

1 MS. ABEL: Okay, we're going across. We
2 have consensus. We're going across. We talked about,
3 in the previous discussions, migration wasn't
4 something that you could really set out to evaluate in
5 an animal model. So it really doesn't make sense that
6 we would say that you have to evaluate it now.

7 And now you've got something that could
8 change sealing and fixation effectiveness. Should you
9 be doing an animal model to try to look at the
10 difference in a modified device compared to the
11 original one with respect to migration? And what we
12 can do here is kind of group migration-related issues.
13 So let's just say when you're looking at migration,
14 you're also looking at the tissue response, and those
15 sorts of things.

16 DR. GREENBERG: I think it depends what it
17 is. I mean, what if you're talking about a drug?

18 MS. ABEL: Well, but whatever the
19 modification is, I mean obviously the amount of
20 information you have to collect is going to be
21 dependent on how drastic the change is. But let's
22 just say you made some sort of a mechanical change

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1 that could affect sealing fixation effectiveness. Do
2 you get good information out of a GLP 20-week animal
3 model?

4 DR. BIANCO: That would depend on the
5 claims of the manufacturer. I mean, if you bring in
6 risk analysis. If the manufacturer is claiming an
7 improvement in fixation, wouldn't you have to evaluate
8 that?

9 MS. ABEL: No, it's just if it could
10 affect fixation or sealing. It has nothing to do with
11 claims. If you make a device modification, and we can
12 all look at it, and you have to say these are the
13 various parameters that could be affected by this
14 change, and this is the testing that we're going to do
15 to evaluate.

16 DR. BIANCO: What was the reason for the
17 modification?

18 MS. ABEL: The reason for the modification
19 doesn't matter so much if it could affect sealing
20 fixation effectiveness.

21 DR. BIANCO: Well, I agree and disagree
22 with you. I think it does matter. If it is related

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1 to claim, and it is related to the impetus behind the
2 modification in the first place.

3 MS. ABEL: But if it could affect it, what
4 do you care what the claim is? If Stuart changed his
5 the same way that Mark changed his, and Stuart made a
6 claim and Mark didn't, would you say they should
7 evaluate their devices --

8 DR. BIANCO: Well, that circumstance, yes.
9 If a manufacturer claims, though, that they have an
10 improvement in fixation that must be evaluated.

11 MS. ABEL: Sure.

12 DR. BIANCO: Okay.

13 MS. ABEL: But that's a separate issue.
14 If there's a claim, you always have to evaluate the
15 claim.

16 MS. ABEL: Dan?

17 MR. WANINGER: I guess I would agree with
18 Lou. I mean, if you're going to have a change that's
19 going to affect migration, you may want to do like a
20 pullout test, or maybe some other bench test. I'm not
21 sure that you'd actually have to repeat an animal
22 study to assess that.

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1 MS. ABEL: And we've already talked about
2 it might have excessive radial force. And that's not
3 going to show up in an animal model anyway.

4 DR. GREENBERG: I think it depends on what
5 we're really looking at, because we're not looking at
6 an animal model to reproduce migration. We may be
7 looking at an animal model for other factors, and it
8 depends on the change. If you're talking about a
9 minor mechanical change to a device that's going to
10 improve the pullout force, that's right. But if
11 you're trying to induce tissue in-growth that's a
12 whole other story.

13 MS. ABEL: And that's fair. And again,
14 that's why I'm saying it's somewhat dependent. But if
15 you made something that was significant enough that
16 you thought that it could really affect the sealing
17 fixation effectiveness in the human, do you do an
18 animal study? Does that give you useful information?

19 DR. GREENBERG: Absolutely.

20 DR. CRIADO: But if we said that you could
21 not look at that to begin with through the animal
22 study, then the answer again would be no.

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1 DR. VIRMANI: But if you made a special
2 change at the anchoring site itself, would you not
3 evaluate migration? Absolutely you will look for it.
4 You cannot make a change in your device which is based
5 on the anchoring and say you don't have to evaluate
6 migration.

7 DR. CRIADO: Whether you would do it in an
8 animal study is the question. Of course you would
9 evaluate it.

10 DR. VIRMANI: I think you need an animal
11 study to say at least that the migration is not seen,
12 or it is seen, especially when you've modified that
13 region.

14 MS. ABEL: But if you've got -- you're
15 building on a platform that already exists. You've
16 got a device that may have some minor migration issues
17 in the clinic, for example. Obviously you didn't see
18 that in your animal model or you wouldn't have gone
19 forward to the clinical with it, because so far the
20 devices that are out there have been tested in animal
21 models. You make a change to make it more robust. So
22 there's no reason to believe that you would be able to

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1 show anything.

2 DR. VIRMANI: But you have to at least --
3 you might not be able to show it, but you have to say
4 that it is negative for it. That, I think, is a very
5 important aspect of it. Supposing you modified your
6 anchoring device and made it into needles. Now you're
7 going to tell me it's not necessary to look at
8 migration? Of course you have to say that it looks
9 anchored and there was no migration observed.

10 MS. DECKER: There are other methods to
11 evaluate that, whether the fixation is impacted by the
12 change. A cadaver aorta would be an example.

13 MS. ABEL: Dan?

14 DR. VIRMANI: Not enough. That is only
15 two it tells you. It does not tell you chronic
16 change. You will have to evaluate in an animal to say
17 there is a change or there isn't.

18 MS. ABEL: Dan?

19 MR. MICONI: I'm Dan. I think the
20 question needs to be answered in the context of what
21 other information is going to be available to address
22 the issue. In the first column where you're talking

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1 about a new device, I think the implication there is
2 that migration resistance will be evaluated on the
3 bench, and it will be validated in clinical trials.
4 Now, somebody comes along and wants to make a change
5 that could potentially affect migration resistance,
6 obviously it'll be evaluated on the bench, and maybe
7 the question we're asking is do animal data, or could
8 animal data suffice to obviate the need to repeat the
9 clinical trials. If the answer to that is no, we're
10 going to have to do clinical trials anyway. If you
11 don't have to do animals for a new device, you're just
12 doing bench and then human clinicals, why do you do
13 animals for modification?

14 DR. VIRMANI: Supposing you saw a defect
15 in the animal, supposing you saw. Then will you go
16 and do a clinical? I don't think so.

17 MR. MICONI: I just don't see any
18 rationale for requiring animals for a modification to
19 a device if you don't require them for the new device
20 to begin with. If you're going to have human clinical
21 data.

22 MR. SMITH: And I would just like to add

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1 real quick that if you look at the rest of the list,
2 there's biological response, there's these other
3 things that you would do an animal model for. If you
4 did a fixation modification, maybe it's a fuzzy tuft
5 at the top or something and you want to see if it
6 heals in better, you're really looking at biological
7 response. You're not necessarily looking at
8 migration. So with this table, the way I look at it
9 it's very segmented. And so for migration, I would
10 say no. But for biological response, I would say yes.
11 Needles or tuft or whatever.

12 DR. VIRMANI: No, but I would say that it
13 is an important negative to say. You will have to say
14 there was no migration. You must, because supposing
15 there is and you don't do a clinical trial.

16 MR. SMITH: But I trust my pulse
17 duplicator better than I do the animal in migration.

18 DR. GREENBERG: We've got a lot of animal
19 data, and none of it has been predictive of migration
20 to any extent. It is a negative test for migration
21 from all the evidence that we have, absolutely.

22 MS. ABEL: And we have definitely seen

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1 migration in the clinics, so you know that it's --

2 DR. GREENBERG: That's correct. So it
3 does not predict that phenomenon in a patient.

4 MS. ABEL: All right. I think we talked
5 about endoleak enough this morning. And I think, as
6 Frank has pointed out, if most of this is, you know,
7 anyway, why talk about the individual modifications.
8 So maybe we should just kind of glance down at things
9 that we think could be of relevance.

10 So biological response. You have a new
11 endovascular graft, but in terms of its -- comparable
12 materials, comparable design, but it is different. Is
13 it necessary to do an animal study? You've already
14 done all your bench testing, you've looked at radial
15 force, you've looked at permeability. Do you get
16 additional information in that circumstance with an
17 animal study, or do you just need to get into a human
18 feasibility study?

19 MR. SMITH: I think if it's a new
20 endovascular graft, a new design or whatever, there
21 are -- we have standard materials. There's PTFD and
22 PET. But there are things that can be done to those

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1 materials to deleteriously affect their biological
2 response. And so if you haven't ever been in the
3 animal before, and you have a new device design, and
4 you have no idea, and it's hard to compare it to
5 what's commercially available, then I could think it
6 to be reasonable to at least be evaluated in the
7 animal for the first time.

8 MS. ABEL: All right. Anyone else?

9 MR. KING: It seems to me, Dorothy, that
10 along with that that one does need some controls with
11 clinical histories associated with them, so that you
12 can draw some comparisons, rather than be looking at
13 a performance without any controls. I think that's,
14 to me, an important part of this protocol.

15 MS. ABEL: And when you talk about
16 controls, which is, you know, farther on in the row
17 here, so it's a good idea to talk about it, do you
18 think you have to have an active control in that
19 study. Or if Rod White's already got a pile of
20 information on the performance of the various devices,
21 you know it's a historical control, you know, what are
22 you talking about when you say a control?

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1 MR. KING: Well, would you have used the
2 same protocol, and the same animal model, with the
3 same size of a device that has a clinical history?
4 Well then, historical controls are sufficient, it
5 would seem to me. But I -- but clearly one does have
6 to look at both the model, and the procedure, and the
7 oversizing, and issues related to that in order to
8 draw those comparisons against the controls.

9 AUDIENCE MEMBER: Dorothy, could they say
10 their name and their background, in addition to their
11 name?

12 MS. ABEL: Why don't we just go around
13 real quick and have people introduce themselves.
14 Because if we do it every time people open their
15 mouths.

16 AUDIENCE MEMBER: Okay, that's fine.

17 MS. ABEL: Is that?

18 AUDIENCE MEMBER: Yes.

19 MS. ABEL: Yes, and we had done that at
20 the last workshop and I totally skipped it this time.
21 Maybe I need to introduce myself. I'm Dorothy Abel.
22 Matt?

1 MR. WANINGER: I'm Matt Waninger. I'm the
2 program manager for Zenith at Cook MED Institute.

3 MR. BORDEAU: Bill Bordeau. I manage
4 animal testing at Cook.

5 MR. KING: Martin King, North Carolina
6 State University, and Universite Laval, Quebec City,
7 Canada.

8 DR. HALLISEY: Michael Hallisey, from
9 Hartford, Connecticut.

10 AUDIENCE MEMBER: Who? Is he an engineer?
11 The guy from Canada.

12 MR. KING: Biomedical engineering.

13 AUDIENCE MEMBER: Thanks.

14 DR. HILBERT: Steve Hilbert, DCD,
15 experimental pathologist.

16 MS. WOODS: Terry Woods from the labs.
17 I'm the one that causes you guys all the trouble with
18 the preclinical testing.

19 MR. REIMSCHNEIDER: I'm Bill
20 Reimschneider. I'm a biologist for FDA.

21 GUIDANT: Kristin Hunnell, Guidant
22 Corporation, in regulatory affairs.

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1 MS. DECKER: Maria Decker, physician
2 training in clinical affairs at Guidant. Have been
3 working with AAA for eight years.

4 ENDOMED: Heath Musley, engineering
5 supervisor for Endomed.

6 MR. CARDELLA: My name is John Cardella.
7 I'm an interventional radiologist, and chairman of the
8 Department of Radiology at the University of Colorado.
9 I'm here representing the Society of Interventional
10 Radiology.

11 COOK, INC.: My name's Craig Lithban. I'm
12 from CSIRO in Australia and I'm a physicist.

13 DR. BROWN: My name is Michael Lawrence
14 Brown. I'm a vascular surgeon from Western Australia.

15 MR. SMITH: My name is Lou Smith. I
16 worked with W.L. Gore as an engineer for the last 20
17 years. And I'm part of the Scientific Advisory
18 Committee for this meeting.

19 DR. GREENBERG: I'm Roy Greenberg from
20 Cleveland Clinic Departments of Vascular Surgery and
21 Biomedical Engineering.

22 MR. BATY: I'm Ace Baty. I work for W.L.

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1 Gore, and I work in product development.

2 MR. BIGGERSTAFF: Chuck Biggerstaff, W.L.
3 Gore for 20 years. Responsible for product
4 development.

5 MR. KIEBEL: Duncan Kiebel, engineer by
6 background, product development manager at Lombard
7 Medical.

8 MR. PHILLIPS: I'm Peter Phillips. I'm
9 engineering director of cardiovascular devices,
10 Lombard Medical. Physicist by background, dangerous
11 knowledge of physiology.

12 DR. WHIRLEY: I'm Robert Whirley, VP of
13 research and development at Trivascular.

14 MR. MESSENGER: I'm Noel Messenger, VP of
15 RAQA clinical at Trivascular.

16 DR. FILLINGER: I'm Mark Fillinger, a
17 vascular surgeon from Dartmouth Hitchcock, with a
18 degree in engineering so enough knowledge to make me
19 dangerous there too.

20 MS. HASTING: Erin Hasting. I'm with
21 Medtronic in the preclinical group.

22 MR. MICONI: Dan Miconi, with Medtronic,

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1 also in the clinical research group.

2 DR. WHITE: Rod White, vascular surgeon
3 from L.A., and I'm full of it.

4 DR. FOGARTY: Tom Fogarty, wine-maker.

5 (Laughter.)

6 MR. RUSH: Scott Rush, development
7 engineer with Cordis.

8 MR. TRENTO: Julian Trento, development
9 engineer with Cordis.

10 DR. CRIADO: Frank Criado, vascular
11 surgeon Union Memorial in Baltimore.

12 DR. CHUTER: Tim Chuter, vascular surgeon,
13 UCSF.

14 MR. RODGER: I am Stuart Rodger. I'm vice
15 president of clinical affairs at Vasutek.

16 MR. STEVENSON: David Stevenson, project
17 engineering manager at Vasutek.

18 MS. GRUNWALDT: I am Marianne Grunwaldt,
19 biomedical engineer, and I'm an intern at the FDA.

20 MR. YU: Well, I'm here from Sydney,
21 Australia, associated with Royal Prince Alfred
22 Hospital, as well as biomedical engineering

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1 department, University of New South Wales.

2 MR. DEHDASHTIAN: Mark Dehdashtain, R&D
3 engineer at Edwards.

4 EDWARDS LIFESCIENCE: Scott Bagans,
5 Edwards Lifescience, regulatory affairs.

6 DR. BIANCO: Dick Bianco, director of
7 experimental surgery, University of Minnesota, and
8 member of ISO committees on vasocardiac valves.

9 DR. VIRMANI: Renu Virmani, cardiac
10 pathology at the Armed Forces Institute of Pathology.

11 MR. LERDAHL: Robert Lerdahl, research and
12 development at Bard.

13 MR. HUDSON: Brian Hudson, quality manager
14 at Bart.

15 MS. UYESUGI: Karen Uyesugi from
16 Endologix. I'm a VP of regulatory and clinicals.

17 DR. SCHRECK: Stefan Schreck, VP of R&D,
18 Endologix.

19 MR. QUIGLEY: Fergus Quigley with Boston
20 Scientific, in R&D.

21 MS. BOLTON: Jennifer Bolton with Boston
22 Scientific, regulatory affairs.

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1 MS. SMITH: I think I'm last. Angie
2 Smith, reviewer for the FDA.

3 MS. ABEL: Dick brought up a good point,
4 there are a lot of people in the room that are
5 actually on the ISO committees. And so maybe if
6 people could just raise their hands if you're a member
7 of the ISO committee for the endovascular grafts and
8 vascular prostheses. So we've got quite a few people
9 involved in that that are here. I'm the convener of
10 that committee. Lou Smith's project leader.

11 So now we all know who our buddy is. We
12 can talk about biological response, and I think what
13 we came up with respect to the new endovascular graft
14 is that it's probably rational that you would want to
15 use some animal studies to look at biological response
16 if it's your first time, new device, whatever. And
17 that we had talked about historical controls, or some
18 sort of a control. At least you should know what you
19 should be expecting to see in your study.

20 The modifications -- well. We can talk
21 about the modifications also I guess. So obviously if
22 you're affecting sealing fixation effectiveness, you

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1 would have the potential of changing the biological
2 response. So if we're going to say that you should do
3 it for a new device, dependent on the magnitude of the
4 change and exactly what was going on, you should
5 consider having to do an animal study if you have a
6 significant change to your attachment. Is that fair?

7 Now on the changes in durability, I think
8 we've all agreed that there's no reason to do animal
9 studies to look at durability. So we can just a big
10 old no down that whole entire column.

11 Okay, if you've got a modified device, and
12 certainly you would want to be comparing your results.
13 If you do an animal study, you want to compare your
14 results from your previous designs. Is that
15 reasonable?

16 Adverse events due to excessive radial
17 force. I think we can kind of group that with it's
18 something you need to be looking for if you did a
19 biological response evaluation. It's something you're
20 looking for but you really can't measure it is what we
21 agreed to before the break. Loss of integrity. We've
22 already said animal models don't really address that.

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1 So wasn't that a quick table?

2 DR. CRIADO: Dorothy, the fact that only
3 excessive radial force is listed and not insufficient
4 radial force. Is that because the latter has not been
5 identified to be a problem or what? What's the
6 rationale for that?

7 MS. ABEL: Insufficient would show up as
8 migration or endoleak.

9 DR. CRIADO: Oh, under a different name.
10 That's where it is. Okay.

11 MS. ABEL: Yes.

12 DR. BROWN: Dorothy? Does it matter if
13 the neck dilates to a certain extent? What are the
14 parameters? The fact you've got radial force, and
15 you've got a certain amount of neck dilatation, does
16 it matter?

17 MS. ABEL: Well, Stuart, can you talk to
18 that at all? I mean.

19 MR. RODGER: Yes. It was a question that
20 we started with was how much neck dilatation is
21 excessive. And maybe I will ask David to respond
22 before I get myself into deep water here. I'll ask

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1 David.

2 MR. STEVENSON: We started out with no
3 idea of what excessive dilatation was. It wasn't
4 something people were talking about. And now it's
5 talked about. People have a clear idea of what they
6 would expect. I'm not sure I can say very more than
7 that.

8 AUDIENCE MEMBER: So you don't know what
9 you saw, is that correct?

10 MR. STEVENSON: Sorry?

11 AUDIENCE MEMBER: You can't define
12 excessive dilatation, so is that what you said? Are
13 you talking about sustained, or temporary via balloon?

14 MR. STEVENSON: Sorry, what we saw was
15 obviously the initial dilatation, when the device went
16 in. But in our first generation device, we also had
17 ongoing neck dilatation, which -- sorry? In a
18 clinical yes. But we didn't identify this in the
19 animal. So we had a great struggle with trying to
20 work out what was excessive, and what was likely to
21 continue. That was the other issue that we had.

22 DR. WHITE: The only reference point we

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1 have is the clinical scenario. And patients with
2 aneurysms dilate their arteries. Excessive dilatation
3 is when the fixation site disrupts. So if it dilates
4 and it doesn't break free, it's okay. If it dilates
5 and it breaks free, it's a failure. And it's the same
6 that we know now.

7 MR. STEVENSON: Or if it dilates and fails
8 to see it.

9 DR. FOGARTY: It's not a failure of
10 device. It's a continuance of pathology.

11 MS. ABEL: But there are certainly,
12 theoretically, and Stuart mentioned, there are devices
13 that do cause or contribute to that.

14 DR. FOGARTY: Well, maybe they oversized
15 or overdilated to begin with, I don't know which it
16 is.

17 MR. RODGER: Yes, but surely if you've got
18 a device that goes in with a balloon, then you are
19 over-dilating. You're dilating at the time you deploy
20 your device.

21 DR. FOGARTY: Well, you can call it
22 dilatations. Others would say it's conforming. So

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1 I'd challenge that. But I don't think we know the
2 definition. If you can't define something, you can't
3 say yes or no. I don't think we can define it.
4 You've got to define it relative to compliance and
5 non-compliance, and you don't know the compliance.
6 And you don't know all the views. You'll see
7 different things in different views. So I think at
8 the end of the day, this is a test of something that
9 can't be measured.

10 DR. CRIADO: So Tom, are you saying that
11 excessive radial force that apparently is not defined
12 may not be bad? Is that what you're saying?

13 DR. FOGARTY: No, I'm not saying that at
14 all. I'm saying I don't know.

15 DR. CRIADO: But then you are saying that
16 it may not be bad, if you don't know.

17 DR. FOGARTY: That's correct.

18 DR. CRIADO: Because here it is assumed
19 that it is bad. Obviously it's giving it a negative,
20 right?

21 DR. VIRMANI: But you don't even know --
22 firstly you're saying that you don't even know how to

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1 define that excessive force. All you know is the
2 result. You don't know for a given size if whatever
3 you're applying the force is that excessive for that
4 size or for that neck. It may be excessive for one
5 neck, may not be excessive for another neck, and
6 therefore you can't define what is excessive.

7 MR. RODGER: We also had -- we had two, if
8 you like, failure modes. The neck dilatation, the
9 excessive neck dilatation, in and of itself wasn't the
10 main problem. It was the migration of the device as
11 a result of that that was the main problem. So coming
12 to define what is excessive neck dilatation, I think
13 it reflects on what the next stage is. If it dilates
14 and stays, and there's no other failure mode, then how
15 big a failure is it? If it dilates and your device
16 moves, then clearly the dilatation was a big issue.
17 But it doesn't bring us any closer to defining it.

18 DR. FILLINGER: But you're back to Rod's -
19 - I think Rod's definition is a pretty good one. If
20 the radial force causes a problem, it's excessive. If
21 it causes the device to erode through the wall, for
22 example, that's a problem. Or if it causes so much

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1 dilatation that it then migrates, that's a problem.
2 So I think that's a fairly reasonable definition of
3 what's excessive.

4 DR. GREENBERG: The problem is that
5 there's no third dimension, or fourth dimension.
6 There's no time. You can see dilatation of the neck,
7 but then how long do we need to look for migration?
8 Because we don't predict based on our clinical
9 knowledge if there's neck dilatation. Eventually
10 things will migrate. We don't know when. So neck
11 dilatation in and of itself is somewhat of a surrogate
12 endpoint is a bad thing. But we could be proven wrong
13 as devices, if dilatation --

14 DR. FOGARTY: Did you say eventually they
15 will migrate?

16 DR. FILLINGER: Well, yes, based on
17 clinical data, neck dilatation is associated with
18 migration.

19 DR. FOGARTY: Only if it breaks the seal.

20 DR. FILLINGER: It's associated, not 100
21 percent. They're linked together.

22 DR. FOGARTY: Well, you said less than 100

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1 percent.

2 DR. FILLINGER: Well, they're linked
3 together.

4 DR. FOGARTY: You think.

5 DR. FILLINGER: No, we know. From
6 clinical trials there's published data. In fact,
7 people in this room published it.

8 MR. SMITH: Not to pick on Dr. Greenberg.

9 DR. GREENBERG: That's okay, I can handle
10 it.

11 MR. SMITH: What would be your definition?

12 DR. GREENBERG: I don't disagree with the
13 definition. I just think that it's a little bit vague
14 because we can't put any sort of temporal component on
15 this. I think that we use neck dilatation as a
16 surrogate endpoint for a bad outcome. As you know,
17 sometimes surrogate endpoints aren't accurate. And so
18 I think Rod's definition is correct. But to say that
19 it's dilatation to the point that fixation is lost, we
20 have to realize that we're applying some time point to
21 loss of fixation.

22 DR. BROWN: If you're relying on radial

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1 force for a fixation, when the device is fully
2 dilated, it will no longer have any radial force
3 because it will be constrained by the fabric. And it
4 will fall out. That's just straightforward common
5 sense.

6 So if it relates to a problem, and the
7 problem is migration if you're relying on radial
8 force, and it's probably a good thing that it
9 continues to dilate while it maintains radial force.
10 It relates to erosion. I think that's a real problem
11 if it erodes out. And it also relates to damage to
12 the wall in some way. But just the dilatation itself
13 may actually be a good thing because it maintains the
14 seal.

15 DR. CHUTER: The trouble with using neck
16 dilatation as an endpoint is that it can have multiple
17 negative effects, yes. I think that's true. But all
18 of those are filtered through performance
19 characteristics of the device. For example, the
20 extent of neck dilatation is probably more significant
21 relative to the diameter of the graft than it is
22 relative to any fixed number. It's probably

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1 significant relative to the fixation mechanisms of the
2 graft. The graft that depends entirely upon friction
3 is perhaps going to be affected a little more by neck
4 dilatation than one that has other mechanisms. The
5 device that becomes incorporated might be affected
6 differently. A device that does not continue to
7 expand, such as a balloon dilated device, is obviously
8 going to be affected differently. All of these device
9 characteristics are going to affect the outcomes of
10 the given degree of neck dilatation. So I don't think
11 that that as an endpoint in itself is of any value.
12 I think we need to look for the effects.

13 MS. ABEL: Well, after all that discussion
14 I think that the bottom line is instead of saying, for
15 example, neck dilatation, I should have said, for
16 example, resulting in disruption of fixation or seal,
17 or in erosion I think the point is well taken. The
18 reason that we had put neck dilatation was because
19 that's something theoretical you could look at in an
20 animal model, you know, remembering that's what we're
21 all supposed to be talking about this morning. In an
22 animal, can you evaluate, can you get information with

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1 respect to whether you designed a device that has
2 radial force that's not well distributed, or that's
3 excessive, or it has something that, to Michael's
4 point, causes an adverse effect on the vessel wall.

5 DR. WHITE: I agree with one exception.
6 If it erodes or necroses the wall, and that's the
7 scenario where you have data. Otherwise, no. It's
8 the adverse effect.

9 MS. ABEL: And so you could put necrosis
10 in with biological response, right?

11 DR. WHITE: Right. But that's --

12 DR. VIRMANI: Necrosis and inflammation
13 both. You can put down, and it could be just thinning
14 of the media and the media may be totally destroyed.
15 And if you have destroyed the media, you're likely to
16 get that in man too. If you see that destruction in
17 animals, you're likely to get the same thing in
18 humans.

19 DR. CHUTER: That's not true. You're
20 dealing with a young, relatively healthy animals.
21 Even animals that may be still growing. I think that
22 to expect that model to behave in the same way as the

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1 pieces of leather that humans have for their
2 implantation sites is -- stretches credibility. I
3 don't think it's of any value.

4 DR. FOGARTY: I'm sure Dr. Virmani
5 understands the constant disagreement between
6 pathologists and surgeons.

7 (Laughter.)

8 DR. VIRMANI: She's well versed with it.

9 MR. CARDELLA: I missed the morning
10 discussion because I was coming from the West Coast on
11 a midnight flight. So I apologize for that. But --

12 DR. FOGARTY: Who are you?

13 MR. CARDELLA: My name's John Cardella.

14 DR. FOGARTY: Okay.

15 MR. CARDELLA: I'm an interventional
16 radiologist.

17 DR. FOGARTY: That's too bad.

18 (Laughter.)

19 MR. CARDELLA: I know. What can he
20 possibly know anyway, right? The discussion here
21 strikes me as a little bit mixed. Are we talking
22 about the radial force that an endograft exerts, and

1 then are we talking about that in a piece of selastic
2 rubber tubing on a bench-top test device. Are we
3 talking about that radial force in a young animal who
4 may have a surgically-created aneurysm, but relatively
5 normal vessels. Or are you talking about the
6 performance of the device in humans with advance
7 atherosclerotic disease, in which case those vessels
8 are not normal. I'm not sure I understand quite what
9 it is that you're trying to test. If this thing's got
10 radial force sufficient to hold itself in a test block
11 on a bench, I don't think that has any meaning at all
12 in a human. And the same applies for an animal with
13 a relatively normal vessel that's just been made
14 aneurismal surgically. Am I missing something here?

15 DR. FOGARTY: This morning you missed.

16 MS. ABEL: We're looking at the failure
17 mode in the clinic. What you see is that there has
18 been -- Stuart was very kind to share his woes with us
19 of having a previous device design that had problems
20 where there was excessive radial force, led to neck
21 dilatation and migration. So that happened
22 clinically. They did not observe that, they did not

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1 figure that out until they got in the clinic. Is
2 there something that we could do to better evaluate
3 that before we get into the clinical in an animal
4 model, because this session is just talking about
5 animal models.

6 MR. YU: Yes, so many already said that
7 there are so many parameters that's on the discussion,
8 and it's very difficult to put either a yes or a
9 blanket no category. Maybe I can suggest an
10 additional category for specific cases, in which case
11 we can add notes like erosion issues, in which case it
12 would become very useful. But where there's any other
13 issues, it's a no.

14 DR. FOGARTY: Dorothy, there's a human
15 model where it's proven that if you push a non-fixed,
16 a rigid, against a compliant, normal artery, you will
17 get an aneurysm. It's called Lamolt Stent. It's used
18 for the thoracic coax. You don't have to repeat
19 anything because it's already been done in a human.

20 Now, I'm probably the only one old enough
21 to remember that shit in this room. But that's the
22 way it is. You don't have to do that again, even in

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1 an animal.

2 MS. ABEL: Okay, well I think from what
3 I've taken out of the discussions so far after the
4 break is that the only time we really identify that
5 you need to be doing additional animal studies, and
6 what you really need to be focused on is the
7 biological response. And although you might document
8 any adverse findings and try to figure out what to do
9 from there, biological response is really what animal
10 models are all about.

11 Now, having said that, we did say that if
12 you've got a brand new AAA device, and you've never
13 been anywhere near an animal model with it, then it
14 may be reasonable to consider doing an animal study.
15 And of course you would be looking at the delivery and
16 things like that. But really the only thing we've had
17 any agreement on even to any level is that biological
18 response would be what you would be focusing on.

19 So what is a reasonable time frame in
20 terms of evaluating biological response? Dr.
21 Hallisey.

22 DR. HALLISEY: Martin and I were just

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1 talking about. Did you also exclude delivery of the
2 device and deployment as a necessity too?

3 MS. ABEL: I guess I just --

4 DR. HALLISEY: Or there's just not
5 agreement on that one?

6 MS. ABEL: Well, it's something that you
7 would evaluate. It's just not that you would
8 necessarily be able to show. If you can deliver it in
9 an animal.

10 DR. HALLISEY: Okay. Then to answer your
11 question, the way I looked at this table that you're
12 doing now is necessity, correct? And the previous
13 page in our book is really I guess you'd call what can
14 animal models do potentially, or what's the utopia for
15 animal models. So what do you need to do to get
16 biological response. And I guess you're saying
17 there's a consensus in the room that you do need to do
18 an animal study, and you're asking me how many weeks
19 to follow it out. I don't know the answer to that.
20 I don't know.

21 DR. VIRMANI: I would do at least one
22 year. Between six months to a year.

1 MS. ABEL: We've got one year.

2 MR. SMITH: I think six months.

3 DR. VIRMANI: Six months to a year.

4 DR. HALLISEY: I would agree Dorothy that
5 when you look at the histology after three months and
6 then six months, and beyond that time there's very
7 little change in our experience in six months. So if
8 you're looking for -- I think six months would be an
9 ideal endpoint.

10 MS. ABEL: And we're looking at just
11 another endovascular graft. It's not anything really
12 wild and crazy, it's just -- it's almost proof of
13 concept in the animal before you go to the clinic.
14 Would you still say six months, or would you say three
15 is more rational for something like that if it's not
16 anything very unique?

17 DR. WHITE: We have no data, again, that
18 the long-term predicts anything. I mean, we've done
19 it out to numbers of years. The long-term data is the
20 same as the short-term data in an animal.

21 MS. ABEL: When you say short-term, what
22 do you mean?

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1 DR. WHITE: Thirty days.

2 MS. ABEL: You think 30?

3 DR. WHITE: Thirty days is no different
4 than five years except that the healing reaction is
5 more in an animal. But that has no correlation to a
6 patient.

7 DR. VIRMANI: But there is. If you look
8 at the data in drug-eluding stents, and if you look at
9 animal data comparing it to human stent deliveries,
10 there is a lag period between the animal --

11 DR. WHITE: But that's not --

12 DR. VIRMANI: -- when humans occur. And
13 therefore the question really is should you see
14 complete healing in an animal before you go to humans.
15 You know, at least you know that in an animal in three
16 months or six months it heals. It is going to take
17 longer in a human being to do the same thing. So you
18 must see complete healing before you are able to go
19 from an animal to a human.

20 MS. ABEL: When we do the clinical studies
21 for vascular grafts and endovascular grafts, it's very
22 common that there are interim sacrifice time points.

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1 And the standards all say 20 weeks with -- specify the
2 interim, 26 weeks, excuse me. And you have to look at
3 how things are progressing. I think it's perfectly
4 rational to believe that you could, with a device that
5 is not drastically different, extrapolate if things
6 are going as planned in the short time to assume that
7 they would continue to perform the same in the longer
8 term. I don't know that you have to wait for complete
9 anything, honestly, from what we've seen with the
10 experience with vascular grafts and endovascular
11 grafts, not stents.

12 DR. VIRMANI: But part of the problem is
13 the way they're assessed. The way they're assessed.
14 They cut in very thick sections. You cannot assess
15 the healing response. People have said this is healed
16 when it is not healed. That's the basic problem is
17 the evaluation has not been very adequate.

18 MS. ABEL: But Dr. Fillinger already told
19 us that healing is not something that we necessarily
20 have in the clinic too. And I think we have to look
21 at what are we trying to figure out. We're trying to
22 see -- there's nothing really unique going on with

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1 this device as compared to the others, so we can --
2 therefore, it's reasonable to expect that it will
3 perform reasonably comparable to the other device, or
4 the other devices. Michael?

5 DR. BROWN: If we go back to first
6 principles, we know that there's a six-weeks period to
7 get healing from the initial injury. And let's assume
8 that some injury occurs when you implant something.
9 And then after the initial response to the injury, you
10 have a period where you get a reactive response. And
11 that's when we get hyperplasia. And we know that the
12 greatest risk period for hyperplasia after placement
13 of an implant is six months. So it's be reasonable to
14 test out to six months with an initial injury
15 response, and the reaction to that.

16 DR. CHUTER: Can I just ask a question,
17 Dorothy? I have in my mind the image that Takoki gave
18 me of all of these devices that have been out there.
19 All of those, presumably, have gone through some form
20 of animal testing. Did any of those animal tests show
21 any biological responses that would have raised any
22 alarm bells? You know, healing or whatever else it is

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1 that we're talking about.

2 MS. ABEL: Perfectly reasonable question.
3 I can't tell you if all of them actually had animal
4 studies because all of them weren't even in clinical
5 studies in the U.S. So I think some, like Mintec is
6 the number one example. I don't know what they did
7 for studies, so I can't tell you what they saw. But
8 their problem wasn't healing related anyway.

9 DR. CHUTER: Well, Mintec is the only one
10 I can think of that really was biologically
11 incompatible. A lot of those patients got quite sick.
12 I was just wondering if any of the animal studies
13 showed that they might get sick.

14 MS. ABEL: I don't know anything about it.
15 It was not in the U.S., so. But as far as --

16 MR. SMITH: I can say for the Gore new
17 device did not show any adverse biological reaction in
18 our study. But I can also say that in development,
19 there are many things that don't make it very far,
20 maybe because of the biological response.

21 MS. ABEL: And that's what --

22 MR. SMITH: Whether that's a good decision

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1 or not, is you know, you'd never get clinical it is
2 decided at some point.

3 DR. CHUTER: It would be lovely to know,
4 you know, because that gives us the other side of our
5 testing.

6 DR. HALLISEY: The stent grafts that have
7 fallen out because of animal testing. I know there
8 are stent grafts that were sort of abandoned during
9 the animal study process because of the biological
10 response. The intimal hyperplasia was too intense,
11 and they developed stenoses, and all the stent grafts
12 in the animals thrombosed.

13 MS. ABEL: That's what I was going to say.

14 DR. HALLISEY: I know direct examples of
15 that. But and the company that abandoned the device,
16 or went to a new device, or stopped even developing
17 any devices. Now, what does that translate into in
18 the clinical setting? Maybe that stent graft, if they
19 had pursued it, would have been a great stent graft in
20 humans.

21 MS. ABEL: I was just also going to say,
22 by the time things get to us, they've already been

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1 through the preliminary evaluations, and so we don't
2 see the negative findings. In the studies that were
3 reported in response to the homework, no one said they
4 saw anything negative, period, with respect to
5 anything.

6 DR. VIRMANI: Because they do all the non-
7 GLP studies before which they don't have to report to
8 you. And they've learned everything in those, and
9 therefore now what they're presenting to you, they're
10 showing healing, and they're saying the bad results
11 were never shown to you.

12 MS. ABEL: Well, first of all, if they
13 have a bad result presumably they do something to
14 modify the device and to address the issue so that
15 there's no reason for me to ever see it. But I think
16 you bring up a good point with respect to do we need
17 these 6-month GLP studies to look at this new device,
18 or is it something that during the development of a
19 device, you should be doing some animal studies to
20 look at the healing. Tom?

21 DR. FOGARTY: Can I recommend a period of
22 anesthesia?

1 MS. ABEL: Now?

2 DR. FOGARTY: Yes.

3 (Laughter.)

4 DR. CHUTER: Induced by what agent,
5 ethanol?

6 DR. FOGARTY: Please?

7 DR. CHUTER: Induced by what agent?

8 (Laughter.)

9 DR. FOGARTY: You can take it too.

10 MR. RODGER: Just going back to the point,
11 the one point that you're discussing here, and that is
12 you specifically said that we're looking at
13 effectively and NE2 -- it's not rocket science
14 different from anything else. So therefore, if it's
15 relatively NE2, then the materials at least are known.
16 So it's likely to be PTFE, PET, whatever.

17 So it's questionable really how much extra
18 information you're going to get from this from running
19 a 6-month study on something that you've probably
20 already tested quite extensively. And we know that
21 the original extensive testing didn't predict clinical
22 failure.

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1 DR. VIRMANI: But you know, there are some
2 modifications that are done. For example --

3 MS. ABEL: This isn't modifications. This
4 is a brand new device.

5 DR. VIRMANI: No, no, while they are
6 actually designing the device. They learn that this
7 produces -- for example, they sterilize it in a
8 particular agent, they clean it in a particular agent,
9 and learn that particular agent produced some reaction
10 in it. So then now they do away with that and not
11 produce a different way of sterilizing that device.

12 Now you learn from the sterilization that
13 if you had done ETRH versus gamma radiation there are
14 different responses you can get. And so there are
15 differences that can be produced. So I think it is --
16 the manufacturers already modify them by the time it
17 comes --

18 DR. FOGARTY: Well, should they not modify
19 them?

20 DR. VIRMANI: I'm not saying not to
21 modify, Dr. Fogarty, I'm basically saying that you
22 need to show a GLP study that it shows that they are

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1 healed. If you show me that they're not healed, you
2 could have taken it to clinical and yet your patient
3 is dead at that time. Then don't come to me and say
4 Dr. Virmani, as a pathologist you don't know what
5 you're doing.

6 MS. ABEL: I'm trying to understand why
7 you would think that it wouldn't heal, if you've got
8 a comparable -- I mean, I don't want to go down the
9 substantial equivalence route, but what -- to Stuart's
10 point, what would lead you to believe that you would
11 have enough of a difference that you would not get
12 comparable results in the clinic, if you had a
13 relatively comparable device? Dick, do you have any
14 thoughts?

15 DR. BIANCO: Yes, I have a lot of
16 thoughts.

17 MS. ABEL: Can you share them?

18 DR. BIANCO: Well, I mean, look.
19 Sometimes what people think are minor modifications
20 end up to have unanticipated consequences. I think
21 it's in all of our interest -- this reminds me of a
22 discussion we had on heart valves about 15 years ago.

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1 It's in all of our interests to verify that the
2 modification doesn't have unanticipated results, vis-
3 à-vis catastrophic failure. And I don't think a short
4 GLP animal study is that burdensome.

5 MS. ABEL: Define short, if you could,
6 please?

7 DR. BIANCO: Sorry?

8 MS. ABEL: Define short.

9 DR. BIANCO: Well, and I don't want to
10 harp on heart valves, but on heart valves we have
11 applied risk analysis in ISO-5840. Depends on what
12 you're trying to achieve. If it's healing, then I
13 think shown -- published many times at 4 to 6 weeks.
14 You must go at least six weeks when healing is
15 completed. And I agree that healing must be complete
16 to evaluate the device. So some devices, 90 days,
17 some devices, 6 months.

18 DR. CHUTER: Could I just bring the
19 discussion back to stent grafts? I mean, we've seen
20 a lot of stent graft failures, and a lot of different
21 failure modes. They didn't relate to healing. They
22 related to corrosion, repetitive stress strains, all

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1 sorts of things, but not to the healing response. If
2 we're focusing our desire for animal studies on a
3 desire to see some pattern of healing, I think we're
4 focusing on the wrong aspect.

5 DR. FILLINGER: I mean, since I've said
6 lots of things, I guess -- the comments that have been
7 made about how you take a material that's well known,
8 it's PTFE or PET or whatever. And Tim, you made that
9 comment about the Mintec grafts, and how for whatever
10 reason, we don't know why, a lot of patients have
11 fevers, and bed chills, and what appear to be sort of
12 adverse consequences. We don't know whether they
13 really were or not. But somehow they seem to be
14 reacting differently to those grafts than other
15 grafts. And it wasn't a new material that had never
16 been used in humans before. It probably had something
17 to do with the way it was handled and treated. And
18 while you're not going to discuss all of those in
19 animal testing, it seems reasonable, and I think the
20 comment was made not burdensome to do some minimal
21 sort of testing just to show that the way we handle
22 this material has not created some unanticipated

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1 effect. I don't think that's an unreasonable thing to
2 suggest.

3 MR. KING: Dorothy, this is Martin King.
4 Just wanted to add that when anyone looks at retrieved
5 devices, and agrees that the variety of healing we see
6 because the patient pathologies are very different.
7 But nevertheless, I think we'd all agree around the
8 table here that for example, if you have a stent
9 inside as opposed to a stent outside, if you have a
10 different permeability of your graft material that
11 allows a different degree of incorporation, of tissue,
12 of the anterior wall. And so you will in fact get
13 different degrees of healing in different styles and
14 models of devices. We've seen endothelialization, for
15 example, in certain devices that haven't occurred in
16 others.

17 And so I do believe that there is evidence
18 to suggest that an animal model that is controlled
19 under GLP conditions would enable you to at least
20 reassure yourself that this new device does not in any
21 way generate potential difficulties that would be seen
22 in a clinical situation. So I don't agree entirely

1 with Stuart that, hey, we're using the same materials,
2 and they're well documented clinically, so what's the
3 big deal, you don't need to do this. I think the way
4 you put the materials together, and the way you
5 assemble it, and the way you deliver it, those issues
6 all impact on the way in which the healing will occur.
7 So I think it would be somewhat irresponsible not to
8 consider including some animal trial.

9 MR. RODGER: I agree, Martin. All I was
10 suggesting was that anything out beyond six months.
11 I wasn't sure what any benefit would be from that.

12 MR. KING: None whatsoever.

13 MR. RODGER: That's what we're trying to
14 get some consensus on was a time frame for this.

15 MR. KING: Beyond six months, you're
16 absolutely right, you're wasting your time.

17 DR. VIRMANI: As long as you can show that
18 they're completely healed. It could even be three
19 months that it's completely healed. You may not have
20 to go to six months. It is possible. There may be
21 some which don't heal at six months. You may have to
22 go up to one year. So if you define it as saying that

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1 it requires complete healing, then you can say that it
2 could be three months to anywhere, whatever is
3 required.

4 MR. BIGGERSTAFF: Excuse me, we seem to be
5 focusing on healing. I think we're trying to -- at
6 least from our point of view, we're looking at worst
7 case. Let's assume there will be no healing, and that
8 whatever time frame, you still have anchoring, you
9 still have sealing, and you've still excluded the
10 aneurysm from blood flow, and you don't have a
11 rupture. That's what we're concerned about.
12 Personally I don't care if it heals, as long as you
13 don't have an adverse biological response -- this is
14 Chuck Biggerstaff from Gore. As long as you don't
15 have an adverse biological response, and you haven't
16 done what the endograft, in this we're talking about.
17 And it's done what you designed it to do, I think it's
18 our duty to design it so in case there is no healing
19 it still functional.

20 MS. ABEL: And that gets back to Michael's
21 previous comment that we shouldn't be saying healing.
22 We should be talking about biological response.

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1 DR. VIRMANI: If you can't produce healing
2 in a normal animal, I disagree with you that you can
3 put it safely in a human being and say there is no
4 healing, human will do the same thing and it'll be
5 safe. I guarantee you it will not be safe.

6 MR. BIGGERSTAFF: Well, which normal
7 animal? We've got 30 years of dog data, and somebody
8 else has got 20 years of --

9 DR. VIRMANI: If you have shown in a dog
10 data, even if it's dog, it could be any animal. And
11 if in an animal, in a normal aorta you've shown no
12 healing at one year, and you put it in a human and
13 you're saying I have very good results in humans.
14 I'll be amazed.

15 MS. ABEL: Michael, you had something you
16 wanted to say about an hour ago, but you're too
17 polite.

18 DR. BROWN: Very minor. I just wanted to
19 make clear in my own mind, we're not necessarily
20 talking about a whole device but a sample piece of it
21 because we're looking for the biological response, not
22 for the efficacy of the device. Is that correct?

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1 MS. ABEL: You know, I think that's the
2 next topic we should hit on. Even if we talk about
3 the duration, we've all agreed that if you do an
4 animal study, you should look for some of the other
5 issues. Whether or not you actually designed the
6 study to evaluate patency, you would look at whether
7 you had any adverse issues with respect to patency.

8 So I think it wouldn't -- I don't think
9 that anyone would agree it makes sense to just test
10 the attachment site. It may be appropriate to do a
11 tube graft as opposed to a bifurcated graft, but
12 that's at least my understanding. When we're talking
13 about doing an animal study, that it would be not
14 necessarily evaluation components, but it would be
15 evaluation of some modified device that's as close to
16 the regular device as it could be.

17 DR. BROWN: I think it would be very
18 different, because if you put the whole device in, you
19 are then struggling with an animal model. Whereas if
20 you take a sample of the device, or a component, you
21 may just have to put a segment in the aorta. So it's
22 a very different experiment to put in the whole

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1 device.

2 MS. ABEL: Sure, I agree with that. I was
3 just concerned that you weren't implying that you
4 would test portions of the device, you know, as
5 opposed to -- and when I say that, cut off half of it,
6 as opposed to just using the aortic segment.

7 DR. BROWN: That's exactly what I'm
8 saying.

9 MS. ABEL: You want to cut off half of it?

10 DR. BROWN: I want to cut off a piece of
11 it and put it in the aorta. Let's say we take a
12 shape, whatever Dr. Hallisey says. Working with
13 shapes is not that easy always. The artery spasm, and
14 they're not so small. But you could take a segment of
15 a graft and implant it in the aorta and see what the
16 biological response is. You don't have to see what
17 the efficacy is, or bifurcated thing, or try and get
18 it down both arteries. All you need to do is have a
19 look at the response inside the aorta, which is only
20 a segment of it.

21 MR. SMITH: I think as long as the segment
22 is large enough to have both the excluded effect,

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1 you're excluding tissue from the internal vascular
2 flow, and the adjacent areas around it. Then it could
3 be a segment. I think if it gets too small or too
4 partial, then you're overwhelming it with good tissue.
5 That's my only response to what you're saying.

6 MS. ABEL: I think we always get back to
7 the whole, you know, you're looking at pieces of the
8 puzzle. I think to try to chop up the one piece too
9 small with respect to we're doing an animal study to
10 look only at healing probably isn't terribly rational
11 either. I think we have to look at -- the scenario we
12 proposed is someone's got a new endovascular graft.
13 It's a new manufacturer, but it's relatively
14 comparable with other designs that are out there. So
15 what is the minimum amount of testing that they ought
16 to do to qualify it before moving it into a clinical
17 study.

18 And I think, although biological response
19 is the only thing that people agreed you can kind of
20 look at in an animal model reliably, it's understood
21 that that doesn't necessarily predict how it's going
22 to function in the clinical. But you can at least

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1 see, is there anything strange happening compared to
2 what has happened with other devices. So it's almost
3 a screening situation.

4 You would also look for delivery and
5 deployment, and any negative effects during the
6 duration of your study, seems like. So if you wanted
7 to look only at tissue response, you know, that would
8 just be one piece of the puzzle. And then you would
9 need to do another study to actually look for, again,
10 the negatives.

11 DR. BROWN: Well, I'm going to agree
12 because you're feeling that we'll suddenly get
13 terrible problems trying to get this piece of device
14 into an animal is terribly different from a human
15 being. It just negates the whole test. So if you
16 take the major component, and you put that segment in
17 the aorta to see what the response is, you would get
18 answers as to whether you produced a biological
19 response.

20 MS. ABEL: Well, I think to Lou's point.
21 I'm not saying you have to take the entire bifurcated
22 device, or design a bifurcated device for the sheep,

1 but you need to have a reasonable amount of the device
2 in there so you can figure out the delivery and other
3 things too.

4 DR. FOGARTY: Yes, I'd like to ask the
5 physicians here. Did we ever figure out why those
6 patients had those febrile responses?

7 DR. CHUTER: No.

8 DR. FOGARTY: No.

9 DR. CHUTER: We didn't. What happened is
10 Boston Scientific bought the company and changed the
11 fabric. And then things just seemed to get better.
12 Those things were being manufactured in the Bahamas,
13 you know? They were probably being --

14 DR. FOGARTY: Well, they were certainly --
15 (Laughter.)

16 DR. FOGARTY: You know, that's politically
17 incorrect. But there are other grafts that also had
18 febrile responses. To my knowledge, they never -- I
19 mean, there's a change in manufacturing, lots of stuff
20 happens, I'll agree to that. But I'm asking did --
21 other than geographic location, did we figure that
22 out?

1 DR. CHUTER: No, they were septic deaths.
2 I mean, these were very high levels of TNF, very
3 septic patients, and some of them died. We haven't
4 seen that since, and we don't know why.

5 DR. VIRMANI: You know, they were
6 reproduced in animals. The same reaction was
7 reproduced in animals in retrospect. Once it had
8 occurred in man, then they went back. And that was
9 just to tell you that you can see certain reactions in
10 animals that you could have missed if you don't look
11 very carefully. So it's a lesson to be learned from
12 that.

13 MR. YU: Can I just add another dimension
14 to this whole discussion of biological responses. I
15 mean, everyone seems to be most focused on the intimal
16 response, the luminal response, the systemic response.
17 The other interesting aspect, talking about biological
18 response, could very well be the arterial wall into
19 other vascular, smooth muscle, the collagen elastin
20 component. And they obviously would have much greater
21 implication to all the subsequent dilatation, or some
22 of the significant endoleak responses.

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1 And while doing this study, but looking at
2 it more carefully in that aspect, it potentially could
3 give us some indicator into all the subsequent
4 progression of whether the neck's going to dilate,
5 there's atrophy, or various other aspects along those
6 lines.

7 DR. GREENBERG: I have a comment that may
8 potentially confuse things even more. But realize
9 that we're sitting here in the United States and
10 applying these certain preclinical testing things to
11 companies that are distributing grafts in the U.S.
12 And the FDA has little, if any, control over what
13 happens outside the U.S. What happens when a company
14 comes with a fair amount of clinical data from outside
15 the U.S.? Can we use that to supplant an animal
16 study?

17 I mean, if you're not concerned about a
18 healing response, you're not concerned about
19 neointimal hyperplasia because you have a year of
20 follow-up in humans from another country, are you
21 going to go back and tell that company they need to do
22 a GLP study?

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1 MS. ABEL: No, we'll go back and tell them
2 to sacrifice some of those humans to get some explant.

3 (Laughter.)

4 DR. GREENBERG: But this is where we have
5 a real problem in making a protocol for animal.

6 MS. ABEL: No, I think that's a very good
7 point, and I think that's when you have to look at how
8 different is the device from others that we're more
9 familiar with it. And if we've seen in the clinical
10 that there aren't any negative findings, it doesn't
11 seem rational to have to go back and do an animal.

12 DR. GREENBERG: Well, and is this a bad
13 message that we're giving companies to use Australians
14 and Europeans before we go to U.S. live animals?

15 MS. ABEL: Well, it's a message to the
16 Australians and the Europeans and the South Americans
17 that they ought to be paying attention to what's going
18 on there. And they should have more rational
19 requirements with respect to the preclinical
20 evaluation of their devices.

21 MR. YU: Doesn't that also depend on the
22 quality of the clinical trial from other locations?

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1 I mean, there's a big variety of the quality.

2 DR. GREENBERG: I don't disagree with any
3 of this, and I think that it would be very prudent to
4 fully evaluate the device in animals before we go into
5 humans. However, that's just not reality.

6 DR. VIRMANI: No, but there is an effort
7 by the FDA to make similar requirements, at least in
8 the western world.

9 DR. GREENBERG: I understand.

10 DR. VIRMANI: So there is an effort.

11 DR. GREENBERG: The question is now we've
12 said there's an effort, we've said there's an issue,
13 but a company comes with 100 patients with a year
14 follow-up. Do we still require that?

15 DR. VIRMANI: Yes. If you want the real
16 answer, yes.

17 DR. FOGARTY: The real answer is there's
18 social, economic, and religious difference, and
19 cultural difference, that that will never happen.

20 MS. ABEL: Did we just get philosophical?

21 (Laughter.)

22 MR. SMITH: My reaction to Roy's scenario

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1 is if there is enough explanted data out to a certain
2 amount of time, and you can show positive human
3 responses histologically, I think that's your best
4 argument.

5 MS. ABEL: But if you have absence of the
6 histological.

7 MR. SMITH: In the absence of that.

8 MS. ABEL: You've got a device that's not
9 drastically different from other things that are out
10 there, I think you look at it differently than if
11 you've got a brand new device with unique
12 characteristics. It's harder for us to sign off on it
13 in the absence of having any explanted analyses.

14 DR. CHUTER: I just want -- we've all been
15 sort of looking back to failure modes that we've seen.
16 And we're talking now grafts that are pretty much
17 plain vanilla, or as close to it as we can make. But
18 I think there is a significant likelihood that in the
19 future, a lot of these skin grafts are going to be
20 loaded up with biologically active agents. You know,
21 things to make them heal into the wall better, and
22 maybe some tetracycline to make the aneurysm behave.

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1 Maybe some antibiotics, whatever. Whatever they are,
2 they're biologically active things. And I suspect
3 that in the future you will be doing these animal
4 studies for the specific reason that the grafts are
5 intended to produce biological effects. You want to
6 just make sure they don't have any unintended
7 biological effects.

8 MS. ABEL: That's completely fair, and I
9 think that you're probably going to be dealing with
10 things like biologics and broadens, and someone is
11 going to have to figure out what that animal study
12 looks like.

13 MR. SMITH: It's hard to hear you.

14 MS. ABEL: Good. When I'm mumbling, you
15 don't want to hear it.

16 DR. CHUTER: So 180 days?

17 MR. SMITH: What's the punch line, I'm
18 just wondering.

19 AUDIENCE MEMBER: Twenty-four hours.

20 MS. ABEL: That's how long we have to wait
21 until -- never mind. If I were to summarize what I
22 heard, first of all, even though biological response

1 is the one thing that people agree that you can sort
2 of look at in an animal study, there's some
3 disagreement as to how relevant that is in terms of
4 extrapolating to the clinical as far as failure modes.

5 So I think what we can agree to is that
6 animal models can be used as a screening mechanism to
7 hopefully weed out exceptionally bad designs, and
8 maybe we'll be able to again give some
9 characterization information so that if you do see an
10 adverse effect in the clinical, maybe you can relate
11 it back. So far, we've not seen anyone being able to
12 do that as far as I know. That once you've done your
13 clinical studies, you've come up with negative
14 results, you retrospectively look back at the animal
15 studies. There still wasn't anything there to suggest
16 that you just missed it.

17 But it's still an option. It gives you
18 characterization information. And especially if
19 you're looking at a modification, maybe you can see I
20 guess when we did our animal studies, and we did see
21 a slightly different biological response, we should
22 have taken heart that that was a potential for a

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1 negative finding in the clinic, but the bottom line is
2 we still have to get to the clinic to be able to
3 interpret the data. Is that? Yes.

4 So as far as what sort of study to do, I
5 think it's kind of a confirmation thing. And that's
6 when I think it's difficult to say we need to get more
7 aggressive with respect to the animal studies. So
8 it's hard for me to sit here and say, okay, from now
9 on when you come in to the agency, we expect you to
10 have an aneurysm model. I mean, even if the aneurysm
11 model had been established, what we've seen so far is
12 that we're not getting predictive information, and I
13 don't know that we should be getting more rigorous.

14 I also don't know that we've heard from
15 anyone that we should be thinking differently with
16 respect to the amount of information that's necessary
17 for a new device. It sounds like you ought to do a
18 little bit of testing in an animal model. And maybe
19 we need to negotiate on an individual basis what those
20 studies will look like, depending on how unique the
21 device is, or depending on what additional information
22 is available. And again, looking at the pieces of the

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1 puzzle, if you have a relatively short-term study to
2 look at delivery and deployment in one animal model,
3 what else do you need to look at in other models, and
4 that sort of thing. So it's still fairly
5 individualized.

6 The duration of study that we've heard
7 about ranges anywhere from 30 days to up to six
8 months, to until we're absolutely certain that there's
9 healing. I think it's rational, again, to look at the
10 individual devices and say, okay, let's look at the
11 study design, let's look at the comparisons, let's
12 look at the controls, whatever, and figure out
13 appropriate interim sacrifices. And maybe we need to
14 do some more creative stopping points for animal
15 studies than we've ever done before. I think someone
16 suggested that it may be, and I think it was Dr.
17 Virmani, that if you see everything has hunky-dory at
18 three months, do you really need to go on to the six
19 months.

20 So we have not done that previously. With
21 our animal studies, with what folks send in to us,
22 they say we're going to do these sacrifices. And

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1 usually at the interim sacrifice times there are fewer
2 animals. So you don't have enough data to really make
3 those sorts of conclusions. So I don't know that
4 we've made any huge leaps and bounds in terms of
5 trying to figure out different ways of handling animal
6 evaluations. But I think at the very least we've all
7 agreed that animal data really gives you just the lack
8 of negative information, and maybe some
9 characterization.

10 DR. CHUTER: Is histology the only thing
11 we're going to be looking at, or are there other
12 things that should be measured in these animals to
13 give us some sense of what's happening?

14 MS. ABEL: What we had talked about as far
15 as the list of potential negative findings is that you
16 would document it. So you're obviously going to
17 document that sort of thing, even though you're not
18 really evaluating patency.

19 DR. CHUTER: What about systemic effects?

20 MS. ABEL: Huh?

21 DR. CHUTER: Systemic things. Anything
22 there that you want to look at?

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1 MS. ABEL: It probably depends on what
2 your device is.

3 DR. VIRMANI: It may be smart to do some
4 blood tests. For sure, I agree with you that -- you
5 know, look at animals who have received the devices to
6 see what is the leukocyte count, has it changed? Has
7 the hematocrit, for example, fallen. I think that's
8 an important thing to look at and it should be
9 incorporated within the design, biological response in
10 a sense.

11 DR. CHUTER: Maybe platelets, maybe some
12 co-ax, some of the worse reactions you could say are
13 a DIC or something like that. It's a fishing
14 expedition that we're on anyway. We don't really know
15 what we're looking for. We may as well cast the net
16 fairly widely.

17 MR. SMITH: Is that you, Tim who said
18 that?

19 DR. CHUTER: What about fishing?

20 MR. SMITH: Yes.

21 DR. CHUTER: No that was David Hartley.
22 I don't fish at all.

1 (Laughter.)

2 MR. SMITH: I do think there's two
3 different types. In a research mode, you do all of
4 that. That's what we're learning, is this a good
5 model, is this a good way to do the study. Is this a
6 preliminary prototype? But when you're down at the
7 final device evaluation stage, GOP for submission to
8 regulatory authority, I think then your scope is more
9 --

10 DR. CHUTER: I think that's reasonable,
11 but we have no control over what things are being
12 looked at in the earlier phase of study. Unless you
13 impose it at a later phase, people are not even going
14 to bother to look for things that might turn up bad
15 findings, maybe they're not.

16 DR. BIANCO: I think another reason to
17 cast your net widely is that it often aids in
18 separating a pre-existing animal disease versus
19 device-related effects.

20 MS. ABEL: So we're adding to our animal
21 requirements the need for blood data?

22 DR. FOGARTY: Dorothy, I think we've got

1 to think about what is possible and what you can do
2 and what is probable. I think Tim can go do all the
3 chemistry he wants. I think it's inappropriate to
4 commit animals to do that because it won't relate.
5 You can get a net as wide as the ocean. I don't think
6 you'll get most of the information, nor fish. The
7 fish will run away from that net because it's so long
8 and wide that they don't get in the net. They escape.
9 You cannot add -- the least burdensome route is the
10 burden the FDA has and we have as physicians.

11 I think you do all kinds of science and
12 exotic tests, but make that part of the regulatory
13 requirement means we're not going to see any devices.

14 MS. ABEL: I don't think just having to
15 measure platelets and hematocrits is going to stop the
16 evolution of man. But I think your point is well
17 taken, is that something that needs to be part of
18 every animal study for endovascular graft and I guess
19 --

20 DR. FOGARTY: Or any human study.

21 MS. ABEL: Well, that's --

22 DR. FOGARTY: Or whether it's doable.

1 MS. ABEL: I think if there was again,
2 looking at the individual device, if there was
3 something related to that device where you had to
4 specifically look at more systemic effects, then maybe
5 it's appropriate to include it. But to characterize
6 your model, that's a whole other issue and that's just
7 outside of our realm of dealing with, doing good GLP
8 studies. I just don't even want to think about going
9 there.

10 It was a nice thought. Thanks for
11 sharing. Are we ready to wrap up?

12 We keep forgetting to ask the audience, in
13 particular, if they have any comments. We're at the
14 point now of wrapping up, so we just had to put
15 something with an animal on it. So the first cow is
16 saying moo and the cow in the back is saying you cow,
17 I was going to say that and I figured we'd have a
18 little bit of that going on.

19 (Laughter.)

20 A little light heartedness.

21 (Pause.)

22 MS. SMITH: I think what we want to look

1 at as far as going back to our objectives that were
2 laid out for this session is to kind of summarize the
3 potential modifications to improve animal studies and
4 also to look at what animal studies should look like
5 in the future. And I think there's been little
6 consensus regarding a lot of the failure modes and
7 attributes. We've kind of honed in on biologic
8 response, specifically, and Dorothy provided a fairly
9 good conclusion a few minutes ago on what that should
10 look like.

11 Are there any other potential
12 modifications that were mentioned throughout the
13 session that should be listed here as a way to improve
14 animal studies?

15 MS. ABEL: Would people agree that we
16 should consider in terms of animal study design to
17 look at the potential for early stopping?

18 MR. BIGGERSTAFF: Definitely.

19 MR. CARDELLA: Another option that hasn't
20 been discussed much that I've heard anyway is there
21 are ways being developed in small animals that you can
22 basically do nondestructive testing of the animals.

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1 You had mentioned earlier that the interval sacrifice
2 numbers were pretty small because you can't do a
3 million animals in the project to start with.

4 One potential suggestion and I don't know
5 if it's modification, but you might begin to allow
6 nondestructive testing of animals and I'm talking
7 about things like CAT, CT scanning, CT scanning
8 profusion, MRI scanning, those types of tests are able
9 to look for things like inflammation, neointimal
10 hyperplasia and those types of things that you might
11 be interested in for this particular session can be
12 done nondestructively. Then you can leave the animal
13 alive and start with a smaller number. I think that
14 might be an improvement that to the extent that you
15 can interrogate the things that you're trying to
16 measure nondestructively, at least some thought ought
17 to be given to that.

18 MS. ABEL: That's interesting. That's
19 good.

20 MEDTRONIC: This is Dan. One of the
21 things we might also look at too is there decided to
22 be a gold standard of animal models. Each animal

1 model offers a different aspect to test and each
2 animal, depending on the length of the study, you
3 know, they offer different applications for maturity
4 of the device, different elements you can't analyze.
5 You start with a small calf and give it a year and it
6 looks like that thing on the stage. Their aorta may
7 have grown a couple of millimeters. You might get an
8 element of migration into that level.

9 But is there -- I mean we're talking about
10 an ideal model. Is there one that we all worked on
11 say greyhounds in the State of California where
12 there's no greyhound racing or something like that.
13 That could minimize the use of animals, different
14 models. Every animal model, everybody might say we'll
15 evaluate device deployment in a calf. We'll evaluate
16 the healing rate in a dog. Something like that.

17 MS. ABEL: In an ideal world, that would
18 be fantastic. The problem is we have so many
19 established companies that have their own
20 methodologies of doing it. Unless we had really
21 strong evidence that one model was absolutely more
22 useful than the others, it's just -- there would have

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1 to be a big group hug and everybody would agree to
2 give up what they know and change the world. But I
3 mean it definitely -- I mean at the very least it
4 would be helpful for new companies if we could lay out
5 what we think would be a rational strategy.

6 Is that fair?

7 DR. WHITE: I hate to keep going back to
8 experience here, but in fact, models are
9 interchangeable because none of them are predictive
10 for what we're looking for.

11 (Laughter.)

12 MS. ABEL: So you're saying they're
13 useless?

14 DR. WHITE: No, I'm not saying they're
15 useless. They're useful for a few animals for the
16 length of time we've said, but the data is
17 interchangeable because none of them are predictive.

18 MS. ABEL: But it would be helpful, you
19 have to agree that if we said evaluate delivering
20 deployment in a bovine, not that everyone has to do
21 it, but if the next person coming along doesn't know
22 anything we said use that animal model and if all the

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1 next people who came along used it, eventually, we'd
2 have a body of information that may be a little bit
3 more comparable.

4 DR. WHITE: So it could be deployment if
5 the size of the animal is an issue, an acute
6 deployment in a bigger vessel. But there's no chronic
7 nature to that. There's nothing chronic to that.
8 That's an acute deployment.

9 MS. ABEL: That was a suggestion and maybe
10 we should be looking at delivering deployment in the
11 bovine and then what else should we be looking at? I
12 think that's reasonable to lay something out in terms
13 of this would be one acceptable approach, not to say
14 that there aren't others.

15 MS. SMITH: As far as what animal studies
16 should look like in the future, it goes back to these
17 comments as well that there is potential for stopping
18 studies early based on what you're looking at and if
19 there are complete vessel response and healing.

20 Is there anything else that we need to add
21 to that?

22 DR. BIANCO: I just need to make one

1 comment about predictability. The primary purpose of
2 my view of this kind of work is to provide an
3 assessment of clinical safety and someone mentioned
4 there's a lot of iterations that go on that fail in
5 animals that we don't talk about because we are under
6 proprietary restrictions. There are some failures,
7 but I would say that there are probably a lot more
8 clinical failures if we weren't doing the animal
9 testing and those iterations.

10 MS. ABEL: Maybe something we should put
11 in our summary in terms of potential modifications to
12 improve animal studies is just to remind people that
13 it is critical to do some early design related what do
14 you call them, verifications? I think actually that
15 can be some of the more critical information. Like
16 you say, it's screening and that's a lot of what we'll
17 get out of these studies.

18 AUDIENCE MEMBER: Is the term * (12:46:29)

19 MS. ABEL: Could you give us one?

20 AUDIENCE MEMBER: Early design
21 development.

22 MS. ABEL: Anything else with respect to

1 what it would look like in the future? I mean just to
2 reflect the potential business?

3 AUDIENCE MEMBER: Just to say I think
4 animal studies have to be taken in context of the
5 entire testing plan and that to look at animal studies
6 is they have to be this because of that. If you don't
7 look at it in the context of what other testing are
8 you doing, what other bench top testing you're doing,
9 cadaver modeling, other things, I think it's a
10 mistake. I think it has to be appropriate in the
11 context of your entire testing.

12 MS. ABEL: That's a very good point and I
13 think we also should document in the context of the
14 other testing but also to the device itself.

15 So what I heard is that we're really
16 individualized plans, depending on what the device is,
17 what you can show with the other testing, what
18 additional information you have available from either
19 prototypes or whatever.

20 Yes?

21 MR. SCHRECK: I'd like to make another
22 comment. When we look at the testing from a design

1 control standpoint, probably for each functional issue
2 when you want to investigate, you can develop a very
3 specific and better bench test model than animal
4 model. But on the other hand, all those models are
5 very specific and typically very narrow in scope and
6 the advantage of the animal model is if you have a
7 certain complexity that you probably can't reproduce
8 on the bench. And you don't necessarily in an animal
9 look for failure modes you already know. It's kind of
10 a check at the very end that maybe there's something
11 else that you have overlooked that you couldn't test
12 for that pops up.

13 So that's why it's difficult to defend and
14 define the specific endpoint for the animal studies
15 because you don't know what you're going to look for.
16 But I think it's a good reality check to do it at the
17 very end. It may not be specific to any particular
18 failure model or any particular function, but it gives
19 you kind of like warm and fuzzy before you go into the
20 kingdom studies.

21 MS. ABEL: I would agree that that's
22 actually a very good summary of the discussion that

1 we've had today. I think for the most part people
2 believe that it is a reality check and it's a good
3 screening mechanism and so I just want to make sure
4 getting back to is there any need to improve the
5 models, is there a need to incorporate aneurisms and
6 stuff like that so it's a more realistic reality
7 check, or does that just make it harder and introduce
8 more questions than answers?

9 DR. VIRMANI: To me, probably that's true
10 that we don't have a very good model as yet as the
11 standard model, but I think our goal should be to
12 develop such a model and if researchers can come up
13 with a good model tomorrow, you may change the way you
14 are evaluating and I think we should put in here
15 saying the goal is to have a better animal model.

16 DR. FOGARTY: Dorothy, are we talking
17 about animal models or bench models or are we mixing
18 them up? I don't understand where we are.

19 MS. ABEL: We're still on animal, Tom.
20 We'll let we know when we switch over to bench.

21 DR. FOGARTY: Okay.

22 (Laughter.)

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1 I thought we were talking about
2 benchmarks.

3 MS. ABEL: Just in terms of when you
4 evaluate a device, you have very specific testing on
5 the bench and the animal model kind of brings
6 everything together, even though it's a * (12:50:16)
7 model. It's something to look at the overall picture.
8 That's why bench came back into the world.

9 DR. FOGARTY: Okay, so it did come back.

10 MS. ABEL: It did. It wasn't a senior
11 moment or anything.

12 DR. FOGARTY: I got to check all the time.

13 (Laughter.)

14 MS. ABEL: Rod, can you help him with that
15 so the whole audience doesn't have to --

16 (Laughter.)

17 MR. BIGGERSTAFF: Actually, I can't.

18 (Laughter.)

19 MS. ABEL: I think what we're trying to do
20 is to refine the word with respect to the goal. I
21 would say develop an aneurismal model, a validated
22 aneurismal model, and then I'd take out the rest of

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1 it. I think if that ever happens, then we can figure
2 out if it's going to give us more information or not.

3 DR. CHUTER: I have some concerns about
4 that last animal model thing. Because you're just
5 introducing a whole new pathology, you know, that
6 doesn't have anything to do with the human pathology
7 you're trying to treat. It's an operated aorta or
8 it's an aorta that's had elastin in it and you know,
9 it may have very little to do with the things that
10 we're interested in this testing because the best that
11 we care about the most is the implantation size, the
12 bits that are actually remote from that.

13 I have some concerns about these
14 aneurismal models because they're not going to be the
15 same as the human and they may be introducing the new
16 pathology.

17 MS. ABEL: Yes, but if someone could come
18 up with one, if someone can feed their sheep, you
19 know, the right foods so that they end up growing
20 aneurisms, then we can talk about whether you gain
21 anything new by testing in that particular --

22 DR. VIRMANI: I could give an example.

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1 For example, we know very little about
2 atherosclerosis. They didn't come up with the mice
3 model in the sense. So I think the future is to draw
4 up such a model. If we can develop it, it's a good
5 goal.

6 DR. CHUTER: That kind of a model looks
7 nothing like the models we have right now. We are
8 very, very far away from that goal.

9 DR. WHITE: I actually take an opposite
10 point of view. I think the modeling has developed a
11 lot of marginal drugs that don't work that get sold.
12 I mean this is the wrong way to go. Human data is the
13 most reliable data set we've got. And we ought to
14 spend our time and effort there.

15 NIH wants to spend money on modeling,
16 that's fine. But it is not a priority, even any more
17 for academia unless you want to spend the rest of your
18 life developing stuff that's not going to go anywhere.
19 And I say that as someone who did that for 20 years.

20 DR. FOGARTY: It's longer than that.

21 (Laughter.)

22 MS. ABEL: Robert, you had a very

1 interesting point during the break. You had mentioned
2 that maybe it would be worthwhile to develop --

3 DR. WHIRLEY: It just seems to me in our
4 discussions about animal models and about the utility
5 of aneurisms that maybe with regard to the clinical
6 performance of endovascular grafts that the luminal
7 irregularity associated with atherosclerotic plaque
8 might be one of the most salient features that's
9 missing from the animal models. And I suggest that if
10 the Agency had a very large budget to develop new
11 animal models, try to develop and incorporate
12 atherosclerosis would be a worthwhile endeavor, but I
13 don't know how to do that.

14 MS. ABEL: But I just think it kind of
15 brings the point, even if you stick in an aneurism,
16 you're still lacking the other and it certainly, if
17 there was more research on trying to develop a larger
18 animal model for atherosclerotic disease, it would be
19 helpful in terms of the aneurism evaluation and also
20 for treatment of atherosclerotic disease.

21 DR. CRIADO: Dorothy, it seems to me that
22 to include as part of a wrap up, as an important goal

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1 to develop a better animal model is counter to this
2 period of the whole discussion this morning. What I
3 heard was the opposite of that, that we should move
4 away perhaps from that, not towards a better model, an
5 animal model that is. How would that be an important
6 goal following this discussion?

7 MS. ABEL: I think that what we're trying
8 to do is capture the opinion of the various people in
9 the room and I would -- this isn't a consensus
10 meeting, necessarily. I think that there are those
11 that believe there may be benefit in terms of
12 developing better models and I don't think that we can
13 necessarily say absolutely not, you don't go off and
14 do that.

15 I also did not hear from the majority of
16 the people in the room that they believe that they
17 would get valuable information from that model, but if
18 it doesn't exist, we can't assess it. So if they
19 would develop it, we can look at it and maybe we would
20 change our minds, but at this point, most people
21 sitting here don't predict that it would be a
22 significant advancement in terms of the evaluation.

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1 DR. CRIADO: It just seems excessive to
2 call it an important goal. That's kind of implicit.

3 MS. ABEL: We said potentially develop a
4 validated aneurism model and potentially develop an
5 atherosclerotic or disease model.

6 So when we document, I think you're
7 absolutely right. I don't think anyone said that's
8 what we got to do to fix the problem, but it's an
9 action item that someone may decide to take. Not you,
10 obviously.

11 Any other thoughts? Peanut gallery?
12 Audience.

13 (Laughter.)

14 AUDIENCE MEMBER: If we're going to --

15 MS. ABEL: Could you use the microphone,
16 please?

17 AUDIENCE MEMBER: My question is if we
18 decide to set a criteria of healing as complete, what
19 are going to be the constituents of that criteria that
20 we're going to say that the graph is complete? And
21 are we going to develop -- is the Agency going to have
22 specific things that they want to see at 30 days, at

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1 90 days, at 180 days in a cow versus a pig versus --
2 I mean are there special things that you have to see?
3 Are there things that if you see them, they're
4 acceptable? Are there things that if you saw them,
5 it's a definite no? And would you -- would there be
6 guidelines for that?

7 MS. ABEL: I would say first of all that
8 there was not consensus, that healing would have to be
9 complete. I think that we had said that for
10 individual devices, that it would be important to come
11 up with a strategy for evaluating the device in the
12 context of the other testing that would be done, that
13 would assess appropriately either the modifications or
14 the device itself.

15 We talked about maybe coming up with some
16 ways to look at interval information so that you
17 wouldn't have to go out to the longer term, if
18 everything looked like it was going status quo. We
19 talked about having controls. All those sorts of
20 things, so the answer to your question is no. I just
21 started with a lot of rambling, but the answer is no.
22 There's no way that the Agency would have the

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1 knowledge base, no offense to my friends over here.
2 But we just -- that's not a humanly possible thing for
3 us to do. And we're not the right people to do it, in
4 my opinion. That could be theoretically again some
5 research that would be useful and we could include
6 that as another potential action item is that if there
7 are folks out there that are interested in doing
8 research take a look at healing response and see how
9 much it varies depending on different devices that are
10 put in and what have you, but I don't think it's that
11 definable.

12 Anyone else?

13 DR. HALLISEY: Dorothy, I don't think the
14 word complete is an appropriate term that we should be
15 using in this forum. Healing is never complete in the
16 vascular graft in the sense that the body has
17 completely accepted them. There continues always to
18 be some long-term chronic response. So I think what
19 we're really saying is we want to see that healing is
20 stable, has reached a plateau. That would be my
21 interpretation.

22 MS. ABEL: Hi, John.

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1 DR. MATSUMURA: I just walked in here late,
2 but I'm looking around at my colleagues here and I
3 don't see Greg Siccard here or some of the -- but I
4 heard from four of my colleagues about the
5 deficiencies of animal models for testing medical
6 devices for aneurisms and the current kind of
7 generation of devices and I would agree with them, but
8 I think when you look down the future, if there is a
9 lot of utility for animal models, if we're going to be
10 doing a hybrid therapy, if we're going to try to be
11 doing biologic modification, like a coded stent or
12 something. Animal models have an enormous role in
13 developing and testing those therapies, if we're going
14 to try Fibrosin, saving aneurism next to improve the
15 healing and use biologics in combination with the
16 therapy.

17 I think there are some animal models that
18 are useful. The murine ones, the transgenics that are
19 being used to test metalpertinese therapy and
20 certainly that data is instrumental for going into
21 clinical trial with pharmacologic therapy for
22 aneurisms which at some point down the line might be

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1 combined with anavascular therapy, so I would agree
2 that the current grafts don't really have a utility
3 really for those models because they don't simulate
4 the problems we view of the current grafts, but I
5 think in the future there will definitely be a role
6 for animal models in what future therapies may lie for
7 aneurisms.

8 MS. ABEL: Tim agrees.

9 DR. CHUTER: I just have to compliment
10 your insight.

11 (Laughter.)

12 I think you were here and heard Tim's
13 suggestion.

14 AUDIENCE MEMBER: We talked earlier about
15 the role of using animal models in testing deployment
16 as a design verification test and it didn't seem like
17 there was a lot of consensus that that was terribly
18 valuable, but to the extent that animal models were
19 really helpful in clinical practice development,
20 hasn't really been discussed. And if you look at the
21 popular press about some of the device issues that
22 have happened in the last couple of years, whether it

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1 was AAA or stent issues, a lot of them have to do with
2 deployment and then undeployment. If something does
3 go wrong, is there a methodology for which you recover
4 the device that is stuck or unopened or the balloon is
5 stuck or what have you. And whether design
6 verification includes the clinical practice, I don't
7 want to create new design dossier requirements, but I
8 think that to the extent that animal studies are
9 really valuable to clinical practice development and
10 that that's an important component of the usability of
11 the whole system and the clinical training component
12 of rolling out a new device.

13 I don't really want to lose the focus of
14 that in our development processes.

15 MS. ABEL: I'm afraid that kind of went
16 over my head because I'm not very familiar with design
17 verification requirements with respect to QSR and that
18 sort of thing, so --

19 AUDIENCE MEMBER: If you look at the FDA
20 submission is a design verification dossier for the
21 most part.

22 MS. ABEL: Right.

1 AUDIENCE MEMBER: Clinical practice, as a
2 component of that has not really been so much of a
3 requirement, but if you look at the body of problems
4 that have resulted recently in devices for
5 implantation, a lot of them are associated with the
6 clinical practice aspects of the device and not so
7 much the design of device itself.

8 MS. ABEL: We certainly look at the
9 clinical studies. I mean, you know, when I say we
10 don't look at the design dossier, it's I don't look at
11 the manufacturing section. Personally, that's not my
12 area of review.

13 But we look at the clinical studies, the
14 sorts of things that you mention with respect to the
15 delivery and deployment failures and stuff were
16 certainly observed in the clinical studies. They're
17 documented. It's in the labeling that these are for
18 problems that you run into and I think what I would
19 suggest is that when you mention it with respect to
20 animal studies, we did not see them in the animal
21 studies. We did see them in the clinical study. We
22 do make sure that that's part of the overall picture

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1 of the information that we have available.

2 Now whether you're suggesting potentially
3 that the clinical should be put into the design
4 verification, you know, documentation for what's it
5 called, quality systems?

6 MR. SMITH: Yes, clinical studies would
7 fall under design validation.

8 MS. ABEL: Instead of verification.

9 MR. SMITH: Verification, you see an in
10 vitro module. That's 95 percent of a verification
11 dossier. So there might be other stuff people can put
12 in, the development of clinical practice in terms of
13 how they're going to train people or whatever, what
14 other incidents do come up, but I agree with you in
15 that. Those things come out of the initial clinical
16 studies of how this really translates into the
17 clinical practice and then the labeling is updated all
18 through the approval process as we very well know. So
19 I don't think we really lose it.

20 And I'm sorry, I don't know who that
21 colleague was, but the popular press doesn't really
22 understand all those details.

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1 MS. ABEL: All right. I think we better
2 break for lunch. And of course, you're on your own
3 for lunch. This is a government-sponsored meeting.

4 (Laughter.)

5 We'll meet back here at 2 o'clock.

6 (Whereupon, at 1:04 p.m., the meeting was
7 recessed, to reconvene at 2:00 p.m.)

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2:12 P.M.

DR. FILLINGER: Okay, great. As you've heard earlier, I'm Mark Fillinger. I'm a vascular surgeon so I'm going to talk about the clinical perspective of sealing and fixation effectiveness as the microphone warms up as well.

I notice there's the clinical perspective and then the scientific perspective, so when I noticed that I said excellent, I can be totally nonscientific.

(Laughter.)

So that's great. So you know, that's right, you get what you ask for.

So basically I also realized this morning that it's not an 8-minute clock, it's a 15-minute clock, so that's okay. But I got permission to go over.

So basically what I tried to do is sort of group this into something catchy. So I put a bunch of things in there to talk about what we know and what we don't know. Basically, we know something about all these things, but we still have a lot to learn so

1 we've sort of divided it into disease, distortion,
2 dynamics, device, delivery, deployment and durability
3 of which I'll talk very little about, since that's
4 going to be talked about later on.

5 But dimensions are something that we think
6 we know a lot about, including things like early on we
7 sort of realize that you have an axial cross section,
8 you get this elliptical cross section that's not
9 really an accurate representation of the vessel. But
10 if you do a slice that's perpendicular to the vessel,
11 you get what appears to be an appropriate cross
12 section, although this is not always a circular cross
13 section. It's close. And if you take the narrower
14 diameter here, most of the time that's correct,
15 although the neck is not always a nice uniform
16 cylinder.

17 But even if we get that right, there's
18 still more to it. Well, of course, there's plaque,
19 whether it's calcified plaque or noncalcified
20 atheroma, it's not only there, it's also eccentric.
21 And then where do you place the diameter measurement
22 then? Well, we sort of know that we measure the outer

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1 wall because that's where the load bearing portion of
2 the wall is, but if we do that and we size the device
3 for the outer wall, then how is it going to respond to
4 this eccentric cross section, this very small cross
5 section for a device that's sized to the outer
6 boundary. So that's a little bit of a problem, as
7 well as sort of -- people who have very sort of
8 individual ways of doing these measurements where you
9 might get at least a couple of millimeters' difference
10 from one person to another. We still have hopefully
11 not too many, but still there are people I know who
12 are using hard copies to do their measurements, even
13 though it's twice the error or an electronic work
14 station, even though electronic work stations to do
15 electronic calipers exist in every hospital that has
16 a spiral CT scanner, it's still being done this way
17 despite the fact that the error is twice as high.

18 Even if you use an electronic work station
19 of whatever type, there is still some inter and intra
20 observer variability that's built in to these
21 measurements. So what we think we're measuring has a
22 certain degree of inaccuracy and imprecision,

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1 basically difficulty in reproducing this. And I won't
2 get into length measurements with angiographic
3 catheters and things like that, but we all know there
4 are a lot of problems with that. And this is sort of
5 something we don't talk about very much, but
6 angulation is always part of any clinical trial. We
7 measure it. We say these are the limits and yet
8 usually the way we measure angles is we sort of get a
9 two-dimensional projection of something and then we
10 sort of look and it's about this many degrees. We
11 just sort of look at it and gasp.

12 And as you can see, this is the same
13 patient and obviously what angle you're looking at
14 makes a big difference or what rotation of the
15 aneurism or what view you're looking at makes the
16 angle look quite different. And the angle can be
17 different depending on where you put these marks. It
18 depends on exactly what part of the neck you're
19 measuring this in. There's a huge amount of variation
20 and yet we say okay, 45 degrees, above this; or 60
21 degrees and that's the limit for this device.

22 And there is a lot of imprecision, even in

1 this, where something that we've all been working at
2 and looking at for a number of years and I personally
3 have done lots and lots of work on this, trying to
4 make this more precise. There is still a lot of
5 imprecision and inaccuracy and these are the things
6 that we're basing our patient selection and our device
7 sizing on. And I just want to sort of re-emphasize
8 that because when we start talking about how we set up
9 bench testing and that sort of thing, basically we
10 have to build in design tolerances is what I'm saying.
11 That's a long way of saying there need to be certain
12 design tolerances because there's going to be slop and
13 depending on who's doing the measurements in some
14 cases more slop than others.

15 Even with the most precise measurements
16 possible, there's going to be disease, calcified
17 plaque, noncalcified plaque or atheroma and thrombus
18 which have the same density on CT, but we sort of use
19 those terms interchangeably, but it's not really the
20 same thing histologically, but nonetheless, we talk
21 about them that way.

22 We've heard a lot about aneurysmal

1. degeneration, the neck is immediately adjacent to a
2 disease portion of aorta that's already dilated.
3 That's why we're doing the procedure in the first
4 place.

5 Inflammation that occurs to varying
6 degrees, I think we've all seen patients after an
7 endograph that get this thick inflammatory rind around
8 them, very infrequent, uncommon, but to some degree
9 there is a degree of inflammation with every endograph
10 placement. Sometimes fibrosis, tissue end growth. We
11 talk about to a great extent earlier. And all of that
12 has variability as well.

13 Looking at this, good neck. Sure looks
14 good. That's about as nice an anatomy as you're going
15 to see. But if we look at this with a 3-D
16 reconstruction, the lumen here in red, the standard
17 sort of thing, atheroma and thrombus in yellow and
18 calcified plaque in white, you can see actually
19 there's more yellow here than there is in the aneurism
20 sac itself. And if you look at the CT slides, there's
21 this eccentric plaque again and so how you look at it
22 gives us a varying impression. If we're looking at

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1 these with angiograms, if we're not looking closely,
2 we may miss or fail to quantify or fail to document
3 potential disease states that may affect the outcomes
4 of the endographs in clinical trials or in our own
5 personal clinical series. And if we don't capture
6 this information and we have a bad outcome later,
7 we're going to miss the boat in terms of better device
8 design down the road and better patient selection and
9 how we should do our imagining. So we have to be very
10 careful about doing these measurements because we know
11 almost nothing about how these eccentric plaques
12 affect the device.

13 How do we quantitate it? Well, you can
14 look at this sort of MIP image, maximum intensity
15 projection, say yeah, there is a lot of calcification
16 there. And that's kind of how we do it now, right?
17 It's like people look at it and go that's pretty
18 calcified. Do we know what that does to the device?
19 No, we really don't know. We just go it's really
20 heavily calcified. Maybe they're not as good a
21 candidate, but we don't really have a way of saying
22 the outcome is going to be this much better or worse

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1 because of this.

2 So maybe we should have some sort of a
3 thing like this where we have -- where we quantitate
4 in terms of a diameter plot. In this case, it's
5 actually cross sectional area converted into a
6 diameter where the lumen again is in red. The
7 thrombus and atheroma in yellow. In this case,
8 calcified plaque is in blue which there's very little
9 of in this particular case, but you can immediately,
10 if you put a device along this and you say okay, the
11 device is this diameter in the trunk and it's this
12 diameter at the distal attachment site, you can see
13 the degree of oversizing immediately with a graphical
14 inlay. You can see even here though with a
15 quantitative measure of the plaque, this doesn't tell
16 you whether it's a focal thick plaque and it's
17 eccentric or a thin rim that goes circumferentially
18 around. So even this doesn't capture all the
19 information. But it's at least a step towards
20 quantitating some of this that might help us again in
21 patient selection and determining device outcomes and
22 problems with devices in terms of getting at sort of

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1 root cause analysis.

2 And that sort of naturally leads us on to
3 distortion and device interactions which I sort of put
4 together and basically that comes from nonuniform
5 diameter at the site of fixation and ceiling. Rarely,
6 rarely, do you see, even that patient that I just
7 showed you that looked like they had a nice, long
8 uniform neck, they did not have a uniform diameter,
9 uniform plaque. They had eccentric plaque that varied
10 along the neck and even the diameter varied to some
11 degree. It's not like an animal that has a nice,
12 smooth uniform neck in basically any case.

13 There's angulation which can be focal.
14 There can be a lot of tortuosity over the entire
15 device which can affect the tension on it. We talk
16 about loads and forces and that sort of thing which
17 this isn't the scientific part, so I won't talk about
18 that. And then the changes over time. So the
19 diameter may increase due to the outward radial force
20 of the stent. It may increase due to natural
21 degeneration of the neck. You may get increased
22 tortuosity due to sac shrinkage.

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1 All of those things are going to put loads
2 on the devices and unfortunately, aneurisms are like
3 snowflakes, no two are identical. So you have to
4 build in again sort of this -- again this sort of
5 concept of design specifications that have tolerance
6 limits because that's all you can do is talk about
7 this bell shaped curve and what percentage of the
8 aneurisms am I going to be able to treat. I have
9 certain design tolerances for the device and I have to
10 pay attention to what is there clinically so I can
11 figure that out.

12 How do I need to design the device and
13 that comes from I think Rod White said, basically our
14 clinical data is really the best information we have
15 about how we're going to design these devices.

16 Just one example of how this sort of
17 distortion occurs with the device, if you have neck
18 angulation, you may want to get the device deployed
19 like this where the top of the device is coaxial to
20 the vessel or the device is coaxial so that the top is
21 perpendicular to the vessel, but depending on the
22 device and your level of experience in deploying that

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1 device, especially if you're a novice, you may end up
2 with a device that's deployed like this. And that's
3 obviously going to affect the long-term durability of
4 that device and its performance.

5 This same amount of curvature here also
6 affects the cross section which may start out as a
7 nice circular cross section of the device, but even if
8 the neck maintains a circular cross section which it
9 often doesn't, as it goes around this bend, even if
10 the aorta is nice and circular, the device likely will
11 not, it will take this elliptical cross section as it
12 goes around this bend. In characterizing that amount
13 of elliptical distortion as it goes around the bend is
14 probably important because that can lead to endoleaks
15 in the short term. It can lead to metal fatigue and
16 fabric wear in the long term. And almost every neck
17 has some degree of angulation and tortuosity and yet
18 very little of our preclinical testing is aimed at
19 figuring out this sort of issue and this problem.

20 Plaque device interaction. Again, the
21 sort of elliptical cross section affects the device
22 differently on different parts of the device. It's

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1 not uniform stresses around the device because most
2 plaques are not uniform circumferential and equally
3 thick all the way around. And you can -- it's all
4 very well and good to say well in my clinical trials
5 I'm not going to let any patients with this cross
6 section in my clinical trial. And you may be
7 successful at doing that. However, as soon as that
8 device is released, you know darn well that a patient
9 with a plaque like this is going to be treated. And
10 in part, because some people just don't pay any
11 attention to the directions which is hard -- you can't
12 get around that. But also, in part, because you get
13 patients who are truly at high risk for surgery. They
14 have a high risk of rupture and therefore their
15 alternative is to place a device in a suboptimal
16 situation or to just observe them until they rupture.
17 And so you get into these difficult situations where
18 you really -- your best option out of three bad
19 options is to put a device into a difficult situation
20 where it may not perform perfectly well.

21 Speaking of doing things like that, the
22 effective proximal and distal fixation length is very