interest in the products.

3 DR. STONE: Thank you. Regarding potential
4 conflicts, my formal position is the Director of
5 Cardiovascular Research and Education at the Cardiology
6 Research Foundation which is a not-for-profit foundation.
7 We do, however, receive pretty much unrestricted support
8 from almost every stent manufacturer.

9 Personally, I also serve as the consultant for
10 several companies that have interest in stents including
11 Guidant, Cardiovascular Dynamics and Endosonics.

12 What I would like to do is five or 10 minutes at
13 most, without slides, is hopefully just make some very
14 common sense appeals to what we see as physicians and
15 interventional cardiologists who are, one, very interested
16 in clinical and basic science research, and two, interested
17 in taking care of patients, just some common sense
18 guidelines for what we think is necessary for this field to
19 move forward and how we would like to see ourselves and
20 others working with the regulatory agencies in this regard
21 in new stent development.

22 You know, I think that we agree in a large part
23 with what most of the previous speakers have said. I mean
24 the time for randomized trials to get a new basic stent on
25 the market I think is past. There is going to be

1 increasingly less and less interest for stent versus stent
2 equivalence trials, and actually when you look at what the
3 confidence intervals are for the delta, the delta is so wide
4 that I think these trials actually will often miss what are
5 important clinically significant differences.

6 I think that does bring us to what a better model
7 would be, which would be using OPCs, and we are all in favor
8 of that, and in favor of using a Bayesian approach, and to
9 be able to add as much older data and new data as possible.

10 The question then becomes where do you get this
11 data from, and I would hope that all the stent manufacturers
12 would allow their data from their previous PMAs to be used
13 for a combined analysis in this regard.

14 I think when you look at the stent versus stent
15 trials, while we agree that you can't compare one trial
16 versus the other because they are all different, you can
17 certainly make some generalizations.

18 If you look just at restenosis rates among the six
19 randomized trials using the Palmaz-Schatz stent -- actually,
20 it was seven -- the restenosis rates vary from 18 1/2 to 26
21 1/2 percent. I mean it is remarkably similar across these
22 trials.

23 I think that if you combine this data, we have
24 characterized what that stent does very effectively, and
25 that could be a basis of new stent improvement since it is

1 unlikely that, at least for 3 to 4 millimeter de novo
2 lesions, that new stents are going to make marked
3 differences.

4 Now, if the manufacturers are not willing to allow
5 their data, either all the Palmaz-Schatz data to be combined
6 or else some of the new stent data to be combined, we
7 honestly actually believe -- and this may be a new paradigm
8 -- that PMA data should be public domain data.

9 I mean the public is benefiting from these stents
10 being put on the market, the companies are benefiting from
11 stents being on the market, and it seems as if this would be
12 a reasonable way to go.

13 A third alternative would be to create a registry
14 of several of the leading stents with angiographic follow-
15 up. Hopefully, there could be government funding for this
16 to actually create the registry that we need, to have a
17 large enough registry of approximately 6- or 7,000 patients
18 to use as a starting point for a Bayesian model.

19 So, that actually applies to 3- or 4-millimeter de
20 novo lesions. A second indication would be the newer
21 subsets that are not yet approved for elective use, such as
22 small vessels and diffuse disease, bifurcations, and it is
23 our opinion that for those indications, you still need
24 randomized prospective trials.

25 However, while we don't yet have a stent that is

1 approved for elective use in small vessels, if we take that
2 as an example, it has been very difficult to do such a
3 trial. I mean clearly we need to use an angiographic
4 endpoint -- I am sorry, let me back up for one second.

5 When we look at what the OPC should be looking at,
6 we also strongly believe that the angiographic endpoint
7 should be the primary endpoint in these studies. I think
8 Jeff made a very convincing argument why that is a strong
9 surrogate of clinical events.

10 I will actually take it one step further, and I
11 will say that clinical events, if anything, are a good to
12 somewhat flawed surrogate for the angiographic endpoint. As
13 we get away from prospective randomized trials and we allow
14 ourselves to use just registry information, we need to
15 harden the science in this field, and the only scientific
16 validated approved way to look at this is going be an
17 angiographic endpoint.

18 The clinical endpoint is all over the place. When
19 you look at these trials, for example, in the Palmaz-Schatz
20 studies where the angiographic endpoint is much tighter, the
21 confidence intervals are much narrower, and there are too
22 many things that go into whether or not a patient has a
23 target lesion or a target vessel vascularization, whether or
24 not the patient has a follow-up stress test or a thallium,
25 what the threshold of the doctor is to do follow-up

1 angiography and follow-up studies, financial incentives,
2 whether the study was done in the United States versus
3 Europe, and also the time to follow-up, which varies
4 markedly as you were shown from six months to 12 months.

5 If you look at, for example, in the one study, the
6 equivalence trial that showed worse restenosis with the new
7 device, the clinical endpoint was much closer than the
8 angiographic endpoint, and partly because the initial
9 clinical endpoint was only six months.

10 So, the angiogram at six months or nine months,
11 but six months as you get the final endpoint, should be the
12 endpoint of these studies.

13 So, for new indications, small vessels, diffuse
14 disease, again, an angiographic endpoint in a prospective
15 randomized trial would be what we favor. A new paradigm,
16 however, would be to allow companies to do these trials for
17 these indications for equivalence as opposed to for
18 superiority with some reasonable degree of equivalence
19 allowed.

20 While, yes, it is true that stents are an implant,
21 they are very different than a silicon breast implant. We
22 now have seven to eight years of data, actually 10 years or
23 more in some cases, from the very first stents that were put
24 in. We are not seeing pseudoaneurysms, we are not seeing
25 them erode through the chest wall. If anything, we are

1 seeing the lumens become slightly larger.

2 We have good long-term data now from Stress and
3 Benestent, and I think the reality is, is the physicians in
4 the United States are going to put stents in as the default
5 strategy. If you look at the way the 2.5 NIR stent is being
6 used, it is being used more for a primary stent in 2.5
7 vessels than it is as a bailout stent.

8 So, to allow an equivalence trial in 2.5's, I
9 think would prompt the companies to be more likely to take
10 the risk and do that trial, and we need the support of
11 industry to answer that important question. I think the
12 feeling is stents are going to be either equivalent or
13 slightly better than angioplasty in small vessels, but if we
14 do the study, we will find out at least if they are not
15 worse.

16 The third point that comes up is orphan
17 indications. What do you do for a covered stent, what do
18 you do, what do you do for a stent that has the capacity to
19 be a lifesaving device, for example, for a patient
20 experiencing a perforation where the only other alternative
21 is an emergency surgery, you know, which, of course, is very
22 risky in that situation in a hemodynamically unstable
23 patient.

24 One possible way to approve new devices for life-
25 threatening indications would be to either, on the basis of

1 carefully examined European studies or after a small number
2 of patients were done in the United States, allow an
3 approval for such an orphan device, but then mandate careful
4 postmarket surveillance with cards returned to the
5 manufacturers and the Agency for every single device put in
6 to make sure it was only being put in for those specific
7 situations.

8 Somewhere in between is large and expanding
9 aneurysms, which also would probably be such an orphan
10 indication, if there is no way to ever do a randomized trial
11 for that.

12 On the other hand, for covered stents, for vein
13 grafts or for large vessels, that would, on the other hand,
14 require a randomized trial.

15 Finally, the last comment I would like to make is
16 that about adjunct pharmacology. I think that it has become
17 increasingly important that we consider the role of adjunct
18 pharmacology when we consider stents and devices, and, in
19 fact, to consider one without the other, I think is also not
20 necessarily considering real world considerations.

21 In this regard, I think it is very important that
22 the device side of the Agency talks to the drug side of the
23 Agency, and, for example, the drug side of the Agency right
24 now has taken the position that to do percutaneous
25 intervention or to treat patients with unstable angina or

1 non-Q-wave MI, often of which in this country, about 60
2 percent lead to percutaneous intervention with devices
3 without IIb/IIIa inhibitors is not acceptable, and, in fact,
4 there have been three trials now of placebo-controlled,
5 IIb/IIIa inhibitors, multimillion dollar trials that would
6 have added a lot of science, that were funded by industry,
7 that have been turned down from the drug side of the agency,
8 and I have talked to them about this.

9 I think most of the people in this room would
10 probably -- many, at least, or most -- would tell you that
11 that is not their opinion, that the IIb/IIIa's are either
12 absolutely mandated or necessary in all patients receiving a
13 stent or undergoing a percutaneous intervention, and for the
14 Agency to make that stance would add somewhere between 500
15 million to about 2 billion dollars to our health care budget
16 depending on all the indications that are covered.

17 So, I think there should be open panels and
18 discussions whenever a device involves adjunct pharmacology
19 from both sides of the Agency.

20 Thank you very much.

21 DR. CURTIS: The next speaker is Dr. Edelman
22 representing ASTM.

23 DR. EDELMAN: I am Elazer Edelman. I am actually
24 from Harvard Medical School and MIT. I should preface my
25 remarks by mirroring what Dr. Stone said. We have worked

1 with all of the major stent manufacturers, and have at one
2 time or another received unrestricted grants or consulting
3 fees from them.

4 [Slide.]

5 Let me go on by explaining to you something that
6 is happening with multiple constituencies principally
7 initiated by the FDA, therefore can be conceived of as an
8 FDA effort, but strongly supported over the last two years
9 by the Office of the Dean of Harvard Medical School and the
10 Provost of MIT, and with the Office of Science and
11 Technology by the ASTM and with our European counterparts
12 and the ISO.

13 The fundamental issue really is what happens when
14 technology demand drives technology development, and what,
15 in general, should be the case is that technology assessment
16 should protect against the dangers. In other words, when
17 you have a potential problem, you should have a mechanism in
18 place for assessing the technology.

19 When the demand drives the development to such an
20 extent that there is an insufficient lag time, there is a
21 potential for great danger to occur.

22 [Slide.]

23 This typically has led to various, as I call them,
24 constituencies to be involved - the Food and Drug
25 Administration as a regulatory body, industry, in and of

1 itself, doing what I think is a very good job in the past,
2 clinicians, both protecting themselves and their patients,
3 and the constituencies, as you heard from Dr. Hirshfeld,
4 American College of Cardiology, but it is only recently that
5 the research community has gotten involved in this effort,
6 and that is what I am going to talk about today.

7 [Slide.]

8 The issues that were brought up, and those that I
9 have announced to address, are one of, first, do preclinical
10 studies. The engineering studies, on the one hand, and the
11 animal experiments, on the other, allow some predictability,
12 so that we could devise more rigorous, more rational, and
13 more streamlined clinical trials, but along the way we have
14 to, as some of the earlier speakers from the FDA alluded to,
15 develop standards.

16 [Slide.]

17 The problem with the field, as it currently stands
18 right now, is that in general there are no standards for any
19 of the preclinical evaluation of these devices. There are a
20 set of guidelines, but they have questionable clinical
21 significance, and what is absolutely maddening to the people
22 who submit a variety of these submissions is that they are
23 unfortunately, by the nature of where they were taken, at
24 times can be perceived of as ambiguous or arbitrary.

25 [Slide.]

1 All of this is not a problem in and of itself, but
2 linked with the following three issues becomes something
3 that has prompted the FDA to ask us to look at this.

4 First, let's recall that most of what goes on is
5 binary, approved, unapproved, safe, unsafe. In truth,
6 though, when we buy a product, we don't look at it as safe
7 or unsafe. Nobody buys a refrigerator, a stereo, or a car
8 because somebody said it was safe.

9 They look at it, and they characterize it, and
10 that has not gone on for devices, and biotechnology in
11 general, and the fundamental academic problem that Harvard
12 and MIT are interested in is how to change biotechnology
13 assessment where using endovascular stents as a test case.

14 The two final issues are very much important, and
15 that is, as we become aware either from case reports or
16 formal postmarket surveillance that there are problems,
17 there is no way of extrapolating for the future or feeding
18 back into this process of evaluation.

19 [Slide.]

20 I am going talk very briefly first about benchtop
21 testing, say one word about finite element analysis, and
22 then say one word about the preclinical assessment just to
23 adhere to the time limits, and I am not at all going to
24 refer to my colleagues who spoke on the clinical side.

25 [Slide.]

1 The guidelines that were published by the FDA,
2 which have been immensely helpful, suggest that we have a
3 10-year simulated testing that look at hoop strength and
4 geometry, but as we begin to look at these things, why is
5 this important if the stent is embedded well within the
6 blood vessel wall.

7 [Slide.]

8 Let's look also for the development of cracks
9 during expansion, after expansion, again, is a crack in a
10 stent of any clinical significance? I raise the questions
11 that beg far greater discussion, but for the sake of time,
12 let's go on.

13 [Slide.]

14 I promised one word about finite element analysis.
15 Finite element analysis is the ability to perhaps use a
16 mathematical model based on a set of boundary conditions
17 from predetermined conditions, and some understanding, for
18 example, of the mechanical characteristics of the stent, a
19 balloon and artery, and a lesion.

20 The problem is that finite element analysis, as it
21 is fundamentally practiced in the field of stenting,
22 predicts deformation using what it presumes to be measures
23 of stress, but you can't measure stress in an artery, you
24 can measure deformation.

25 We may be focusing on the very wrong thing.

1 Perhaps what we should be measuring, and what we should be
2 looking at, is what are the mechanical characteristics of
3 the stent and its interaction on the artery, so that we can
4 predict the internal forces.

5 In other words, what is most important in the
6 engineering evaluation of the stent - is it the force that
7 it imparts on the blood vessel wall or the
8 deformation/injury that it imposes?

9 [Slide.]

10 Let me also talk now about dimensional changes.
11 The current guidelines would suggest that we look at
12 dimensions before and after expansion, what is a 7-
13 millimeter stent in its expanded and unexpanded state. But
14 the truth is that most of the injury that occurs early on is
15 during expansion.

16 [Slide.]

17 One of the things that we have learned in our own
18 laboratory, and data that we have published, is that the
19 form of expansion, both spatially over the length of the
20 artery and temporally, over the time of expansion,
21 correlates very directly with the injury that it is formed
22 and the neointima that is developed in animal models.

23 [Slide.]

24 The characterization that currently exists is
25 binary. Let me show you why that might be a problem.

1 Imagine that we had two devices. They could look like this,
2 and there could be some environmental condition, let's call
3 them umbrellas, so under a sunny condition, the umbrella
4 should shield the sun, and under rainy conditions, the
5 umbrella should shield out the rain.

6 Well, which is the better device, that which
7 shields out more sun or that which shields out more rain?
8 It really depends on where you put your threshold, and what
9 you begin to understand is that we should be characterizing
10 these devices to a far greater extent than just simply
11 approving whether they are good or bad.

12 [Slide.]

13 Let's look at this. We could say that a red stent
14 has a certain number of pass and a certain number of fail,
15 and it could look identical to a yellow stent with the same
16 degree of pass and fail, but in truth, if one looked at it
17 in what we call in continuum dynamics a probability
18 distribution of those events, you can see that these stents
19 or devices or umbrellas may be behaving in a very different
20 manner.

21 [Slide.]

22 It was this that motivated us to begin to work
23 with the standards community, with the Office of Science and
24 Technology, with a large faculty at Harvard Medical School
25 and MIT to assist the FDA and industry in standardizing PMA

1 submissions, but also to aid and, in this case, Dr.
2 Hirshfeld and Dr. Barry Shariff and Dr. Spencer King have
3 helped us involve the American College of Cardiology in
4 terms of aiding in clinical decisionmaking.

5 Finally, although I am not going to talk about it
6 today, we have spawned a major effort at our universities of
7 initiating an institute devoted totally to biotechnology
8 development.

9 [Slide.]

10 We have proposed to the FDA a three-tiered
11 approach. The first is one of general characterization that
12 we would, in concert with ASTM, look to see what can we
13 characterize. Then, after we have completed that task, we
14 will look to see which of these characterizations are
15 clinically relevant, and mindful of the fact that we still
16 need to be within the approval business. We need to provide
17 at the end of the day what can be used for approving the
18 market introduction of a device.

19 [Slide.]

20 The tack we have taken is to identify, involve,
21 and funding of key players. We have been aided, as I said,
22 by critical people like Dan Chwirut, Bram Zuckerman, Semih
23 Oktay, and many other people at the FDA, many people in
24 industry, many people in academia. I have put their names
25 in your packet, I am not going to go through them, and we

1 have begun to identify the testing characteristics, and we
2 have begun to identify the tools, metrics, and measures, as
3 well the procedures, that can be done.

4 One of the frustrating things again in looking at
5 these approval submissions is that not only do you have very
6 many different parameters that are submitted to characterize
7 a stent, but you also have very many different procedures
8 for potentially measuring the same parameter.

9 [Slide.]

10 I am going to skip over this other than to say
11 this really is part of a very large process that is going on
12 now at Harvard and MIT, looking at instrument, software,
13 diagnostics, therapeutics, imaging, and environmental
14 exposures, not just for devices alone.

15 [Slide.]

16 What we have done in concert with Dan Chwirut is
17 to involve the American Society for Testing of Materials,
18 and there is a subcommittee which Dan I had head, the
19 Subcommittee F4.04, which now has three subcommittees
20 looking at the material characteristics, the dimensional
21 analysis, and operational performance of these devices,
22 breaking down now for the first time into three formal
23 categories the way in which an endovascular implant can
24 behave.

25 [Slide.]

1 These are in your packet, I am not going to go
2 through them other than to say that we have had involvement
3 by industry and by academia, first, Dave Jacobson and later
4 Daniel Cox have chaired the Dimensional Analysis
5 Subcommittee, and are beginning to formulate in a series of
6 meetings, the next of which will be tomorrow morning, what
7 are the parameters we should be looking at and how they
8 should be measured.

9 [Slide.]

10 In the very same way, Dr. Palmaz, Dr. Julio Palmaz
11 has led the effort, again with a large representation from
12 industry, from ex officio members of the FDA and academia
13 are looking at what are the ways of analyzing various
14 materials, and he has done an absolutely magnificent job of
15 bringing this all together, both for standard stents and for
16 what is now coated stents.

17 [Slide.]

18 Finally, Semih Oktay is working with us, in
19 particular, Jim Squires and myself at our center to try to
20 understand what are the parameters that go into the
21 operational definition of a stent.

22 [Slide.]

23 Now, let me close by just touching on preclinical
24 assessment.

25 [Slide.]

1 The guidelines state that animal models should
2 reflect the type of lesion to be evaluated in the clinical
3 study. Well, this is a human coronary artery, and this is a
4 porcine coronary artery after it has been stented.

5 [Slide.]

6 The studies say that we should use atherosclerotic
7 models rather than normal animals, however, other models may
8 be utilized with adequate justification, and this presents
9 two problems.

10 First, this is a native coronary artery and here
11 is the diseased coronary artery, so clearly, there is a
12 marked difference. Clearly, it is virtually impossible to
13 reproduce the human lesion in the animal, but there presents
14 a further problem, and that is we need to use this lesion,
15 and virtually this lesion alone, because it is almost
16 impossible to reproduce this kind of lesion time after time.

17 [Slide.]

18 The response to injury is a probability density
19 function unto itself. Here, I have drawn it as a normal
20 distribution. That means that the mean response to injury,
21 the mean amount of thickening of intimal hyperplasia, of
22 proliferation, of inflammation and thrombosis sits right
23 here, but there are extremes on either side.

24 [Slide.]

25 If I do this twice, then, I get a 3-dimensional

1 probability density function, and here I have drawn it as
2 symmetric. In other words, I have drawn it that the first
3 lesion has no impact on the second, but that, in and of
4 itself, may not be the case.

5 [Slide.]

6 What this fundamentally means is that animal
7 models are not used to predict human disease. They are here
8 to help us unroof biological mechanisms. They can, in fact,
9 tell us trends about the way in which stents may behave if
10 taken in the general context of what we know about
11 engineering principles and of how they are performed in
12 clinical trials, but if one makes the mistake of trying to
13 use them alone and in a vacuum, we will not be able to
14 reproduce the findings in the human trials.

15 [Slide.]

16 We cannot reiterate the human substrate or
17 recapitulate the human condition, and we can only, though,
18 examine fundamental mechanisms.

19 [Slide.]

20 In closing, if we are to go from standards to
21 predictability, we will need to have an integrated approach
22 that takes advantage of all of the elements of assessment
23 from benchtop testing to finite element analysis, to
24 preclinical animal models, to clinical trials with both pre-
25 and post-market surveillance.

1 I must close again by simply acknowledging that
2 although I am presenting this material, it represents the
3 sum of work over the last two years of very many
4 individuals.

5 Thank you.

6 DR. CURTIS: Thank you.

7 I am not aware of any other members of the general
8 public who wanted time to speak. We are going to hold the
9 industry presentations until after the break. So, let's go
10 ahead and take a break now and reconvene at 10:15.

11 [Recess.]

12 **Industry Presentations**

13 DR. CURTIS: Next, we are going to have the
14 industry presentations, and the first one is going to be
15 Gary Johnson from Guidant Corporation, representing HIMA.

16 Again, you need to state I guess your financial
17 interests in these products.

18 MR. JOHNSON: I am an employee of Guidant
19 Corporation.

20 [Slide.]

21 Good morning. My name is Gary Johnson. I am Vice
22 President of Regulatory Affairs, Clinical Research, and
23 Quality Assurance for Guidant Corporation's Vascular
24 Intervention Group.

25 I am here today representing the HIMA ad hoc

1 Interventional Cardiology Group.

2 [Slide.]

3 This group is made up of representatives from the
4 following companies: Arterial Vascular Engineering, Boston
5 Scientific, SCIMED; Cordis Corporation, Guidant Corporation,
6 and Medtronic Corporation.

7 First, I wanted to thank FDA and panel for the
8 opportunity to meet and discuss the possibility of
9 developing preclinical and clinical standards for coronary
10 stents. We truly do believe this type of collaborative
11 effort between FDA, industry, and the medical community
12 allows us to bring value-added technologies forward in an
13 effective and efficient manner.

14 What the HIMA Committee wanted to do today was to
15 comment on the questions that FDA asked panel to review. As
16 this time, we do not have final answers to these questions,
17 but did want to provide you some early industry perspectives
18 on them.

19 [Slide.]

20 The first question is: Can we define the standard
21 coronary stent based on engineering design characteristics?

22 We definitely feel there is a possibility here,
23 and as you have already heard today, there is already an
24 ASTM Committee working on doing this.

25 They have phased their activities, has already

1 been presented, as well, and we think we need to also
2 incorporate a request of them to actually come up with an
3 engineering definition for a standard stent.

4 [Slide.]

5 The second question that was asked was: What
6 acute clinical performance characteristics best define a
7 standard coronary stent?

8 [Slide.]

9 To really answer this question, we had to come up
10 with a very crude frame of what we thought a standard stent
11 was, and again this is just something for discussion. We
12 said a standard coronary stent would have the stent features
13 of being stainless steel and balloon-expandable, in
14 diameters of 2.5 to 5.5, and in lengths from 8 to 32
15 millimeters.

16 The standard indications would be for de novo and
17 restenotic lesions, saphenous vein grafts, and abrupt and
18 threatened closure, and, of course, would have to be in
19 conformance with the ASTM standards and recommendations when
20 they are developed.

21 [Slide.]

22 Given that, we think that the clinical performance
23 characteristics which best define a coronary stent would be
24 technical success, which is defined as device success and
25 procedure success; post-procedure diameter stenosis, post-

1 procedure MLD, subacute thrombosis, and 30-day MACE, and
2 looking at the long term endpoints, we think it should be 6-
3 month MACE, 6-month target vessel failure, target vessel
4 revascularization or target lesion vascularization, and one
5 that is left off here is angiographic endpoints.

6 [Slide.]

7 The next question we wanted to address is: Can a
8 combination of engineering design characteristics and/or
9 acute clinical performance be employed?

10 We think definitely the answer is yes, we think
11 this is most appropriate for product modifications, but to
12 really do this, we need to determine, in conjunction with
13 ASTM Committee, what the standards performance
14 characteristics for stents would be.

15 [Slide.]

16 The next question we want to address is: For what
17 clinical questions should we continue to perform randomized
18 controlled trials?

19 We think when there is new questions of safety and
20 efficacy, we need to have randomized trials. This would be
21 in the case of a significantly new stent design, such as a
22 mesh or covered stent, significant new materials, such as
23 polymers, and radically new indications as we have discussed
24 today, maybe in small vessels and long lesions.

25 [Slide.]

1 The question was: Based on the consistency of
2 results in completed trials to date, should we consider the
3 use of non-concurrent controls?

4 We think the answer is definitely yes, there is an
5 opportunity here. Company specific data from randomized
6 trials and/or the most recent registry can be used to
7 support minor design changes in those stents with the
8 creation of company specific OPCs.

9 This would have the advantage of rapid
10 introduction of next generation stents, provide an incentive
11 for continuous improvement of those stent platforms, and
12 incentive to conduct scientifically sound clinical trials
13 furthering medical science in other areas.

14 [Slide.]

15 Looking at industry OPC, the question was: Can we
16 develop an industrywide objective performance criteria?

17 We think again this is definitely a possibility,
18 but there are several hurdles that need to be overcome that
19 have also been addressed today.

20 First, the clinical data is held confidential for
21 six years post-PMA, so we have to work out a way in which
22 this data could actually be utilized for this purpose for
23 all the industry members.

24 Then, we have to decide which stents would be
25 included in the OPC, would it be all the currently approved

1 stents or some subset of them, and that is an important
2 question.

3 [Slide.]

4 Third, stent clinical trial results are still
5 moving in our opinion, have not yet stabilized. It is true
6 that over the last two years, most of the stent trials
7 showed very consistent results, but you have to remember
8 that those trials were really designed to show equivalence.
9 That was the purpose of them.

10 But if you broaden out that window a little bit
11 and you look at the Palmaz-Schatz results in the recent
12 randomized trials, the results improved substantially over
13 the original approval data of the Benestent and Stress
14 trials, if you look at SAT and target vessel
15 revascularization.

16 We also believe there is ongoing improvements in
17 stent design, stenting technique, and medications, and we
18 have to be careful that we don't recognize a "worse"
19 performing stent with an OPC due to changes really in the
20 auxiliary care.

21 So, those are just some of the challenges. We
22 think they definitely can be overcome, and we can work with
23 people in doing this, but we have to make sure that we are
24 recognizing those challenges.

25 [Slide.]

1 Looking at the long term endpoints of six months,
2 the question was asked: What is the best candidate for
3 valid surrogate endpoints?

4 We definitely feel today that angiographic
5 restenosis rate is a great surrogate endpoint. It offers a
6 lot of advantages from a statistical endpoint, as well as
7 consistent with the bigger is better theory.

8 How can we validate a continuous measure? We
9 think this can definitely be done through statistical
10 modeling of the currently available data from clinical
11 trials.

12 [Slide.]

13 How can we validate an earlier endpoint, example,
14 30-day MACE?

15 Again, we think statistical modeling of a 30-day
16 MACE compared to long term results of the current clinical
17 trials would allow us to do this.

18 [Slide.]

19 The question was: Could alternative approaches to
20 design analysis be considered?

21 Again, we think definitely there is opportunity
22 here, looking at different statistical methods, such as the
23 Frequentist and Bayesian approaches referred to today can be
24 employed, and the use of previously established surrogates
25 for specific stent designs for approved stents, and the

1 development of company specific or industrywide OPCs would
2 offer great advantage.

3 [Slide.]

4 The next question is: Could we integrate
5 postmarket surveillance or post-approval studies into the
6 approval process?

7 We believe definitely this is a possibility, but
8 it is probably more appropriate for modifications to the
9 label or provide additional user information versus
10 establishing the safety and efficacy of the device.

11 [Slide.]

12 The next question was: For new indications for
13 previously approved stents, can we reduce the size of
14 adjunctive registries?

15 We think there is opportunity here, as well, with
16 the use of Bayesian statistics, we can not only maybe use
17 this statistical model to approve minor changes in stent,
18 but also minor changes in indications. This may be
19 difficult, though, for brand-new indications, and we need to
20 continue to evaluate continuous variables, surrogate
21 endpoints, and continue to conduct postmarket evaluations.

22 [Slide.]

23 The last question was: What is the most
24 appropriate interpretation of peri-procedural CPK enzyme
25 bumps?

1 That was something we definitely wanted to the
2 panel on.

3 In closing, on behalf of the HIMA ad hoc
4 Interventional Cardiology Group, again, we wanted to thank
5 FDA and the panel for the opportunity to talk about this
6 important issue, and we look forward to working with both of
7 you on trying to set up the appropriate OPCs for stenting.

8 Thank you.

9 DR. CURTIS: Before you step away, the issue is
10 going to be coming up about using the data that has already
11 been available as a database, and, you know, a lot is going
12 to depend on whether industry is willing to share data with
13 other members of industry.

14 I doubt any member of the panel would have a
15 problem with that approach. I think probably the FDA would
16 be happy if there was some allowance for some of this data
17 being shared, because they can't go beyond what the law will
18 allow them if the manufacturers are against the idea.

19 I think the problem that comes up is that, you
20 know, a lot of times whatever a particular company is
21 interested in doing depends on self-interest. I mean if you
22 have got all the stent data, it gives you an advantage over
23 the guy who doesn't have any yet, and you may not be so
24 willing to share it, but then if some other kind of
25 technology comes up, and somebody has got it, oh, you would

1 love to be able to share it, because it gives you some
2 easier entry into it.

3 How willing is industry going to share the data,
4 and, you know, particularly I don't see J.J. listed there.

5 MR. JOHNSON: That was just an oversight. It's
6 not that they are not willing. Cordis is on there.

7 Obviously, that is a very big question, and it is
8 very difficult to answer at this time. I think during the
9 HIMA Committee meetings, I think everybody from industry who
10 has part of this data was very open to developing OPCs, but
11 were reluctant to just turn the data over for analysis, but
12 really wanted to be part of how the OPC was going to be
13 created and turn it over as appropriate.

14 So, I think there was a great deal of openness,
15 but it would definitely have to be interactive process.

16 DR. CURTIS: I think that is at least a good place
17 to start from, because if there is openness and willingness
18 to share, but it has to be worked out, well, then that is
19 fine, it can be worked out. It wouldn't really matter a
20 whole lot if we decided that it would be great to share all
21 the data if nobody was willing to.

22 MR. JOHNSON: Right. I am more than welcome for
23 anybody from industry in the audience to comment if they
24 would like, as well.

25 DR. CURTIS: Thank you.

1 MR. JOHNSON: Thank you.

2 DR. CURTIS: The next industry presentation is
3 going to be by Dr. Elliot Barnathan from Centocor.

4 [Slide.]

5 DR. BARNATHAN: Good morning. I would like to
6 thank the members of the panel and the FDA for the
7 opportunity to share our thoughts and data with you on the
8 following areas for consideration in stent trials.

9 DR. CURTIS: Would you mind stating your financial
10 interest in these products?

11 DR. BARNATHAN: I am an employee of Centocor.

12 DR. CURTIS: Okay.

13 [Slide.]

14 DR. BARNATHAN: First, I will briefly review the
15 effects of interventions including abciximab on vascular
16 biology as well as the effects of these interventions on
17 clinical endpoints. My presentation will include our
18 thoughts on CK/CK-MB elevation and its association with late
19 mortality.

20 I will also review the results of several clinical
21 trials with abciximab, focusing on our most recent trial,
22 the EPISTENT trial, which is the largest coronary stent
23 trial performed to date. Finally, I will offer some
24 concluding remarks about the design of future coronary stent
25 trials.

1 [Slide.]

2 ReoPro or abciximab is a chimeric monoclonal
3 antibody which blocks both the glycoprotein IIb/IIIa
4 receptor, shown in orange, and the alpha v beta 3 receptor,
5 shown in purple, on the surface of the platelet, as well as
6 alpha v beta 3 receptors found on both endothelial cells and
7 on smooth muscle cells.

8 [Slide.]

9 By virtue of this dual specificity, abciximab has
10 multiple mechanisms to potentially affect the vascular
11 response to injury. First, it blocks fibrinogen binding and
12 thereby potently inhibits platelet aggregation.

13 Second, it inhibits thrombin generation on the
14 platelet surface and finally, it inhibits smooth muscle
15 migration and proliferation via its inhibition of alpha v
16 beta 3 which is up-regulated on smooth muscle cells in
17 response to vascular injury.

18 [Slide.]

19 This slide is adapted from one shown recently at
20 the American Heart Association meeting by Terry Ferguson
21 from the University of Texas. Angioplasty clearly induces
22 an acute vessel wall injury, resulting in platelet
23 deposition, followed by thrombus formation which can lead to
24 myocardial injury.

25 Platelet embolization can also occur causing

1 obstruction in the microvasculature, and may result
2 information microthrombosis, which may further worsen the
3 injury.

4 This may request in either Q wave or non-Q wave
5 MIs. Vessel wall injury also results in neointimal
6 proliferation leading to restenosis, which may have a
7 contribution from the reorganization of thrombus. This can
8 be measured angiographically or clinically as the need for
9 target vessel revascularization or TVR. MIs may also be
10 associated with late mortality.

11 [Slide.]

12 Let's look at how stenting may improve this
13 picture. The major effect has been to reduce restenosis or
14 TVR. However, there has been no effect on reducing either
15 MI or late mortality.

16 [Slide.]

17 Let's look at abciximab. For abciximab, there is
18 a modest effect on restenosis possibly via its effects on
19 alpha v beta 3.. There is a potent effect on reducing
20 platelet deposition neighborhood subsequent events,
21 including a reduction in MI, and there have been trends in
22 most trials to a reduction in mortality.

23 [Slide.]

24 If one looks at the combination of abciximab and
25 stents, one can imagine potent effects on each of the

1 consequences of vessel wall injury, resulting in decreases
2 in TVR, in MI, and possibly late mortality. The association
3 between post-procedural MI and late mortality has been shown
4 in most, but not all, studies. I would like to review some
5 of that data briefly now.

6 [Slide.]

7 This slide depicts the results of three series
8 with late follow up, from the CAVEAT trial, as well as from
9 series from the Cleveland Clinic and the Washington Heart
10 Center. While the definitions for small and large
11 infarctions varied among these series, in each case with
12 follow up from one to more than three years, there was a
13 graded increase in late mortality with those having larger
14 enzyme rises, shown in yellow, having the greatest increased
15 risk of death.

16 We have seen a similar close association in a
17 metaanalysis performed with three of our large pivotal
18 trials. I would like to share with you, in brief, the
19 results of several trials with abciximab.

20 [Slide.]

21 Shown on this slide is the primary endpoint by
22 intention to treat in three large Phase III, placebo
23 controlled trials of abciximab. In the EPIC trial, shown on
24 the left, there was a highly significant 35 percent
25 reduction in the primary endpoint of death, MI, or urgent

1 intervention.

2 In EPILOG, which studied a reduced dose of
3 heparin, there was a 56 percent reduction, and in the most
4 recent trial, EPISTENT, the addition of ReoPro to stenting
5 reduced the same composite endpoint by 51 percent, a highly
6 statistically significant result. We have also recently
7 performed a metaanalysis of patients receiving stents in
8 abciximab trials prior to EPISTENT with similar results, as
9 shown in the next slide.

10 [Slide.]

11 Presented here are the results for death or MI at
12 6 months in stented patients from EPIC, EPILOG, and CAPTURE.
13 As you can see, there was a 53 percent reduction which
14 achieved a p-value of 0.05 in this small sample size of 529
15 patients.

16 [Slide.]

17 This slide demonstrates the results for TVR alone
18 at 6 months. The left two bars, the results for all 5,491
19 patients in these three trials, is shown with a significant
20 3 percent absolute reduction. To the right, you can see
21 that, although it did not achieve statistical significance
22 due to the small sample size, these patients receiving the
23 stents in this trial had a 4.8 absolute percent reduction in
24 TVR.

25 [Slide.]

1 Therefore, to address the value of combining
2 stents and abciximab in a wide population receiving elective
3 coronary stents, we designed the EPISTENT trial.

4 Parenthetically, I would remark this is probably the last of
5 the Frequentist Ferrari trials in this area.

6 [Slide.]

7 2,399 patients with coronary anatomy suitable for
8 stent implantation were randomized to receive either a stent
9 plus placebo with standard weight adjusted heparin,
10 abciximab and a stent, with low dose weight adjusted
11 heparin, or abciximab and conventional angioplasty with the
12 same low dose heparin regimen.

13 The primary endpoint was death, MI or urgent
14 intervention at 30 days. Additional clinical and
15 angiographic follow-up was performed at 6 months and
16 mortality was assessed at one year.

17 [Slide.]

18 This slide shows the Kaplan-Meier plots of the
19 primary composite endpoint of death, MI or urgent
20 intervention at 30 days. As you can see, most events tended
21 to occur early, with a significant reduction in both
22 abciximab groups. There was a 5.5 percent absolute
23 reduction or a 51 percent relative reduction in the stent
24 and abciximab arm, but there was also a significant 35
25 percent relative reduction in the angioplasty and abciximab

1 arm as well.

2 [Slide.]

3 This slide shows the incidence of MI at 30 days,
4 broken down by the size of the infarction. As you can see,
5 it was the large non-Q wave infarctions, shown in blue, with
6 a greater than 5-fold increase in CKMB that was the major
7 component, although trends for reduction were seen with Q
8 wave and small non-Q wave infarctions, as well.

9 [Slide.]

10 This slide shows the major bleeding rate in the
11 trial. Importantly, bleeding was not increased, and if
12 anything, decreased, but not statistically significant in
13 the two abciximab treated groups. This confirms the results
14 of the EPILOG trial which demonstrated no increase in major
15 bleeding when abciximab was used with low dose weight
16 adjusted heparin.

17 [Slide.]

18 This slide shows the results at 6 months for death
19 or MI. As you can see, the benefit is maintained in both
20 groups, with a 5.8 absolute percent reduction when stents
21 and abciximab were combined, as shown in blue.

22 [Slide.]

23 If one looks, however, at death, MI or TVR, the
24 more conventional MACE endpoint at 6 months, one can see an
25 interesting pattern, with the early benefit here in the

1 angioplasty and abciximab group, disappearing by 3 months,
2 while the curves remain significant different from one
3 another for the two stent groups, with a 5 percent absolute
4 reduction.

5 Therefore, utilizing this MACE at 6 months has
6 obscured the maintained benefit seen for death and MI at 6
7 months in the angioplasty and abciximab group.

8 [Slide.]

9 This slide shows the results for TVR alone at 6
10 months. The combination of abciximab and stents is shown in
11 red, was associated with an 18 percent reduction from 10.6
12 percent to 8.7 percent. That was not significant, but both
13 stent groups did better than the angioplasty group, shown in
14 orange, confirming the results of prior trials,
15 demonstrating a decrease in TVR at 6 months with stenting.

16 [Slide.]

17 This slide shows the results for TVR at 6 months
18 in a prespecified subgroup, diabetics, who tend to do worse
19 with stenting. As you can see on the left, there is an
20 excess TVR of 16.6 percent in diabetic patients receiving
21 stents alone, compared to the non-diabetics.

22 The combination of stents and abciximab, shown in
23 red, completely neutralized this excess, reducing the TVR in
24 half to the 8 to 9 percent range shown in non-diabetic
25 patients. To provide a mechanistic insight into these

1 clinical results, we performed an angiographic substudy on
2 the first consecutive 900 patients enrolled.

3 [Slide.]

4 This slide shows the early gain, late loss and net
5 gain in the angiographic substudy as a whole, with stent
6 alone shown in purple, stent plus abciximab in red, and the
7 balloon plus abciximab in orange. As you can see, both
8 stent groups fared better than the angioplasty group in
9 terms of early gain, but both were worse in terms of late
10 loss. However, the combination of abciximab and stenting
11 provided a significant improvement in net gain from 0.73 to
12 0.86 mm.

13 [Slide.]

14 As with the clinical data, if one looks at the
15 diabetic patients, the results were more dramatic
16 particularly with respect to net gain, where there was a
17 significant increase from 0.55 to 0.88 mm.

18 In the last few minutes I would like to share with
19 you perhaps the most significant findings from the EPISTENT
20 trial.

21 [Slide.]

22 On this slide is the analysis of all randomized
23 patients in terms of one year mortality. As you can see,
24 there is a 58 percent relative reduction or a 1.4 absolute
25 reduction which was statistically significant.

1 [Slide.]

2 This slide depicts the mortality at 30 days, 6
3 months, and at 1 year. As you can see, although mortality
4 is an uncommon event, the best strategy for saving lives
5 would appear to be the combination of abciximab and stents,
6 with a steadily increasing absolute reduction in mortality
7 from 3 to 7 to 14 lives saved per 1,000 patients treated.
8 This finding in the EPISTENT trial is not isolated and has
9 been seen in other trials.

10 [Slide.]

11 This slide depicts a metaanalysis of several
12 trials comparing abciximab bolus plus 12 hour infusion in
13 treated patients with placebo in terms of mortality. As you
14 can see, the point estimate for each trial is to the left of
15 the center, suggesting a mortality advantage.

16 If one pools all balloon-treated patients, there
17 is a significant reduction, as shown here. Interestingly,
18 although there were fewer patients in the pooled stent
19 comparison, shown here, the results are even more
20 impressive.

21 Overall, there was a reduction of 36 percent in
22 terms of mortality, which is highly significant. From these
23 data, we conclude that the benefits of abciximab and
24 coronary stents are truly additive and that the combination
25 does save lives.

1 [Slide.]

2 Based on the information I have shared with you
3 today, we would like to offer the following considerations
4 for future device trials.

5 First, with respect to CK/CKMB evaluation, post-
6 procedural MIs identified by increased CK/CKMB have been
7 associated with late mortality. Therefore, we propose that
8 CKMB measurement is important, and that it should be done
9 systematically. We have consistently used a 3-fold
10 increase to define a non-Q wave MI, and would propose that
11 this be used as an industry standard.

12 [Slide.]

13 Second, with respect to the selection of
14 appropriate endpoints, we would suggest that the different
15 coronary interventions may have differing effects both on
16 vascular biology and on clinical endpoints. The composite
17 endpoint of death, MI or TVR at 6 months may obscure
18 differential effects on death or MI versus those on TVR
19 alone. Therefore, both the composite and the components
20 should be evaluated. Finally, TVR at 6 months is concordant
21 with angiographic evaluations.

22 [Slide.]

23 Finally, regarding the use of adjunctive therapy
24 in stent trials, the data I have presented today
25 demonstrates that the effects of abciximab and stents are

1 additive, and that the combination reduces mortality.

2 Because abciximab is the only GPIIb/IIIa inhibitor
3 that has been tested and been shown to be effective as an
4 adjunct to stenting, and because abciximab possesses unique
5 pharmacologic attributes compared to the other IIb/IIIa
6 inhibitors, we propose that abciximab be included as
7 adjunctive therapy in coronary stent trials.

8 Finally, we propose that the combination of
9 abciximab and stents become the standard against which new
10 devices are compared.

11 Thank you for your attention.

12 DR. DOMANSKI: I have one question for you. That
13 was a very nice presentation. Thank you. It was very
14 clear.

15 One sort of minor point from your standpoint, but
16 major perhaps from ours, is the combination of death, MI and
17 target vessel revascularization performed actually pretty
18 poorly because it obscured the mortality benefit of the PTCA
19 plus abciximab.

20 Can you comment on that? I mean it strikes me.
21 Does it strike you or maybe anyone else?

22 DR. BARNATHAN: I think it depends on whether or
23 not you are interested in evaluating a stent or you are
24 interested in evaluating antiplatelet therapy. I think in
25 terms of stents, using TVR alone is a good endpoint. I

1 think when you are having a therapy that has effects both on
2 TVR and on death or MI, or an effect only on death or MI,
3 then, by lumping in TVR, you can obscure both death or MI.

4 DR. DOMANSKI: I guess that is something that it
5 might be worth briefly revisiting, though, because, of
6 course, the problem with that endpoint is it takes one very
7 soft endpoint and combines it with two very hard and
8 important ones.

9 I mean it is one thing to redilate somebody, it is
10 another thing to have them have an MI or die, and I guess I
11 would be interested in, as time goes by, just hearing from
12 everybody and kind of thinking about that endpoint one last
13 time.

14 DR. BARNATHAN: I think the one thing that is
15 unquestioned, at least in terms of the IIb/IIIa data and
16 abciximab in particular, is that death or MI as a particular
17 endpoint has been very consistent and has been preserved out
18 to long time points, 6 months, for example.

19 DR. VETROVEC: If you exclude the unstable
20 patients in that study, does the data still hold true?

21 DR. BARNATHAN: Yes. In point of fact, a third of
22 the patients were stable, and Mike Linkhoff at the American
23 Heart Association presented the data on stable, and in point
24 of fact, the results are equivalent for stable or unstable
25 patients.

1 DR. CURTIS: Thank you.

2 DR. BARNATHAN: Thank you.

3 **Open Committee Discussion**

4 DR. CURTIS: We are going to move on to the panel
5 discussion now.

6 Does any member of the panel want to make any
7 general or opening comments as we get started? To me, it
8 seems the best way to go about discussing this is to go
9 through the questions that have been posed for us, and it
10 will cover every issue as we go along.

11 [No response.]

12 DR. CURTIS: No one has anything to say yet.

13 Let's go ahead and put up the first question.

14 The first question being posed to us is to define
15 the standard coronary stent.

16 Can we define it based on engineering design
17 characteristics such as: materials used; the range of
18 diameters; a stent-to-free surface area ratio; elastic
19 recoil; percent shortening; and radial strength?

20 I think the point here is that if we are going to
21 have differences between new designs and standard designs,
22 then, we have to know what it is we are calling a standard
23 design that might allow a different approach to evaluation
24 compared to the randomized clinical trial that has been used
25 the past.

1 Does anybody want to make any comments about that
2 first question and kick it off? Go ahead.

3 DR. OESTERLE: I am confused about this. I mean
4 we have some real experts here that know more than I do and
5 particularly Dr. Edelman, but it seems somewhat naive to
6 list it like this and think that this is sufficient. In
7 fact, we do know that these stents actually injure the blood
8 vessel when they are deployed, and that injury I think is
9 quite variable, and it is not simply related to these
10 variables, but how the stent is cut, whether it is a flat
11 surface, whether it is a coil, and as we look at some of the
12 stents that have already been approved, there are some
13 stents that do have significant variability in their
14 restenosis rates, and we think that it is related to not
15 just the materials or the range or these things here, but
16 actually some issues about when they are deployed, how they
17 injure the artery, what pressures, a variety of things like
18 that.

19 So, I guess I am a little confused about how you
20 expect us to take this approach. I mean it seems much more
21 complicated. I don't know if maybe Elazer wants to say
22 anything more about that. He is probably the world's expert
23 on this particular issue as I see it, but it seems a little
24 naive.

25 DR. CURTIS: Well, I have to agree that I am not

1 an expert in this kind of thing either. Maybe a better way
2 to look at this might be to say what would a stent have to
3 be like so that it wouldn't be a standard stent, what would
4 make something different enough that you wouldn't include it
5 here."

6 Maybe that would be helpful, because I don't think
7 I could just sit here and list, well, if it is 2.5 to 4.0
8 mm, then, that is standard. There are other experts who
9 could probably come out with that better, but maybe just
10 some thoughts about would different materials make a stent
11 different enough, that it wouldn't be treated this way, you
12 know, rather than stainless steel, some other material were
13 to be used, would that be different enough.

14 I think it would be because you can't predict how
15 another material is going to work.

16 DR. BRINKER: I think that one easy
17 straightforward thing that one might entertain is to take
18 the list of the range of these specific variables for each
19 of the stents that are approved for the indication that this
20 new stent seeks, and that gets out of some muddy water in
21 relationship to the coil stent, but if a new stent is for
22 the elective implantation for limitation of restenosis, it
23 could be considered standard if it falls within the range of
24 the already approved devices. That would be a first cut
25 approach, it seems to me.

1 Again, the specifics of the engineering are things
2 that haven't been worked out in the past, so that pending
3 some dramatic revelation as to which of these factors may or
4 may not be important, and even so, the factors may not be
5 analyzable very well in single format.

6 They might be a combination of these things that
7 might act one way and a combination of them that might act
8 another way, but for our purposes, for the definition of
9 what might be considered reasonably equivalent in terms of
10 the spectrum of engineering to what has already been
11 approved, I think you know what has been approved, you know
12 the range of that, or something that is approved for that
13 specific indication, I think that you have a reasonable
14 starting point, and then when the engineering gets to a
15 state of higher knowledge and agreement, one could work from
16 there.

17 DR. CURTIS: Does anybody from the FDA want to
18 comment on the rationale behind this question or how
19 specific you are looking for in terms of some of these
20 answers here?

21 DR. SPYKER: Well, in Section 4 of your panel pack
22 there is a good deal more detail that the ASTM team has put
23 together, and those of you who care to comment on this kind
24 of question, would be well-advised, I suppose, to look more
25 critically at those, like starting on page 432 are the

1 details of those.

2 MR. CHWIRUT: My name is Dan Chwirut. I am an
3 engineer in the Office of Science and Technology, CDRH.

4 Just to add a little bit, there has been some
5 discussion in the ASTM, for example, the use of stainless
6 steel. The gold standard is the Palmaz-Schatz stainless
7 steel, is elastoplastic traditional material is a better
8 definition of that.

9 Is the panel comfortable if we included stainless
10 steel, elgiloy, tantalum, materials like that, as opposed to
11 nitinol or shape-memory alloys, which are a totally
12 different class of materials with a totally different set or
13 problems?

14 Can we exclude, as Dr. Brinker said, nitinol,
15 shape-memory materials from the definition of standard,
16 while including traditional elastoplastic materials? That
17 would be one good starting point, I think.

18 DR. CURTIS: Dr. Edelman, why don't you go ahead
19 because I would like to hear -- I think part of the question
20 here is does a standard coronary stent have to fulfill six
21 different characteristics, or is one or two of those more
22 important than some of the other ones, what is the key thing
23 that would define a stent that is similar to previous ones.

24 DR. EDELMAN: As Mr. Chwirut alluded to, these are
25 the very issues that we have been struggling with for a very

1 long time, now upwards of two years. What you are seeing
2 here is that this technology got way ahead of its
3 assessment, very much ahead, so we are dealing with a
4 clinical definition of a device, an engineering definition
5 of a device, and we are trying to correlate the two, and we
6 don't have any data to correlate them, and we don't even
7 know what the tools are.

8 So, the best answer right now is to really go
9 back, as Dr. Oesterle said, to some of the first principles
10 and to see if we can (a) reduce the device to, first, its
11 indications, and second, its fundamental parts, and that is
12 why the ASTM has taken the tack of saying stent is composed
13 of materials, it has finite dimensions, and it performs in a
14 certain way, and the best that we can do at start is to try
15 to characterize those things.

16 Then, once we have characterized them in a
17 standard fashion, because there is no standard way of
18 characterizing any of those elements, we can then look to
19 see whether any of those characteristics have any relevance
20 to the clinical performance.

21 Right now I would take an eagle's eye view of this
22 in what in medicine we call the difference between lumpers
23 and splitters. So, I would prefer to be a lumper here and
24 begin to try to broaden the definition from an engineering
25 point of view and to limit it from a clinical point of view,

1 because that is the only way we are going to be able to get
2 our hands around this.

3 So, the specific answer to your question is a list
4 like this will do injustice to us because it may be
5 exclusionary or it may be too focused, and what we should
6 try to do is try to just break it into the broadest
7 components and then work from there.

8 DR. CURTIS: Cindy.

9 DR. TRACY: I think there is a problem of
10 practicality here that we are dealing with. If you just
11 take sort of the global picture and look at the results of
12 the different stents, it doesn't appear as though there is a
13 major difference using one stent versus another so far, so
14 although there may be very different parameters involved
15 with the different stents, I think Jeff's idea of starting
16 out with, well, this is what is approved, sure, figure out
17 what their exact mechanisms or properties are, but to then
18 use that as a comparative basis is probably a reasonably
19 practical way to start.

20 Otherwise, if we have to go back to start from
21 some very basic definition of structure and function, it
22 doesn't seem like we are any farther along than where we are
23 right now. In fact, practically speaking, we are somewhere
24 even farther behind than where we are right now.

25 So, I think if you are looking for a practical

1 place to start, what you have is what you have, and a
2 comparison against those different things, those parameters
3 that are understood about what is approved at this point is
4 probably a very good starting point.

5 DR. EDELMAN: One thing that you can do is to
6 decide on a clinical definition, and then decide on an
7 engineering definition, because the clinical definition
8 doesn't require anything about performance or anything about
9 the way in which it is shaped.

10 Then, you can go back and address the issues as to
11 why stents, which do perform differently on the benchtop,
12 and do perform very different in animal models, have not
13 shown the difference in clinical trials.

14 You have heard the world's experts behind me
15 explain, I think, that equivalency trials are not designed
16 to show superiority.

17 DR. DOMANSKI: I guess the thing that strikes me
18 is that there is an interaction, though, of these devices
19 with the vessel wall, and there are certain things you have
20 to do, for instance, in terms of just staying open or hoop
21 strength, or wherever, and beyond that, it probably doesn't
22 make any difference.

23 I guess maybe one could think about it in terms of
24 what it has to do to keep a vessel open, and do the
25 parameters based on that. I am not sure I know the answer

1 to how to do it. If I were doing it, as far as doing the
2 engineering from the ground up, I would say, gee, why do we
3 really need to do this, and use that as some kind of a
4 standard.

5 DR. CURTIS: I think one of the key issues was,
6 you know, if you come up with a new stent, how is it going
7 to be evaluated, and I think, if I can try to interpret
8 this, one of the reasons for trying to make these decisions
9 about what is standard, is that something that is not
10 standard would require a different sort of evaluation than
11 something that is called standard.

12 You could get into engineering things although I
13 haven't got the foggiest idea how I would figure out how
14 much elastic recoil was okay, but on the other hand, you
15 know, another way to look at it is that, you know, what is a
16 stent, and a stent is a device that is designed to be put
17 into a coronary artery and expanded to keep it open.

18 The idea about that, the point of that is to keep
19 the artery open and then down the road that we are hoping
20 that we are going to have fewer deaths, fewer MIs, and fewer
21 revascularizations, less restenosis.

22 So, that is really what the point of a stent is,
23 and we have data already available on results to be expected
24 from the stents that are already on the market. If a new
25 stent comes out that is a millimeter longer than what the

1 standard definition is, or has a slightly different diameter
2 than the other ones, why does that necessarily have to kick
3 that out into something brand-new, and maybe in a roundabout
4 way, I am getting to saying what you were saying, is that if
5 you are very narrow about your definitions, you know, the
6 following parameters define a standard stent, anything else
7 is not a standard stent, well, then, that is going to be
8 somewhat limiting because then you are going to have to meet
9 those very specific design characteristics in order to allow
10 the equivalence trials and using the database, if we get to
11 that point and talk about that, whereas, something that is
12 outside of that realm then would still need a randomized
13 clinical trial where you have to compare it one to one with
14 another stent.

15 I am not sure, just thinking about it, that I
16 really see that that is necessary, that is a stent is a
17 stent and it is designed to do for the clinical indications
18 of a de novo stenosis or a restenosis, you know, we are not
19 getting into new clinical indications.

20 If it is a standard clinical indication, and it is
21 a new stent, but a somewhat different design, can we conduct
22 the trials is the same way and think of them as equivalence
23 trials.

24 I am not talking about the engineering aspects of
25 it. I am sure there is going to be some bench testing where

1 you are looking at recoils and strength, and all the rest of
2 that sort of thing, but in terms of how it is done with the
3 patient. I am not sure, just thinking out loud, how
4 important that is going to be, which then gets down to
5 trying to come up with a very specific definition as to what
6 is standard and be limited to that, I don't know how
7 important that is.

8 DR. GILLIAM: I don't think that it is necessary
9 or even possible that we could sit here, come up with
10 numerical parameters or even any listing of things that are
11 considered part of the standard coronary stent, because they
12 are quite variable already.

13 I mean maybe even the shape. I mean we can down
14 to maybe a certain type of mesh is better than a spiral or
15 those things, and those things may have nothing to do with
16 it at all.

17 I hesitate, however, to go to strictly the
18 clinical indication used because it has been suggested very
19 strongly that the vast majorities in the real world are put
20 in for, if you will, off-label usage, and I am more
21 concerned with somehow to maybe come up with a definition of
22 stent, and maybe use the materials and looking for things
23 that might make a difference.

24 I can understand the use of other, I guess for
25 lack of a better term from a clinician is, active metals

1 that, say, maybe exert pressures, and they may pose risks
2 that we have not any way of knowing about until they are
3 used, but we are basically saying that we have a metal
4 device that we put in a vessel, that is expanded and left
5 there, and essentially, we know what certain metals are that
6 have not been associated with any problems being implanted
7 in the body, I think that might be the first step in
8 defining a standard coronary stent.

9 I don't think that we need to say that it has to
10 be -- radial strength may have nothing to do with it. I
11 mean I don't know how much we can say that. I don't know
12 that anybody knows that.

13 DR. CURTIS: Does anybody from industry want to
14 comment on this issue? If I remember correctly, one of the
15 slides before did show an attempt to define a standard
16 coronary stent so I guess we have got that information.

17 DR. EDELMAN: Let me just suggest the following
18 thing, and that is that nobody would in our shoes, from the
19 people I represent, say that the engineering is not
20 important, but what they are saying now is that there simply
21 is insufficient data to understand what are the clinically
22 significant characteristics of the stent.

23 Second, that we have to divorce the issues of
24 quality control from ease of use, from performance, and you
25 do need to go through this exercise, because otherwise we

1 will be further mired in the future in evaluating not one,
2 or five or 12, but countless numbers of devices, and as they
3 take on additional functions, such as the release of
4 compounds or energies or codings, this will become all the
5 more important.

6 I go back, though, to saying that it is okay to
7 start by insisting that the devices be made within certain
8 tolerances. It is okay that when you say it, that you have
9 a dimension that it functions in a specific way, and that
10 when it opens, it opens within a certain confidence
11 interval, and that when you have a metal that you actually
12 specify the characteristics of the metal, that there be a
13 certain purity to the metal.

14 It is okay to divorce some of the operational
15 issues, hoop strength, elastic recoil, percent shortening,
16 radial strength from some of the other very many issues that
17 go into making any device, and that is what I think that we
18 are suggesting.

19 DR. GILLIAM: If I understand what you are saying,
20 and maybe this is how I have sort of this morning come to
21 believe, that we may want to list a number of parameters
22 that any company should test and list, knowing right now
23 that we don't have a clear idea that anything you list the 6
24 parameters here, or maybe 600 other different parameters
25 that are probably routinely tested by engineering of these

1 companies, whether they are important or not, but if we can
2 say that there are several things that we can guarantee that
3 every stent or proposed stent list its characteristics, that
4 if we later found out that some parameter fell out and
5 caused a problem, then, we can certainly begin to identify
6 outlier standard stents, if you will.

7 DR. BRINKER: I think we are losing the
8 perspective of the question, and maybe, Dan, you can help
9 redirect this, maybe I am wrong.

10 I thought that what you wanted was an agreement or
11 some starting place for a stent to be called standard, and
12 starting place would be before it goes into a person or an
13 animal, and once it is called standard, it could then be
14 considered for a rapid kind of clinical evaluation, and
15 something that falls outside of whatever parameters are
16 called standard would have to be examined more carefully
17 perhaps, not in an accelerated fashion.

18 One of the problems we are getting into, I think,
19 is trying to set engineering guidelines for any stent, and I
20 think you have asked us an unfair question. The easier
21 question would be that the companies come to you with the
22 appropriate engineering information that you deem necessary
23 for any stent device, and on the basis of their study and
24 your interpretation of that, you determine whether this is a
25 significant deviation from what already exists to require a

1 full clinical or a more obtrusive clinical evaluation, or
2 whether this generally conforms to what you would consider
3 state-of-the-art or accepted stent technology, engineering
4 technology.

5 There is a give and take on your part. I mean it
6 would be very difficult to write down every specific thing
7 that we would consider a baseline for an engineering
8 standard stent. There might be a tiny difference. As you
9 suggested, maybe a millimeter longer, maybe that's okay,
10 maybe it's not. Maybe a different material that is so
11 similar, and there is abundant evidence of this material in
12 other uses, that just because it wasn't included in our
13 first guesstimate, you would have no problem with.

14 I think that we, as clinicians -- and I think
15 everybody here basically is a clinician on the panel --
16 would say that the engineering business is your business,
17 and that you have a better idea of what might be considered
18 at this stage of the game standard and acceptable than we
19 do.

20 DR. CALLAHAN: I would like to address that
21 because I think what you have captured is why we are here.
22 Why we are here is that to the credit I think of the
23 engineering staff that is already doing it, notwithstanding
24 that there is not principles yet understood about how to
25 design probably stents to begin with, but we have now

1 allowed a number of stents out on the market, half a dozen
2 or more, and we have collected clinical data. Clinical data
3 doesn't seem to show that there is much difference, if any,
4 between those stents that are out there.

5 So, we can continue going along the way we have
6 now, and we haven't seen many adverse effects,
7 notwithstanding that we don't understand some of the basic
8 engineering, but we are trying now to lower the bar, if you
9 will, for other stents that are coming along.

10 Now, for the new stents we will continue to
11 analyze it and hopefully learn some fundamental principles
12 as we are going along to apply. Now we are looking at me-
13 too stents, second family, second generations, and saying
14 since their clinical endpoints, as measured by equivalency
15 now, and that is a question that comes up later on, doesn't
16 seem to make too much difference.

17 So, is there not a fast track or lowered bar for
18 us to deal with? We know that -- and I probably as well as
19 anyone from an engineering background -- know we don't have
20 fresh principles to detect which is the most important, but
21 those that are out there so far at least are doing an
22 adequate job.

23 So, we are looking for you to try to make the
24 segue between what is a clinical endpoint and what your
25 segue or slot factor is between something we could call

1 standard, and I think Dan Chwirut gave you like one option,
2 that there is families of materials that seem to behave
3 similarly, at least as we have seen so far, and that is one
4 type cut.

5 DR. BRINKER: And I would agree with that, and
6 what I would say is you are there and you can tell me there
7 is family of materials that behave the same way, I don't
8 know that except for you telling me that, because I am not
9 an engineer, and I would say, well, if you are satisfied
10 that they behave the same way, I am satisfied that they
11 behave the same way, and if you can tell me that there is a
12 range of hoop strengths that seem satisfactory to me in such
13 a design, then, I am satisfied that that would qualify for a
14 lower bar for the clinical track, because you are asking
15 people -- what I said before was that the easiest thing to
16 do is just take the range of what is already out there, and
17 what I think I heard your response was with the family
18 materials question is, well, maybe there is some leeway that
19 you can recognize, and the sponsor can present to you that
20 would be acceptable to you, and just by us defining more
21 strictly a standard stent, and not giving you that wiggle
22 room would be defeating the purpose, I think.

23 DR. STUHMULLER: Can I make a comment and I will
24 ask Dr. Callahan to clarify this? I think the context of
25 this question, I mean the Agency recognizes that the panel

1 members are primarily clinicians, and the intent of a panel
2 meeting is to get input from experts in the area, but the
3 panel meeting also provides a public forum for industry to
4 be on record, professional societies to be on record, and
5 members of the public, and this question in part is intended
6 also to elicit input from industry and the other groups as
7 part of the public record.

8 One of the issues that industry is concerned about
9 is a level playing field, and that the same standards are
10 applied uniformly across all sponsors, and so this question
11 in part gets at that intent of what, from an engineering
12 perspective, what is the least approvable unit in terms of
13 the engineering requirements.

14 That is in part what the intent of the question
15 is. Will you agree, Dr. Callahan?

16 DR. CALLAHAN: Yes, that is fairly stated.

17 DR. BAILEY: I am getting the sense from the data
18 that there is a handful of stents out there that have been
19 approved, and they have a variety of values of these six
20 parameters. That is not a lot of information, but to the
21 extent that we see, we haven't seen any impact on the
22 clinical outcomes.

23 It doesn't seem fair then to say that the area
24 mapped out by these six stents defines what -- I mean one
25 would tend to extrapolate and assume that there doesn't seem

1 to be much, we haven't found the place where the behavior
2 falls off, and so it seems inconsistent to say that based on
3 the very few models we have out there we can define what is
4 acceptable, so I like the idea of going to the functional
5 basis for saying what is the standard performance on a
6 hopefully easily measured immediate of six-month result.

7 DR. LASKEY: To that point, are we all comfortable
8 with the variability and performance of the P-S stent, the
9 same exact instrument in different populations and different
10 studies? I think, Rick, you showed some data which
11 indicated that the clinical performance and the outcomes are
12 variable, they don't track right on.

13 DR. KUNTZ: I think this is a great discussion.
14 If you don't have any engineering measures or metrics that
15 you can actually determine what the predictability is going
16 to be, then, we have to use a Frequentist framework to study
17 things, that is, start from square one, and that is what we
18 have done so far.

19 If you want to be able to then go a little bit
20 faster, the next thing is to set up an objective performance
21 criteria, which is a pooled data, which is basically a
22 measure of what the acceptable performance criterias are,
23 that is how safe it is, what is the safety endpoint, and
24 what is the restenosis endpoint.

25 That becomes just a fixed line, and you can do a

1 registry to compare against that. That still has no bearing
2 on engineering.

3 If we say that we will accept anything below 15
4 percent restenosis rate, and anything less than a 2 percent
5 acute death or thrombosis rate, engineering characteristics
6 are still 100 percent variable. We just do sufficient
7 sample size and measure them.

8 If you really want to get into the real pathways
9 that go fast, it's the ability to borrow data, and that is
10 in a Bayesian context or using a smaller sample size, and
11 that does require some input from engineering, that does
12 require us to say we are going to use this stent and borrow
13 some data, because we think that some of the data so far
14 already tells us about the stent.

15 So, we only have to add a little bit more. In
16 that way, the engineering aspect becomes very, very
17 important, and I would say that actually we do know a little
18 bit about stents.

19 Right now I would submit that the stainless steel
20 316 slotted tube, that is balloon-expandable, is a very,
21 very common predictable stent, and that we can look to the
22 endpoint and look what happens.

23 I think that once you get to an open stent, a
24 coiled stent, one made of nitinol, they are less predictable
25 at this point, and that is a very practical observation that

1 we can look at, and therefore those stents might not be
2 prime time for using these borrowed techniques for rapid
3 pathways.

4 So, I think that we can come up with some common
5 sense approaches, which is that the next slotted tube,
6 stainless steel, balloon-expandable stent probably doesn't
7 require us to have a huge Frequentist approach to go forward
8 because we have so much good data so far, and that all you
9 have to do is be able to use the other patient
10 characteristics to predict the variability, that is, lesion
11 length, stent length, diabetes, LAD location, and vessel
12 size, and once we have those, I think we can get very, very
13 predictable with even up to 150 or less patients.

14 DR. OESTERLE: Could I ask just for a point of
15 clarification, and maybe Dr. Edelman can do this, maybe not,
16 but I just want to sort to get back to the point I made
17 initially, which is the sort of naive nature of this is that
18 my belief is that how you cut these stents is not an
19 unimportant issue, and that how you cut the stents and what
20 their edges are like plays some role in what the ultimate
21 target vessel revascularization rate is likely to be.

22 Peter Fitzgerald is here from Stanford. He has
23 looked at these issues, I think from intravascular and
24 ultrasound, and clearly there are edge effects of these
25 stents. That was really the only point I made early on, is

1 that materials that are used is not enough, in my opinion,
2 that you really have to kind of ask -- and I am not the
3 person to answer this perhaps -- how did you cut the stent
4 and what did the edges look like.

5 A good example, of course, is the P-S stent,
6 Palmaz-Schatz stent, which had an articulated ridge and
7 therefore had four edges instead of two, and is probably why
8 it is not as good a stent as the Guidant Multilink, for
9 example, of the NIR stent, or a variety of these things, but
10 do you get the point I am making here?

11 DR. EDELMAN: I do. In a situation of agreeing
12 with everything, I mean in a sense, and that is, I firmly
13 believe that how you make a stent makes a difference. I
14 also do agree with Dr. Brinker that the question at hand is
15 what do you do when the next device comes out, but there is
16 this overwhelming mission that we have to deal with, and
17 that is how we are going to evaluate this moving target.

18 So, yes, I think, though, that the best that we
19 can suggest for now is to divorce quality control,
20 manufacturing, and tolerance issues from operational issues,
21 because you don't really know anything about the operational
22 issues.

23 So, you have to insist that the devices be made,
24 be made well, and be made to specification, and that
25 shouldn't be dismissed as a minor statement because there

1 really are very few standards right now for that.

2 When you extrapolate that, when you begin to bring
3 that forward, you get into what Dr. Kuntz is talking about,
4 and that is we have a wealth of data with existing
5 technologies, and then when we purposely change something,
6 not by accident, and not by whim of the manufacturing
7 techniques, but when we purposely change something, when
8 does it become a major change.

9 There are data to suggest already from the
10 clinical trials that are published, and the clinical trials
11 that are coming out, that the stents are beginning to
12 diverge in their performance, but it is still not enough to
13 suggest what the important parameters are.

14 DR. VETROVEC: It might be helpful, Dan, if you
15 could give us some perspective about how the Agency has
16 handled other medical devices. I mean hip prostheses are a
17 device that clearly must have different metals involved and
18 different issues and characteristics, and what has been
19 required and what is the equivalency there.

20 Have you got a sense of that?

21 DR. CHWIRUT: I don't know which Dan you were
22 referring to, but I may know more about orthopedics than Dr.
23 Spyker. There is a historical subset of alloys that have
24 been used in orthopedics that have been grandfathered. Most
25 of that stuff was around before FDA started regulating

1 arthroplasty devices. That is not a very good model to
2 choose from.

3 As new alloys came on, new titanium alloys, et
4 cetera, they were minor perturbations, and other than
5 biocompatibility issues, I think we were very comfortable
6 accepting those. Probably the biggest divergence was in
7 design when they went from cement fixation to porous
8 coating. biologic fixation, et cetera. Those were
9 nonsubstantially equivalent prospective clinical trials, et
10 cetera, which have since been downclassified into Class 2 as
11 we gained information.

12 I don't think that is a good area where we can
13 learn from for this particular application.

14 MS. BUCKLEY: I am Donna Buckley again. I am a
15 mechanical engineer for the FDA. I would like to take a
16 little different perspective on this question. It is
17 actually probably better seen as a part, the first part of
18 three questions in Questions 1, 2, and 3.

19 From a general or practical approach, if we are
20 going to adopt alternative clinical trial designs for stents
21 that would be considered standard, where do we start, and as
22 a reviewer at the FDA, there are different ways to start.
23 You can start by saying it is standard based on engineering
24 characteristics, and as I mentioned earlier, if you are
25 going to use those things alone, we have to know a whole lot

1 more than we do right now.

2 We have to, as Dr. Brinker mentioned earlier, look
3 at the range of performance characteristics of stents that
4 are currently marketed. We can't even do that right now
5 because the tests aren't standardized.

6 So, one number from one manufacturer is totally
7 noncomparable to a number from another manufacturer, so we
8 would need to first identify what would be a relevant
9 characteristic to compare, and then standardize the test
10 methods to be able to put it inside the framework of what we
11 have seen before, and then we would need to come up with
12 some type of criteria whether or not we use clinical
13 judgment to decide whether or not a minor difference in one
14 category is going to kick it out of the standard stent
15 category.

16 So, the intent of this question was really -- my
17 goal for answering this question is where do we start. If a
18 new manufacturer comes in and says I have a standard stent,
19 is it going to be based on engineering characteristics, how
20 do we do that, and if we want to go that route, we need to
21 do a whole lot more.

22 If we are going to start as the second question
23 indicates, should we look at acute clinical performance
24 characteristics? If so, how do we practically deal with
25 that? When the sponsor comes in, we don't have the clinical

1 data yet, so we can't call it standard.

2 Is a feasibility trial in order? How do we handle
3 that? Or as the third question kind of leads to can we in
4 the effort of trying to move things along as best we can, as
5 quickly as we can, and as much as the science will let us at
6 this point, merge what we know from some of the general
7 basic design characteristics of coronary stents right now
8 with some acute clinical performance characteristics, and
9 maybe a feasibility study.

10 I am just suggesting that the third question might
11 need some type of a creative approach where we would merge
12 those two things together in an effort to maybe define a
13 coronary stent in that fashion.

14 So, the nature of the question really wasn't to
15 ask you what the number cutoff is for recoil, it was just
16 kind of a general question to bring to your attention that
17 we need to kind of address this issue and what comes first
18 and in what ratio, engineering and clinical, and how do we
19 balance that, so maybe it is best read within the context of
20 the subsequent two questions.

21 DR. BRINKER: The parameters that you have, for
22 instance, when anybody submits a stent to you, you have
23 certain general engineering parameters even though the
24 individual tests may vary that you require of them. Is that
25 not correct?

1 MS. BUCKLEY: Yes.

2 DR. BRINKER: And when they give you supporting
3 testing to conform to those parameters, you either accept it
4 or reject it, I assume, based on some interpretation.

5 MS. BUCKLEY: And that leads to some of the things
6 that we are facing right now, because we are dependent on
7 the sponsors to justify pass/fail criteria for each test as
8 clinically based as they can make it, because right now I
9 would personally characterize these tests as more
10 characterization based as opposed to real good feeling this
11 is going to perform really, really well.

12 So, that is another thing that we would need to
13 tackle is to come up with pass/fail criteria for each test
14 that is really grounded in a clinical foundation.

15 DR. CURTIS: I think the problem right now is that
16 you have got a bunch of stents out there, and you could list
17 what their characteristics are, what you have got already,
18 what their diameters are, recoil, that is available.

19 Nobody knows if the characteristics of those
20 stents are sufficient, necessary, ideal, is more recoil
21 better, is more recoil worse and so really, all you know is
22 what is available already.

23 I think one important thing is going to be
24 developing your testing methods. You want to at least be
25 able to have standardized testing, so that anybody who comes

1 before you with a stent has tested it in a certain one,
2 gives you a certain answer that you can compare it.

3 That would have to be developed in conjunction
4 with some of the other groups that are represented here
5 today, and still that is just characterization, it still
6 just tells you what is available.

7 I don't think clinical performance really is
8 something that defines the standard stent, because that is
9 an outcome. That is what you are going to study and try to
10 find out. I think it is going to be easier for us as a
11 panel here to say, well, how much restenosis is acceptable
12 and what kind of clinical outcomes are we looking for at six
13 months. I think we could probably develop some consensus
14 about that, but that it the result of your testing.

15 In terms of defining a standard stent, you have
16 got to do that before you do your clinical study, because
17 then you are either going to go the fast track, compare it
18 to the database type thing, or a prospective randomized
19 clinical trial, because it is not standard.

20 In either case, the outcomes are supposed to be
21 somewhat comparable we hope, so I don't think that that
22 definition is going to tell you what a standard stent is,
23 and any stent is going to be something that is supposed to
24 keep an artery open, so we know that that is the intent of
25 it. I think it is going to be more design characteristics

1 than anything that define that.

2 DR. DOMANSKI: Anne, could I ask you a question
3 about that? I guess I am impressed that there are a lot of
4 data out there about the stents that currently exist, and
5 certainly they can, in an engineering sense, be
6 characterized, so that something that doesn't vary very much
7 in terms of what you are putting up on the board from what
8 is already out there, it might be expected to be a
9 "standard" stent, that is, it behaves substantially the
10 same.

11 So, I am not so sure there aren't the data out
12 there to do some characterization anyhow. Now, it may be
13 that there are properties of these stents that aren't being
14 measured by this that are important clinically, that we just
15 don't recognize, but really, if you are going to make, as
16 Jeff suggested, a judgment about, gee, this isn't much
17 different, it's a half a millimeter longer, well, obviously,
18 if it is half a millimeter longer, it probably doesn't make
19 any difference, and you would probably judge that it
20 deserves a fast track.

21 But, you see, that is characterizable in a more
22 quantitative way in terms of what is up on the board there.
23 It is the same material, it is shortened about the same
24 amount, it has about the same area ratio, and, yes, it's a
25 half a millimeter longer, but you can characterize these

1 things, and we do know something about the performance as it
2 correlates with the engineering.

3 Now, that doesn't mean that something that has
4 vastly different engineering characteristics might not
5 perform just as well or better, but you at least would have
6 some sense that is already quantified, so I am not so sure
7 that it is completely divorced from performance or
8 completely unquantifiable.

9 You are going to quantify by judgment anyway
10 somehow if you are going to put it on a fast track. There
11 may be others, but this looks like something that can be
12 characterized and characterized semi-quantitatively to me.
13 I mean what is your reaction? You are actively doing
14 engineering.

15 MS. BUCKLEY: The first step is to get some input
16 as to what are the biggies, and as Dan mentioned a little
17 bit earlier, where do we start, do we start with the
18 material? Do we restrict it to stainless steel, and if we
19 restrict it to stainless steel --

20 DR. DOMANSKI: I don't know if you have to
21 restrict it to stainless steel. There are a couple of
22 devices out there. When you know how they perform, now, if
23 I come in with some alloy that you have never seen before,
24 then, that strikes me as perhaps being different, but you do
25 know how stainless steel performs, and you do know how a

1 couple of other materials perform. I don't think you are
2 quite that in the dark.

3 DR. GILLIAM: Are there variations? The ones that
4 we have now, you just looked at these six things, I mean you
5 know what all these parameters are for those devices out
6 there. Are there huge variations?

7 MS. BUCKLEY: Well, that is part of the question.
8 We are not sure how these separate engineering
9 characteristics correlate to clinical outcome.

10 DR. GILLIAM: Forget the clinical outcomes. I
11 guess what I am asking is looking at the engineering
12 parameters, is there a great variation of the ones that we
13 have already approved?

14 MS. BUCKLEY: It depends how you define great. I
15 mean from an engineering standpoint, I would say maybe not,
16 but that is exactly what it is, maybe not, there is no
17 quantitative approach to it, because I can't compare
18 numbers. There is different methodologies, different
19 techniques. Even for something as maybe fundamental from an
20 engineering standpoint, the ability of the stent to withhold
21 or hold up the vessel, the hoop stress, and we have a test
22 that we ask for in our guidance document, radial strength,
23 to evaluate that.

24 Because of the way perhaps it is defined in the
25 guidance document, sponsors interpret that differently, so

1 even some sponsors put a stent in a tube and vacuum it, and
2 when it collapses, that is the radial strength.

3 Another manufacturer might use a pressure such
4 that you get a 5 percent permanent deformation or reduction
5 in diameter, so there is some serious difficulties, and I am
6 not saying that we won't be able to tackle these things, but
7 we would have to take a pretty methodical approach to be
8 able to pool this information together to make generalized
9 statements about it.

10 Right now we look at each application
11 independently. The sponsors have their own testing and
12 their own pass/fail criteria. Unless we see something that
13 is incredibly anomalous or that we have concern that there
14 might be some safety issues with that, we look into that a
15 little bit further.

16 DR. DOMANSKI: But radial strength is something --
17 you know, it would be interesting to hear some of the
18 industry people speak to this issue, too, as a matter of
19 fact. This doesn't sound like that intractable a problem.
20 It looks like you could fast-track an awful lot of stents
21 based on just looking at things like radial strength, and so
22 forth.

23 Does that make sense? I would be interested in
24 hearing whether that makes sense to the industrial guys.

25 DR. FITZGERALD: Mike, I think there is a bigger

1 picture here in the sense that you have to decide whether
2 you are going to actually set up a fast track and whether
3 you are going to use some borrowing power from historical
4 cohorts to fast-track these new types of stents.

5 If you decide that that is a pathway, then, I
6 think you could take the six stents that you have available
7 now, you could look at the coefficient of variance of all
8 these with respect to your specific parameters, and that is
9 your standard stent for developing a framework for your
10 Bayesian criteria for evaluating clinical endpoints,
11 whereas, if it falls outside of your spread of what you have
12 today, and you are saying, well, all the manufacturers
13 define it differently, but can't we come up with a standard
14 that you take all the stents that are out there today and
15 find out what the variation is with the one single test?

16 MS. BUCKLEY: Sure, and that is part of what we
17 are getting at. We are not saying that this isn't doable.
18 We are saying for this to be doable, we have to do some
19 things first, standardize the test, so that we can take a
20 look at these things together, and that is ASTM's goal to
21 really facilitate that effort, so that we can get a global
22 perspective.

23 DR. FITZGERALD: But for us, you know, I am an
24 engineer, but, of course, I am the wrong type of engineer.
25 I don't know anything about material sciences, but I do know

1 that you have a bunch of materials out there that you can
2 get quantitated in a focused-by-focused group, and that then
3 is your standard.

4 So I think, again, the big picture. If we adopt
5 that we are going to go fast-track, then, I think you have
6 to use what we know, and we have a lot of knowledge as the
7 framework for setting up with respect to these parameters
8 that you are talking about.

9 DR. DOMANSKI: But, Peter, how can you not go
10 fast-track? I mean how can we leave the bar -- look, I do
11 randomized trials for a living, and, yes, I was an engineer
12 once, but just from a common sense point, this field is
13 evolving rapidly, and one wants to get these newer and
14 better stents on the market, not vice versa.

15 So, I didn't think there was any question that we
16 wanted a fast track, is there?

17 DR. FITZGERALD: No, I don't think there is, but I
18 am just saying if we do decide that, then, I think this
19 becomes an easier question to answer.

20 DR. STUHLMULLER: Perhaps, Dr. Callahan, could you
21 clarify this, I mean from an Agency perspective, we had to
22 start somewhere. There was a guidance document that got
23 published in 1994 that listed a series of tests that cover
24 engineering concepts that we felt needed to be addressed.

25 We are now X number of years later, and is our

1 approach still reasonable within the context of what was
2 initially started, and how do we refine that. Is that
3 reasonable?

4 DR. TRACY: Yes, that's reasonable, but is there a
5 problem in trying to define these things on an engineering
6 basis when there is such a variety of pass/fail criteria on
7 the currently manufactured devices, and when there are a
8 variety of different ways that these things probably react
9 within vessels, but the final outcome is really the clinical
10 outcome. So, I agree with the basic principle of saying,
11 yes, define what is an important recoil parameter, certain
12 parameters that are probably agreeable upon, however, I
13 wouldn't make it too restrictive because it seems that a
14 variety of different tests have been done, materials have
15 been used, designs have been manufactured that still give
16 basically the same outcome.

17 So, I don't think it would be reasonable to have
18 those pass/fail be so restrictive that something that is a
19 little bit different -- and I don't think it is a matter of
20 a quarter of a millimeter -- but I think there may be some
21 other difference that you don't want to exclude that
22 possibility of going forward by being too restrictive in the
23 pass/fail criteria that you have come up with.

24 DR. GILLIAM: And I would submit right now, what I
25 am hearing at least, we are not sure that the devices we

1 have in any measured way are comparable from an engineering
2 standpoint on a lot of these parameters. Is that basically
3 what you said?

4 MR. CHWIRUT: I think everybody would agree there
5 is a significant difference from an engineering perspective
6 between the Palmaz-Schatz and the Walstent with respect to
7 some of these characteristics.

8 DR. DOMANSKI: But it establishes actually that
9 may be good, not bad, because the clinical performance of a
10 pretty wide range with respect to those parameters, and that
11 actually helps. It makes it easier, not harder, for the
12 next manufacturer to come through.

13 DR. GILLIAM: It may be that none of these
14 parameters, you know, we have hit the edge of it. I mean we
15 have pretty much sailed around in a big ocean, maybe we
16 haven't pushed the envelope, and I guess if you ask the
17 question, when I first looked at it, can we use engineering
18 criteria to define a standard stent, I said, well, I think
19 those are definitely criteria, I can just simply say yes to
20 answer the question.

21 Now, what those are and how restrictive they are,
22 it sounds like we don't have the first hint of data or even
23 designed a standard list of tests to do this with at this
24 point.

25 MR. OKTAY: Perhaps we made a mistake by putting

1 those six specific characteristics out there for you. I
2 think that we may be sidetracking a little bit. In Donna's
3 conclusion slide, as you can see up there, we really need to
4 first identify clinically relevant design performance
5 characteristics.

6 That is where our struggle is coming from to start
7 with. That is why we work with the ASTM to identify those
8 parameters, and then maybe perhaps we can standardize in
9 vitro test methods just to identify, just to test these
10 characteristics, and then maybe we can come up with
11 pass/fail criteria.

12 So, maybe you shouldn't really concentrate on as
13 much to those six characteristics because, as Dr. Oesterle
14 indicated, there could be differences between wire versus
15 tubular type depending on the design of the stent itself.

16 So, I think that our initiative with ASTM would
17 help us to identify those, hopefully, in the near future.
18 That is all I wanted to say.

19 DR. STONE: I don't think this is all that
20 difficult. I want to echo and expand a little bit on what
21 Peter Fitzgerald said.

22 What I think we are all saying, I mean I would
23 disagree a little bit with these conclusion in that I don't
24 think either the bench without clinical, or clinical without
25 the bench is going to be sufficient.

1 So, we are trying to come up with a set of
2 standards which will say okay, this is similar enough to
3 what we have already got that we know is working, that now
4 we can do a fast-track kind of a study. I mean that is all
5 we are trying to say, and if it deviates from those
6 standards, then, forget it, no fast track, you have now got
7 to do a standard prospective randomized trial after you have
8 met all the other standard bench tests that we want.

9 So, I think you can very easily look at that list
10 of six, and you can have a panel that would come up with
11 four more if you want, and say these are the characteristics
12 of the stents that are performing well in the market.

13 You can say the surface area coverage has been 18
14 to 16 percent between the stents. If anything falls more
15 than one standard deviation out of that range, you know, as
16 Peter was saying about coefficient of variation, then, we
17 need to do a prospective randomized study.

18 You can say the standard stent that we have is
19 either a multicellular slotted tube or corrugated ring
20 stent, that is the stent that is performing well. I don't
21 think there would be too much disagreement that is the
22 standard stent.

23 An interesting discussion of topic would be is it
24 all 316L stainless steel or can we say any material with
25 elastoplastic properties would be adequate. I think that

1 would be a little more in-depth discussion.

2 So, I think you can look at all these parameters.
3 Does it need to be electropolished or not, et cetera, and
4 all you are trying to do is get a certain comfort level
5 where you think this will probably meet the standards of the
6 stents that are out there that are performing well, such
7 that we are comfortable to take it to the next level. It
8 still has to behave in a clinical trial, it just doesn't
9 have to be a prospective randomized clinical trial.

10 So, my suggestion would be that you could do this,
11 you need both, and to come up with a working group that
12 would actually sit down, look at all the data, look at all
13 the characteristics, decide what your range would be.

14 I also agree leave a little bit of wiggle room on
15 any given characteristic, such that if a manufacturer comes
16 in and says, well, this fell a little bit out of your
17 parameter, but this is why we think it should be included,
18 that the panel that would make the decision to allow or not
19 allow fast track would have the authority to let them go
20 ahead.

21 DR. CURTIS: I think that is a very nice summary
22 of what the issues have been. May I ask, too, whether the
23 industry representatives, are you willing in principle to
24 have the ASTM clarify some of these engineering aspects, the
25 testing and standardization issues?

1 I am getting a nod yes.

2 DR. BAILEY: Let me just offer. If we specify
3 ranges of parameters within which there is a very different
4 way of being able to get approval, aren't we pretty much
5 guaranteeing them that that is the framework in which all
6 future stents will be developed?

7 DR. DOMANSKI: I don't think you are. I think in
8 the past, we, or at least I for years have pushed the
9 randomized trial as the gold standard for comparison. I
10 don't think that is really going away, but one has to
11 realize that that tool isn't necessary for everything, and
12 what they are trying to do is separate out the things for
13 which that very high bar or high hill to climb isn't really
14 necessary.

15 So, I don't think you are throwing away the gold
16 standard, you are just saying it doesn't --

17 DR. BAILEY: But we are providing a very strong
18 incentive to stay within those parameters.

19 DR. GILLIAM: But we are also providing incentive
20 to not be within those parameters, because if we assume that
21 the standard stent, if you will, only provides a certain
22 level of clinical usefulness, and you can prove that, if you
23 will, a nonstandard stent is better, that gives you a
24 distinct marketing advantage, as well, so I don't think that
25 it necessarily guarantees that we will stay with the

1 standard stent any more than someone looking in
2 electrophysiology, I mean once we have said that a VBI
3 pacemaker was approved in a certain way, I mean it still
4 hasn't stopped the companies from producing more and more
5 complicated devices.

6 DR. DOMANSKI: Yes, and our business isn't to --
7 at least FDA -- I don't perceive their business as being
8 stimulating this or that, but rather providing a regulatory
9 bar that protects the public, and the question is how high
10 should that bar be, and the bar should only be as high as
11 necessary to protect the public.

12 It doesn't have to do with motivating competition.
13 If we can protect the public with a bar that is lower, the
14 bar ought to be lower. It looks like for a lot of these
15 stents, it ought to be lower, but maybe not for all of them.

16 DR. TRACY: It also is a reasonable way of
17 providing something against which to compare a newer
18 technology, so I think that is something that, in the EP
19 field, we have always faced as a real problem, there is
20 nothing to compare against.

21 So, if we have a reasonable bar and we have a
22 variety of different things against which to compare as the
23 standard, I think that only would serve to spur the industry
24 to develop new technologies.

25 DR. CURTIS: Last comment I hope.

1 DR. HIRSHFELD: I would just like to a comment as
2 a clinician. I think in terms of calibrating the weight
3 that you assign to this phase of the evaluation process, I
4 think you have to be careful not to undervalue the clinical
5 performance assessment, because traditionally, when a new
6 stent reaches the point where we can put it into people, the
7 first couple of times you use it, you know what you are
8 dealing with. It is very clear to the user whether this is
9 a well-performing stent or whether this is a clunker.

10 So, I would think that the way that this issue
11 should be calibrated -- which I would hope would simplify
12 FDA's task -- is that the role of this is to basically
13 ascertain that this is a safe device to enter clinical
14 trials, and so I think that that would simplify the degree,
15 the rigor that you would have to apply to the engineering
16 analysis and make it easier for you to design pass/fail
17 criteria.

18 I would think the gold standard would be once it
19 gets into clinical use, that people will instantly recognize
20 the value or lack of value of the design.

21 DR. DOMANSKI: I don't think you can instantly
22 recognize the value of these things. I think that
23 significant differences are often relatively small, far too
24 small to see in any one practice, let alone the first few
25 applications of it. That, I do have a problem with.

1 DR. GILLIAM: I would tend to agree because on a
2 lot of devices, it may not show up a problem until after
3 they have been in for a while.

4 DR. CURTIS: Why don't we move on to the second
5 question. The comments have come up several times that you
6 can't divorce this from clinical performance.

7 What acute clinical performance characteristics
8 best define a standard coronary stent - (a) treatment of
9 specific-vessel diameter range and lesion length range; (b)
10 stents which provide a particular post-procedure diameter
11 stenosis; (c) a subacute thrombosis rate; (d) a 6-month
12 major adverse cardiac event rate based on survival analysis;
13 or (e) any other characteristics?

14 DR. BRINKER: I think that it really takes a
15 working group to sit down and go over published data and
16 their own practices, their own feelings what is the minimal
17 level. I think all these are pertinent, and they are, I
18 think from my own opinion, all relatively easily gotten at,
19 but I don't think we should attempt to do them at this panel
20 meeting.

21 It doesn't pay the kind of service that these
22 kinds of questions are meant to represent for us to try to
23 come up with quick answers. I think a panel of experts from
24 the professional societies that are involved can be much
25 more helpful.

1 DR. CURTIS: I am not sure that I agree with that.
2 I think that again may make this more complicated than it
3 has to be. There is a specific range of vessel diameters
4 that has already been studied in stents.

5 DR. BRINKER: The criteria that this should be a
6 Stress-Benestent kind of inclusion criteria for the test,
7 you really want it, as Rick suggested, to make to level the
8 playing field, you really want to look at the Fairlane kind
9 of performance, but the other aspects of what would you
10 consider a minimum subacute thrombosis rate, et cetera, I
11 don't think that that is something that we should say at
12 this panel meeting is set in stone.

13 I think that really takes some deliberate and
14 specific review, and I think you need a panel of experts to
15 do that.

16 DR. DOMANSKI: Jeff, I think that is right in
17 terms of putting a number on that, but I think there are
18 certain things this panel can do. For instance, I would
19 like to hear -- and I don't have any answer to this at this
20 moment -- but I would like to revisit, for instance, the
21 issue of the endpoint. You know, this MACE thing is a very
22 clever acronym. I am not sure that I like it for that
23 reason, as a matter of fact. But I would like to revisit
24 whether it makes sense to use that as the endpoint.

25 That is the kind of big ticket item we can do. I

1 am not sure I can give them a percentage about what we
2 should accept. Anyway, before this is over, I want to hear
3 people readdress that one.

4 DR. BRINKER: There are other issues, as well, and
5 one is that MACE has been a primary endpoint for most of the
6 stent trials, and to say that you want to throw that out,
7 there may be a surrogate, but I am not sure that you are
8 interested in that particular thing, and I don't think we
9 can, as a panel, reach a conclusion at this sitting.

10 I think that what we can do is to realize that
11 there has to be certain inclusion criteria, and if we are
12 talking about an accelerated kind of trial, using inclusion
13 criteria to be presumably compared with prior data should be
14 aimed at the same inclusion criteria that has been standard,
15 in fact, the same that still exists on the labeling of the
16 approved stents.

17 DR. CURTIS: I think what the first part of this
18 question is asking, that (a), there are group of diameter
19 ranges and lesion length ranges that have been studied in
20 the stents that have been studied in the stents that have
21 already been approved, and it is simple enough to say that a
22 standard coronary stent, if it is going to be fast-tracked,
23 and the bar is going to be lowered, as we said, that that is
24 what it is going after.

25 This isn't the Fairlane Ferrari discussion here,

1 because you are not getting into other types of lesions that
2 you are trying to treat.

3 DR. BRINKER: Length of stent is critical, and
4 that is a Ferrari --

5 DR. CURTIS: What I am saying is that in terms of
6 defining a standard coronary stent for a fast-track type of
7 trial, you could define ahead of time that certain diameter
8 ranges of vessels and certain lesion lengths would be
9 included in that, and then if somebody wanted to use a stent
10 for a longer lesion, that is a not a fast-track type of
11 trial, it is something you have got to look at differently,
12 that's all.

13 DR. BRINKER: That has already been done in the
14 stent, Benestent, and every stent trial have already --
15 FDA's stent trial -- have already predicated at least on a
16 comparison group the inclusion criteria, and I believe that
17 those are acceptable and not an issue.

18 The issue is everything from (b) down to (e), and
19 I think that requires some thought and discussion. It
20 shouldn't be addressed at this meeting.

21 DR. OESTERLE: Can I ask for a point of
22 clarification, Dr. Curtis?

23 DR. CURTIS: Yes.

24 DR. OESTERLE: It seems like we have made this
25 transition from looking at engineering criteria to clinical

1 criteria, and it is easy for me to concede that I could hold
2 a stent in my hand and say, yes, this looks like a standard
3 stent, but, in fact, each one of these stents, when they
4 become a clinical tool, have to be delivered, and it seems
5 like we have either ignored or perhaps I have been asleep,
6 but we have not really talked about the delivery devices for
7 these stents, which play I believe again a huge role.

8 Maybe I am a minority player in this, as I believe
9 the stent design is actually, in terms of injury patterns of
10 each stent, will be important.

11 I also think that the delivery devices play a huge
12 role in this, and we have seen this recently with the NIR
13 situation, but that is one adverse event type of thing, but,
14 or course, there is at least a considerable number of people
15 who are doing clinical cardiology who believe that the type
16 of balloon material and the type of balloon that the stent
17 is mounted on actually probably has as important a role in
18 terms of the short and long term clinical outcome as the
19 stent itself.

20 Somehow I don't sort of hear any issues about
21 delivery devices in the context of these questions, and how
22 is the FDA dealing with that.

23 DR. FITZGERALD: I would actually second that
24 partly because I think Steve taught me how to do
25 interventions, but when I look at this question, that is the

1 first thing I think of. When you look at an angiogram and
2 you are right there, the first thing you think of is whether
3 you can get it there, and can you get it there with a
4 minimum amount of trauma and the maximum amount of ease.

5 I think, to answer your question, Anne, with
6 respect to is this a standard stent. In the same context
7 that we have been talking about Question No. 1, I think (a)
8 is the only one that is really applicable, because we don't
9 really know what SATs are for this type of stent.

10 We really don't know some of these others, so in
11 this acute clinical performance, No. 2 question, I would say
12 deliverability and treatment of specific vessel diameter
13 range and lesion length range are the important points.

14 DR. SPYKER: We explicitly put that in Question
15 10, but we would be happy to discuss it at any point.

16 DR. STUHLMULLER: I think to try and put this in
17 context -- and I will ask Dr. Callahan to clarify this again
18 -- I mean the legal construct we work within in terms of how
19 efficacy is defined in the regulations, is that the device
20 needs to provide clinically significant results in a
21 significant portion of the patients based on its intended
22 use.

23 So, the issue is, is can you define a standard
24 stent based on its indication for use, because that is, from
25 a regulatory point of view, we have got to look at it, does

1 it provide clinically significant benefit.

2 I think can you then, based on what has been done
3 in terms of the indication for use, come up with clinical
4 criteria that support that, because that is what we have to
5 look at. Would you agree, Tom?

6 DR. CALLAHAN: Yes, that is sort of an overview,
7 and that is probably what we can best get from this panel.
8 Obviously, we are working closely with ASTM, and we are
9 hoping that as we methodically plod along, we will know a
10 lot more about these, but the main issue I think before us
11 is the question of a bar.

12 We can continue to do what we are doing, and
13 stents are going on the market, and they are being -- to
14 date, there haven't been any major problems with them. So,
15 I think you can best probably generate questions around the
16 endpoints. If delivery should be included in every one of
17 these questions, as it is later on, we should be including
18 that as well.

19 I think we need some big ticket items that we
20 should be specifically watching for in these trials.

21 DR. BAILEY: It seems to me one thing that is
22 going to be difficult in setting the bar here as far as
23 dividing the devices into those that can be fast-tracked, is
24 that if these clinical endpoints depend on patient and
25 lesion characteristics, then, you have to adjust for those,

1 unless you are going to say that the worst possible patient
2 or lesion has to be your standard.

3 DR. STUHMULLER: I am not sure I like the term,
4 you know, from an Agency perspective fast track, because
5 these are not going to be expedited reviews. I think the
6 concept here is what is an appropriate, least burdensome
7 study design within the context of the law that demonstrates
8 safety and efficacy for a device.

9 Personally, I am not sure I agree with the term
10 fast track.

11 DR. BRINKER: It just takes less time to say.

12 DR. STUHMULLER: But I think again, you know, the
13 context of Question 2 is how do you define safety and
14 efficacy within the range of the devices that have been
15 approved, and can that data, in terms of how we have
16 previously defined safety and efficacy, be extrapolated to
17 the future evaluation of stents, and I think that is the
18 context that this question is --

19 DR. DOMANSKI: It may do one thing, though. You
20 know, if we use these clinical performance criteria, in
21 fact, it may encourage manufacturers. What it may encourage
22 them to do is to use relatively low risk patients because it
23 is difficult to define precisely where they stand in the
24 risk spectrum, but I guess that's okay.

25 DR. BRINKER: But that is what every other stent

1 trial used. We are getting off the mark here. All these
2 should fall into either objective performance criteria or
3 they can be used as endpoints for the Bayesian type analysis
4 that was suggested before.

5 This isn't rocket science. All we want to do is
6 to allow the same kind of clinical arena to look at the
7 stent performance as we have for the other stents, and I
8 think that the specifics, my problem with (b) through (e)
9 are really asking for -- except for (e) -- is specific
10 numbers, for OPCs, I would guess. I don't think that is
11 this panel's best time spent, but I do think that we should
12 look at the full range of endpoints including successful
13 delivery that have been asked for in previous studies.

14 DR. CURTIS: Just to try to move someplace with
15 this, I think what we are talking about are new stents that
16 are me-too's. You know, a new company comes out, me-too, I
17 want to have a stent and I want to be able to use it.

18 Well, what are you going to study that in? You
19 are going to study it in the discrete proximal stenosis and
20 look at your outcomes, in which case, then, a standard stent
21 ought to be the targets for treating that should be proximal
22 discrete stenosis in the major coronary arteries.

23 Nobody is going to come out with a me-too stent
24 that they want to stick in a bifurcation of something, or
25 down in a small vessel, or any of that. All of that is

1 going to be a different kind of approach to a clinical
2 trial.

3 So, I think that just by using the stent trials
4 that have already happened, and, in general, they have been
5 discrete proximal stenosis or restenosis would be fine,
6 then, that defines what a standard stent is trying to treat.
7 That is going to be that type of clinical trial, using the
8 OPCs or whatever else you are talking about.

9 DR. FITZGERALD: I think this has to do a little
10 bit with what Rick was talking about. If we are going the
11 least burdensome study design road, then, it is going to
12 depend upon what power you are stealing from and what those
13 endpoints are.

14 So, I think that has to come more from what Rick
15 thinks about this.

16 DR. KUNTZ: If you take a stent that has been
17 studied in a Palmaz-Schatz randomized trial, and then put it
18 into a registry with the same labels, it will perform twice
19 as bad, and this is why. Right now we have shown about four
20 stents are equivalent to the Palmaz-Schatz stent, but there
21 are no Palmaz-Schatz labels on the shelves anymore.

22 Now, why would that be? That is because these
23 stents are better, and everybody knows they are better, and
24 they perform better, and they do more difficult lesions, and
25 that is what people use them for. If you study them in the

1 registry, you will get longer lesions, more diabetics, more
2 LAD location. You will have more complex disease, longer
3 stent lengths. All these things double and triple the
4 restenosis rate, so to have a fixed OPC derived from the
5 vanilla Palmaz-Schatz stent is completely irrelevant to
6 measure the outcome of stents that are good for patients
7 upfront.

8 So, what I would suggest is to have an OPC derived
9 from an multivariable model, that is one that can be
10 adjusted for those effects that mask and match those factors
11 that the registry are unique about.

12 Now, the data set has to be derived from ranges
13 that will be the projected future registry. That is, you
14 have to have a fair number of long lesions in order to be
15 able to predict long lesions. You can't extrapolate too
16 much longer along the scales upfront here.

17 But that is the beauty of having potentially
18 pooled data set, is that you can actually tailor-make a data
19 set with every one of those (b) through (d) criteria
20 predicted that is fine-tuned for the unique characteristics
21 of the registry data set because whether the criteria are
22 established and fixed by the IFUs or not, people still use
23 them in different ways, and it is very hard to say that
24 someone didn't violate the protocol to go into it by saying
25 that their lesion was slightly longer or less than, say, 15

1 mm.

2 As a matter of fact, if we do strict core-lab
3 analysis of people who fit into protocol requirements, it is
4 only about 80 percent or 70 percent. Thirty percent are in
5 one way or another off of the core-lab measurements.

6 So, I think that that is the issue here is that
7 this is an approach for an easier pathway, not fast track,
8 but easier pathway for approval, that would use a single-arm
9 study, but it has to meet some criteria for us to study
10 that, that is, I think the engineers have to tell us that
11 this is a somewhat comfortable stent to do, and we have to
12 do this dynamic pooled data set that we can fine-tune to
13 mimic the unique characteristics of the patient and lesion
14 characteristics and factors that make up the prospective
15 registry in order to meet all those endpoints to measure.

16 DR. VETROVEC: It just seems to me, although all
17 of that is true, you are going to start having all kinds of
18 complications in terms of statistical complications, it
19 seems to me, as to whether or not you are dealing with
20 apples or oranges.

21 I realize you are trying to get rid of that, but
22 it also seems to me that somewhere, knowing that 30 percent
23 of patients already in the stent trials don't quite fit,
24 that it wouldn't be unreasonable to say that the registry
25 data for the stent would only include or the analyzable data

1 would only include those patients that fall within the sort
2 of standard vanilla characteristics of the stent or of the
3 trial designs that we have looked at so far, and exclude
4 those patients for analysis that are more complicated.

5 So, you would look at the patients who hopefully
6 70 percent of them were really 15 mm long lesions that were
7 3 mm in diameter, and so forth, and analyze that, and then
8 you could have criteria that are based on the approved ones
9 that are there today.

10 It would seem to me that would be a place to start
11 for me-too stents that would be fairly simple.

12 DR. CURTIS: And in terms of the other questions
13 on here, although I don't think any of us on the panel wants
14 to plug some numbers into that, nor do I think it is as
15 complicated as requiring some panel to convene, once you
16 know your data set that you are using for comparison, you
17 know the range of subacute thrombosis rates that have been
18 seen, you know the ranges of major adverse cardiac events
19 that occur, and again, the idea that you have got to be
20 within one standard deviation for that to be acceptable is
21 probably I think a good way to go with that.

22 Hopefully, we will come to that a little bit later
23 in the discussion about what is the OPC or where are we
24 going to get the data set from, but the data set is going to
25 give you what your parameters are right there.

1 DR. STUHLMULLER: I guess again to put it in
2 perspective, I mean if the panel is not willing to provide
3 specific numbers, do you conceptually agree that, you know,
4 within the regulatory framework that we work in, that these
5 types of endpoints would provide reasonable assurance that
6 in a significant portion of the patients, you are going to
7 derive clinical benefit, because that is the legal
8 definition that we have to meet for efficacy and for safety,
9 does it provide reasonable assurance that the potential
10 benefits outweigh the risk.

11 That is the regulatory construct, and so what we
12 are asking is your clinical opinion on how to meet those
13 definitions.

14 DR. TRACY: It depends on what Anne was getting
15 at, what is the data set against which we are comparing
16 things. If we are looking at the NHLBI dynamic registry,
17 that is something different from looking at the currently
18 available data from the approved studies, and I am a little
19 bit concerned about what the six-month MACE data is giving.
20 It there really some important information that is being
21 obscured by just looking at that information.

22 So, I think it depends, yes, I think there are
23 some definable outcomes, but I am not sure where to get the
24 data against which to compare, and I think how you define
25 your outcomes is going to be dependent on which data set you

1 are looking at to make your comparisons.

2 DR. CURTIS: I think they are going to be acute
3 angiographic results. I think six-month adverse events is
4 an important endpoint. The one that is not specifically
5 listed there, although I am not exactly sure what subacute
6 thrombosis is supposed to mean there, the issue came up of
7 angiography at six months as a surrogate endpoint instead of
8 or in addition to MACE.

9 I actually was a little bit surprised to see that
10 touted, and the reason I say that is I have been at other
11 panel meetings where the idea of doing repeat
12 catheterizations on patients after valve surgery in order to
13 follow up on what happened to them, was considered extremely
14 burdensome and unrealistic.

15 Here, there were some thoughts earlier today about
16 angiography as a good way to go, because then you will see
17 exactly what is going on with the stent. I think it is
18 always a good way to look at it if, in the studies, the
19 patients are going to be willing to undergo that repeat
20 catheterization in six months in order to take a look at it.

21 Any thoughts on that?

22 DR. DOMANSKI: I guess the question is six months.

23 DR. LASKEY: It is also angiography at the
24 completion of the procedure as a way to obviate the need to
25 do down-the-road angiography, because that is predictive of

1 down-the-road events.

2 The problem with six month or nine month or 12
3 month angiography is this animal called the oculostenotic
4 reflex where the endpoint here is really not independent of
5 the means to assess it, so that there is a lot of strength
6 to the argument that a post-procedural angiogram within the
7 proper methodology can be predictive of events down the
8 road.

9 Now, how you want to define TVR, and so forth, is
10 another issue, but I don't think anyone is suggesting six
11 month angiography as a hard --

12 DR. CURTIS: I wouldn't be pushing it unless
13 interventionalists at this table were.

14 DR. LASKEY: It is cumbersome and patients these
15 days are increasingly reluctant to come back.

16 DR. FITZGERALD: I think it is a continuous
17 variable that has some power, especially as you begin to
18 shorten the sample sizes and you end up looking at and
19 relying more on statistics. I think having more objective
20 criteria increases your statistical power especially as you
21 go in this with small sample sizes.

22 I would say early on, as we experiment with this
23 least burdensome study pathway, that we might encourage it.
24 Just in hearing all the comments this morning, we are all a
25 little confused about what really are the criteria we are

1 going to use for this pathway, and I think it might make
2 sense early on to use a continuous variable to strengthen
3 that cohort.

4 DR. STONE: I have got two comments. I think both
5 clinical outcomes are important, but I think again we need a
6 very hard scientific approach. We are talking here about
7 ways to fast-track -- and I know it's not really fast
8 tracking, but it is easier to say that -- ways about at
9 least shortening the regulatory process to get a new
10 implantable device on the market.

11 As you heard earlier, we can do studies using the
12 power in continuous function analysis with 175 to 200
13 patients with follow-up angiography, have very tight
14 confidence intervals that we know, at least from a point of
15 restenosis, which is the best core that we have of target
16 vessel revascularization, that gets rid of all the other
17 clinical problems inherent in that measure.

18 That, I don't think is too much of a public burden
19 to ask for, 175 to 200 patients before we are approving a
20 new implantable device in a human being. I think that it is
21 for that amount of money, you know, you are talking on
22 average about \$1,500 for 200 patients. That is certainly
23 something that start-up companies should be able to expend,
24 and it is nothing that I think is unreasonable.

25 On the other hand, we obviously have to look at

1 safety issues and clinical outcomes, as well. I am
2 concerned that if we don't have angiography and all that it
3 takes is six-month clinical events, you are going to get
4 into big issues on how you are defining MIs, and more
5 importantly, how you define target vessel revascularization,
6 and you are going to have all the companies and all the
7 investigators trying not to cath their patients, you know
8 letting a little bit of angina go on and on until you get to
9 that magic six-month endpoint, and I think there is going to
10 be too many ways around it and too many other variables in
11 the system.

12 I also agree with the comment that we have to
13 separate MACE. I mean death, if you have got a death rate
14 of 5 percent or 8 percent, but the target vessel
15 revascularization is 8 percent less, so the MACE turns out
16 to be the same, to me, that is not equivalent outcome, and
17 they are very different. The mechanisms can be totally
18 different.

19 So, I think again what needs to happen is there
20 needs to be a working group that says what are the important
21 points that we want to look at. We need to look at
22 deliverability, we need to look at death, we need to look at
23 MI, however we define MI -- that is a whole other issue --
24 you know, clinical target vessel revascularization, it
25 should track with angiographic restenosis. I think that is

1 important, but I strongly feel that 200 patient for
2 angiographic follow up is not too much to ask for before we
3 approve an implantable device.

4 DR. VETROVEC: I just might make the comment, at
5 least in our experience, if you pay for angiographic follow
6 up, most patients will do it. I think patients will do it.

7 DR. POPMA: I am going to make one statement first
8 and then we are going to kind of jointly make a statement.

9 First, all the randomized clinical trials right
10 now, to the point about is it ethical to do angiography, in
11 fact, all of the randomized trials now for stent approval
12 all have angiography locked in as part of it, so we are not
13 really doing anything outside of what we are already doing.

14 I think Dr. Laskey makes a very important point
15 about when the angiogram done and how to avoid the
16 oculostenotic reflex, and there has been a lot of work
17 primarily out at Beth Israel Hospital and elsewhere that has
18 suggested that if you back out the angiogram to nine months,
19 that, in fact, perhaps you can get away with all the
20 clinical events that would occur symptomatically early on.

21 The joint comment I think that we would want to
22 make is that it seems as if there is going to be some
23 hesitation on the part of the panel to actually nail down a
24 number, but to me, that is almost what we would have to do
25 if we are going to offer as an alternative to industry a

1 registry format. They are going to have to know what type
2 of patients to include.

3 I guess what we would say is, both myself as part
4 of the Society for Cardiac Angiography and Intervention --
5 and Dr. Hirshfeld can comment in just a second -- is that
6 maybe the societies could come together and give you some
7 numbers that you would feel more comfortable with, because
8 you may have some limitations about what data you can
9 actually look at to come up with your numbers.

10 I would wonder if that would be useful thing for
11 the panel.

12 DR. HIRSHFELD: To reiterate that but, at the same
13 time, to qualify this by saying that I don't think either
14 Jeff or I are empowered to commit our organizations at this
15 moment to do this, but I think we would be interested to
16 know whether FDA would find this to be a constructive input,
17 and if so, then, I think we should explore it.

18 DR. BRINKER: I agree that the professional
19 societies would be most helpful in this. I also agree with
20 Warren's statement, Jeff, that somehow we have to get around
21 -- it's great if you do a controlled study, that you feel
22 that the oculostenotic reflex is going to be a wash between
23 the two groups.

24 Actually, I wanted to do a study with the B-stent,
25 in which the control group would not get angiograms, and

1 only the investigational stent would get angiograms, and the
2 biggest hurrah that came up was, well, this is going to
3 drive up your target lesion revascularization to a degree
4 that you will end up having a worse case scenario.

5 There are methodologies that lessen that burden by
6 making the investigator commit before the angiogram, things
7 of that nature, which might be used, but it is not a small
8 concern, and I would agree with the nine-month angiogram
9 rather than the six-month angiogram for a lot of reasons,
10 even though this may prolong the total study a little bit.

11 DR. CURTIS: I think it is important for us to
12 take a break now. I would like to adjourn for lunch and be
13 back at 1:30.

14 [Whereupon, at 12:20 p.m., the proceedings were
15 recessed, to be resumed at 1:30 p.m.]

AFTERNOON PROCEEDINGS

[1:30 p.m.]

DR. CURTIS: We will start again on the panel discussion.

Question No. 3 really related to Nos. 1 and 2, and I just want to go past that and move onto a new topic.

No. 4. For what clinical questions should we continue to perform randomized control trials? Before that, in our panel pack, the question is raised, what are the clinical trial design options for a previously unstudied stent design which fits into the definition of a standard coronary stent.

So, after all the deliberations this morning, if there was some agreement on what a standard coronary stent is, what kind of specifications it meets, then, what kind of a clinical trial design should be performed for that?

Let's start with this question here. For what clinical trials should we continue to perform randomized controlled trials?

I will open that up for discussion.

DR. DOMANSKI: How about any one for which the stent being studied is not a minor variation of prior stents?

DR. CURTIS: So, a significant deviation from current designs would be one reason why you would still have

1 a randomized controlled trial.

2 DR. TRACY: A stent that is going to be used to
3 deploy something, either radiation or medication or some
4 other therapeutic goal of the stent that is tied along with
5 the stent.

6 DR. DOMANSKI: I meant to sort of put that under
7 that roof.

8 DR. CURTIS: So, new indications, too.

9 DR. VETROVEC: Certainly for all the new blood
10 vessels, I mean new vessel sizes, small vessels.

11 DR. CURTIS: Small vessels.

12 DR. VETROVEC: Long lesions. I guess there is the
13 intriguing question that we haven't really addressed is
14 suppose the stent is outside of what we consider the optimal
15 standards, but the manufacturer says but in conjunction with
16 the IIb/IIIa, let's say, it will give equivalent results. I
17 mean I can see that question coming forward, that there is
18 some synergism that might change it, and I think in that
19 circumstance, you would have to prove it.

20 DR. CURTIS: I agree with that.

21 DR. BRINKER: I am not sure I agree -- I mean I am
22 not sure that if a stent says I can give you the same
23 results as an already approved stent, but I require an
24 adjunct therapy with it, I am not sure what the proof would
25 be. The randomized study would have to be against the

1 approved stent with the adjunct, as well as the new stent
2 with the adjunct, which presumably would be a no-win
3 situation.

4 In other words, I don't think that a new stent
5 that is going to be as good as an old stent only with an
6 adjunct to it, has got much of a chance. On the other hand,
7 I would require a randomized controlled trial for any stent
8 that is wishing to label its superiority claim to the
9 existing stents.

10 DR. DOMANSKI: They never do that, though, Jeff.

11 DR. BRINKER: They may.

12 DR. DOMANSKI: But they never do because you don't
13 have to go that far to get the thing on the market, and that
14 is all they ever care about.

15 DR. BRINKER: No, no, if someone were to do this,
16 that would required a randomized controlled trial. Let's
17 put it that way.

18 DR. CURTIS: Probably the interventionalists here
19 could answer this for me, but are there stents that are on
20 the market that have already been approved for the
21 indication for use in, say, bypass grafts, and some of these
22 other, because I am noticing in the proposed labeling there
23 are some statements to that effect - discrete lesions,
24 restenotic lesions, I am sure all of them have that
25 indication, but are there already approved devices with the

1 indication of being used in, say, saphenous vein bypass
2 grafts?

3 DR. OESTERLE: If I could ask for a point of
4 clarification over here.

5 DR. CURTIS: Okay.

6 DR. OESTERLE: Maybe I missed the point of what
7 this means. The idea of streamlining the regulatory
8 process, so that we can get stents more quickly to the
9 market, if our goal is to have a bunch of wannabe's, which
10 has been mentioned here several times, I am not sure that is
11 what the interventionists or the American public really
12 want is another 10 look-alike stents, and there is no
13 question that we could design a streamlined process for
14 bringing in their 10 stents that look a lot like the NIR
15 stent.

16 It seems to me that what most people actually
17 doing this procedure in the Unites States have wanted is a
18 streamlined process for bringing in stents that really add
19 value. You could say let's just open it up and get a bunch
20 of wannabe's and treat these things like a commodity, and
21 therefore this has value because it will drive the costs of
22 stents down dramatically.

23 That is true, but I would suggest that with six or
24 seven companies already on the market, that that price will
25 come down anyway. What we have really been missing is a

1 process that --

2 DR. STUHMULLER: Excuse me. Just from an Agency
3 point of view, I want to clarify that. The issue is, is
4 from a legal point of view, we are obligated to work with
5 manufacturers who want to market a device, and the issue is
6 if it happens to be a similar device, and there is 10 of
7 them out there, we are in no position to tell that company
8 no, they can't.

9 DR. OESTERLE: I understand that.

10 DR. STUHMULLER: So, the issue is, is what we
11 need from the panel, is what do they consider to be valid
12 scientific evidence for the evaluation of the stent. You
13 know, the issue at hand is not whether there is 10 stents
14 that are similar. The issue is if the 11th manufacturer
15 wants to come on the market, we are obligated to work with
16 them.

17 DR. OESTERLE: I understand that, but that is a
18 pretty low goal for this committee, and it seems to me that
19 you could maybe raise the horizon a little bit by asking a
20 more valuable question, which is what can we do to get
21 useful stents into the marketplace, because we obviously
22 have a lot of missing gaps in our stent armamentarium that
23 need to be filled, and the question is do they all have to
24 go through RCT's in order to be approved.

25 That philosophy or that ethos can totally change

1 how you answer these questions because we could easily
2 decide what we need to get 10 more wannabe stents on the
3 market. I think that would be easy for this panel to do in
4 an hour, but it is a much more difficult question to look at
5 a stent and say this stent looks reasonable, how could we
6 streamline the evaluation of this, and get it into the hands
7 of people, so we can help people. It's a different
8 question.

9 DR. BRINKER: Why is it a different question? I
10 mean let's assume that the company that makes the new stent,
11 and it's more easily deliverable, let's say, and it may have
12 markers on the end, and you might want to have that stent,
13 because you can't see the stents we have now as well as you
14 would like to, for instance, and that would come under the
15 same rubric, if everything else was the same, as these
16 wannabe stents.

17 DR. OESTERLE: That is not what I am looking for
18 is a stent with two more markers on it. I mean I am talking
19 about sort of probably more significant engineering
20 modifications that would make these more useful and bypass
21 grafts more useful, and small vessels, and, of course, I
22 mean the concept here is that, well, those are all
23 automatically randomized clinical trials, and the question
24 is, is that really true, isn't there a way that we could
25 look at the fundamentals of the engineering design, say,

1 look, this is a reasonable design.

2 We know we do have a data set, a large data set on
3 small vessels who were inadvertently entered into these
4 trials, and maybe we could actually streamline the approval
5 of even a stent that is not within the boundary of what we
6 consider a standard stent, and that is a different question.
7 It's not just to put more markers on it.

8 DR. BRINKER: It is a different question, and in
9 prior panel discussions, the importance of looking at small
10 vessels as a paradigm for a new indication, is really
11 focused on the ability to show that small vessels do better
12 with the stent, too, not just perform equally to a balloon
13 angioplasty, and I think that, in fact, there was at least
14 one trial that was unfortunate, that would have given the
15 answer, that was halfway done, that was stopped by the
16 sponsor because they got a small vessel stent approved under
17 a bailout indication or will get it approved under a bailout
18 indication, which is a lot less onerous, and we don't
19 actually have the data that we need to, to know whether
20 stenting in a vessel that is 2.5 mm or less is beneficial.
21 I don't see how you are going to get that data.

22 DR. OESTERLE: I am not here to debate with you,
23 Jeff, about whether we should be doing it in small vessels.
24 It is a broader comment than that. I mean I agree that you
25 could pick any of these vein grafts, bifurcations, small

1 vessels, and argue this point for the rest of the afternoon.

2 I am just saying are we interested in shortening
3 that process in any way or looking at ways to do that by
4 looking again at fundamental engineering issues that Elazer
5 and people have brought up earlier, or are we really just
6 honestly just talking about wannabe stents.

7 DR. TRACY: I don't see how we could look at any
8 engineering issue and decide based on that, that a stent
9 probably would work okay in a small vessel or any of the
10 other issues that you mentioned.

11 I think the real question is for those sorts of
12 things, saphenous vein bypass grafts, bifurcations, small
13 vessels, is there any reasonable way to get at safety and
14 effectiveness for a new stent short of a randomized clinical
15 trial, and I am not sure there is enough data around to tell
16 you how small vessels behave that you could use, as we were
17 thinking for the larger vessels and for the standard
18 coronary stent we talked about earlier.

19 DR. OESTERLE: I think, I don't know, I mean that
20 is just what I do for a living, I mean every day, and I
21 think that there is enough people who believe, who are doing
22 interventions every day, that we do have an understanding of
23 the problems of stenting in some of these so-called off-
24 label sites that we probably could do something short of a
25 randomized clinical trial.

1 I am not trying to argue this point. I have
2 already more of the time than I meant to here, but I am just
3 confused about the process because I am afraid that what we
4 are heading for is just sort of the mediocrity, we are going
5 to get a bunch of stents that look like the NIR stent, and
6 look like the Multilink, and that we will have 10 more of
7 those, and is that really why we are here, is that what we
8 want to do.

9 I understand John's point that you have an
10 obligation as an agency to be fair to all these wannabe
11 companies, but I mean it somehow seems not a very sublime
12 pursuit.

13 DR. CURTIS: I think the idea is that we are going
14 to try to recommend the least burdensome thing that protects
15 the public, and accomplishes what we want to accomplish.
16 The thing about the wannabe companies, yes, there is a need
17 to have that process be as simple as possible, but yet
18 answer the questions.

19 If there are other indications for which it
20 wouldn't be necessary to do a randomized clinical trial,
21 then, we ought to put that out on the table here. We are
22 not here to eliminate that. I am not sure there is.

23 DR. TRACY: Maybe, Steve, the question that you
24 are asking, is there some way to expedite things that are
25 novel, and I think that probably part of what we should be

1 considering is in Question 5 and 6 in terms of are there
2 other endpoints that we can look at other than gathering
3 thousands and thousands of patients, are there surrogate
4 endpoints, and so on, that might be appropriate to use that
5 would, in effect, expedite.

6 So, I think there are two goals that we have. One
7 is to expedite the look at me, I am just like the other guy,
8 and also help expedite the newer devices, and I think we are
9 coming to the newer stuff.

10 DR. DOMANSKI: But I do think it is important to
11 say. I think it is important to join the discussion by
12 saying from my point anyway that if there is a question, I
13 think that one shall fall in the camp of doing clinical
14 trials. I don't think -- you know, you may do it all day,
15 I don't do angioplasty all day, but I do angioplasty, and I
16 don't know how it behaves in small vessels, and I think that
17 is a legitimate question, and I think there are others, so I
18 think if the question is extant, I think the controlled
19 trial should be the gold standard.

20 I just don't think when the stent goes another
21 quarter of a millimeter in one direction or another, it has
22 a slightly different balloon behind it, that one necessarily
23 needs a big controlled trial for it, but I do think for
24 small vessels you do, and for novel devices and novel
25 applications of those devices, I think we should force it.

1 DR. CURTIS: So, novel devices, novel
2 applications, small vessels. Anything else anybody wants to
3 point out as still requiring a randomized clinical trial?

4 DR. DOMANSKI: I suppose radically different
5 lesion -- well, different lesion morphology from what we
6 have approved the thing for in the past. That shouldn't
7 usually be a problem because these companies usually get it
8 out on the market for a simpler lesion morphology, and then
9 it is there and you can use it for the multivessel disease.

10 I suppose if somebody came in and wanted the
11 indication, they would have to prove it was okay.

12 DR. CURTIS: For saphenous vein bypass graft, do
13 you need a randomized clinical trial?

14 DR. DOMANSKI: I think we now have one.

15 DR. BRINKER: There has only been one, and there
16 has never been another one.

17 DR. LASKEY: It also depends on the device. There
18 may be novel devices out. The vein covered stent was used
19 this morning as an example.

20 DR. CURTIS: I am just saying for various
21 indications, you know, just give some recommendations here,
22 because I don't know this as well as some of the other
23 members of the panel.

24 DR. DOMANSKI: There is one trial out there, I
25 guess, Jeff, for the saphenous vein.

1 DR. BRINKER: But what has happened is for a
2 regular stent, after the first trial, companies have been
3 allowed to have a registry, and that seems to be a
4 legitimate form of validation for saphenous vein, for
5 routine type stent.

6 Now, if you are looking at novel technology, like
7 a covered stent or some sort of bioabsorbable device in any
8 site, or a stent that has a proposed different mechanism of
9 operation for one reason or another, those would very well
10 require randomized trials.

11 DR. CURTIS: Have the previous trials that have
12 been done, been done in native arteries, and then everybody
13 just go ahead and uses them in saphenous vein grafts, or
14 part of the trial included saphenous vein grafts, and they
15 got a labeling for saphenous vein?

16 DR. BRINKER: The more recent trials after the
17 SAVE trial, the stents that came into clinical investigation
18 usually had a saphenous vein graft registry arm.

19 DR. CURTIS: As part of the clinical trial?

20 DR. BRINKER: As part of the clinical trial, and
21 that is a nonrandomized registry, as well as an acute and
22 threatened bailout arm, which was also nonrandomized.

23 DR. CURTIS: So the main trial would be randomized
24 against some other stent?

25 DR. BRINKER: Right.

1 DR. CURTIS: And then there would also be patients
2 having implants, and then the final indication would include
3 all of those.

4 DR. BRINKER: Yes, assuming that the stent
5 performed well. There is one situation in which the stent
6 actually did not perform as well in the randomized portion
7 of the trial, and was not pursued, to the best of my
8 knowledge, for that indication, but is available for the
9 acute bailout situation.

10 DR. CURTIS: So, then if you had another standard
11 coronary stent that was going to be studied, and the main
12 goal was the large vessel, kind of typical lesion, even
13 including these other things like threatened closure and
14 saphenous vein bypass grafts, all of that could be done,
15 comparing it to some sort of a database, you are saying,
16 rather than a -- would you say that?

17 DR. BRINKER: I hadn't thought. I would guess
18 that if one were to include saphenous vein grafts as an
19 indication, one would want to include a portion of the
20 clinical trial, nonrandomized trial.

21 DR. GILLIAM: Jeff, are any of these devices
22 presently approved for saphenous vein grafts as an
23 indication?

24 DR. ZUCKERMAN: The FDA can answer that question.
25 The labels for all the approved stents are included in your

1 panel pack, but to make it simple, as Dr. Brinker was
2 explaining, for a new stent, PMA trial right now. The core
3 database consists primarily of patients with large vessel de
4 novo lesions. You talking about a 600 to 800 patient
5 randomized trial.

6 Concurrent arms at the manufacturer's discretion
7 have included parallel arms for abrupt and threatened
8 enclosure, saphenous venous graft lesions, and restenotic
9 lesions.

10 Now, there are several practical problems
11 regarding randomized trials in the SVG and restenotic
12 patient population that we have seen previously. Presently,
13 they center around the rate of patient accrual as opposed to
14 how quickly patients can be accrued that have de novo
15 lesions.

16 DR. BRINKER: So, the question that was asked is
17 if you get your stent approved and you have had a saphenous
18 vein graft registry, will you get labeling for the saphenous
19 vein graft.

20 DR. ZUCKERMAN: If it met the performance criteria
21 that were established a priori during the initial planning
22 stage. However, there is another part to that question
23 regarding what is approved for saphenous venous graft
24 stenting, especially when it comes down to the new question
25 of what is going to be the controls for the saphenous venous

1 grafts covered stents, and that is, right now our coronary
2 stents for SVG location are I believe only approved up to 4
3 mm. The question then is what type of control would you use
4 in a 3- to 5-mm diameter saphenous venous graft population
5 that you might want to use covered stents in.

6 DR. BRINKER: Do you understand that in the
7 saphenous vein graft population, since the predicate stent
8 was only available in 3 to 4 mm, that there is no experience
9 beyond 4 mm, so that becomes a potential question.

10 DR. CURTIS: That sounds like a potential question
11 for a randomized clinical trial design.

12 DR. BRINKER: For all the reasons that Bram had
13 suggested randomized clinical trials for saphenous vein
14 grafts are difficult. Again, since there is no predicate
15 stent, you would have to randomize against a balloon
16 angioplasty, if you are just looking for bigger stents, and
17 that is not much of a viable methodology, and I think that
18 is something that the Agency -- I mean the larger stent size
19 is something that the Agency will have to come to grips
20 with.

21 The covered stents are a whole other issue, but I
22 would hope that stents that are validated, larger stents
23 that are validated outside the saphenous vein graft could be
24 rapidly adopted with a minimal registry trial to the
25 saphenous vein, so that we can get that out of the way.

1 DR. FITZGERALD: I think size and length that is
2 well understood will chronicle engineering descriptors that
3 are similar to what our database is, and the only variable
4 you have is length and/or size. I think those are the type
5 of trials that should stay away from randomized clinical
6 controlled trials. I think those are the ones that should
7 be accelerated.

8 DR. CURTIS: So, you want them accelerated because
9 we don't have anything currently on the market that would
10 work for that indication, but yet you think it would be
11 acceptable in that kind of a trial to implant them, and then
12 be comparing them to a database or some sort of a data set
13 that is already available.

14 DR. FITZGERALD: Not a covered stent. I am not
15 sure about that because that is a different biology and
16 biological variation that is going to surround itself there,
17 but certainly the same type of stent that was just for an
18 indication of a 5 mm and an NSVG graft is important, and I
19 don't think in need of a randomized trial.

20 DR. OESTERLE: Peter, what are the limits on
21 diameter and length where you think that maybe there will be
22 questions?

23 DR. FITZGERALD: Well, I think that length needs
24 to be curtailed a little bit. I don't think we could extend
25 that to say 80 mm long stents, but for the factors that we

1 are talking about, a few millimeters on each side and a
2 millimeter increase in width, I think those are within the
3 spread of what people can be comfortable with.

4 I think long stents get into a problem because the
5 biology is pretty aggressive in that situation.

6 DR. OESTERLE: I actually don't see any problem
7 with extending the diameter almost at will since we have had
8 plenty of experience with large bore stents that have been
9 nothing but favorable always.

10 The issue of length is a much more critical issue
11 I think in terms of whether people are going to just
12 randomly accept that, but I don't see any problem with
13 having a 6-mm stent in diameter, but when you start
14 lengthening, I mean where does it stop. I don't know. I
15 would pick something in the range of 45 or 50 mm in length.

16 DR. BAILEY: In these registry comparisons, what
17 would be the comparison, to what treatment?

18 DR. FITZGERALD: For?

19 DR. BAILEY: For saphenous vein grafts.

20 DR. FITZGERALD: For size?

21 DR. OESTERLE: Well, it would have to be balloon-
22 only since we don't have stents, unless you totally use an
23 off-label peripheral stent.

24 DR. BRINKER: You could use the experience with
25 stents smaller. I mean there is no reason why you couldn't

1 compare a 6-mm stent to the results achieved. In fact, you
2 would probably get better results with the 6-mm.

3 DR. BAILEY: What would you be looking for, better
4 results?

5 DR. BRINKER: No, equivalence, just basically
6 safety.

7 DR. CURTIS: Let's go on to Question No. 5.

8 Comparators. Based on the consistency of results
9 in completed trials to date, could we consider use of non-
10 concurrent controls based on published/public domain (or
11 proprietary) data including: (a) matching of patients
12 individually from an appropriately comprised large register;
13 (b) comparison of individual or cohort results to
14 appropriate statistical models of patient response; the use
15 of predefined or "patient adjusted" objective performance
16 criteria?

17 We have been kind of skirting the issue of
18 comparing new designs in a clinical trial to a database, and
19 the question is what is the database, what would be the best
20 kind of database to use? I think some of this is going to
21 get directly into what the manufacturers are going to be
22 comfortable with.

23 One suggestion I could make is that there is a lot
24 of data that has been available from all the PMA
25 applications. It sure would be nice if people could have

1 access to that, and would that be the ideal, any new
2 manufacturer would have access to that data, and be able to
3 use that to compare their new stents to?

4 DR. BRINKER: When you asked the question what is
5 the optimal methodology, and I think that Rick suggested the
6 optimal methodology, and that is to look for the specific in
7 a large document, the database, separated out patients in
8 terms of the criteria that we know overtly affect outcome
9 and correct for that. I think that would be ideal.

10 The least acceptable, to my mind, would be the
11 construction of objective performance criteria based on the
12 prior inclusion criteria for stent trials in terms of
13 length, type of lesion, et cetera, and then hold the sponsor
14 responsible for assuring that the patients that are
15 recruited pretty much conform to those inclusion criteria.
16 Otherwise, it would be probably to their disappointment that
17 their results won't be as good.

18 DR. CURTIS: What is the source of the data,
19 though?

20 DR. BRINKER: That is what I was suggesting
21 before, that I think that you get people from societies, the
22 ACC and the Society for Cardiac Angiography and Intervention
23 together, and develop a panel that is based on experiential
24 and published data.

25 The one thing I would agree with Steve on is that

1 you could pretty much say what a rate of successful
2 delivery, rate of subacute from thrombosis, rate of MACE
3 will be, what you would take as minimally acceptable.

4 I don't think there would be a problem if you put
5 a bunch of interventionalists in a room for a bit to come up
6 with data that pretty much reflect that. Obviously, again,
7 it would scientifically more pleasing to have the kind of
8 analysis that Rick was suggesting, but I think that this
9 could be done, and we are going to have almost assuredly
10 angiographic analysis at 6 or 9 months in the study group
11 that would further meet predefined criteria.

12 DR. CURTIS: Then, those objective performance
13 criteria would be developed from published studies then
14 basically.

15 DR. LASKEY: There are some OPCs which we never
16 thought of, or we thought of, but we didn't do much with,
17 but I think which are more apparent now with newer
18 generation devices, and they relate to the technology
19 itself. I think some of the acute clinical criteria are
20 pretty cut and dried, but some of the other aspects to these
21 procedures, such as deliverability, catheter related
22 embolization or maldeployment rates need to be carefully
23 looked at because these are things which do occur with a
24 frequency greater than zero, and I think we need to set
25 limits for what is acceptable and safe, as well, for new

1 devices, with unsheathed devices, and so forth, so I think
2 there are issues now which didn't pertain sheath system, the
3 PS system.

4 DR. CURTIS: How would you go about defining what
5 was acceptable and unacceptable?

6 DR. LASKEY: Well, again, you can look at what is
7 out there, either in the trial experience or in the real
8 world experience, i.e., registry data, and that assumes that
9 everyone actually carefully tabulates these data.

10 Certainly, that is true in the trial literature
11 where you can set confidence limits for acceptability of
12 maldeployment or embolization rates, but I think that is
13 something that really needs to be looked at, as well.

14 It is not simply a matter of reaching for another
15 device because your first one didn't get where you wanted it
16 to go. I think that needs to be worked through, but I think
17 that that information is available, to answer your question.

18 DR. TRACY: If you think about databases, and you
19 think of where the data comes from, there is multiple
20 different types of databases. There is the data that is
21 collected by the companies that so far have been accrued for
22 the approval of these different devices, and, yes, there
23 were certain inclusion and exclusion criteria, and that by
24 its nature, in comparing a novel technology to this, or even
25 a novel indication, you are going to have problems.

1 If you want to compare a device that elutes
2 ReoPro, how are you going to compare that with something
3 that has already approved? However, at least you have the
4 satisfaction of knowing that that data was obtained clean.
5 There were specific criteria that were being asked for,
6 specific things that went into the database, that you have
7 confidence in that information.

8 Then, you have the types of registry databases,
9 which is if one day I get a good result, I might turn it in,
10 if the next day I get a bad result, I might not turn it in.
11 So, I have very little confidence in historic registries as
12 being something that is worthwhile comparing things to.

13 The third type of database would be something, you
14 know, comparing to the literature. You have got the top
15 investigators doing their very best job, which probably has
16 nothing to do with somebody else doing it somewhere else, so
17 I am not sure that that is comparable or worthwhile.

18 Then, you have the idea of taking the patients
19 that were in these protocols that were -- and this is
20 burdensome I know -- but if you have patients that were
21 enrolled in a study to get the device approved, and you
22 continue following them, and you ask the manufacturers to
23 obtain some kind of data on those ongoing patients and
24 expanding indications, you might get better information, but
25 I just don't think it is simple to find a good database

1 against which to compare things, but I would make the strong
2 plea that the best data is probably the stuff that has been
3 obtained by the companies so far for the approval of these
4 devices, and if somehow that information could be in the
5 public domain, and somehow be comparable and used otherwise,
6 it would avoid a whole lot of problems in the future, the
7 same kind of problems that we keep running into the arena of
8 electrophysiology.

9 It has something that the industry has to at some
10 point recognize the benefit of. They may not get the
11 benefit immediately, but they will get the benefit long
12 term.

13 DR. CURTIS: To go along with that same issue, I
14 think that what is not going to work is simply to use any
15 data that is more than six years old, the issue about that
16 that then becomes then public domain, because the stent
17 results from six years ago are not comparable to what people
18 are going to get today, and you are going to set the bar way
19 too low if you say, well, all you have to do is be as good
20 as the stent was back in the early 1990s.

21 So, that is not going to be good enough by itself.
22 Now, if we can get some of this data that has been submitted
23 as Dr. Tracy said, and be able to use it if there is a
24 general agreement among the manufacturers, and there was
25 some talk earlier, working with the FDA to decide how to go

1 about doing that, that probably is going to be the best.

2 DR. POPMA: I guess I am getting old enough that
3 now I can be a historian about stent registry approval, and
4 that sort of thing, but there is one stent that was approved
5 off a registry for abrupt closure, and that is the Wichter
6 stent, and that was a comparative analysis from the NACI,
7 New Approaches to Coronary Intervention registry with a GR-
8 1. This was back before there were many other bailout
9 devices, and that stent I think has kind of come and gone in
10 terms of its popularity. Dr. Detre has left, but this is a
11 good plug actually for the dynamic registry.

12 If the FDA was serious about capturing what is
13 happening across the board in a number of different centers
14 with contemporary stent use, the dynamic registry, which
15 will start the next set of enrollment in February, is a
16 perfect way to capture that information, because that gives
17 both acute outcomes, as well as target lesion
18 revascularization rates, and if the randomized data isn't
19 readily available from the companies, I think there are
20 other databases that are contemporary, that would be very
21 useful for the panel to consider as contemporary control
22 group, because then you do have the raw data for the
23 multivariable models that Dr. Kuntz has suggested.

24 DR. GILLIAM: Are you suggesting that in every
25 deployed stent, being enrolled in such a database?

1 DR. POPMA: Well, there will be 2,000 patients,
2 and I will bet, although it was 60 percent stent use the
3 last go-around, knowing from our institution it is going to
4 be 75 or 80 percent stent use right now, which gives a
5 pretty good denominator of stent use. There will be 1,500
6 patient acquired over a 6-week period of time, that will
7 have undergone stent use with the currently approved stent
8 designs, and the majority of those are going to be from the
9 major manufacturers that we know now.

10 I would be willing to guess that in February,
11 there is going to be a lot less JJI stent use, and a lot
12 more of the other major manufacturers that are currently
13 approved.

14 That system is already in place. You know, that
15 whole registry format and that system is already in place.
16 It is an NIH-sponsored study. It seems to be an ideal
17 setting to allow some contemporary OPCs to be created. I am
18 sorry Katherine had to leave because I think it's a great
19 plug for what she is really developing.

20 DR. CURTIS: And then that dynamic registry, is
21 that as good as trying to get the PMA data released into the
22 public domain?

23 DR. POPMA: That is actually an interesting
24 question. Maybe it's better.

25 DR. OESTERLE: It goes back to what Rick Kuntz was

1 saying. If you look at the new generation of stents coming
2 out, people are pushing the applications of those stents,
3 because the question is we are not really looking for
4 another NIR stent, we are looking for something better than
5 a NIR stent, or better than Multilink.

6 So, people get access to it, and they are going to
7 be more aggressive with it than they would the original JJ
8 stent, because it is just much easier to deploy, and
9 theoretically, a new design is going to be appealing as a
10 more easily deployed stent.

11 So, the people are going to be more aggressive,
12 and the results are not going to be as good. Rick made this
13 point this morning, and I think he is absolutely right.
14 Whereas, if you take a registry like the dynamic registry,
15 people are going to practice their practice, and they are
16 going to try to get a stent wherever they can.

17 You are really going to see the limits of what
18 stenting can do in 1999, because the groups that are in this
19 are pretty aggressive groups, and you will see them using
20 them off-label, it will be in the registry, and I think you
21 will get a pretty good idea.

22 DR. POPMA: But the de novos, you can still tease
23 out the de novo lesions or the very simple lesions, the
24 straightforward lesions out of that dynamic registry. They
25 are not all going to be super complex lesions, so I think

1 you still could develop the registry.

2 That actually is very useful in the Wichter
3 analysis that many people here were part of, is that you
4 really could add the data in and run a multivariable model
5 and test specifically whether the stent was associated with
6 a good or bad outcome.

7 DR. CURTIS: The issue of off-label use leads into
8 a question for Dr. Callahan. Are we going to be able to
9 combine off-label and on-label use and use this registry
10 data?

11 DR. CALLAHAN: When we get into that kind of data,
12 what you will get from the data has to be applied to
13 everybody. We have no way of -- with an off-label use,
14 everybody may very well have to have -- the data may have to
15 be robust enough, so everybody can have that data, and we
16 will have a problem looking at it if there is not enough of
17 a specific type of stent in there to have that, what do we
18 do? If there are 20 stents out there in the database, the
19 registry has primarily 5, what do we do with the other
20 because they are all off-label use. I am not sure how we
21 would handle that.

22 DR. CURTIS: Let me ask something else. This is
23 NHLBI. Does that mean it's public domain, and you have full
24 access to it, or does that have to be worked out?

25 DR. CALLAHAN: If it's NHLBI --

1 DR. DOMANSKI: They do not have access to it
2 necessarily until it's released. After a certain amount of
3 time, all of those data are released to anyone who wants it,
4 but nobody gets it until that point including the FDA.

5 DR. CURTIS: Do you know what kind of time frame
6 you are talking about?

7 DR. DOMANSKI: A couple of years after the trial
8 is completed usually.

9 DR. CALLAHAN: We have other trials going on, not
10 in the stent area, that are NHLBI- sponsored or cosponsored,
11 and the endpoints that they are looking for, again, it's the
12 question of concept versus specific. They are usually
13 looking for conceptual to answer a question, are valves of
14 this type good for this population, so they want the data
15 out for a longer period of time.

16 DR. DOMANSKI: That is not to say we couldn't give
17 it to them or something, but just, you know, it's not a
18 priori theirs just because it's government.

19 DR. CURTIS: The other thing I am thinking about
20 is that if we are just into wave one now, and you are saying
21 two years after -- I would imagine at a minimum, wave one is
22 finished, then, unless there were some sort of agreement,
23 there might not be access to that information for two or
24 three years.

25 DR. POPMA: If I could just speak to that point

1 for just a second, I can't speak for the dynamic registry,
2 but I can tell you that is why Katherine was here. I mean
3 the idea is that we have all been very much involved in with
4 respect to NACI.

5 That is exactly why NACI was set up, so that we
6 could do cross-device comparisons, and there was unanimity
7 amongst the investigators who were part of NACI, that this
8 is exactly what we wanted to do.

9 So, I think if this was a proposal that would
10 really come from the FDA panel members to the dynamic
11 registry investigators saying this is a facilitated
12 mechanism, I am not sure that there would be that same data
13 delay.

14 DR. DOMANSKI: No, I think there wouldn't
15 necessarily for NACI. That would be easy to arrange. I
16 think where you get a group of investigators together to do
17 a clinical trial, you would have more trouble.

18 DR. CURTIS: The other distinction here is nobody
19 is looking to look at that data to publish anything, you are
20 just looking at it to compare.

21 DR. DOMANSKI: Once you put it on the market, I
22 mean once you put it out there, anybody can publish anything
23 they want. I am sure you will see a lot of metaanalyses
24 come out of that, which is fine, I mean that is what it is
25 there for. It is great it is in the public domain, it's

1 just that if we run -- take something non-threatening, BEST
2 -- I mean the whole world is not going to have access to
3 those data until a certain amount of time elapses, and the
4 people who did the thing are going to have the primary shot
5 at writing the papers.

6 DR. CURTIS: So, the dynamic registry, that idea
7 might be one approach to having a patient comparison group
8 or working through the issues with the manufacturers and the
9 PMA data that is already available.

10 In either event, there are published studies on
11 the stents already, too, which could help you develop
12 objective performance criteria. I think they are all valid
13 ways of approaching this issue.

14 Let's go to No. 6.

15 DR. BAILEY: I think if you could compare the
16 different databases, too, that would give you some idea of
17 how reliable the results are, if they are robust when you
18 use different databases.

19 DR. CURTIS: Long-term endpoints. The primary
20 endpoint currently used is 6 months. What are the best
21 candidates for valid surrogate endpoints? How could we
22 validate a continuous measure, for example, angiographic
23 percent diameter stenosis at 6 months, which could have a
24 corresponding smaller sample size? How could we validate a
25 earlier endpoint, for example, 30-day MACE?

1 I think what we are going to come to primarily is
2 the need for, the desirability of, and the timing of
3 angiography at some point after the initial procedure, and
4 then the issue of MACE and the timing of that. If there are
5 any other valid surrogate endpoints, that should be brought
6 up now, too.

7 DR. BAILEY: You are talking about a surrogate
8 endpoint for what, for 6 month angiographic results?

9 DR. CURTIS: Or MACE, anything else. I didn't
10 make up the question, but in terms of surrogate endpoints,
11 is there something else that would be valid to use as an
12 endpoint that would give you just as much information as
13 those listed, are those the ones we should have, and is that
14 the right timing.

15 DR. BAILEY: I guess I would prefer calling it an
16 alternate endpoint if the implication is that learning about
17 this endpoint as a surrogate would tell us the information
18 we need about the clinical endpoint.

19 DR. CURTIS: I think that is what was meant by the
20 term surrogate.

21 DR. TRACY: I guess that the clinical endpoints
22 are so variable depending on other parameters, that are not
23 being affected by the stent, that may be, in this instance,
24 the surrogates are actually the better endpoints to be
25 looking at, and if people are saying that performing cath at

1 6 months is not an onerous, you know, not an impossible
2 thing to do, then, perhaps if there is good validation that
3 these things really do correlate with other types of
4 outcomes, that would be important, then, angiographic data
5 at six months is probably appropriate, especially I think if
6 the MACE information is making it difficult to ferret out MI
7 and mortality, and other things that may not be clear from
8 that data, then, maybe the angiographic data is the
9 appropriate primary endpoint.

10 DR. FITZGERALD: I don't think you can loosen the
11 input and loosen the output at the same time. I think if
12 you are going to loosen the input for studies to be
13 facilitated a little bit more efficiently, then, I think you
14 have to tighten up the endpoint, and I think tightening up
15 the endpoint would mean, at least for me, 9-month
16 angiographic follow-up with continuous variables for MLD.

17 I think we have seen and have learned from a lot
18 of these trials that there is a lot of variation between
19 MACE, the clinical endpoints, and some of the hard-core
20 objective data, and I think to go ahead and either postulate
21 another surrogate endpoint here is not appropriate since we
22 are already loosening up the trial to start out with. I
23 think we tighten up the endpoint.

24 DR. OESTERLE: Peter, you have been remarkably
25 quiet about intravascular ultrasound. For people who don't

1 know, Peter is probably one of the top three or four people
2 in the world in the techniques of intravascular ultrasound.

3 One of the issues that I have kind of wondered
4 about, about stents and how you evaluate stents -- and this
5 gets back to some issues that were brought up in the first
6 question about what should be some of the standards for
7 recoil, and really the issue is what is the recoil in vitro,
8 and there are some things that I sometimes worry about from
9 the world of quantitative coronary angiography. We have one
10 of the world's experts here in Jeff Popma on that.

11 Maybe the two of you could say a few words about
12 this, because I have wondered always about this and whether
13 we are really learning everything we need to learn from
14 angiography and would we actually get a lot more incremental
15 information that would be even more precise by doing
16 ultrasound analysis.

17 Again, for people in the room who don't do this,
18 it might sound barbaric, but it is a pretty straightforward
19 and nonbarbaric event, not that expensive. Do you have any
20 thoughts about that?

21 DR. FITZGERALD: For those who don't know,
22 intravascular ultrasound is a catheter-based tool that goes
23 in and from with inside the artery, gets a view of the
24 plaque and the stent and the vessel itself.

25 I think it does provide very useful information

1 that is complementary to the angiogram. I do, however,
2 worry about two factors, and that is the methodology of how
3 you actually analyze these at core laboratories and the
4 biological variation that is inherent to the measurement
5 that you are making.

6 I don't think that there is enough experience
7 right now with intravascular ultrasound to be able to
8 characterize the methodology and the biological variation,
9 so that we can postulate effective sample size if you are
10 going to make intravascular ultrasound the primary endpoint.

11 So, part of the reason I am being quite a little
12 bit about intravascular ultrasound, although I believe it is
13 very important for mechanistic understandings, I don't think
14 it is mature enough yet to be used as a primary endpoint.

15 Certainly, we have seen many trials that have used
16 it as a secondary or even a tertiary endpoint. I think that
17 is important, especially as we get into some of the targeted
18 restenosis therapies for in stent restenosis, knowing
19 exactly what is going on at the edges of the stent.

20 Again, intravascular ultrasound is the perfect
21 tool to understand those mechanistic flavors, but we don't
22 know enough about intravascular ultrasound to make it a
23 primary endpoint, and that is why I am still a believer that
24 the continuous variable of the angiogram should be.

25 I do, though, support that ultrasound should be

1 subset studies with well thought out information that you
2 are going to derive from the ultrasound, and I think several
3 of the trials have intravascular ultrasound incorporated,
4 but keep it beneath the wraps and keep it as a secondary or
5 tertiary objective.

6 DR. CURTIS: Is it not true that most of the stent
7 trials that have been done already where there was
8 angiography, that it was done at six months?

9 DR. BRINKER: More recently at nine months.

10 DR. CURTIS: More recently at nine.

11 DR. BRINKER: Yes.

12 DR. CURTIS: I am just wondering. You have
13 expressed that opinion I think twice now about the nine
14 months, and maybe that is the general consensus, but I just
15 wanted to bring it up. Is it really important to wait that
16 long?

17 DR. BRINKER: I actually like the idea, and if you
18 looked at -- I don't know whether it is your data, Jeff, or
19 Rick's -- that show that the accrual of actually events
20 between six and nine months, or actually between six months
21 and a year, was not small, and that is a bit of anathema to
22 most of us who feel like that if you didn't get anything by
23 six months, you were home free.

24 I like the nine-month idea, and I agree you,
25 Peter, exactly both about the angiography and about

1 reserving IVUS, since most of the other stent studies did
2 not use IVUS as a significant endpoint, and that IVUS -- you
3 have to do an angiogram basically as part of IVUS anyway.
4 It is not something that you can say, well, I am not going
5 to do any coronary angiography, I am just going to stick
6 this thing in here without even looking in the coronary.

7 So, if you have the angiographic data and you have
8 it at nine months, I think that is the best that can be
9 done, and I am hoping actually that maybe we could, in the
10 future, get away from the angiography all together, which
11 might be a little bit different than most people think, but
12 again, if you just allow me to say that for the look-alike
13 stents, the me-too stents which you may or may not have a
14 great deal of enthusiasm for, but for a company that is
15 looking to do that, we are subjecting patients to a clinical
16 trial.

17 There is not much in it for them to get a me-too
18 stent, and if this also requires them to undergo a non-
19 clinically indicated angiogram, one wonders about the ethics
20 of this, if it is just to get a similar, but brand-different
21 device approved.

22 So, I would hope that over time we could be better
23 at the way we do things, and sort of like angioplasty, not
24 require any invasive follow-up once we get into the mindset
25 of being more comfortable with stents.

1 DR. CURTIS: The major way we are loosening things
2 up is by not having a randomized trial design for these me-
3 too things, where you don't have to have one patient get the
4 me-too stent and one patient get a standard stent. That is
5 the thing that is changing in terms of indications for doing
6 the procedure, the types of vessels you are talking about,
7 that is all the same.

8 I kind of wonder whether or not, well, you defer
9 to the interventionalists about how to go about doing this.
10 The issue with the MACE, the major adverse clinical events,
11 the points raised up there about 30 days, you know, is a 30-
12 day MACE follow-up, a 9-month angiography a good way to go?

13 DR. BRINKER: If you do 9-month angiography, you
14 are going to get 9-month MACE pretty much. I think that the
15 major reason we do angioplasty is to help alleviate angina.
16 We may think we are doing it, but there is no real data that
17 most of the angioplasty we do saves lives or prevents
18 myocardial infarction, at least over a year.

19 The primary reason is angina. That is why, from a
20 safety point of view, I certainly don't want an excess
21 number of deaths or infarcts in a stent case, I am most
22 concerned actually about whether the stent is doing its job,
23 and that is predictively eliminating angina.

24 That is why I think that the TLR is a major
25 concern for me, and I think you would only know that at

1 later follow-up.

2 DR. DOMANSKI: I feel compelled to weigh in on
3 this MACE business again. It's a great acronym, but I think
4 it is not a great endpoint, and I am concerned about the FDA
5 using it for the following reason.

6 If you look at the trials other than EPISTENT, the
7 trend is towards increased mortality and MI in all of them
8 with stent placement. In fact, if you use the endpoint
9 MACE, it looks very good because you add this target vessel
10 revascularization, which is an extraordinarily soft endpoint
11 which can be manipulated very easily because these trials
12 aren't blinded.

13 So, what you do is you take two very bad things
14 and you drown out their effect in a composite endpoint that
15 includes one thing that is strongly positive. The truth is
16 that perhaps the more honest way of doing it is to throw
17 away the death plus MI, and simply use target lesion
18 revascularization, because frankly, that is all you are
19 doing anyway. I don't think it is a good endpoint, and I
20 think the FDA needs to track that death plus MI as an
21 endpoint quite apart from target vessel revascularization.

22 It would be very interesting to see a good
23 metaanalysis, as a matter of fact, of that across the
24 trials. So, I really think that is a problem.

25 DR. CURTIS: So, don't lump all three together.

1 DR. DOMANSKI: You know, there is only one good
2 reason to lump them, and that is to make the death plus MI
3 problem go away or appear to. Otherwise, why lump them? I
4 mean the only thing that is working is target vessel
5 revascularization, so just use that as your endpoint.

6 DR. BRINKER: I don't have a problem with looking
7 at them separately, but we have to remember how we are
8 looking at stent versus stent. In the older days, we were
9 looking at stent versus angioplasty, and where the immediate
10 effects or the hospitalization effects were important in
11 terms of the difference between death and at least
12 myocardial infarction, urgent surgery, things of that
13 nature.

14 Now that we are comparing two stents, there is a
15 wash pretty much between the acute complications of
16 angioplasty, and therefore, the target lesion
17 revascularization becomes more important.

18 DR. DOMANSKI: I think what you have got is trials
19 that are simply underpowered to show the more important
20 endpoint, which is death plus MI. I don't think it is a
21 wash at all. I think they are underpowered studies.

22 The way you make it look better is you pick an
23 endpoint that you have the power to do, that makes something
24 else, the complications look innocuous, which is what has
25 been done.

1 DR. BRINKER: But we are looking at stent versus
2 stent. If there is a reason to think --

3 DR. DOMANSKI: Well, you don't know the answer,
4 though, Jeff. If you are doing that, maybe you ought to be
5 looking at death plus MI and stent versus stent with
6 suitably powered studies. I am being a little bit the
7 devil's advocate, but I am pointing out that MACE is a poor
8 endpoint in my view, and that is why.

9 DR. LASKEY: Jeff, if we follow through with your
10 reasoning, why don't we just wait 12 months to see if the
11 patient has angina, and if not, then, we are back to the
12 clinically driven endpoint, and are the events enough to
13 statistically defend that? Agreeably, they are increased
14 between six and 12 months, so now you have a little more
15 power to detect what previously was undetectable.

16 DR. BRINKER: The first part of your question, I
17 think that again from my probably too long experience with
18 the panel here, I would like to see at least a subset of any
19 patient getting a new stent, even if it's a me-too stent,
20 see an angiogram to make sure there is nothing deleterious
21 like an aneurysm or wearing out or something, that is
22 totally unpredictable by any of the usual kind of
23 engineering and baseline clinical data.

24 So, I would like to have at least a caution of
25 those patients. On the other hand, despite my difficulty

1 with asking patients to undergo angiography, again, for
2 something that is clearly not necessarily in their best
3 interest, unless we are I think very disappointed in how we
4 look at angina, and I don't know that we have a good
5 comparator by which we can say that the recurrence of angina
6 at nine months is less or the same in this group that is not
7 going under angiography as it was in the other group of
8 previous stents.

9 Even target lesion revascularization, for all the
10 things we said before, suffered a bit from the fact that
11 there was angiography. So, my bet would be if you don't
12 angiography, and if you have a group of investigators who
13 have a vested interest in seeing this new stent perform very
14 well, there will be minimal target lesion revascularization,
15 and when you are looking at a smaller cohort of patients, to
16 begin with, I think that that is potentially a dangerous
17 proposition.

18 DR. CURTIS: I think that is an excellent point.
19 I think we have to look at death and MI because those are
20 major adverse things that can happen to a patient. On the
21 other hand, none of these new stent trials are going to be
22 powered enough to tell a difference, because they are all
23 going to be small.

24 So, then you are left with, in terms of the major
25 clinical events, you would follow that target lesion

1 revascularization, which is a very soft endpoint, which can
2 be manipulated, and in which case then I think you are left,
3 as you said, with catheterization in at least some of the
4 patients.

5 DR. BAILEY: Could you just try to get more
6 objective measures of angina?

7 DR. CURTIS: That is a good question.

8 DR. BRINKER: We have gone through that stress
9 test. Many of our patients have more than single vessel
10 disease, even though one vessel is the only thing that is
11 being operated on, and the stress tests are just not that
12 good. I think most of us, when we considered other stent
13 trials in the past have pretty much given up on the thought
14 of the stress test as being the defining parameter.

15 DR. GILLIAM: Do you think nine months is enough
16 to consider long term? Maybe I am just again bringing
17 electrophysiology into this, but we don't consider nine
18 months particularly very long. I understand the acute and
19 the immediate when we look at restenosis, but if you look at
20 so-called long term complications of the devices that we
21 implant, that probably are going to stay there forever, I
22 don't think any of us have figured out a way to get these
23 things out.

24 DR. BRINKER: The only problems that have been
25 associated with stents really have been restenosis and

1 occlusion.

2 DR. GILLIAM: How do we know?

3 DR. BRINKER: In the 10 years that people have
4 been looking at these things.

5 DR. OESTERLE: Ten years of experience, and no one
6 has ever reported a late complication of a stent. To my
7 knowledge, I have never seen stent erosion, stent migration.
8 He is right. We know that from probably several million
9 stent implantations.

10 DR. BRINKER: And there is a diminishing return in
11 terms of picking up new restenosis. I think nine months is
12 an excellent compromise, and even more to the point, none of
13 the other angiographies were required in other stent studies
14 after nine months. Clinical follow-up is often asked that a
15 year, but you can file before a year clinical follow-up.

16 DR. OESTERLE: Do you think it is fair to ask for
17 nine months? Jeff Popma did most of the angiographic
18 analysis on a lot of these trials, but most of them were not
19 nine-month trials. It seems they are going to confound the
20 data once again to all of a sudden in learning in nine
21 months now, when we have had six months for everybody else.

22 DR. BRINKER: I think it is nine months for the
23 last couple of trials. Is that right, Jeff?

24 DR. POPMA: Yes. Some of the trials were designed
25 earlier for nine-month angiographic follow-up, but because

1 of speeding of the PMA process, some of the angiograms were
2 done earlier within the window period, so it is probably not
3 fair to say that we have had any angiographic follow-up
4 right now. The mean is at nine months. I think they have
5 tended to be earlier even though they were designed to be a
6 little bit later than that.

7 From what we know from stenting, however, what we
8 see at six months is the same or the angiogram gets a little
9 bit better over the nine to 12-month period of time. There
10 is almost retraction of some of the tissue within there as
11 we looked at some of the serial angiographic studies.

12 The real issue is does the six-month angiogram
13 pollute the clinical decisions made about target vessel
14 revascularization, so that if one looks at a six-month
15 angiogram, sees there is a 60 or 70 percent stenosis, says
16 that must be tight even though the patient is asymptomatic
17 and has a negative exercise test, and then dilates it, then,
18 we get an overgenerous target vessel revascularization rate.

19 I think the main reason to back out the angiograms
20 is not to get a different number from the follow-up
21 angiogram, I think they will be pretty much the same, but to
22 avoid the pollution of the clinical decision based on seeing
23 the angiogram.

24 DR. OESTERLE: I am guessing that people who look
25 at this at nine months and see a 70 percent are less likely

1 to dilate than they would have at six months?

2 DR. POPMA: But that patient, by that period of
3 time, the angiogram is done after the clinical endpoint is,
4 so they would have come back with recurrent symptoms or with
5 a positive exercise test and undergone early angiography.

6 The whole point of the 270-day or the nine-month
7 angiogram is that the clinical endpoint is assessed before
8 the angiogram is done, and then you do the angiogram to do
9 the mechanistic correlation.

10 DR. OESTERLE: Jeff, of course, had mentioned that
11 he would be measuring MACE at nine months when you did the
12 angiogram. Did you say that?

13 DR. BRINKER: But you made your clinical decision
14 a week before the angiogram, say this patient does not have
15 an indication for revascularization no matter what the
16 angiogram shows, that that clinical arm, that follow-up
17 stops, and then a week later he gets his angiogram.

18 DR. OESTERLE: I can guarantee you that what he
19 decided and what he did are going to be two different things
20 in that situation.

21 DR. CURTIS: Why couldn't you do that at six
22 months as well as at nine months, end your clinical data at
23 six months, and then do the angiogram the next day?

24 DR. POPMA: You could except that when we don't do
25 angiograms, we know that there is a continuation of clinical

1 presentation that relates to target site revascularization
2 that occurs out to 210 and probably 240 days. So, even
3 though we think the angiogram has stabilized, Dr. Kuntz, in
4 his slide earlier on, had mentioned the reasons why there is
5 a clinical delay, but in point of fact, only two-thirds of
6 the events have occurred right at six months, and that there
7 is still another third of the events that occur after six
8 months up until nine months.

9 In fact, in STARS and some of the other data sets
10 from the randomized trials, they even go up a little bit
11 further, even out to 12 months, but most of the events are
12 finished by nine months.

13 So, you could exactly as you have suggested, to
14 have the patient come back at six months, measure the
15 clinical endpoint, and then do the angiogram, and call that
16 the mechanistic correlation.

17 The problem with that is that you would be missing
18 a third of the events that would occur if you continue the
19 trial out to nine months.

20 DR. CURTIS: Let's say we do it after nine months.
21 Is there good comparison data available? Because you were
22 saying a lot of the patients, even though it was designed to
23 go out to nine months, had their angiograms earlier. If we
24 don't have a large group of patients --

25 DR. POPMA: We do have those because you can

1 follow them out. The only issue is about the pollution of
2 the early angiograms on those nine-month clinical events,
3 but they were really performed with the same ascertainment
4 rate in both groups.

5 DR. CURTIS: We don't have nine-month angiograms.

6 DR. POPMA: We don't have nine-month angiograms,
7 but we have nine and 12-month clinical data, which is the
8 same between the two groups, and if the same number of
9 angiograms are performed in both cohorts, then, the same
10 amount of pollution should occur in both events, unless
11 there are investigator bias, which we have not been able to
12 show so far.

13 DR. CURTIS: I am just a little bit concerned that
14 we are trying to design a trial here where we can compare
15 what is happening now to a large group of patients who have
16 already been in some sort of a database or registry, but now
17 we don't really have that if we are changing --

18 DR. POPMA: It will depend upon the database, and
19 I will just use this as an example. If you went to use the
20 dynamic database, which does not have angiographic follow-
21 up, then, whatever registries may want to tack onto the
22 dynamic registry are going to have to have clinical follow-
23 up as the primary endpoint.

24 If, however, we say we have got enough information
25 and we are comfortable about the correlation between the

1 six-month angiogram and the nine- and 12-month clinical
2 events, where we would allow a stent to come through just
3 with that registry format, then, we would have to do OPCs or
4 benchmarks based on the current data that has already been
5 done, and then you have to use societies to help give us
6 what those benchmark guidelines would be, so there is
7 clearly two different things.

8 DR. OESTERLE: Let's just take the Multilink.
9 Wasn't that six-month data on Multilink?

10 DR. POPMA: Maybe Gary can speak to that. It's a
11 little complicated, so I will let Gary speak to that.

12 MR. JOHNSON: By the protocol, it was supposed to
13 be nine month, but indeed it was something less than that,
14 about eight months, because people were even brought in
15 sooner.

16 DR. POPMA: That didn't seem so complicated.

17 DR. STONE: I think some of the confusion may be
18 because we are trying to design endpoints here that will
19 satisfy our desire to want to look at every single endpoint,
20 but what I would suggest is to make this much simpler.

21 I think that some of us have tried to make a
22 cogent argument that the angiographic endpoint is going to
23 be the hard science here, and that there is a lot of
24 problems with the clinical endpoint. So, what I would
25 suggest is that at six months, we know that by six months

1 restenosis has stopped pretty much, and as you have heard
2 there may be a little bit of retraction beyond the six-month
3 period, what I would suggest is using the six-month
4 angiographic endpoint as the marker of a stent to reduce
5 restenosis, and that is what TLR or TVR is a surrogate of.

6 So, if we are happy with that as the primary
7 endpoint, we can get angiographic follow-up at six months.
8 We don't care as much about TLR or TVR. It would be nice to
9 track it and look at it, but that is not what we have to
10 base approval on.

11 The second issue is death and myocardial
12 infarction, and I would agree wholeheartedly with Dr.
13 Brinker's comments that none of the stents decreased death
14 or MI, but, in fact, all the stent versus stent trials, even
15 the large randomized trials are woefully underpowered to
16 show differences in death or MI.

17 So, no matter if we have a 400-patient registry,
18 we are not going to be able to expect differences in death
19 or MI. All you can have a working group do is pick a
20 certain kind of confidence interval, so that as long as
21 death and MI is not above 4 percent or 5 percent, or
22 whatever, you will be happy that that is reasonable based on
23 your bench data, that that is reasonable to go ahead and
24 approve it.

25 So, again, I think if we could agree that the

1 angiographic endpoint should be the primary endpoint, I
2 personally don't see a reason to push things to nine months
3 because I can then make the argument let's push things to 12
4 months, and, in fact, you have pushed it two years, then,
5 you can really answer your clinical question that that is
6 not the goal here. It is to say when will the stent be safe
7 to be able to allow it to go on market.

8 DR. FITZGERALD: Just to make the comment that I
9 wasn't being so adamant, if I misspoke, the nine month was
10 sort of secondary, and the one thing I do want to
11 reemphasize is I just like having an MLD, a measurement, as
12 the distribution that you are going to compare it to the
13 parent distribution, which you have a lot of data on, and I
14 think it is important to have that be the endpoint in this
15 trial format. Whether it is six or nine months, I think we
16 have to let the statisticians help us with that, but the
17 nine month, at least will help sync up, adjust for that
18 phase delay that we have seen between the clinical findings
19 and the objective findings.

20 DR. LASKEY: So, what do we do with two different
21 endpoints on the same patient? What do we do with six-month
22 data and nine- or 12-month data, and which do we have more
23 credibility in?

24 DR. OESTERLE: I think everyone has said, Warren,
25 that most of the people believe that the six-month

1 angiographic follow-up is the least ambiguous marker of
2 outcome. I think that has been said here clearly by
3 multiple people that it would be nice to be able to do this
4 by nine-month TVR or TLR, but I don't think anyone is
5 suggesting that that is what we should be doing or at least
6 the majority of people are not suggesting that.

7 DR. BRINKER: I am not sure I am not suggesting
8 that. Again, going back historically, it is always seen
9 that clinical events have rule the decisionmaking because it
10 is what is actually happening to the patient, and this would
11 be setting a bit of a precedent to say that angiography at
12 six months will establish the safety and efficacy of a
13 stent, not that I am opposed --

14 DR. OESTERLE: No one said that was going to
15 establish the safety. It was just an issue of what is an
16 appropriate surrogate, a less ambiguous surrogate for TLR.
17 That has nothing to do with safety.

18 DR. BRINKER: Let's say efficacy. The problem I
19 have with that is that why not, for the covered stents, or
20 for any other device, for that matter, say that six-month
21 angiography should be the primary endpoint of these studies,
22 and I am not sure. Maybe it should be, and I think that
23 dissociating the clinical events and clinical follow-up, and
24 making the angiography the primary endpoint, may be
25 problematic.

1 DR. OESTERLE: I think that is correct if you have
2 a completely novel stent design and a novel indication.
3 Again, we are talking about something that we know a lot
4 about. We have a huge data set already on it, so this is
5 really a different issue from covered stents. I wouldn't
6 bring that in and confuse the issue. It is a different
7 conversation altogether.

8 DR. CURTIS: I think we have beat this six- to
9 nine-month thing to death, and what I would like to do is go
10 ahead and move on and see if we could cover one more
11 question before we take a break.

12 No. 7. Design and Analyses Options. Could
13 alternative approaches to design and analysis such as
14 borrowing of strength (Bayesian) or appropriate choice of
15 confidence intervals for equivalence studies be considered?

16 Anybody who understands that question is free to
17 answer it.

18 DR. BRINKER: That excludes me. I think it is
19 worthwhile pursuing other forms of summarizing it and
20 analyzing, presenting the data. I would encourage the FDA
21 to pursue the Bayesian framework, particularly as a way of
22 perhaps getting a better understanding of the level of
23 evidence that they want to have.

24 There really isn't that much controversy as might
25 be suggested in the packet between Bayesian and Frequentist.

1 Some Bayesians believe in randomized trials, as well.

2 I think it is not whether to use a Bayesian
3 analysis or not. The question is what studies need to be
4 done and even if you are doing a Bayesian analysis, you need
5 to separate the information that comes from your study. It
6 is a perfectly judgmental question how much you are willing
7 to trust prior data. You don't get something for nothing if
8 you use the Bayesian approach. There is no magic that
9 occurs. You get exactly as much information as you put into
10 your prior.

11 So, obviously, different people will have
12 different opinions about the validity of the prior. So, it
13 is more a question of whether you formalize this prior
14 information or whether you sort of do it internally based on
15 your own personal experience.

16 It would be nice to have perhaps a conversation
17 about this, but I don't think is perhaps the right forum for
18 it other than to say that it is certainly worth pursuing.

19 DR. ZUCKERMAN: I don't see Greg Campbell here
20 from FDA, so maybe we can help you a little bit more with
21 what was implied by this question.

22 The panel up to now has considered the OPC idea in
23 lieu of a randomized trial for a wannabe stent, for lack of
24 a better definition. However, I believe Dr. Campbell would
25 like you to consider another option which one does assume

1 the Bayesian approach would be, for example, a 3 to 1
2 randomization of new stent to the control.

3 The advantage to the manufacturer there would be
4 because you would have the control running in that trial,
5 potentially, if there were changes in lesions approach,
6 i.e., a lot of protocol deviations, the manufacturer could
7 be somewhat protected, et cetera.

8 I mean right now the panel has looked at two
9 extremes, one as staying with the randomized trial, at the
10 other end is adoption of OPCs, but potentially there is
11 something in between. In fact, this was pretty widely
12 discussed at the Bayesian meeting that the Agency put on
13 last month.

14 DR. BAILEY: That is certainly important to
15 educate people as to the other possibilities, the
16 intermediate possibilities as far as preserving some
17 semblance of randomization.

18 I think it is important not to assume that the
19 randomized trial is inherently burdensome. Certainly the
20 ones that look for very rare clinical endpoints are going to
21 be very large, but we have talked about other endpoints that
22 have much more precision, and it is important to separate
23 the issue of randomization, the randomized trial versus no
24 randomized trial versus how you analyze the data. I don't
25 think we should get carried away with discarding the idea of

1 randomization.

2 DR. CURTIS: I think that approach, the 3 to 1
3 type of randomization ratio is a perfectly acceptable
4 alternative way to handle this. I think we would all agree
5 with that.

6 DR. BRINKER: Is it possible that there might be
7 more than one option for a manufacturer to choose from?

8 DR. ZUCKERMAN: I think that is the key point, one
9 size doesn't fit all. There might be some advantage to
10 considering a Bayesian approach. I think the key point made
11 at the meeting last month was that if a manufacturer does
12 want to go with a Bayesian approach, we do need a lot of
13 planning upfront to really look at the clinical trial
14 design.

15 However, we have recently approved a stent
16 partially utilizing a Bayesian approach, and as mentioned
17 here, we are looking forward to continuing to develop
18 potentially this pathway.

19 DR. BAILEY: I am sure it is intended that it
20 would be very important to understand the Frequentist
21 properties of your resulting procedures, not just the
22 Bayesian one.

23 DR. VETROVEC: This might actually be very good,
24 because once you get through Questions 4 to 8, one of the
25 questions is going to be how might you apply the same issues

1 to stents that have mild to moderate variations from
2 currently accepted stents.

3 This might really be the intermediary to handle
4 that type of problem or that issue.

5 DR. CURTIS: Let's look at the eighth question,
6 then, because that kind of ends this group of questions we
7 have been asking.

8 How could we better integrate postmarket
9 surveillance to contribute evidence to the approval process?
10 How can we best utilize registries such as NACI?

11 What kind of postmarket surveillance would be
12 useful, interesting, necessary?

13 DR. LASKEY: You are leading us with the way the
14 question is formatted. I would take away the message that a
15 registry is the way to do this and that a NACI registry,
16 which is probably the most contemporaneous, would be the way
17 to go for postmarketing.

18 Whoever wrote this question, I think wanted the
19 reader to get the concept of registry equated with
20 postmarketing surveillance, and it's successful. That is
21 the way I interpret this, and I actually agree with it. I
22 think that it is a very useful form, although the economics
23 of it are formidable, I would think.

24 DR. TRACY: Once you start looking at postmarket
25 surveillance, you are stuck with clinical outcomes, which is

1 fine. I don't know enough about the NACI registry to know
2 that it is really everything out of those centers, that it
3 really is as good as it seems to be, and I would have to
4 rely on other people to tell me that it really is capturing
5 all the data from these different centers.

6 But the postmarket surveillance, it does seem
7 possible that you could be very specific about what pieces
8 of information you want to collect and what patient
9 population, over what time, and I think that would be things
10 that would be of interest that would be definable, death,
11 MI, other things that would be quite obvious, that would be
12 important to continue observing.

13 DR. OESTERLE: I am kind of confused. When a
14 device is approved -- I am sorry if this is stupid -- but
15 once a device is approved, then, you are going to do some
16 postmarket surveillance as a rule, right, that usually comes
17 after approval of the device?

18 But you are asking how that is going to contribute
19 to the approval process. It seems like there is an internal
20 irony here that I am not getting. The device is approved,
21 you do postmarketing surveillance, and you want to know how
22 that information is going to contribute to the approval
23 process?

24 DR. CURTIS: I think the way I read it is that if
25 you have postmarket surveillance, which then was data that

1 was gathered, could you then use that data --

2 DR. OESTERLE: For the next device? I don't know,
3 it doesn't seem very fair, because then you are asking the
4 next company to jump through a hoop that the previous
5 company didn't.

6 DR. VETROVEC: I may be wrong -- and the FDA needs
7 to correct me -- in the most recent revision of the FDA
8 process, there is some encouragement to do more
9 postmarketing surveillance as a tradeoff to more long-term,
10 premarketing studies with the idea that the Agency could
11 conceivably change the decision on a device late.

12 DR. CALLAHAN: I think that is an overextension,
13 that the postmarket approval and postmarket surveillance is
14 intended to supply data much as is indicated or inferred in
15 this process, but the premarket process, the new law was not
16 meant to dilute the premarket process in lieu of a
17 postmarket, but just to recognize that there is different
18 data sets and that perhaps the postmarket data set, as is
19 inferred here, could feed back into the premarket, not in
20 lieu of.

21 DR. TRACY: I think six months, I mean we have
22 been talking about endpoints that are six and nine months
23 long, which as Mike pointed out, for EP, that would be
24 nothing since our procedures take a month to perform. You
25 know, by six months out, you have hardly gotten any

1 information. So, for these procedures, if you have approval
2 based on six to nine months worth of data, I think it is
3 important to know what happens at 12 and 18 and 24 months,
4 and I think that may perhaps not affect it, may not be a
5 hoop that the next company doesn't have to meet the 24-month
6 data, but that may be information that is very critical in
7 understanding what these devices actually do.

8 DR. OESTERLE: I don't have any argument with
9 that. I am just saying that it doesn't help with the
10 approval process per se. It is clearly valuable
11 information.

12 DR. GILLIAM: It may help if we find that 24 and
13 36 months out, there may be some adverse clinical events
14 associated with stents, that because we have not looked at
15 it in any really precise way that could show itself.

16 We say that stents have been around for 10 years,
17 and we know that they don't have any problems, but do we
18 know that? Have we looked to see? For instance, something
19 as simple as the coronary artery bypass graft surgery in
20 people with stents versus people without stents?

21 Is there an increased complication rate in people
22 who have stents?

23 DR. OSTERLE: I think those data are available,
24 frankly. What you are suggesting is correct which is that
25 if we put a stent in and, eight or nine years later, we find

1 out that it is defective, simply like the Bjork-Shiley
2 valve, it becomes a recall, basically, and that becomes a
3 surveillance issue for those people in the FDA and all sorts
4 of people get involved.

5 That would be appropriate. But that wasn't the
6 question. The question was how does it help in the approval
7 process, a completely different issue.

8 DR. GILLIAM: Other than it identifies potential
9 things. I think the Bjork-Shiley valve was approved but,
10 certainly, the fact is that we were, in some ways, watching
11 for potential complications for it.

12 I am suggesting that there could, perhaps, be
13 complications associated with a stent given that we are not
14 looking at them in any real way. You don't have to have a
15 stent fly out of the chest for it to cause problems two to
16 three years after it is in. I mean, I don't know.

17 DR. STUHLMULLER: I think part of the intent of
18 this question, and maybe Bram and Dan can clarify this, is
19 it gets at the issue of, the labeling says that data exists
20 for up to point X and is part of this the issue, then, that
21 you are going to get X plus Y so that you come up with a new
22 time frame so you can revise the labeling.

23 Is that part of the intent of the question and is
24 postmarket studies a reasonable way to alter the labeling?

25 DR. ZUCKERMAN: Yes. Let me review for you what

1 is currently being required for the approved stents.
2 Essentially, we require that at least 75 percent of the new-
3 stent cohort be followed yearly out to five years. In that
4 cohort, we would expect that there would be a continuance of
5 independent clinical adjudication of events and also that
6 angiographic films for revascularizations be sent back to
7 the core laboratory.

8 The potential incentive to have good postapproval
9 follow up up to five years would be the question that we ask
10 the panel, what potential additional labeling indications
11 could a manufacturer receive. Right now, the indication is
12 for six months.

13 DR. BRINKER: How big is the cohort usually that
14 is being asked for for a long follow up?

15 DR. ZUCKERMAN: If we assume that the average
16 patient in trial is about 300 to 350 patients, about 75
17 percent of that. So that is about 250 or so.

18 DR. BRINKER: I have been in a lot of stent trials
19 and I don't remember anybody asking me for five-year follow
20 up on any of my--maybe I am just one of that lucky
21 25 percent.

22 DR. ZUCKERMAN: No; I hope you are one of the
23 better centers that is going to be asked.

24 DR. GILLIAM: Is going to be asked?

25 DR. ZUCKERMAN: Should have already been done.

1 But this is a condition of approval, that we continue follow
2 up yearly.

3 DR. BRINKER: It seems to me that the same type of
4 conditional postmarket surveillance should be applied to
5 this group of patients as well. And they would eventually
6 earn the same labeling. I think that the implication that
7 there should be a specific group that could do this, like
8 NACI or CRO or something like that is probably not
9 appropriate.

10 It seems to me that if they are part of the study
11 group, that the sponsor should bear the responsibility for
12 doing that.

13 DR. ZUCKERMAN: Just as a case example, that has
14 happened with respect, for example, to the Palmaz-Schatz
15 stent. Initially, the label talked about the six-month
16 data. Now, the one-year data is referenced in the label.

17 DR. CURTIS: Why don't we take a break now and
18 reconvene at 3:20.

19 [Break.]

20 DR. CURTIS: Question No. 8. There is a
21 subsection underneath it that is in our panel pack where we
22 were asked to readdress the questions for a minor or
23 moderate modification to an already approved stent. I have
24 no intention of going back through each question
25 individually about that, but I think, just in general, since

1 the preceding questions had to do with whether or not a
2 randomized controlled trial was necessary, what kinds of
3 comparisons you would use, endpoints and design analysis
4 options, let me just see if anybody has any thoughts about
5 what you would say about a minor or moderate modification to
6 an already approved coronary stent.

7 One thought I had about this is that if you had a
8 stent that was already approved and there was a minor design
9 modification to it, to get back into the cath issue, I don't
10 think you would have to have a whole set of patients cathed
11 because of that if you were following up a group of patients
12 if it were truly a minor modification in the design. It
13 depends on what your definitions are there.

14 Moderate modification probably well could require
15 that. But, in terms of everything else that was listed
16 there, in terms of having a patient cohort you followed,
17 comparing it to some sort of a database, registry, OPC,
18 whatever, I don't think there would be really much of a
19 difference whether it were a minor or a moderate
20 modification except for the thought I had about not needing
21 to cath patients for a minor change in the stent design.

22 Any other comments?

23 DR. GILLIAM: It comes down to, I guess, what is a
24 minor modification. Maybe I am just too simplistic. I
25 mean, it is a piece of metal that expands and sticks in the

1 vessel. I don't know. Maybe there are minor modifications
2 they can make of them now but it seems like if you change it
3 in any real way, it is a pretty major stent change.

4 DR. CURTIS: You have to have definitions for what
5 that is. I would imagine anything different about the
6 stent, at all, is a modification.

7 DR. GILLIAM: But if you change metals--

8 DR. CURTIS: That is not minor.

9 DR. GILLIAM: I wouldn't consider that minor, if
10 you change mesh design or--that is, essentially, another
11 stent. I guess if you can see by making it a millimeter
12 longer or something to that nature.

13 DR. TRACY: I guess so, Rosie. We have three
14 electricians arguing about what the difference between--come
15 on. If an engineer told me that metal X was the same as
16 metal Y in every single parameter of functionality and so on
17 and so forth, I would have to rely on their judgment.

18 But if you have something that is going to radiate
19 the vessel, some kind of a thing that is radioactive, that,
20 I think anybody would agree, is a major modification. I
21 think that is the kind of decision that somebody who
22 understands the engineering of these devices would have to
23 make that kind of a distinction, but I think what Anne said
24 is if it really is minor, then the hoops should be pretty
25 minimal.

1 If it is a major modification, then your
2 randomized trial may be, with some Bayesian modification, 3
3 to 1 randomization or something like that depending on how
4 big the difference is between what you are looking for
5 approval on and what is already approved.

6 DR. CURTIS: Let's move on to new indications for
7 a standard coronary stent. "For other indications,
8 restenotic, saphenous-vein graft, abrupt and threatened
9 closure, could we reduce the size of adjunct registries
10 through alternative methods of statistical assessment, for
11 example Bayesian?"

12 Question No. 9 is, "What is the appropriate
13 clinical-trial design for expanding the indications for a
14 standard coronary stent to restenotic lesions, small
15 vessels, saphenous-vein grafts and acute myocardial
16 infarction?"

17 We did kind of deal with this already. My
18 impression, from what the interventionalists here on the
19 panel were saying, is that when stents are studied, they are
20 studied for restenotic lesions and saphenous-vein grafts and
21 abrupt and threatened closure and that small vessels are the
22 major place where, maybe, standard stents are not currently
23 being studied.

24 DR. BRINKER: I think that if the gist of the
25 question is how can we work in some significant

1 representative sample in a non-randomized study to allow for
2 some confidence in giving the same approval for this stent
3 as other stents, I like the idea on the previous slide of
4 using some directed enrollment and making sure that the
5 cohort that you choose has enough of these indications to be
6 able to be looked at with some degree of confidence to data
7 that Rick Kuntz would gear up from his analysis of similar
8 kinds of registries and correct for patient parameters.

9 This is not going to be easy when you limit the
10 total number of patients, but I am not sure that you really
11 have to--by doing away with the control group, I am not sure
12 that you have to really limit the total number of
13 investigational-device patients very much at all.

14 In fact, the onus is on the control group and if
15 that is gone, you could keep basically the same size or
16 minimally different size groups and that should enable you
17 to use the same sort of methodology as for the previous de
18 novo ideal-lesion group.

19 As far as acute myocardial infarction, I don't see
20 that that should be segregated out. That, to my way of
21 thinking, shouldn't be considered a separate entity. Small
22 vessels, as I said before, I think that deserves at least
23 one good study.

24 DR. VETROVEC: May I ask how is it that there are
25 at least two stents on the market that are 2.5's already?

1 Can you explain that versus kind of this quandary that we
2 are saying nobody that small stents work?

3 DR. ZUCKERMAN: The labeling for those two stents
4 is for abrupt and threatened closure, not for de novo
5 stenting.

6 DR. CURTIS: Let's move on to No. 10. "When would
7 clinical data be appropriate to establish safety and
8 effectiveness of a modified stent delivery system and what
9 type of study design would you recommend?"

10 We talked a little bit about stent delivery
11 systems before but we have not really concentrated on that.
12 So here is our opportunity. How does the stent delivery
13 system fit into the issue of studying a stent? Does it
14 change anything about the way we design the trial? Is it
15 the same?

16 DR. LASKEY: The best example is the one mentioned
17 earlier where the transition from sheath to sheathless
18 systems occurred. Now that the vast majority of systems out
19 there are sheathless, there is this risk of technical mishap
20 or maldeployment or whatever euphemism is applied.

21 But I think that pertains to acute safety data so
22 that is pretty hard data, I would think. That should be a
23 fairly straightforward type of analysis up front.

24 DR. CURTIS: So, in other words, with your acute
25 outcome data, you are going to be studying the stent

1 delivery system as well as the stent.

2 DR. LASKEY: That's correct. I think it just
3 addresses the safety aspect of the procedure and the device
4 rather than efficacy. I'm not sure that the delivery
5 system, although Steve alluded to things that we really
6 don't understand, that may be important but, at least from
7 the very rough-cut look, clearly the delivery system and its
8 complexity or simplicity relates to the safety and
9 deliverability of the device.

10 DR. CURTIS: What about if you changed the stent
11 delivery system but you had the same stent.

12 DR. OSTERLE: I think it is a real issue. This
13 question, I keep reading it as what clinical data would be
14 appropriate, not when would they be appropriate. I think
15 the real issue is what types of clinical data would be
16 appropriate to evaluate the safety of the delivery device
17 because, again, my belief in using stents is that the
18 delivery device plays a major role not only in the acute but
19 in the long-term efficacy of the stent.

20 To give you an example is some stents are mounted
21 on balloons that are quite a bit longer than the stent,
22 itself. The balloon might be semi-compliant so that when
23 you deploy that stent, you actually have a lot of damage to
24 the vessel that is unstented on each end of that stent.

25 Other stents are delivered on balloons that are

1 modified so that, actually, the balloon tapers at the ends
2 of the stent so that you don't really have a lot of balloon
3 hanging out. We have never really looked at this very
4 critically, but I think it could play a role that is not
5 trivial in the TLR/TVR, more importantly, of the case.

6 So the question isn't when would these data be
7 appropriate since, of course, the answer would be always in
8 terms of establishing safety and efficacy of any stent. But
9 the question is what kinds of data would be helpful in terms
10 of trying to separate out stent delivery from the stent,
11 itself.

12 One of the questions for some of these stents
13 "wannabe" companies is that they may come into the market on
14 the "wannabe" balloon, as well. This, it seems to me,
15 becomes very problematic for the FDA, is to take a new entry
16 into the stent market who maybe comes in on a new balloon as
17 well and we don't know anything about the safety
18 characteristics of the balloon that is mounted on this
19 stent.

20 It is kind of a morass. I asked this question
21 this morning and I am still confused about it because, if
22 you do modify the stent-delivery system, you can very
23 seriously modify the safety and efficacy of the stent,
24 without question.

25 DR. BRINKER: The real question is do you need to

1 gather other information that isn't ordinarily gathered.

2 DR. OSTERLE: That is why I said the question
3 should be what data not when would it be, what data would be
4 appropriate if you modify it.

5 DR. BRINKER: I am not sure that, actually, you do
6 need much more data to cover all the bases. If you know the
7 successful delivery data, yes/no, and you have any adverse
8 effects, yes/no, and then you have the restenosis--

9 DR. OSTERLE: Let me give you an example, to
10 answer this question. Let's say that you just blindly look
11 at TLR, or TVR is a better example, and you change the
12 delivery system but don't change the stent. Lo and behold,
13 your TVR goes up. One erroneous analysis of that might be,
14 "Gee; that stent isn't very good," when, in fact, the excess
15 TVR was related to modification of the delivery catheter
16 with, perhaps, restenosis at the ends of the stents which
17 you would never know unless you actually did follow-up
18 angiography on everyone because they would all have
19 recurrent angina, one due to, perhaps, a stent-design
20 problem and the other due to delivery.

21 They are very different and you wouldn't know
22 that, necessarily, simply by measuring angina at the end of
23 six months or nine months.

24 DR. BRINKER: You would know that there was a
25 difference. If you are looking at clinical endpoints or the

1 angiogram, you would know that either there was an increase
2 in clinical endpoints over what you would anticipate is your
3 threshold or you would know from the angiogram that there is
4 a peculiar restenosis pattern similar to what we encounter
5 with the radioactive stent.

6 DR. OSTERLE: Only if you do the angiogram.

7 DR. BRINKER: I assume that we are talking about
8 with the context of what we have already discussed which
9 included the angiogram and some sort of clinical assessment.

10 DR. OSTERLE: You never agreed to that, though.

11 DR. BRINKER: Pardon me?

12 DR. OSTERLE: You never agreed to that the last
13 time around.

14 DR. BRINKER: Oh, yes; I did. I agreed to the
15 nine-month angiogram and a day-before clinical assessment.
16 You never agreed to that.

17 DR. VETROVEC: The other question that we haven't
18 dealt with, though, that gets at this issue is the percent
19 of time that an additional stent has to be placed at the
20 stent margin which might be a marker of what you are talking
21 about, the number of times you significantly dissected the
22 stent margin which required you to put another stent in.

23 I don't know how you would look at that and I
24 don't even know what the baseline number for that is but
25 that would get at what you are talking about and maybe

1 looking at the incidence of--Peter is not here but that may
2 even be an IVUS issue that would really be a subset of
3 patients IVUSed right at the time to see the incidence of
4 dissection right at the stent margin.

5 DR. BRINKER: Again, George, we are asking for
6 data now that we haven't asked for for other stents. I
7 think that you should really think about what we need to do
8 compared to what we have done in the past. I think these
9 are not scientifically irrelevant issues but, from a
10 clinical point of view, if there was a big difference in the
11 way a system was performing, we should be able to detect
12 that using the same kind of scenario that we are using now.

13 DR. VETROVEC: Let's suppose, over the next six
14 months, it turns out that one of the stents on the market
15 has a recognized increased incidence of distal stent tear.
16 I don't know that this is going to happen, but let's just
17 suppose that. Should we, then, act for the next six years
18 that we don't know that that is an issue and not, in some
19 way, incorporate that into trying to make the process better
20 for future stents for patients?

21 DR. BRINKER: I think if you find a problem that
22 is existent and you work out the reason why that occurs,
23 that that new knowledge should always be used to direct your
24 thinking about everything. On the other hand, to say that
25 there is a hypothetic that there might be a problem.

1 Of course, we have had this hypothetical before. We
2 had the hypothetical when we had longer balloons. We had the
3 hypothetical when we had long balloons that were high-pressure
4 balloons. We haven't found, at least, anything that is very
5 clinically discouraging about this. I am saying why make
6 the bar higher on a hypothetical right now?

7 DR. VETROVEC: Except to ask for the data in some
8 way.

9 DR. BRINKER: The asking for the data, other than
10 those that you get from the clinical experience, to say that
11 we now want to IVUS the stent and the end margins because of
12 the hypothetical problem that there might be an end stent
13 dissection, and we don't have that for a routine in our
14 previous stents that we have evaluated and it doesn't seem--
15 I rarely IVUS now my stents and I don't think you do,
16 either. You might.

17 So I think we ought to think a little bit about
18 saying, "Well, there is a 'me too' stent, I think we ought
19 to IVUS these endpoints to see that there is no problem."

20 DR. TRACY: How often does it actually happen that
21 there is a stent that is out there that company then says,
22 "I am going to put it on a different delivery balloon."

23 DR. OSTERLE: It happens all the time.

24 DR. TRACY: When that happens, is it such a
25 dramatically different--doesn't that change the whole

1 character of the device if you think of the device as the
2 balloon plus the stent? Does that change the character? I
3 guess the real issue is at what point does the character of
4 the device change enough that it warrants some kind of
5 investigation to be sure that you are not using a different
6 device with different complications and different outcomes.

7 DR. OSTERLE: I don't represent the FDA but I have
8 been around for every device iteration with stents.
9 Generally, the balloon materials change but the performance
10 of the stent rarely, if ever, changes because of the
11 platform it has been mounted on. It is usually an issue of
12 balloon-compliance characteristics and the kinds of
13 pressures that you can deploy it at.

14 To my knowledge, the FDA has never really--if it
15 is an approved balloon, I am not sure they have really asked
16 for anything unusual. Bram, have you?

17 DR. CURTIS: What happens with a modification to
18 the delivery system?

19 DR. ZUCKERMAN: We can talk about all different
20 modifications. For example, with our initial experience of
21 putting high-pressure balloons directly to stents, we asked
22 for clinical data at least out to 30 days. For other
23 modifications can be a small change in the catheter design,
24 we might not ask for any clinical data.

25 It really depends on the type of change. Another

1 change that we might see is a new mechanism for more
2 securing the stent on the balloon on an unsheathed system.
3 There, we would ask for clinical data.

4 Another part of that is, for some of the
5 modifications where we ask for clinical data, because a lot
6 of the adverse events occur quite acutely, although we have
7 been asking for 30-day or 14-day data, can we really make an
8 endpoint in hospital?

9 DR. OSTERLE: Is that a question or statement?

10 DR. ZUCKERMAN: It is a question.

11 DR. OSTERLE: I think you can, particularly if you
12 are talking about a new--you have alluded to this that some
13 of the companies, Cindy, for example have made balloons that
14 have little bumpers on the end to keep the stent from
15 falling off. These are fundamental changes that I think the
16 FDA has every right and should ask for acute information
17 about, the safety of that kind of modification as opposed
18 to, maybe, blending their nylon a little bit differently
19 which is, again, less of an issue.

20 But I don't see any problem at all with asking for
21 acute deployment data and getting it.

22 DR. BRINKER: I think the question was can you
23 limit it to acute deployment data as opposed to prolonged
24 observation? If I were to follow your argument--

25 DR. OSTERLE: I would say no.

1 DR. BRINKER: How long would you want to look to
2 see the effects of a bumper?

3 DR. OSTERLE: Not necessarily a bumper but, again,
4 if you are changing the compliance characteristics of the
5 deployment balloon or the lance and stuff, then again you
6 are looking at TVR, whatever you want to call that, six or
7 nine months. I think you would like to have some data about
8 that.

9 It doesn't have to be randomized but I think you
10 need some information on whether that modification--there
11 are a lot of people who believe that some of the recent
12 changes in the balloon delivery characteristics of some of
13 the major companies that, without getting into the specifics
14 of companies, that these have led to adverse outcomes and we
15 ought to have data on that if that is really true.

16 DR. GILLIAM: About what percentage of time do you
17 expect to have nondeployment or an escaped stent with these
18 delivery systems?

19 DR. OSTERLE: This gets back to that first
20 question about sort of the operating parameters and what we
21 were going to--and I agree with Jeff that if you put ten
22 interventionalists in a room, we could probably all come to
23 a number. We have at least two or three here I could ask.
24 It should be, really, less than 1 percent, don't you think,
25 Greg?

1 DR. STONE: Yes; I think so.

2 DR. OSTERLE: But it is not less than a half a
3 percent. I think probably 1 in 100 stents are lost even in
4 good labs. If I look at just my experience of supervising
5 major laboratories, it is kind of once a month or so someone
6 sends one of these things someplace they wish they knew
7 where it was.

8 DR. GILLIAM: So if you saw a delivery system that
9 changed and you expected it to not be as well, if it were
10 3 percent, it may take some time before you would ever
11 notice it.

12 DR. OSTERLE: That is why I am saying we would
13 like some data on this. And it would have to be acute
14 hospital data. But it is not going to take a long time. If
15 it is going to be more than 1 in 100, it is not going to
16 take more than a few months to recognize there is a problem
17 and that has really been the history of, I think--the stent-
18 delivery platform failures that I have been aware of
19 generally have declared themselves in the first two or three
20 months for all the semi debacles or major debacles that some
21 of you may know have occurred over time.

22 DR. TRACY: It seems to me that if you inflate
23 something at a much higher atmosphere in one model versus at
24 a lower atmosphere in another, that is not something you are
25 going to get information on in the first 30 days. That

1 seems like something you will get information on much later.
2 Is that fair to say?

3 DR. OSTERLE: There are two different issues. One
4 is the acute safety of balloon rupture because they have
5 changed the material. Again, not to bring up names, but
6 there have recently been some balloon ruptures with one of
7 the companies in their stent-delivery system and that stuff
8 is found out usually right on the spot.

9 It is not a late problem. It is an immediate
10 problem which is different from some of the TVR issues which
11 may be related to how the balloon comes up on the ends of
12 these stents. So you need both. You need the acute
13 hospital data and you need the TVR data to ask a fundamental
14 question.

15 I think the minor changes in balloon nylons and
16 sort of tips, softness and things like that, are not a
17 really big deal anyone would really care about.

18 DR. CURTIS: Let's go on to No. 11. "What is the
19 most appropriate interpretation of peri-procedural CPK
20 enzyme bumps--that is, non-Q-wave MIs. Currently, we have
21 defined a non-Q-wave MI using the WHO criteria, CPK two
22 times normal with a positive MB fraction. Should the
23 definition be changed to CPK MB more than three times normal
24 or some other alternative?"

25 DR. OSTERLE: Those are two questions. The first

1 question is kind of unrelated to the second one. I think it
2 is fundamentally asking what do we think about CK bumps, I
3 guess, which is a huge source of debate amongst our friends
4 and colleagues, which is really different from what should
5 the definition be.

6 If you want my opinion, I think the definition
7 should be three times normal. But the question is what is
8 the appropriate interpretation of that.

9 DR. CURTIS: So if your CPK MB goes up more than
10 three times normal, it is a non-Q-wave MI.

11 DR. OSTERLE: Yes. To that extent, the
12 interpretation is yes, that is a non-Q-wave MI. But I
13 thought this question was asking really what is the
14 implication of it, I guess, is a little different. The
15 fact, it is diagnostic of a non-Q-wave infarct but the real
16 issue about these things brought up this morning by our
17 ReoPro guys is whether that really is a long-term issue for
18 us that should be a source of obsession and concentration.

19 DR. DOMANSKI: In terms of diagnosing it, though,
20 what it means is straightforward.

21 DR. OSTERLE: Right.

22 DR. DOMANSKI: What it means is that there is
23 myocardial necrosis.

24 DR. OSTERLE: Correct; no ambiguity.

25 DR. DOMANSKI: The more there is, the worse that

1 is. Those are what, I think, the data suggest; that is, the
2 more, the worse.

3 DR. OESTERLE: No argument about that. But this
4 argument in the world of interventional cardiology doesn't
5 center around the acute issue. It centers around whether
6 the CK leaks have long-term implications for the patients.

7 DR. DOMANSKI: Well, yes, I guess so. But,
8 entering into that debate for a moment, then, clearly
9 somebody who has a twice-normal elevation has had myocardial
10 necrosis based on the procedure. Clearly, also, that is
11 probably a relatively smaller MI than somebody who has had a
12 five times normal problem.

13 But it certainly seems to me to be a complication
14 of the procedure and there is a continuum. So it is not a
15 mechanistic difference. With one-and-a-half times normal,
16 one would expect to have to have to follow an enormous
17 number of patients for an awfully long time to see a
18 mortality difference.

19 But it is still something that didn't work well
20 with the device and I guess you would worry that the next
21 one was going to be ten times normal.

22 What do you think?

23 DR. OSTERLE: I don't disagree with what you are
24 saying. There is no question that when the CK goes up, that
25 is evidence of necrosis. There is no ambiguity about that

1 whatsoever and that more CK is worse than less CK. So the
2 question is whether we should define a point where everyone
3 agrees it is clearly abnormal. The point is it is clearly
4 3X. I think most people in the world would say yes, that is
5 abnormal.

6 DR. DOMANSKI: Most people would also say twice
7 normal is abnormal, I think. Steve, wouldn't they?

8 DR. OSTERLE: I don't know.

9 DR. LASKEY: It depends on what it is related to
10 down the road as well. There are these benign leaks and
11 there are not-so-benign leaks.

12 DR. BRINKER: We also have to look at the context
13 of what we are looking--if the patient comes into the
14 emergency room and they draw a CK and it is twice normal, he
15 is admitted as a non-Q, usually. But, for us, 15 to
16 20 percent of the time we get a CK elevation, we
17 euphemistically called it other things, and there is some
18 myocardial necrosis.

19 The real question for us, as Steve suggested, is
20 what is the long-term down side to this and are there ways
21 that we could limit this.

22 DR. OSTERLE: That is what the first question is
23 that I was sort of getting to. I think that what you are
24 saying is how do we interpret these things. We obviously
25 interpret them as infarct, but that is sort of a tautology.

1 I don't think that is why they are asking this question.

2 DR. BRINKER: This is such a tough question that
3 the real issue, from the regulatory point of view, I hope,
4 will be if we can label something for a comparator kind of
5 thing--that is, how does one stent meet to another stent--
6 and we want to list adverse events and we want to include
7 MIs, what would we think is a CK or maybe it should be a CK
8 MB or whatever, or maybe it should be some combination of
9 both.

10 But what should be threshold which classifies an
11 elevated CK as a myocardial infarction just for no other
12 reason than to compare one endpoint to another endpoint in
13 two different stents. I hope that is the reason for this
14 question.

15 If that is the reason for this question, again, I
16 think that two, three or five could be used and I think that
17 three is a good number for our purposes because it implies,
18 perhaps, a subconscious threshold about comfort with sending
19 the patient home within twenty-four hours after doing this.

20 But other people would disagree with this. I am
21 not sure if it is of great importance that that same panel
22 that helps with the other criteria endpoints could help with
23 making a number valid for you.

24 DR. KUNTZ: Just to make a couple of comments.
25 The CPK two times normal positive MB fraction is derived

1 from a late 1970s Health Organization definition of MI. In
2 those days, they didn't have a quantitative measure of the
3 MB fraction that was qualitative. It was like a litmus
4 test.

5 The quantitative measure of MI was the CPK which
6 was, as you know, a non-specific muscle enzyme issue. That
7 needs to be changed. It is antiquated. Nobody uses it but
8 the FDA. That needs to change tomorrow. It should be a CPK
9 MB issue. As a matter of fact, you probably will miss the
10 window for MBs because we will move into troponins.

11 So the last fifteen years where everybody has
12 using MBs needs to be switched over.

13 The aspect about where the threshold is, I think
14 that the real question is what are you going to do with that
15 data. I think you should measure every CPK MB because I
16 agree with Dr. Laskey that this is a continuum. MBs are
17 mass measurements of volume of leaky enzymes from a heart
18 all of which, by all science, represents myelonecrosis.

19 If you have an elevation that you can
20 statistically say is above the normal noise zone which is
21 defined at every laboratory, you should measure it and you
22 should report it. We do in all of our trials. When you do
23 it carefully, you find out that, in stent cases, between 20
24 and 25 percent of cases will have an abnormal elevation, one
25 determination above one times normal, will have about

1 14 percent above three times normal MB.

2 It is a very frequent event and it should be done.
3 We can compare those directly among groups by comparing
4 their curves.

5 The real question comes down to what is the
6 measure of CPK MB that enters into a MACE combined endpoint.
7 That is the critical issue because I don't think a CPK of
8 one times normal, just for argument's sake, is equal to
9 death in an equally weighted combined endpoint. Maybe not
10 two times MB either is.

11 So when we have this situation of trying to
12 understand how we process this, I think we should have a
13 high threshold for MI that meets the same combined MACE
14 endpoint that we are looking at with gross measures of how
15 well something does with safety that has the same endpoint
16 as emergency CABG or death and then have a separate measure
17 of the display and spectra of CPK MBs measured on every
18 single patient that can be a comparator between stents, and
19 they should be evaluated separately.

20 DR. CURTIS: What would that be, though?

21 DR. KUNTZ: The laboratories are difficult to do.
22 We have wrestled with this in measurements that we have done
23 in over 6,000 patients in multicenter trials. Many
24 laboratories won't measure an MB until CPK is elevated. It
25 is a rule of the lab. You can't break it.

1 Other laboratories will measure MBs on everybody
2 if you ask them to. We would prefer everybody to have an MB
3 measurement because that actually is something that has a
4 somewhat normal distribution and you can compare them.

5 Statistically, if you look at the CPK MBs when
6 they are only measured after a CPK is elevated, you have
7 this very pathological distribution of a bunch of zeros and
8 then some continuum in about 25 percent of the cases. That
9 is very hard to model because it doesn't fit any parametric
10 distribution. You have to do very bizarre, nonparametric
11 bootstrapping techniques to understand sample sizes.

12 So we would prefer to have MB elevations measured
13 on everybody and there should be something maybe stated from
14 the FDA so that hospitals will do this and fall in line. I
15 am afraid what is going to happen, though, is, in the next
16 year or so, we are going to have better measures of troponin
17 which are going to be much more sensitive and actually more
18 specific in the measurements up front here.

19 So I think, again, the spectra of a population
20 randomized to A or B or a registry should be displayed for
21 everybody to see with all of the displays, the one to three
22 times normal, three to five, five to eight and so on so we
23 can really get a sense of how often this is occurring
24 because, even when you dichotomize the CPK MBs, you find
25 that there are some distributions which are kind of funny.

1 Somebody could have a 10 percent greater than
2 three times normal MB and most of them could be clustered in
3 the 5 to 10 percent range and others could be clustered in
4 the 3 to 4 percent range. They are completely different.
5 Their bell-shaped curves will be different and they will
6 show them.

7 So I think the question is that I think we should
8 measure this on people. We advocate this for trials because
9 it is myocardial injury. I don't know that the injuries are
10 sufficient to put into a major adverse cardiac event. At
11 some level, it has to be decided. I think three times
12 normal MB is not equal to the other components of the major
13 adverse cardiac event. I think it should be a little
14 higher.

15 But, on the other hand, I don't think we should
16 sweep it under the rug. We should report it in a separate
17 part of the table with a whole display of the MI profile so
18 that it can be evaluated separately.

19 Again, I think, following Dr. Domanski's comments,
20 we need to deconvolute this combined endpoint issue so we
21 can look more intelligently at their separate components and
22 try to get them so that we are intelligent enough to look at
23 those separate components and make a decision and not have
24 to lump them all together.

25 DR. CURTIS: I think what this gets to is labeling

1 this because if we call these peri-procedure or CPK leaks,
2 that doesn't sound bad to anybody and that probably would be
3 a minor problem down at the end of the list of things that
4 were collected in the clinical trial.

5 Once you put the label "MI" on it, it is part of
6 MACE. So I don't have any problem with collecting that data
7 going above three times the normal value for an MB; yes,
8 that is abnormal. You have got necrosis. What at what
9 level do we call it worrisome, something that needs to be
10 tracked, something that you have got to call an adverse
11 event.

12 DR. KUNTZ: I can give you a little bit of a
13 background on that because that has been the subject of a
14 lot of interest in the last few years. Obviously, there is
15 a variety of interpretations about that and a lot of it is a
16 link that has been set up between this link and death later
17 on.

18 There are a bunch of philosophies that I don't
19 want to go into, but the fact of the matter is that we don't
20 have the luxury of dichotomizing MIs anymore. They are a
21 continuous measure. If you measure them carefully, you will
22 find that you have them in about a quarter of the patients
23 that you treat.

24 If you use athrectomy, they are about 35 percent.
25 So if we call every elevation that is statistically above

1 normal representing true myelonecrosis as an MI, one-quarter
2 to one-third of the patients that everybody treats is having
3 a heart attack. So we can't use that threshold.

4 On the other hand, where you draw the line, three
5 or five times normal, really comes down to how you measure
6 the effect of an MI. We know that LV function doesn't
7 change until it is about eight to ten times normal or in the
8 Q-MI range, that that is when LV function can be detected.
9 That is the MI literature.

10 We know that the mortality of risk of MI is
11 usually in first 24 hours and it declines down to six
12 months. That usually is associated with very large Q-MIs
13 from all the thrombolytic studies. Therefore, you can use
14 those thresholds to determine whether it is a really beefy
15 MI or not.

16 I think, to answer Jeff's comment, in the
17 emergency room when you see someone who comes in with one or
18 two times normal CK MB, you are not admitting that patient
19 because of the injury that they sustained from that, you are
20 admitting them because they probably have a large clot on a
21 plaque which is going to be the widow-maker to follow
22 through.

23 You do that as a preventive measure, to cath them
24 and see what they have or to stabilize them. That is not
25 from the injury sustained, I think, from the one or two

1 times normal.

2 DR. BRINKER: But you do call it an infarct, a
3 subendocardial.

4 DR. KUNTZ: You do call it that but most people,
5 clinically, are not worried about that patient being
6 injured. They are worried about that patient having the big
7 one. When you treat someone who has a proximal LAD stenosis
8 and remove the stenosis that you could see by angiography,
9 it's gone, and then they have the same one to two times
10 normal, it is a different feeling because that patient has
11 sustained the same injury but doesn't have that looming
12 stenosis waiting to cause a problem.

13 DR. DOMANSKI: Of course, one could look at that
14 and say that the reason you are having trouble showing--in
15 fact, the reason that the trials were trending towards
16 increased mortality plus MI with the stents was because you
17 were having just that, you were producing myocardial
18 necrosis--and, of course, your MACE endpoint looks good
19 because of the revascularization, because of the target-
20 vessel revascularization, being less of a problem, but you
21 weren't able to show a difference for that reason; that is,
22 you were destroying heart while you were doing it.

23 And then, they add the ReoPro to it and, all of a
24 sudden, it looks better. And it looks better because maybe
25 they had less myocardial necrosis.

1 DR. KUNTZ: The stent-versus-stent studies were
2 using the CPK two times normal definition not the CPK MBs in
3 their MACE definition because that was the FDA requirement.
4 The CPK elevation does not rise to the same level as CPK
5 MBs. As a matter of fact, they rise differentially.

6 If you have a two times normal or greater CPK
7 elevation, that is usually a large heart attack associated
8 with an MB of about five to ten times normal. So, while the
9 ReoPro studies measured CPK MBs above three times normal,
10 they are a lower threshold of a CPK of two times normal seen
11 in the stent studies.

12 So, in a way, we were sweeping a little bit of
13 those MIs under the rug.

14 DR. DOMANSKI: But I am talking about EPISTENT.
15 EPISTENT looks better because they add the ReoPro.

16 DR. KUNTZ: Yes; it does. You're right.

17 DR. DOMANSKI: That is the point. The point is
18 they infarct. They don't show any improvement in death and
19 MI; in fact, just the opposite. Then, all of a sudden,
20 things like a whole lot better when you appear to be
21 preventing a MI with ReoPro.

22 DR. KUNTZ: Right. I think that that is the
23 debate about those trials is that if a lot of the MIs that
24 are being prevented with something like the IIb/IIIa
25 inhibitor are tiny MIs that don't have--small MIs; I am

1 talking about between one and five times normal MB--that
2 don't have major consequences on the patient, that they need
3 to be dissociated from the deaths and repeat
4 revascularizations in the first three days or six months
5 that are big events and costly events for society.

6 I think the real debate comes down to what Dr.
7 Oesterle said which is that there is an association in some
8 trials with CPK elevations and late death. However, as we
9 all know, the field of epidemiology decides whether
10 associations are causation or not and there is a lot of
11 debate whether that is cause or whether that is totally
12 confounded by atherosclerosis where patients with different
13 levels of atherosclerosis are more likely to have both CPK
14 elevations and also more likely to have an MI three or four
15 years later which kills them.

16 So these are the big debates. I think, Mike, that
17 you hit it right on the nose that, basically, those small
18 levels are really the question about how important they are
19 to reduce.

20 DR. TRACY: It seems that that is one of the
21 things you could follow with outcomes. It is a continuum.
22 Somewhere in there, you have two times elevation and
23 positive MB versus three times MB elevation. You could
24 report what the actual information is and then follow it
25 over time and see whether there is any difference in

1 mortality long-term because nobody, I think, would argue
2 that there is some myocardial necrosis at either of those
3 levels.

4 It is just a question of how relevant that is and
5 that is information that you can find if you are maintaining
6 postmarket surveillance and some type of ongoing information
7 gathering.

8 DR. BARNATHAN: I would just like to reinforce
9 some of what Dr. Kuntz mentioned and then just share a
10 little bit of data particularly relevant to that.

11 We have looked at a pooled meta-analysis from the
12 EPIC, EPILOG and CAPTURE studies where we did exactly what
13 was just suggested and looked at the mean values for less
14 than one, one to three, three to five, five to ten, and
15 greater than tenfold for the people using MB and, if MB was
16 no available, using CK.

17 I think what you can notice here is that it is a
18 continuous function with death at six months. This is
19 mortality at six months. As one goes up in the amount of
20 the cardiac enzymes, there is a fairly clear function. This
21 is not whether or not they received abciximab. This is all
22 patients in the trial.

23 So, at least from our data and I think at least
24 about nine or ten other studies with the exclusion, perhaps,
25 of both which I guess Rick could comment on, most studies, I

1 think, have demonstrated this association although we agree
2 it is not proof, per se.

3 I think the EPISTENT trial where one does have the
4 randomized comparison of the addition of abciximab to lower
5 them and then, in addition, saw a reduction in mortality, I
6 think, closes the loop.

7 DR. OSTERLE: You think it closes the loop?

8 DR. BARNATHAN: Yes.

9 DR. OSTERLE: You may think that but I don't think
10 everyone else thinks that. There is an enormous debate
11 about that.

12 DR. BARNATHAN: It begins to close the loop.

13 DR. OSTERLE: Maybe. Maybe for your company.

14 DR. BARNATHAN: There were just a few other points
15 I would like to make. The other is an agreement with what
16 Dr. Kuntz said. I think there is complete agreement that
17 the collection of CPK MB is an association of infarction.

18 [Slide.]

19 When one systematically measures CK, CK MP, shown
20 on the bottom versus when one doesn't systematically measure
21 it in all of these trials shown on the top, in general what
22 you see and, again, it depended on the levels that one used,
23 but it was approximately 9 percent when one systematically
24 measured whereas it was about 3.5 percent when one did not
25 systematically measure.

1 So until we really do understand what are the
2 actual data and the implications, we would also argue that
3 it is relevant and important to measure it systematically.

4 DR. STONE: This really is very complex and I just
5 want to expand on a few of the points that have been made.
6 Along with these elevations in CPKs, we always used to think
7 of an infarct as a clinical process. It was CPK and it was
8 chest pain and it was EKG changes.

9 Now that we are looking for these CPKs and these
10 troponins, as has been said, we find a lot of patients who
11 have myocardial necrosis, and I will give you that it is
12 myocardial necrosis, but without clinical events, without
13 anything that you can see on the angiogram, without EKG
14 changes.

15 So the question really is what does it mean and
16 how distressed do we need to get and how distressed do we
17 need to make our patients and what do we do as far as
18 labeling and implications for stent-v-stent trials.

19 As Rick was saying, there are a lot of
20 associations that can occur with CPK elevation that may
21 secondarily explain the CPK elevation. We just presented
22 data from our group at the last American Heart meeting in
23 about 1,000 consecutive patients, that when you look at
24 clinical factors, procedural factors and by intracoronary
25 ultrasound, the amount of plaque burden, the amount of

1 plaque in an artery, is a predominant determinant of CPK
2 release, even during an otherwise totally uncomplicated
3 angioplasty procedure.

4 Let me make it a little more interesting and more
5 complex and I will describe some data has been accepted for
6 the ACC meeting in March. This is preliminary because we
7 are still in the throes of cleaning this to make sure it is
8 100 percent accurate, but this is the way the abstract is
9 going to read.

10 We have got about 8,000 patients, consecutive
11 patients, who have undergone percutaneous interventional
12 procedures in native coronary arteries with two-year follow
13 up in whom CPKs were tracked at 8, 16 and 24 hours after the
14 procedure.

15 What we found in those 8,000 patients was that a
16 CPK MB greater than two times normal is present in
17 30 percent of patients, greater than three times normal in
18 20 percent of patients. This is pretty common. There was
19 an association between the height of CK MP and early in-
20 hospital mortality.

21 When we look at cumulative late mortality, though-
22 -that is, again, 1.8 years with actuarial techniques--we
23 find a weak relationship between the CPK MB release and late
24 mortality. Where it gets interesting, and this is what a
25 lot of other studies have not done, is when we corrected it

1 by multivariate Cox proportional hazard regression
2 techniques for age, gender, diabetes, et cetera, we find
3 that the patients who are dying late are the patients who
4 are old when they start and the patients who have diabetes
5 with unstable angina being borderline.

6 In that model, the CPK MB, no matter how you cut
7 it or slice it, was no longer a determinate of late outcome.
8 So, in other words, the CK MB release and mortality it
9 determined in older patients, in diabetic patients, unstable
10 angina with thrombus-burden lesions, and long diffuse
11 lesions from the earlier study.

12 So the issue, then, really becomes which of those
13 are really important. Clearly, some of these CPK releases
14 are important and preventing them would be very important,
15 and to characterize if the stent causes it--if a stent
16 closes a vessel and you get a massive anterior MI, that is,
17 obviously, an important event.

18 If everything goes perfectly well, you have no
19 other problems, but the CK goes up to 350 and the MB is four
20 times normal, I don't know that that has any prognostic
21 importance at all.

22 What I have not yet seen in EPISTENT, which would
23 close the loop, would be how much of the morality reduction-
24 -and this is just one study showing the mortality reduction-
25 -but how much mortality reduction was related to the

1 preventing of CPK events in those patients. That hasn't
2 been related yet and has multivariate modeling been done in
3 that study.

4 It is also only one study. It is a phenomenal
5 study and it is very provocative. We clearly and
6 dramatically need to have that study repeated either with
7 the same or different drugs. So, to try to summarize what I
8 am trying to say, this is a very complex field, as Steve was
9 saying, and there are a lot of different opinions as to the
10 importance of these events.

11 In BOAT, in STRATUS, when you looked at patients
12 with good angiograms, CK release, there was, like, no
13 mortality at one year. It meant nothing. When you look at
14 EPIC, some of the implications of CK MB release is early.
15 Then it's flat. Then, all of a sudden, at eighteen months,
16 it starts jumping again.

17 Pathophysiologically, I don't understand that and
18 that is not what I was taught during medical school. So the
19 electrophysiologists can maybe add something to that. The
20 bottom line is this is not an easy issue. I think we need
21 to call most of these things--if you want to call them
22 myocardial necrosis, it is. If you want to call them CPK
23 leaks, it is.

24 When we think of myocardial infarction, I agree
25 with Dr. Curtis, your comments, that we have got to be very

1 careful and we have got to come up with something that is
2 high enough probably based on a total CPK level as well.

3 Last comment, because I can tell you as a clinical
4 cardiologist, I don't see too many patients coming in with
5 infarcts and congestive heart failure that really affect
6 their prognosis that have a CPK of 200 and the MB of
7 40 percent. They always come in with a CK of 1,000 or 2,000
8 or 3,000 and a proportionately, or somewhat
9 disproportionately, elevated MB.

10 Finally, remember that weight lifters, when they
11 do their curls, they are getting muscle necrosis. But that,
12 for them, at least, wasn't necessarily a bad thing. In
13 fact, it stimulated some good things to happen. I am not
14 saying myocardial necrosis in the heart is a good thing to
15 get. I would rather not get it than get it, but I think we
16 have to be very careful when we have all the implications
17 associated with what those bumps mean.

18 DR. ANDERSON: Kevin Anderson from Centocor. I
19 just want to respond to some of this in that I have done a
20 lot of the morality analyses with ReoPro. Again, another
21 preliminary analysis looking at exactly what Dr. Stone was
22 asking about was to try and associate the excess enzyme
23 elevations as to explaining the late death mortality.

24 It does look like it does explain some portion of
25 it although not, I would say, the majority of it. In other

1 words, among those who had enzyme elevations, that does
2 explain some of the excess mortality in the stent group
3 without ReoPro compared with the stent group with ReoPro.

4 In terms of one other thing Dr. Stone brought up
5 was the very late mortality. I just wanted to mention in
6 passing that there is no real interaction in terms of
7 looking at the proportional hazards for mortality early
8 versus late.

9 In one study, the advantage maybe turns up between
10 six months and one year, one study between two months and
11 six months, another study after eighteen months. But,
12 overall, the appearance is that there is a very consistent
13 reduction in mortality that is consistent over the entire
14 time, that if you look for any time interaction that is
15 statistically significant, you don't find it there.

16 So I am not saying that I have proof of anything.
17 I think that the enzyme elevations probably are relevant.
18 They may not be the entire explanation. I wonder a little
19 bit if twenty-four hours is enough for measuring enzymes
20 although I don't think anybody is going to measure them much
21 longer.

22 In particular, I would say ReoPro probably has a
23 graded effect in terms of platelet blockage over time.

24 DR. CURTIS: I think the bottom line on this is
25 that a Q-wave infarct is important. It is always going to

1 be important, that the CPK MB ought to be over three times
2 normal in order to be considered abnormal.

3 The percentages in the trials with the non-Q-wave
4 MIs were small anyway. It may not be necessary to make a
5 big change in how we call it because everybody in the room
6 here realizes that these small leaks that get above normal
7 may have some implications, maybe they don't.

8 Let's move on to No. 12. "Any other clinical-
9 trial issues you would like to raise for consideration?"
10 Does anybody on the panel have anything else they want to
11 bring up? We have had a pretty free-flowing discussion with
12 industry and the public here. Is there any other comment
13 anybody in the audience wants to make now?

14 MR. JOHNSON: I just wanted to reiterate from
15 industry's perspective our willingness to work with FDA on
16 the development of these standard test methods for assessing
17 stents as well as on objective performance criteria.

18 As I mentioned earlier, there is a HIMA committee,
19 RASTM committee, already set up to do this and we are very
20 active in that and we will continue to pursue. As a matter
21 of fact, there is another meeting tomorrow on that.

22 We would also like, after we have an opportunity
23 to read the transcript from this panel meeting and update
24 our senior management, have a meeting with FDA and HIMA,
25 talk about what the next steps are. We are committed to do

1 that within the next 60 days. So we think that would be a
2 good step forward with this effort and we appreciate
3 everyone's participation and help.

4 DR. OSTERLE: Gary, can I ask you a question?
5 Again, I am pretty ignorant about this process, but there
6 seem to be a lot of people questioning whether the companies
7 would cough up their PMA proprietary data. I never really
8 got a sense of a direct answer from you on that.

9 MR. JOHNSON: We didn't come up with a direct
10 answer. I think it is a very difficult question and it
11 obviously is a concern to any industry when they have paid a
12 lot of money to generate this data how they release it.

13 There was a general consensus, though, of all the
14 manufacturers that had it that they wanted to participate in
15 this effort and that they were willing to work with FDA on
16 the development of OPCs. But they wanted to do that in a
17 very controlled way. So we just wanted to make sure we
18 understand how the data was going to be used and how we
19 would participate in the development of an OPC versus just
20 turn the data over.

21 DR. OSTERLE: This reminds me of the Harvard
22 faculty process where it looks like a bunch of the heavy
23 people are at the top and all the worker bees are below. I
24 notice on this HIMA that it is all the major stent
25 companies. Are the start companies part of HIMA?

1 MR. JOHNSON: Yes. There are a variety of
2 companies as part of HIMA. Maybe Bernie wants to comment on
3 the companies that were involved.

4 DR. OSTERLE: The people who stand to potentially
5 benefit from this as much as you do are, of course, some of
6 these undercapitalized or less capitalized companies. Are
7 they actually represented by HIMA in any substantial way?

8 DR. LIEBLER: Bernie Liebler from HIMA, Director
9 of Technology and Regulatory Affairs. HIMA membership runs
10 from the very largest companies down to companies that
11 basically don't even have a product to sell. These meetings
12 were open to everybody.

13 DR. OSTERLE: What is the percentage of non-
14 publicly held companies that are part of HIMA?

15 DR. LIEBLER: I don't have the statistics.

16 DR. OSTERLE: Is it a lot? Is it a little?

17 DR. LIEBLER: Actually, we have many, many, many
18 more very small companies than we do very large companies.
19 The majority of our membership, if you count individual
20 entities, are small. You have got to realize, on the other
21 hand, that the majority of dollars in a place like HIMA,
22 just like it is in the industry itself, is concentrated in
23 the very large companies. That is just a simple fact of the
24 way things play out.

25 Aside from the people on the list that you saw,

1 there were other companies that were on our list or
2 distribution. They were informed of this. If we continue
3 with this effort, if we work with the FDA in a joint working
4 group or anything, they will also be given the opportunity
5 to participate.

6 DR. CURTIS: Thank you.

7 We are going to end up with the stent labeling
8 proposal. It says, "Please comment on the labeling template
9 for the standard coronary stent which was developed with
10 input from sponsors, panel members and reviewers." It is in
11 section 2 of the panel pack. It goes on for several pages.

12 We are obviously not going to go through this
13 line-by-line but if any of the panel members had specific
14 comments they would like to make--it is a template. It is a
15 general kind of format for a stent labeling with some
16 shifting of information from device description to clinician
17 use information and also shifting some of the warnings and
18 precautions to the clinician use information are the primary
19 differences.

20 DR. OSTERLE: I just had one question about this
21 on page--it is No. 4 under warnings and precautions. It
22 says, "Do not perform stent placement unless emergency
23 coronary bypass-graft surgery is available at that
24 facility." I don't think that reflects standard practice or
25 at least evolving practice. I was wondering how specific

1 they want us to get into that.

2 But just as a point in fact, that would be sort of
3 an unusual--although, perhaps, that has been required in the
4 past, that is clearly not what is going on in the community.
5 As you are well aware, I'm sure, there are people doing
6 primary angioplasty all over the United States right now
7 where stents are an integral part, and it seems like you are
8 taking the one thing that makes angioplasty in these setting
9 safe which is access to stents and taking it off the label.

10 I think that is problematic because, in fact, that
11 is what is going to happen in America. It is already
12 happening. People are using stents to do acute MIs all over
13 the place where they don't have access to bypass surgery.
14 You don't want to take that away because otherwise--and I
15 think angioplasty in the same acute MIs is unsafe in these
16 facilities.

17 DR. SPYKER: It is currently in all the labels,
18 but we are here to hear your comments like this and your
19 suggestions. How would you reword it?

20 DR. OSTERLE: I wouldn't have it in there.

21 DR. TRACY: Somewhere along the line today,
22 somebody present information on the need for acute
23 revascularization as 0.4 percent. Maybe just simply stating
24 that somewhere in there, that the need for acute bypass
25 operation is 0.4 percent, let it stand at that.

1 I agree, though. To require access to CABG for a
2 0.4 percent incidence seems to be a little bit extreme, I
3 think.

4 DR. BRINKER: One easy way to get it out, since
5 most of the professional guidelines, the ACCHA guidelines,
6 suggest at least that elective angioplasty be carried out
7 where there is available surgical support that you could
8 introduce the term nonemergent or elective stenting should
9 be carried out when--

10 DR. OSTERLE: Those guidelines are subject to
11 change, as well.

12 DR. BRINKER: But so is this label. As soon as
13 the guidelines change, I think the labeling can change. The
14 one thing you don't want to do, necessarily--I don't think
15 you want to do--is suggest that people should, in stand-
16 alone clinics, be doing coronary angioplasty and stenting
17 electively.

18 DR. VETROVEC: I am categorically doing
19 angioplasty outside a center without backup surgery. On the
20 other hand, I am not sure it ought to be in the warning
21 label. It seems to me the question is how do you use the
22 stent, not where you use it.

23 DR. OSTERLE: I agree.

24 DR. VETROVEC: It doesn't affect the use of the
25 stent per se, and this is a label that defines the stent

1 usage. It is sort of editorializing on a larger issue, it
2 seems to me. Don't get me wrong. I am against doing it in
3 those settings, but I am just looking at it. The same as
4 the label doesn't say in stent that is approved for
5 emergency bailout that it can't be used in other
6 circumstances.

7 So why tie the hands of the angioplaster in a way
8 that you don't tie industry.

9 DR. BRINKER: A stent that has not been approved
10 for elective angioplasty is not labeled for elective
11 angioplasty, I presume.

12 DR. VETROVEC: But it is not negatively labeled in
13 that regard; is that correct?

14 DR. ZUCKERMAN: Correct.

15 DR. GILLIAM: But we did the same thing with the
16 pectoral implant of a defibrillator at one point. We said
17 it was not to be pectorally. So I am not sure that that is
18 not without precedent plus to state something that is in
19 line with current practice.

20 DR. LASKEY: It is a larger issue than an anatomic
21 issue, though. This is political, social, cultural as well
22 as clinical.

23 DR. GILLIAM: The same argument as was made about
24 the defibrillator implant.

25 DR. BRINKER: The other thing, Warren, is that all

1 the data that goes to support the stent use that is also in
2 the labeling is essentially referable to situations in which
3 there are certain safeguards including surgery. So we have
4 used that in the past to qualify these statements.

5 Does the balloon have a labeling similar, just a
6 coronary balloon?

7 DR. ZUCKERMAN: I believe it does.

8 DR. CURTIS: George, would you be in favor of
9 leaving out that line altogether? Is that what I am
10 hearing?

11 DR. VETROVEC: Yes. I don't think that is
12 relevant.

13 DR. CURTIS: So several opinions that that line
14 ought to just be out altogether.

15 DR. SPYKER: What about the first bullet, then,
16 which is only physicians who receive appropriate training?

17 DR. VETROVEC: I think that is a different issue.
18 That is saying you need to know how to do stents to do it.
19 It doesn't say where you learned.

20 DR. CURTIS: I can't imagine that an untrained
21 physician is going to have a good outcome from a stent in an
22 emergency situation. I think the patient is better off
23 without it altogether.

24 Other comments?

25 DR. VETROVEC: There is a statement here that

1 says, "Do not use the new Stent 100 in the treatment of
2 'blank' lesions as the safety and effectiveness have not
3 been established." I guess I would ask what do you envision
4 putting there? Would you really say because it wasn't
5 approved for--

6 DR. SPYKER: Restenosis, for example.

7 DR. VETROVEC: Restenosis, that you are going to
8 put that label in there?

9 DR. SPYKER: Correct. That is what we have
10 typically done.

11 DR. DOMANSKI: That is an interesting point. It
12 is what has typically been done but maybe that is not such a
13 good idea. It is one thing to approve something for a given
14 use. It is another thing to discuss it for other uses. As
15 time goes by, whether the FDA has approved it or not, some
16 of these things, in fact, become reasonable uses out in the
17 community.

18 I am just talking about quality assurance and
19 stuff like that rather than regulatory approval. So I am
20 not so sure the FDA wants to get in the business of saying,
21 "This is not safe," or do they want to just tell you what is
22 safe and effective. That is an interesting point, actually.

23 DR. SPYKER: One of things that I had never
24 previously appreciated but that we do use labeling for is to
25 provide incentive to get good science done. This is one of

1 the ways in which we do that. This would be, in part, to
2 put a clear advantage to the sponsor to continue the
3 studies.

4 DR. DOMANSKI: But even after it was demonstrated
5 in the New England Journal in a wonderful study, if they
6 didn't apply for regulatory approval, regulatory approval
7 wouldn't be forthcoming. So I guess the science could be
8 there and the label would remain.

9 I never thought about it before, but it is a good
10 question.

11 DR. VETROVEC: Let me ask another--because on
12 another device that we were discussing, one of the concerns
13 of the panel was that the problem is once this device is
14 approved and out on the market, everybody is going to use it
15 for off-label circumstances. We were told that we couldn't
16 consider that. That didn't determine whether a device was
17 out there or not.

18 In a sense, that does encourage manufacturers to
19 get things approved for one reason knowing that they will
20 get used for four others. So they take the easiest way to
21 get it on the market.

22 On the other hand, putting a statement like this
23 in there disadvantages not the device company but the
24 angiographer because if there is a problem, the angiographer
25 is suddenly in court with an attorney reading this statement

1 from the package insert but, despite what Michael may have
2 said, there may be a study in the New England Journal that
3 suggested it was okay.

4 I just kind of would ask about the fairness of
5 this about who it is helping and who it is hurting. I don't
6 know.

7 DR. TRACY: I think that is an excellent point.
8 The only person who is getting hurt in this situation is the
9 person who is doing it where it says very clearly, "Do not
10 use." If it needs to be stated there in any way, leaving
11 the "Do not use" out would probably be appropriate and just
12 saying what it has not been tested in because it does put, I
13 think, an unfair burden on the operator.

14 DR. VETROVEC: I would suggest saying, if you are
15 anxious to put that in there, to say something, "Data
16 relating to efficacy in 'blank' types of lesions has not
17 been established."

18 DR. SPYKER: That is what we have down on page 2-
19 9, section 7-2. That is precisely the point of that
20 section. It is a list of situations where data does not
21 support safety and effectiveness. There is a whole spectrum
22 of use. Something might be put in the indications in some
23 cases, "Do not use in young children." It depends on what
24 we believe is appropriate for protecting the public health
25 and incenting good science.

1 We can hear your comments. That is a perfectly
2 legitimate suggestion.

3 DR. CURTIS: On page 2-10, you talk about patient
4 counseling information. A lot of what is listed there is
5 actually obtaining informed consent. I don't think a
6 physician is going to it right or not do it right based on
7 anything that is listed there.

8 It may be best to shorten that list, as you were
9 suggesting anyway. I think the issue about taking aspirin
10 or other antiplatelet agents is a nice thing to put in there
11 and make sure that is very clear. Maybe stent-failure
12 symptoms, a lot of the rest of that, explain what is going
13 to be for the procedure and afterwards. I don't think it is
14 really necessary.

15 DR. VETROVEC: Can we look at page 2-5 which is
16 called adverse events. This was written, as I read it, at
17 least, with the concept that this would be for randomized,
18 multicenter trials. I am wondering if, for some of the new
19 paradigms that we talked about, if this is going to need to
20 say things like instead of control stent, composite control
21 group, or other issues.

22 DR. SPYKER: Of course, we typically have not done
23 a difference in a statistic in a situation like that but
24 present confidence intervals for each. So that is exactly
25 right.

1 You have commented on the columns. If there are
2 any comments on the rows, are there things that are left out
3 of those rows that you think should be included? The thing
4 that immediately came to mind was Rick's suggestion about a
5 continuous measure of MB increase. I would love to see
6 something like that included, for example.

7 But any other comments from the panel?

8 DR. LASKEY: Just to be careful what time frame
9 you specify because most patients are home within 12 to
10 18 hours now, at least in the elective setting. So I think
11 unless you are going to call them back, it is a real issue.

12 DR. SPYKER: So you are suggesting that we be more
13 detailed in the footnote? What are you suggesting?

14 DR. LASKEY: I think we need to get what we can
15 get. If we ask for 24-hour CKs, we are probably not going
16 to get it.

17 DR. CURTIS: Any other comments?

18 DR. ZUCKERMAN: One additional comment regarding
19 to restenotic lesion, since it was brought up. In the
20 indications, we now have a statement that says, "patients
21 with symptomatic ischemic disease due to discrete de novo
22 and restenotic lesions in native coronary arteries," et
23 cetera.

24 The reason why it is written that way is that, up
25 to this point, we required a different dataset for

1 restenotic lesions which has been hard to accrue given the
2 current data which does not, necessarily, suggest that
3 restenotic lesions are a predictor of further restenosis.
4 Would anyone on the panel suggest that it should just read,
5 "Due to discrete symptomatic lesions," or should that
6 descriptor still be in?

7 DR. CURTIS: Where is this?

8 DR. ZUCKERMAN: Page 2-3, the first indication.
9 There has been a traditional demarcation up to now of
10 separating de novo and restenotic lesions as if they might
11 be two separate datasets.

12 DR. BRINKER: I would agree that you could treat
13 them as one dataset.

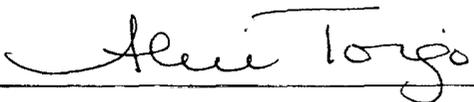
14 DR. CURTIS: If there are no other comments, I
15 think we could stand adjourned for today. Thank you
16 everybody.

17 DR. SPYKER: Thanks very much.

18 [Whereupon, at 4:30 p.m., the meeting was
19 adjourned.]

C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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