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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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WORKSHOP ON PRECLINICAL TESTING FOR ENDOVASCULAR
GRAFTS

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WEDNESDAY, JULY 28, 2004

The workshop came to order at 9:00 a.m. in the Grand Ballroom of the Hilton Washington, DC North, 620 Perry Parkway, Gaithersburg, MD. Dorothy B. Abel presiding.

Steering Committee:

Dorothy B. Abel
Marianne Grunwaldt
Angela C. Smith

Scientific Advisory Committee:

Mark M. Dehdashtian
Stuart T. Rodger
Louis J. Smith
Matthew S. Waninger, Ph.D.

PRESENTERS:

Michael J. Hallisey, MD
Mark F. Fillinger, MD
Robert G. Whirley, PhD

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2001N-0463

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TR3

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

2 9:09 a.m.

3 MS. ABEL: Welcome to our workshop on the
4 preclinical testing of endovascular grafts. And we're
5 going to start out by introducing Donna Bea-Tillman,
6 who is our office director in Office of Device
7 Evaluation. And I'm not going to say anything else
8 about you.

9 MS. BEA-TILLMAN: Well, good morning, and
10 thank you all for coming here. I know Gaithersburg is
11 not the sort of vacation spot of the world, especially
12 on a rainy morning. I've heard several travel horror
13 stories. I won't share with you my own. Actually we
14 came, my husband and I just spent the past week in
15 Nova Scotia, and got home last night.

16 It was interesting because it seems like
17 I can never get very far away from the work I do here
18 at FDA. We were up in Nova Scotia visiting, and we
19 went to this Highland village. It's kind of a neat
20 place. They recreated Scottish life around the turn
21 of the century, and they had built homes and shops and
22 things like that. We were standing in the general

1 store, and I was looking, and there were bales of
2 flour, and tins of hard tack, and all that other stuff
3 that those hardy pioneers ate.

4 And on the shelf was Dr. Johnson's Tonic.
5 And it purported to cure pretty much everything under
6 the sun. And there were a couple of other salves and
7 powders and things, all from the early 1900s. And I
8 was standing there thinking, gosh, we've really come
9 a long way, kind of reading it and chuckling, and this
10 tour group came in the door behind me. It was a bunch
11 of senior citizens from the U.S. And I heard one
12 gentleman say to the other that he had just had some
13 surgery, and he had gotten one of those new-fangled
14 stents. Now I'm too sure what stent he was talking
15 about. I think it was probably one of the drug-
16 eluding coronary stents. But it was kind of funny to
17 stand there, the juxtaposition between these tonics
18 and things that claim to cure all kinds of diseases
19 and then hearing somebody talk about what I would
20 consider probably one of the most novel medical
21 devices we have on the market right now.

22 And you're tempted to think, gee, we've

1 come a long way, we've answered all the questions.
2 But I think it's really important to not stop because
3 we certainly still have a long way to go. And I think
4 this workshop today is certainly one of the steps
5 we're taking in trying to continue to move forward.

6 The agency has a new initiative that you
7 may or may not have heard about called the Critical
8 Path initiative. And the idea behind this is to try
9 and speed the time between product initial development
10 and product availability on the market, the idea being
11 that there's this critical path between product
12 concept and actually getting things out there to
13 benefit the public health. And I think that this
14 workshop fits really nicely into that initiative,
15 because preclinical testing is a really -- tends to be
16 a very important and sometimes a big stumbling block
17 for companies trying to move products from the
18 preclinical and concept phase out into the market.

19 I think that there are several ways in
20 which your work here today can have a direct impact on
21 basically moving these devices to the market more
22 quickly. The first of these obviously is in the area

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1 of trying to start clinical trials as quickly as
2 possible. If our past experience with endovascular
3 grafts has taught us anything, it's that our
4 preclinical experience has not always been very
5 predictive of clinical experience with these devices.
6 And my understanding is that one of the goals of this
7 workshop is to try and develop test methods and
8 strategies that can try and make that preclinical
9 testing experience more predictive of the ultimate
10 clinical experience. That would certainly help in
11 enabling us to begin clinical trials more quickly,
12 being able to have clinical trials that answer the
13 important clinical questions that we need, and not
14 having devices fail unexpectedly.

15 I think the second area in which this
16 preclinical testing could really have a big benefit is
17 in trying to develop mechanisms to make us able to
18 better predict the long-term behavior of these
19 devices. Clinical trials are necessarily short.
20 Nobody is going to be very happy if FDA decides that
21 clinical trials for permanent implants need to be five
22 or ten years because that's how long patients really

1 have them. And so it's very important that we have,
2 I think, preclinical testing that sort of fills in and
3 enables us to be able to say, well, we've got a year
4 of clinical data on this device, we've got some really
5 good preclinical durability testing which makes us
6 feel confident that this device which has performed
7 well clinically for a year is likely to perform well
8 clinically for 10 years. And so I think that's
9 another area where there's a direct impact on the
10 patient.

11 And then finally, another area that we
12 frequently hear a lot about is how to deal with
13 changes to devices. As our old center director Dr.
14 Feigal was fond of showing, medical devices follow
15 this kind of total product lifecycle concept, and that
16 you don't just have one device that you put out there
17 and that people buy for 10 years. You develop a
18 device, and pretty soon your competitors are nipping
19 at your heels, and you've got to make changes to it,
20 make modifications. Your customers are asking for
21 changes. You need different sizes. You've got
22 manufacturing issues which make it important for you

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1 to make changes to it. And the importance of being
2 able to evaluate those changes without having to
3 repeat costly clinical trials I think is something
4 that we are interested in, and you are obviously
5 interested in as well.

6 So I think that there are a lot of ways in
7 which the work that you all do today and tomorrow here
8 can be directly applied to the sort of critical path
9 of getting these devices from the bench, basically,
10 into the patient. I commend you for coming here, and
11 I'm sure you all are going to do a lot of good work.
12 And I think I will turn the podium back over to
13 Dorothy. Thank you.

14 MS. ABEL: Okay, well I can pretty much
15 skip my presentation because Donna Bea covered
16 everything. Well, obviously this is intended to be a
17 very informal situation, so if I get a little bit
18 sarcastic, please don't take it personally. It's just
19 who I am, and that's just the way it is. So I want to
20 have some good discussion and interaction, and not
21 stand on ceremony other than -- the only real rule is
22 that -- sure. I just assume I yell so loud anyway.

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1 I get to shut anybody up that I don't like what
2 they're talking about. That's kind of the big role.
3 So don't be surprised when that happens.

4 (Laughter.)

5 MS. ABEL: I want to acknowledge Angie
6 Smith and Marianne Grunwaldt who helped as far as
7 organizing this meeting. And then we also have the
8 Scientific Advisory Committee. We had to come up for
9 a name for these guys, that came and met with us
10 several times, helped put together the information
11 that you see in front of us. Rest assured that we
12 didn't show them any of the individual work
13 assignments that were submitted from the companies,
14 but they did help us to organize and figure out kind
15 of how we could direct the conversation today. So
16 thanks to everybody who helped out with that.

17 What we're going today is hopefully
18 describe the -- well, right now I'm going to describe
19 the purpose of preclinical testing, just to reiterate
20 the things that Donna Bea already talked about. And
21 then assess how we've been doing so far, identify the
22 basic design requirements for endovascular grafts that

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1 will be a focus of this meeting, and then describe the
2 workshop game plan.

3 So as Donna Bea mentioned, what we're
4 looking to do with preclinical testing is evaluate
5 performance, providing the data on device function and
6 in animals, prior to getting into the clinical. We're
7 also trying to predict the longer-term clinical
8 performance. And also to characterize. And to expand
9 a little bit on what she said, I think we're trying to
10 characterize in order to identify the root cause of
11 any subsequent failures also. But then certainly, in
12 accordance with what she was saying, when there are
13 device modifications it's very useful to have the
14 characterization so that you can identify the
15 additional tests, or new tests, or repeated tests that
16 are necessary. And also, again, to look for the root
17 cause of failures observed in either of the designs.

18 I wanted to mention this because I think
19 it's important to think in the context of what we're
20 discussing today, that we're not only looking at what
21 do you have to do in order to make FDA happy to get
22 into a clinical study, or to get a PMA approved; that

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1 we really are looking at the bigger picture of what
2 preclinical testing can do for us.

3 So how well have we done so far? As Donna
4 Bea mentioned, we haven't been terrible but we
5 certainly have a long list of clinical events that
6 weren't predicted by the preclinical testing. As far
7 as predicting longer-term clinical performance, I'd
8 say the same is true. The longer-term clinical
9 information we get, the more we learn that we didn't
10 find out about in the preclinical testing. And as far
11 as characterizing the device or the modified device,
12 we do reasonably well at that, but it's extremely
13 inconsistent between the manufacturers, and so that's
14 another thing that we would like to be able to attempt
15 to do, is kind of get everyone up to speed and have
16 the bar set pretty high. Everyone's doing it the same
17 way. So there's obvious room for improvement, hence
18 we're having this workshop.

19 I just wanted to provide a background in
20 terms of what we were thinking with respect to why
21 we're talking about the different areas that we're
22 talking about today. And the way I see it is you have

1 to be able to get a grip. So that's, you know, it
2 doesn't matter how great your device design, if you go
3 to put it in and you've got a patient that's not
4 selected appropriately, that doesn't have a long
5 enough neck, or that's so angulated that you can't
6 possibly get the seal zone that you need, it doesn't
7 matter how great the device is. You've got a failed
8 situation there. And so of course, delivery and
9 deployment goes along with that.

10 So we'll be talking about some things with
11 respect to patient selection that's not necessarily
12 preclinical testing. It has more to do with trying to
13 control you guys and making sure you use these things
14 right. But also, testing to the extremes, and so
15 making sure that when you do your testing, you look at
16 the angulated necks to see if you are able to actually
17 get a grip. And then you need to hold on. So you
18 have to have adequate attachment strength, whatever
19 you want to call it, whether it's with active fixation
20 or radial force, once you get it there, it needs to be
21 able to stay there. And of course you can't have any
22 leaking, or it's not going to do any good with respect

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1 to excluding your aneurysm.

2 Then we get into maintaining strength. So
3 once you're there, it doesn't do any good if it falls
4 apart. It can slide right out again. And then
5 maintain performance under changing physiologic
6 conditions. And this is probably the biggest
7 challenge that we face with endovascular grafts in
8 that we just don't know what to do about the fact that
9 we have dilating necks, the aneurysm morphology
10 changes, and how do you incorporate that into your
11 design and into your testing?

12 I put this slide up just to remind
13 everyone that there's a wide variety of devices that
14 are out there, and everyone is attempting to address
15 these different issues in different ways. And so when
16 we talk about trying to get everyone on the same page
17 with respect to testing, it's a pretty significant
18 challenge given the diversity of devices that we're
19 dealing with here.

20 So as you all know by now, we've got four
21 sessions that we're going to be having. We've got the
22 animal studies first. Then we'll talk about sealing

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1 fixation effectiveness, device integrity, and then
2 finally more of a wrap-up session tomorrow afternoon.
3 I just want to acknowledge that there's a lot of
4 cross-over with these sessions. There might be some
5 redundancy, but that's to be expected.

6 So our approach is to look at what's been
7 done in the past. We did a lot of that through our
8 work assignment that you have in your binders. And
9 then we're going to identify the clinical failure
10 modes that could and should be evaluated in the animal
11 testing, and in the bench testing to evaluate the
12 sealing fixation effectiveness, and the testing to
13 evaluate implant integrity. Then we want to identify
14 potential modifications in these test methods, and
15 determine what additional information is needed to
16 implement the improvements that we've identified.

17 So as far as the session structure, we're
18 going to have one or two presentations just to get
19 everyone on the same page with respect to what we're
20 supposed to be talking about for the morning or the
21 afternoon. I'll provide a brief summary of the
22 compiled work assignment, and we'll give an

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1 introduction to the tables for the session. Then
2 we'll have discussion with scheduled audience
3 participation. And we'll be doing all this real-time
4 with Angie documenting everything. And just so you
5 all are prepared, and if you get bored, just watch
6 Angie's face while she's typing because she has these
7 great expressions. It'll help the day go a little bit
8 better hopefully.

9 So we can go ahead and get started, then,
10 with our Session 1. So I would like to introduce Dr.
11 Michael Hallisey, who's going to provide our
12 background information for this.

13 DR. HALLISEY: Thank you, Dorothy. I'd
14 also like to thank you for inviting me to speak today,
15 and compliment you on what you guys have done at the
16 CDRH and the FDA. And my perspective on it is from a
17 clinical perspective. Although I do a lot of animal
18 lab studies, my bigger concern now is the clinical
19 application of devices. You've done a great job in
20 developing these devices and giving guidance to what
21 is safe and effective. But out there in the
22 community, not always the safest clinical application

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1 of those devices. And the devices are going into the
2 hands of everyone, and that has not been well
3 controlled.

4 I'm going to talk today about animal
5 studies. And just basically what's been done and what
6 can be done in the future. I'll talk about some of
7 the previous animal studies that we performed, and
8 focus this on abdominal aortic aneurysm, because
9 there's been a lot of studies working with grafts and
10 stents, in particular, in animals. I'll identify the
11 animal models, what's not been evaluated by these
12 models, identify some of the improvements that can be
13 made to the animal studies, and what future animal
14 studies could look like. And hopefully there'll be
15 some standardization in the community as far as
16 evaluating a stent graft. And I'll give an example at
17 the end.

18 What are the goals of any abdominal aortic
19 aneurysm stent graft? First and foremost, from a
20 clinical issue is can we avoid rupture? Do we avoid
21 rupture of the abdominal aortic aneurysm? A lot of
22 patients will ask, you know, I had a stent graft

1 placed in January of 2002, and my aneurysm was five
2 centimeters in size, and it's still there, Doctor, and
3 it's still five centimeters in size. And we tell
4 patients that's a good thing. I mean, not all
5 aneurysms are going to shrink. The aneurysm didn't
6 rupture. We consider this a successful result.

7 We also want to avoid repeat
8 interventions. If you place a stent graft, you want
9 to be able to evaluate that you're not going back in
10 for a groin hematoma, which is a simple thing,
11 removing the hematoma from the groin, or going back in
12 to balloon-dilate an area of intimal hyperplasia at
13 the end of the stent graft. Or something more
14 complicated, like putting in extension cuffs. Those
15 are under the category of, say, an endoleak, or
16 restenosis. Now, some endoleaks that exist, it's
17 debated in the clinical community whether they cause
18 a clinical problem or not. I mean, do you have -- if
19 you have an endoleak in a patient, some of them are
20 just not treated, and that's up to the clinical
21 physicians that are in certain areas. Around the
22 country they don't treat them, but some of them do.

1 What I don't know has been adequately
2 evaluated in animal studies is if an animal has an
3 endoleak, is it significant? And in a patient, are
4 all endoleaks significant? And then you have to ask
5 the question, can you evaluate that in an animal
6 model?

7 So again, the single most important goal
8 for the stent graft is to avoid rupture. You all know
9 about the morbidity and mortality of a clinical
10 rupture of an abdominal aortic aneurysm. But imagine
11 if you were a patient who had an 8-centimeter
12 abdominal aortic aneurysm, and I told you that it's
13 going to rupture in two weeks. A stent graft device
14 is going to be placed, and the abdominal aortic
15 aneurysm ruptures, is there a way to test if that
16 stent graft will hold, number one. Number two, if the
17 stent graft is placed, will the aneurysm avoid that
18 rupture in two weeks? That's something that has not
19 been adequately tested in animal models.

20 Now, can you test it? Yes you can. I
21 think it can be done, and that's what I want to
22 present to you today, some recent data that's been

1 published that I really like, and I'd like to submit
2 it to you to consider.

3 The answer the patient wants to hear is
4 that same answer. They want to know, Doctor, I am not
5 going to die from a ruptured aneurysm, or I'm going to
6 go to another hospital. And it's similar to the story
7 that your assistant just mentioned about being in Nova
8 Scotia. Patients coming in now, and they are
9 demanding a stent graft. They've got an abdominal
10 aortic aneurysm, Mark knows this probably very well.
11 They're coming in, I've got an abdominal aortic
12 aneurysm, they may have been to three or four other
13 institutions, maybe not, but they want the stent graft
14 to repair their aneurysm. And they want the answer
15 that their aneurysm's not going to rupture.

16 Now, the ideal model for testing stent
17 grafts would have all these characteristics. It would
18 mimic the size of the human arteries that we're
19 putting them into, mimic the tortuosity of the iliac
20 arteries or the atherosclerosis that's in the iliac
21 arteries. It would mimic the elastic degradation that
22 you see in the aorta in the presence of an abdominal

1 aortic aneurysm. Patients who have abdominal aortic
2 aneurysms, some of them have those collaterals, the
3 mesenteric arteries and lumbar arteries, and does your
4 model for testing a stent graft have those arteries as
5 well? And an important feature of that is if they do
6 have the collaterals, how are those collaterals
7 situated? Are they in the presence of the aneurysm,
8 or are they flush to the aortic wall? Because there
9 is a difference. I'll show you what that means in a
10 minute in an animal model.

11 Or you can test, in a very simple animal
12 model, can you safely deliver the device. That can be
13 done in just, say, a canine model where you just take
14 the animal, and you deliver the device under
15 fluoroscopic guidance. You're testing the safety of
16 the delivery. Then of course you want to test the
17 thrombogenicity, coagulation, fibrinolysis of the
18 animal in response to the stent graft.

19 Now, when you look at the previous
20 studies, certain factors come into play. And there
21 are really two major factors: your choice of your
22 animal species, and the choice of the vessel you're

1 going to study. Are you going to use an abdominal
2 aortic aneurysm or are you just going to use the
3 native aorta of the animal. If you want to test
4 healing of the stent graft, or the coagulation, or the
5 response, or the thrombogenicity of the stent graft,
6 you may use just a tube stent graft in an abdominal
7 aorta of a canine. That may be sufficient for the
8 objectives that you set out to do. So you'll meet the
9 goals that you may have set out to do by using that
10 type of model. But in contrast, you may want to
11 actually test where you're excluding the aneurysm of
12 the stent graft, in which case you have to create a
13 model of abdominal aortic aneurysm.

14 So no one animal and no one model right
15 now matches a human for the perfect study of stent
16 grafts, but we can get closer to what we're doing,
17 because right now in the community a lot of people are
18 doing different types of modeling. And if you look in
19 the notebook, I looked there earlier. I looked at
20 some of the data, what you submitted from the
21 companies, and what you're using, and it was pretty
22 well spread out in one of the categories, whether

1 using canine, sheep, or pigs in the evaluation of
2 stent grafts.

3 Now, if you look at the animals
4 themselves, each animal has different reactions, has
5 different advantages to the stent graft. The
6 primates, of course, have clotting and fibrolytic
7 systems that are very close to humans. Same with the
8 calf and the sheep. The calf has an advantage that it
9 has a good vessel size. The sheep the same thing with
10 the size. You can get a sheep up to -- an aorta up to
11 18 millimeters. A lot of you know that the human
12 aorta is probably on the average of 22 to 24
13 millimeters in size.

14 The dog has some advantages in that its
15 spontaneous endothelialization on prosthetic surfaces,
16 it lacks that which is similar to humans. It's very
17 slow in reacting, which is similar to humans. And it
18 has a tendency towards hypercoagulability.

19 The size of the animal is also a benefit,
20 because the sheep, you get real large, and if you're
21 doing your animal studies in a fluoroscopic lab, it's
22 sometimes hard to penetrate the sheep. And the same

1 thing happens with the pig, the last animal. The pigs
2 can grow very fast. And you can start out with a pig,
3 you place your stent graft in it, and then 12 months
4 later you do another evaluation of it and you can't
5 penetrate because the pig's gotten too large.

6 Now, there are some disadvantages. The
7 cost of both the primates and the sheep can be
8 prohibitive. I'm sorry, the cost of the primates and
9 the calves can be prohibitive. Now for sheep, we did
10 a number of studies with sheep, and Q fever was a
11 problem for our hospital as far as the animal
12 laboratory created -- because of the zoonosis Q fever,
13 it can be spread to humans. There was a big concern
14 about using sheep in our evaluations.

15 The dog can be costly, especially if
16 you're in a state that has dog racing. Some of the
17 dog racing states have limited use of the greyhound.
18 The greyhound might be one of the best dogs to use if
19 you're trying to study a stent graft. Why? Because
20 the size of the aorta is a better size aorta than,
21 say, your typical mongrel dog, or even a German
22 Shepherd. I mentioned the pig, the size can be a

1 problem. And also, the pigs can be more fickle with
2 anesthesia.

3 Now, all these animals, with or without
4 abdominal aortic aneurysms have been utilized for the
5 study of stent grafts. And what have we learned, and
6 what is important? Well, sheep have the larger aorta.
7 They can grow up to about 13 millimeters on average,
8 and occasionally you get a sheep that's 16
9 millimeters. They have good access sites, not great,
10 but good access sites for delivery of devices. You
11 can test delivery of devices. They tolerate
12 anesthesia. In fact, the sheep can consume a lot of
13 anesthesia. It can be very difficult to get them to
14 lay still. And they can go on for hours. Your
15 procedure can take forever and they still tolerate it.
16 But they can be expensive, and the Q fever can be
17 prohibitive at some institutions to evaluate. The
18 clotting is a little unpredictable, so you have to
19 watch their activated clotting times. And they can be
20 prone to tail paralysis. And if you're putting a
21 stent graft in that's bifurcated, what happens is you
22 can cover that sciatic artery and end up with a fair

1 number of your sheep with paralysis of the tail. Your
2 stent graft is fine, but unfortunately that artery is
3 a larger artery than in humans.

4 The bovine species, a bigger aorta, 18
5 millimeters. Their fibrolytic systems are closer to
6 humans than the canine, the sheep, or swine. But
7 again, their size can be tough as far as working with
8 fluoroscopy. And they can be expensive.

9 The swine are inexpensive, but they have
10 a smaller aorta, 8 to 9 millimeters. And what that
11 means is you may have to modify your stent graft in
12 order to test it in the aorta. Now, that may produce
13 a failure mode that you don't expect, and it may
14 actually reject your stent graft. Let me expound upon
15 that. If you take a hypothetical stent graft, and you
16 miniaturize it, you may actually make that stent graft
17 in, say, the swine, when in fact in a human it may be
18 just right. So you've got to remember when you're
19 testing these in the swine, again, you're not getting
20 the exact thing you're getting in humans. The swine
21 do grow fast, and they don't tolerate the long
22 anesthesia like I mentioned the sheep do.

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1 Canine are easy to handle. Their aorta is
2 about a 9-millimeter, 10-millimeter aorta. You can
3 get up to 12 if you use the greyhound, as I mentioned
4 earlier. They do tolerate anesthesia. It's been
5 recommended by the Ad Hoc Committee of Joint Councils,
6 the SVS and ISVS, as the animal of choice. It has a
7 good fibrolytic system. It can be expensive, though,
8 which is a disadvantage. But there are two distinct
9 characteristics which make it a good model for
10 abdominal aortic aneurysm or just for studying stent
11 grafts. They don't have that spontaneous
12 endothelialization, which is closer to humans, and
13 it's relatively unpredictable as far as their
14 hypercoagulability. And it tests your device. Is it
15 thrombogenic? Is it going to result in clotting of
16 your device? One of the most important failures that
17 you will test when you introduce your new stent graft
18 into animal testing is occlusion. Does your device
19 occlude? And you come back a month later and you've
20 got a thrombosed aorta and iliac arteries is a very
21 disappointing event.

22 Now, there are several different models.

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1 So on top of the animals, we talk about what models
2 you use. The anterior patch model is one of the most
3 common models. The aorta is isolated here. A
4 surgical procedure, you do an aortomy, and then you
5 sew an elliptical patch onto the aorta. On this side,
6 on the left side, on your right side, that's a patch
7 of a Dacron in this case. But you can use vein, you
8 can use rectus fascia, you can use Jejunum. This is -
9 - on your left side is a patch with Dacron. And what
10 I would have you note is that you see a lumbar artery
11 on the opposite side of the patch over here. And that
12 artery is flush to the aortic wall. Your aneurysm
13 does not have any of those collateral vessels because
14 you've removed them during surgical implantation and
15 creation of your aneurysm. So although you have an
16 aneurysm, the collaterals that might produce endoleaks
17 in the clinical setting is different than what you see
18 in the clinical setting. Here, the endoleak, if it
19 develops in the animal, is flush to your stent graft
20 wall. You may actually falsely, thinking that you can
21 exclude those endoleaks because you had immediate
22 apposition of your stent graft to that wall.

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1 On the right side of the screen you see,
2 this is a Jejunum patch, and you can see some thrombus
3 in there. There's contrast. The white area and the
4 black area inside there is thrombus that's developed.
5 And a lot of abdominal aortic aneurysms in humans have
6 that thrombus in there.

7 The second model is an interposition
8 model, which is an artificial graft which you
9 basically exclude the aortic segment and replace it
10 with an aneurysm. You can make them into any shapes,
11 and you can make them into very large sizes.
12 Ironically, when you put this in there, you completely
13 remove any collateral. So it's unlikely you're going
14 to get an endoleak of the more common endoleaks, like
15 a Type II endoleak where you've got the mesenteric
16 arteries and lumbar arteries coming in because you've
17 already taken them out of the circulation. In
18 addition, you can get shrinkage of this aneurysm
19 because you've done a surgical procedure, fibrosis,
20 around your newly created aneurysm, shrinks it.

21 The third model I'll mention to you is the
22 transluminally created abdominal aortic aneurysm

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1 model, in which you take a Palmaz stent or a balloon-
2 expandable stent here and you dilate that into the
3 aorta of a canine. The canine aorta is rather
4 muscular, and when you dilate it, the aneurysm forms
5 in the shape of the balloon that you've used. It
6 preserves the collaterals, which you can see here,
7 inside the aneurysm, here and here. You can get up
8 to, I note, twice the aortic size. And it's all done
9 percutaneously. Some advantage of this is that you
10 can actually do -- you can create three or four of
11 these in a day, these aneurysm models. And it can all
12 be done percutaneous. And I believe that you can
13 actually create your aneurysm, it's a stable aneurysm,
14 and then put a stent graft in there right away. You
15 can do that as your next procedure.

16 Now, what's not been evaluated? And
17 really, this is some of the guidance that we're
18 looking for today. Endoleaks is one area. If you
19 believe endoleaks is a significant problem, and in
20 some institutions in the clinical setting it is a
21 significant problem. I refer to this article here
22 where they only looked at nine dogs, but they created

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1 anterior vein patch AAA, that patch AAA I mentioned.
2 And what they did is they put in a Teflon-coated stent
3 graft that had holes in it in order to create the
4 leakage. And then they followed with aortograms.
5 Seven of them, seven of the animals, developed the
6 abdominal aortic aneurysm and the aneurysm continued
7 to enlarge. They followed them. They all had the
8 Type III endoleaks that had been artificially created.
9 And later when they evaluated them, they had Type I
10 and Type II leaks. So it's an interesting model for
11 evaluating endoleaks.

12 The next, and this is probably one of the
13 most important studies, and this is the one I referred
14 to earlier, a study by Maynar, published in CBIR in
15 2003. And they presented an animal model using
16 peritoneal patch, a AA peritoneal patch. And the
17 abdominal aortic aneurysms showed further growth. In
18 fact, 15 out of the 27 pigs that they did this in
19 ruptured within two weeks. They were stable after the
20 procedure, but then they later died within two weeks
21 of the procedure. There was statistical significance
22 in the pigs that had aneurysms that were longer than

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1 six centimeters. And I think this could be a good
2 method for testing of a stent graft, because in the
3 pig model you can create your aneurysm. You know it's
4 going to rupture relatively predictably within two
5 weeks. You place the stent graft there. If you
6 change the course of events, then you may have a
7 viable stent graft in humans. Again, I'm getting back
8 to the clinical setting, and I'll talk about that in
9 a minute with an example.

10 The third thing that you'd like to study
11 is restenosis. And this is two studies that I mention
12 here, JVRR-2002 and JVR-2001. They basically took
13 different stent grafts and put them into sheep and
14 canine, respectively, and looked at vessel patency,
15 looked at intimal hyperplasia and tissue reactions.
16 Again, this is a way you could study the stent graft
17 without having to put an aneurysm into the animal
18 model.

19 Now, potential modifications for the
20 future. We could take the same animal models, and do
21 multiple stent grafts. That's not been done
22 adequately. You could take the same stent graft and

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1 put in multiple different animal models. And then we
2 need to evaluate the impact of endoleaks. We still
3 don't know a lot about what the impact of endoleaks
4 are after stent graft. Because by placing a stent
5 graft in the clinical setting, we've created a whole
6 other problem. Or is it a problem? As I said, some
7 clinical institutions don't believe it's a problem.

8 Now, it'd be great to study abdominal
9 aortic aneurysm rupture with and without a stent graft
10 in place. So let me give you as my last slide future
11 animal studies. We have a hypothetical. We have a
12 new stent graft that we have, and that some of you
13 have envisioned, or your companies have envisioned, in
14 this room. We'll call it AN-U-Guard. And I don't
15 know if that's the name of a stent graft. I hope it
16 isn't.

17 First of all, you want to get this thing
18 to market, and you have a business plan on how to do
19 it. It needs to be miniaturized in order to put it
20 into some animal studies. Now, keep in mind, this may
21 invalidate your AN-U-Guard. It may actually -- you
22 may actually reject your stent graft, and this has

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1 happened, I know this has happened, where there have
2 been viable stent grafts that have failed in the
3 animal models. And you may think, well, it's not a
4 good stent graft, but in fact, it may still be. We
5 just don't know.

6 I would recommend that in the community
7 someone out there try to duplicate Maynar's study. If
8 this model is a valid model for the evaluation of
9 stent grafts, if you have a predictable tendency to
10 create an abdominal aortic aneurysm, and you know that
11 abdominal aortic aneurysm's going to rupture within
12 two weeks, and you place your stent graft. You
13 exclude the stent graft, you don't have endoleaks, the
14 dog lives another year. You've got a viable stent
15 graft for the clinical setting.

16 That's the answer the patient wants to
17 hear. They want to know, is their answer not going to
18 rupture in two weeks? They want to know that they're
19 not going to have to go back into the hospital and
20 have another angioplasty, another stent. This is what
21 they're after, okay?

22 If that model is validated, I recommend

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1 using that model. If not, until then, I would suggest
2 using the canine model. Take 20 abdominal aortic
3 aneurysms in the canine model that's transluminally
4 created. If you're just trying to develop a stent
5 graft for safety and efficacy and intimal hyperplasia,
6 delivery of device, you don't have to use the animal
7 with the aneurysm already created. But these two
8 models are good for future animal studies in which
9 you're really, truly testing what the clinician wants
10 to know and what the patients wants to know.

11 Thank you very much for your attendance,
12 and thank you for your attention.

13 (Applause.)

14 MS. ABEL: Well, that brings up an
15 interesting additional thought, just with respect to
16 basic research in animals versus what you need to do
17 as a company to evaluate your advice prior to going to
18 clinical. So I think we'll have some good discussions
19 on it.

20 So as I had said, I'm going to give a
21 little bit of background on what was included in the
22 binders. And then we can just go into having some

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1 open discussion. I'm not going to read to you, you'll
2 be glad to know, but I just wanted to emphasize what
3 Dr. Hallisey already said, there were quite a large
4 number of studies that were distributed over the
5 various types of animals.

6 So we had 23 studies, 235 animals, and 288
7 implants. Most of the implants were straight devices.
8 Most of them were aortic. There were only a few that
9 were implanted and surgically created aneurysms. And
10 the duration of the study varied, obviously, with
11 respect to the animal models, but also just in terms
12 of what people were looking for.

13 Failure modes seen clinically that
14 theoretically you would want to be able to evaluate in
15 an animal model are listed on this slide, and in your
16 packet. And what you can see as far as the bottom
17 line is that there is diversity in terms of what
18 people thought that they actually could look for in an
19 animal model. Everyone thought they could look for
20 loss of patency, for example, but after that it's
21 fairly divided in terms of what everyone thought they
22 were seeing.

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1 As far as the results that people gave us,
2 no one reported any delivery and deployment failures
3 in their animal studies. There were no problems with
4 patency. Those who evaluated migration didn't see any
5 migration. And there were no significant adverse
6 effects of the prosthesis on the vessel wall. So the
7 bottom line is these were all basically negative
8 studies. They put them in, and there wasn't anything
9 terrible that came out.

10 Limitations of the animal models that
11 people identified were the size limitations, the
12 human/animal anatomical differences, the fact that
13 there are no clinically relevant aneurysm models,
14 their different biological responses, different
15 insertion methods, and the rapid growth of animals.

16 So now I'm going to be filling in some
17 tables with some specific directed questions with
18 respect to animal models. And we'll have Angie go
19 ahead and describe those, and we'll get to work.

20 MS. SMITH: Okay, based on the information
21 that was provided indicating that attributes in
22 failure modes listed here, being migration, endoleak,

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1 on down. We want to look at specific questions, which
2 I think Dorothy is going to bring up on her screen,
3 that are abbreviated here, that we want to answer
4 based on the limitations and potential improvements.

5 And to do that we're going to work -- we
6 broke up the table into several different slides so
7 that we had some more room to work. And we're going
8 to annotate the human characteristics and limitations.

9 MS. ABEL: Stuart's touching the
10 equipment.

11 MS. SMITH: Let me see if I can get it.
12 I can change the view, maybe.

13 MS. SMITH: So while she's fixing the
14 view, you could just take a look at the list of
15 headings that we have on the other slide. I want to
16 look at the human characteristics that were not
17 present in the animal model. For example, the neck
18 angulation, changes in morphology, and that sort of
19 thing, that may be important in evaluating each of the
20 attributes or failure modes. So we're going to talk
21 about patency first, then we'll talk about migration.
22 And within this discussion, obviously if you have more

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1 general points we might let you speak your mind. But
2 we want to be able to get these tables filled out,
3 too.

4 Then we want to talk about the additional
5 limitations inherent in the animal models, size
6 limitations, tapers, those sorts of things that we
7 touched on, and that Dr. Hallisey spoke of. And then
8 could and should the attribute of failure mode be
9 evaluated in an animal study. So is it really
10 rational to think that you can evaluate patency for an
11 endovascular graft in an animal model. And then
12 additional information regarding the attribute or
13 failure mode would be obtained from a more complicated
14 model. So when I say "complicated model" I guess what
15 I'm thinking of are the sorts of things that Dr.
16 Hallisey just talked about with incorporating the
17 aneurysms.

18 And then what additional information would
19 be needed to make a more realistic animal model, and
20 how could this model make the results more difficult
21 to interpret. So what are the benefits of doing
22 something a little more complicated, and what are the

1 downsides.

2 MS. SMITH: Okay. So the first attribute
3 or failure mode that we want to look at is patency.
4 And the first question we're asking is what human
5 characteristics are missing in evaluating that failure
6 model.

7 MS. ABEL: So clearly, atherosclerosis is
8 not present in an animal model. So that's a key issue
9 with respect to patency. Are there other things that
10 are not in the animal model that could affect patency,
11 that because they're not there makes it difficult to
12 evaluate. Mark?

13 DR. FILLINGER: Tortuosity and angulation.
14 Most stent grafts are large-vessel failures. And fail
15 to degradations.

16 MS. ABEL: Would everyone agree with that?

17 MS. SMITH: What are the additional
18 limitations for patency? I guess to evaluate patency.

19 MS. ABEL: I'm not sure that there's
20 anything really in addition. You know, patency is
21 probably a very simple example that we can get started
22 on just to get you understanding kind of the exercise

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1 that we're trying to go through. But does anyone have
2 any other thoughts with respect to evaluating patency
3 in animal models? Martin?

4 MR. KING: Dorothy, some analysis of
5 animal models has included the use of elastin or
6 enzyme to break down the elastin membrane within the
7 arterial wall, and therefore do create a, quote,
8 "natural" aneurysm within the animal model. And some
9 of those are reliable and less reliable. But I'm just
10 thinking that approach does, in fact, change the
11 morphology of the arterial wall, and therefore is more
12 likely to mimic the disease state in the clinical
13 situation.

14 I don't know if anyone's had experience of
15 using this approach. I know Dr. Hallisey didn't
16 mention it. But it has had some success, but not
17 necessarily reliable success.

18 MS. ABEL: But even in that circumstance,
19 would you truly be able to evaluate patency? Is that
20 an endpoint for your study, given the fact that you
21 don't have the atherosclerotic model, you don't have
22 all this stuff going on. Just specific to patency

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1 right now.

2 MR. BIGGERSTAFF: I was just going to add
3 that we've done animal trials in sheep and in cows,
4 and I think in both of these, anecdotally we would say
5 that they've been more proficient at clotting than
6 humans have been. So whereas we have seen clotting
7 occurring in blockages in some of our implants in
8 animals, we've not seen equivalent responses in
9 humans. So I'm not very convinced that I would
10 interpret a clotting response out of an animal as
11 being representative of a human.

12 DR. GREENBERG: Yes, I think one of the
13 other issues is that the animal -- the histologic
14 response to a graft in an animal differs from that of
15 a human. And so if the animal's likely to have a
16 higher degree of neointimal hyperplasia or something
17 else from a graft which is going to then cause
18 something to clot, then we've essentially gotten a
19 wrong answer on our patency. And I've actually seen
20 the number of companies where they've embarked on an
21 animal trial to show patency of something that you
22 know will work in a human because it's not so

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1 different than what we already have, that have then
2 stopped their studies because it induces neointimal
3 hyperplasia in perhaps a dog, or a pig, or a sheep.
4 And it almost dissuades us from using an animal model
5 to look at patency because these other factors aren't
6 controlled.

7 MS. ABEL: Does anyone agree with Roy? I
8 personally think that that makes some sense, and I
9 think although in an animal model you would want to
10 document patency, you wouldn't necessarily say I've
11 got a new endovascular graft. The first thing I have
12 to do is evaluate it to make sure that it stays open.
13 Again, thinking of AAA, not for treatment of occlusive
14 disease. So what do people think? Who believes that
15 you have to evaluate patency in an animal model in
16 order to be able to be prepared to go into a clinical?

17 MR. BIGGERSTAFF: It's not hugely
18 important. I mean, the materials being used are well
19 tried for graft materials anyway. So the general
20 patency characteristics are quite well known. So the
21 real issues are more to do with mechanics, and
22 crushing, and kinking, and that sort of thing.

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1 MS. ABEL: And I think it would be fair to
2 say if you did see a problem with patency in your
3 animal model, then you may need to do some additional
4 studies to see what it was related to. If you did
5 have a novel material, something that wasn't as well
6 understood. Is that fair? What was that?

7 DR. WHIRLEY: Maybe you've got the wrong
8 animal.

9 MS. ABEL: Are you volunteering to be the
10 next animal?

11 (Laughter.)

12 DR. WHIRLEY: I think it's you.

13 MS. ABEL: Just checking.

14 DR. WHIRLEY: I've got a series of
15 attorneys lined up.

16 (Laughter.)

17 MS. ABEL: Dr. Hallisey, you had actually
18 mentioned evaluating patency. Would you agree with
19 what I'm summarizing, or is there still disagreement
20 with respect to patency?

21 DR. HALLISEY: I don't fully understand
22 what -- I'm not who was saying it, but are they saying

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1 that they could take -- test a stent graft in, say, a
2 canine, and they had 10 animals, and they all
3 thrombose. They'd still find that an acceptable
4 experiment? Just because it was miniaturized? And
5 that because the materials used were already proven to
6 be safe?

7 I think you still have to prove patency in
8 the animal model with your new device somewhere. If
9 you have 10 animals, and you put all 10 in, 10 new
10 stent grafts in there, all thrombose, I think you've
11 got a problem.

12 MR. BIGGERSTAFF: Sure.

13 DR. HALLISEY: Well that's fine, but you
14 see, that doesn't mean that you can approve it at the
15 FDA.

16 MS. ABEL: But I think, like you said, it
17 would almost be a proof of concept study. If you do
18 that study and it fails, that's not the study that
19 you're reporting. And you didn't design that study
20 necessarily to evaluate patency. But if you fail
21 patency, you're going to have to figure out what
22 happened.

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1 DR. HALLISEY: Correct. And I think you
2 should report that, because there may be a problem
3 with your device, or modify your device and then prove
4 that it can be patent, in another model or something.

5 MS. ABEL: If people could use their
6 microphones it'd be very helpful. And if you could
7 just say at least your first name because not
8 everybody knows each other. But go ahead.

9 MR. SMITH: Okay, this is Lou.

10 (Laughter.)

11 MR. SMITH: Patency is the broad issue.
12 Thrombogenicity is the material issue.
13 Thrombogenicity can be tested in several lab tests not
14 even in an animal. If you're using materials of known
15 properties, and you've confirmed their thrombogenicity
16 outside of the animal model, then you're into patency
17 as a result of the mechanics, like Dr. Fillinger was
18 speaking. And I think that's the only thing you can
19 really get out of patency, is there a mechanical
20 reason why 10 out of 10 just clotted, or is there a
21 surgery reason. That was a joke, but a real answer.

22 MS. ABEL: Is that fair?

1 DR. HALLISEY: That's fair.

2 MS. ABEL: Okay, thank you. Well I don't
3 -- I mean, I would say that the answer is no. Would
4 we agree that the answer is no? I mean, it's
5 certainly something you look for in your animal study.
6 If something goes awry, you need to figure out what's
7 going on. But you don't have to prove patency in an
8 animal model to be able to say you've got a reasonable
9 device to move forward into the clinic. Thank you.
10 I'm sorry, I can't -- this room setup, I'm still
11 having a tough time getting used to it.

12 MR. YU: I just want to caution the
13 evaluation of that last set of data. You have to be
14 able to determine whether it's the device or the
15 animal model. So I'm assuming your controls in the
16 study with 10 clotted experimental devices were both
17 open, were all open. That way you can focus that it
18 is an experimental device issue, not a laboratory or
19 a technical issue. So you have to use controls.

20 MS. ABEL: Well, you have to do a root
21 cause analysis, figure out why you had the failure.
22 And I think controls would be an option in terms of a

1 way to do that. Yes?

2 DR. VIRMANI: Renu Virmani. I think it is
3 important to do animal experiments, and it's very
4 important to show that you're not getting excessive
5 amounts of new intimal formation. If you're getting
6 excessive amounts of new intimal formation in a normal
7 animal, imagine what will happen -- and you're getting
8 thrombosis. Imagine what would happen in a human. So
9 I think to say that animal models don't teach us
10 something is absolutely absurd. I don't care what the
11 device is, it still teaches you safety in many ways.
12 It may not teach you 100 percent safety, but it is
13 much better than not having one animal model.

14 And I think of course there are
15 limitations of the animals. I'm not trying to say
16 that the animals give you all the answers, but they do
17 give you certain things that you cannot take the
18 device directly to a human being and say, we've tested
19 the stent, we've tested the graft, in different ways,
20 in different configurations it will work in a human.
21 That is absolutely not true. There are many things
22 which come into play, information being a very

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1 important aspect of it, which you will learn. If you
2 observe appropriately, you can learn very well in an
3 animal model that you will get inflammatory reaction.

4 DR. GREENBERG: Could I just respond, and
5 are we allowed to use specific examples? I'm going to
6 use an example, just to say that this -- I agree with
7 Renu in terms of the need for an animal model to a
8 certain extent. But I think it's important when
9 you're doing a study design that someone else had
10 brought up the issue of a control. Because the
11 control will tell us what we know happens in a human.

12 And let's just take, for example, not to
13 pick on the Gore folks, but a ViaBond. Let's say we
14 know that we have a clinical trial on a ViaBond in an
15 artery, and we have a certain incidence of restenosis
16 and neointimal hyperplasia formation. And if you're
17 testing another endovascular graft, and you put a
18 known endovascular graft in the contralateral artery,
19 and you have a degree of restenosis there that exceeds
20 that of a human, your basis becomes a comparison with
21 the control, not a fundamental thing. Because with
22 Mike saying if 10 out of 10 grafts occlude, that may

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1 or may not happen in a human. I mean, I can't buy
2 that. And if three grafts occlude, that's not an
3 acceptable result in a human, but it may be acceptable
4 in an animal study. And so it's important to use a
5 control that we know how it behaves in a human, and
6 use that as the comparison for the animal study.

7 MS. ABEL: And I would say that's easier
8 to do with a peripheral device, I think, more than our
9 AAA devices, where you can't put multiple devices
10 within the same animal. It's a little more
11 complicated. Rodney, do you have something?

12 DR. WHITE: I think for conventional
13 materials, the animal patency is a secondary issue.
14 There's lots of patency, it's not the material. It is
15 some other factor. So it is a secondary
16 consideration.

17 MS. ABEL: I think that's fair, and I
18 don't think anyone's saying that we're not requiring
19 an animal model, it's just is the animal model -- if
20 you get 100 percent patency in your animal model, does
21 that really tell you anything about the potential
22 performance in the clinical? And we're all saying

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1 that we'll get later to looking at biological
2 response. There's no question that's something that
3 we have to talk about also, but right now we're just
4 in terms of patency. So what we noted on the slide
5 now is that it's kind of a secondary endpoint.

6 So I guess what I would say, again, is
7 that you look for it. If you do have a loss of
8 patency we need to evaluate what happened, but I think
9 that's different than saying it's patent here,
10 therefore it's good. Is that fair?

11 We had already -- Martin, you had
12 mentioned the other potential model. We had touched
13 on the concept if we have a more complicated model, is
14 there anything we can do in terms of a model to
15 improve it with respect to our evaluation of patency,
16 and is it really necessary?

17 DR. GREENBERG: No.

18 (Laughter.)

19 MS. ABEL: All those in favor? All right.
20 Thank you. We thought patency would be an easy one.

21 (Laughter.)

22 MS. ABEL: Okay. Migration. And so we're

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1 looking at human characteristics that are not in the
2 animal model that could make it less than optimal to
3 evaluate migration in terms of trying to predict
4 clinical performance. Rod?

5 DR. WHITE: There's a lot of differences.
6 The healing's different, and dogs don't have
7 aneurismal disease. And that's the underlying issue
8 that you can't assimilate, and to spend those
9 resources to do it is not realistic.

10 MS. ABEL: So we might as well just -- You
11 know, what we're trying to do is get to Column 3,
12 where we're saying could it be evaluated in an animal
13 model. And so in order to get to that point, I think
14 we have to look at what does an animal model look like
15 compared to the human anatomy that you guys see. And
16 when do you end up with a migration issue in the
17 human, would be a good place to start. Mark?

18 DR. FILLINGER: Well basically, an animal
19 model doesn't have angulation or atherosclerotic
20 plaques, or that sort of thing. You can test pullout
21 force, which is an important issue related to
22 migration in a normal, uniform animal vessel, and

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1 that's at least a start toward evaluating issues
2 related to migration. I don't think it's a great --
3 I mean, it's not the be-all and end-all, but at least
4 it tells you something about the device. If it has an
5 inadequate pullout force in a healthy animal vessel,
6 it's not going to be adequate in an angulated,
7 diseased human vessel.

8 MS. ABEL: Right. So that's looking
9 specifically at a different type of in vivo, or well
10 not in vivo. It's a different type of in vitro study
11 using tissues, as opposed to, okay, again we've got
12 our 20 animals or whatever they are. Is there reason
13 to believe that if you put an endovascular graft in
14 there that you can figure out if it's going to be
15 migrating in humans. And so why do devices migrate in
16 humans.

17 DR. VIRMANI: It has more to do with the
18 atherosclerotic process itself. And the vessel wall
19 anatomy is quite different in the presence of
20 atherosclerosis, so therefore it would be very
21 difficult to evaluate that in animals. However,
22 knowing that, I think if supposing the device migrates

1 in a normal vessel wall, you're in great trouble. I
2 would never put that device in a human being. So I
3 think it should be evaluated in an animal, even if it
4 doesn't tell us whether it will or not in a human.
5 But if it does in an animal, we know it's going to be
6 terrible in a human.

7 MS. ABEL: But it's still kind of the
8 secondary observation.

9 DR. VIRMANI: Yes.

10 MS. ABEL: If you see it, you have to
11 figure out why, but you can't say I put it in, it
12 didn't move in the animal model, therefore it is good.

13 DR. VIRMANI: Yes.

14 MR. RODGER: From Sydney, Australia. And
15 the other issue that's worth considering is the flow
16 volume velocity in say a typical infra-renal aorta
17 vessel. It is only about 10 millimeters. That's
18 going to have a lower momentum, flow momentum, and
19 friction in that area. And also, typically it will
20 still use the same identical compact length of, say,
21 2 centimeters, 1.5 centimeters in such a small area.
22 So the force ratio is completely different. So

1 invariably you are adding a major significant safety
2 factor by using the same attachment lengths. So it
3 would be worthwhile considering scaling everything
4 down in that respect.

5 DR. VIRMANI: The other thing to consider
6 is you could have a better animal model than a normal
7 aorta. You could have an aneurismal model. They do
8 exist. And therefore it is possible within -- if you
9 place that device within one or two centimeters, it's
10 something that you have to consider because that's
11 what happens in human. Rather than putting it in a
12 normal aorta. It really will tell you very little.

13 MS. ABEL: So if you use an aneurismal
14 model in an animal, could you evaluate migration such
15 that you would be able to determine it didn't migrate,
16 and that aneurismal model, it's unlikely that it would
17 migrate in the clinical?

18 (Chorus of Nos.)

19 MS. ABEL: And the reason not? Everyone's
20 saying no here. Rod?

21 DR. GREENBERG: Over time, the morphology
22 in the patient changes. The aneurismal process

1 continues, and if there's regression, it's a
2 complicating factor. And there is no animal model
3 that will assimilate human atherosclerosis. They
4 don't live 70 to 80 years. I mean, you can do
5 anything you want, but we're not going to get there.
6 And the other issue is that when we met 10 years ago
7 and made up definitions for all these things, and the
8 migration definition was what everybody uses. That
9 distance from a fixed anatomic landmark. And what we
10 didn't include at that time was the understanding that
11 the untreated segments elongate and dilate, and that
12 the length of fixation is critical. And that's
13 another parameter, maybe, in migration, is fixation
14 length, and how does the impact -- or the mechanism of
15 fixation. But there are independent issues other than
16 just, you know, a distance from a landmark. Because
17 that changes without the device moving in the vessel.
18 And it's related to the anatomic changes. So the
19 definition of migration we need to change.

20 MS. ABEL: I'll put that down as an action
21 item. Anything from this side of the room? Sorry.

22 COOK, INC.: I think with regard to

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1 migration, the animal model or the animal tissue is
2 very important in terms of testing what your fixation
3 does in the way of damage. That's where it's really
4 useful. Is what you're using going to cause a tear,
5 or a split, or some problem like that. So it's not
6 whether it migrates, but what the problems are
7 associated with what you're using.

8 DR. CHUTER: Also, at least the kind of
9 aneurysm models that were described earlier by Dr.
10 Hallisey are the geometry that don't create much
11 pressure drag, and so they wouldn't create much
12 displacement force. You would need one at the
13 bifurcation, or if it's not in the bifurcation, you
14 would need some significant angulation through the sac
15 to create significant displacement forces.

16 MS. ABEL: I've seen a few hands go up in
17 the audience. You guys can go up to the microphones.
18 We can break the rules.

19 MR. YOR: Hi, Frank Yor. I just felt that
20 what you might be able to evaluate in an animal study
21 is really acute type of migration, or acute type of
22 damage to the aorta. But anything that involves

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1 progression of the disease is just out of the question
2 that I know of.

3 MS. ABEL: So it would be deployment
4 related?

5 MR. YOR: Exactly. It's more a deployment
6 migration as opposed to even short-term migration.

7 MS. ABEL: That's fair. All right, any
8 more thoughts on migration? The way I would summarize
9 our discussion with respect to could it be evaluated
10 is again, that it's something you should look for. If
11 you see it, you should figure out why it's happening.
12 And I would agree with Michael that it's something
13 that we have to look at the effect of the attachment
14 on the vessel. But that's not necessarily looking at
15 migration. Is that fair?

16 Okay, moving on to endoleaks. It's
17 interesting that you mentioned quite a bit in your
18 talk about endoleaks. And so I think this will be a
19 good discussion. I thank you for setting the stage on
20 it. So what characteristics are missing? We've
21 already, in the presentation, shown that depending on
22 how you create an aneurysm model, you may obliterate

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1 any possibility of having a Type II endoleak. And if
2 you don't have an aneurysm model at all, do you get
3 endoleaks in an animal model? And so, do you get Type
4 II endoleaks even in absence of an aneurysm. I don't
5 know.

6 DR. GREENBERG: It doesn't seem likely.

7 DR. VIRMANI: If there is blood between
8 the graft and the vessel wall, it is very hard to
9 evaluate whether there is truly occurred at the time
10 of implant, or it occurred after, since it doesn't
11 resolve. Those are some of the problems.

12 But if you see fresh blood, that is
13 something you should look for, and perhaps you should
14 be able to say that we did not observe fresh blood.
15 That would tell you something. It may not tell you
16 everything, but it'll tell you something. And most of
17 the times it will be absent, I think, but it doesn't
18 mean that we shouldn't look for it.

19 DR. CRIADO: That probably largely relates
20 to the sizing strategy. Because if you oversize it
21 enough in a vessel that is not aneurismal, chances are
22 the device will be up close to the wall and obliterate

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1 all the branches. So you will not expect to get a
2 back flow endoleak.

3 DR. VIRMANI: That's why I think aneurysm
4 models are a must rather than doing without the
5 aneurismal model.

6 MS. ABEL: So let's talk about the non-
7 aneurismal model first. So in a non-aneurismal model,
8 what is not there with respect to --

9 DR. WHITE: The aneurysm.

10 (Laughter.)

11 MS. ABEL: Thank you. That's helpful,
12 thank you. I'm glad you're all paying attention. The
13 really good news is there's a transcriptionist so
14 you'll be able to read it later.

15 So the missing human characteristics.
16 Obviously we're missing the aneurysm if we don't have
17 an aneurysm model. But also, I'm assuming again that
18 it's healthy tissue. So you don't even have a neck.
19 So you don't have the issue of -- I mean, hopefully
20 you can get a seal in healthy tissue.

21 DR. GREENBERG: Right. Without an
22 aneurysm, you don't have anything to exclude. So if

1 you don't have anything to exclude, then there's
2 nothing to leak. And there's nothing to migrate. So
3 if those things occur in a non-aneurismal model, then
4 you do have an issue.

5 DR. VIRMANI: I think it's important to
6 have the negative, to be able to say there were no
7 endoleaks observed. And it's a secondary. It
8 wouldn't be a primary.

9 MS. ABEL: Yes. Well, that's -- that goes
10 along with the others that we talked about. So it's
11 a secondary. It's an observation sort of thing. If
12 you see it, you've got to figure out what's going on
13 and report it. So then let's talk about what would be
14 learned if we used an aneurysm model. And there are
15 a lot of different aneurysm models that were presented
16 earlier and discussed afterwards.

17 Are you actually able to incorporate the
18 things that were missing in the -- are you able to
19 incorporate the human characteristics by creating an
20 aneurysm. So you now have a neck and an aneurysm. So
21 you've done that. You've got an aneurysm. So what
22 are some other issues? Robert?

1 DR. WHIRLEY: In an animal model, even if
2 we put in an aneurysm, you still have absent the
3 effects the atherosclerosis, luminal irregularity, and
4 angulation. Our clinical experience suggests those
5 are all significant factors in the prevalence of
6 endoleaks.

7 MS. ABEL: So, got all those?

8 MR. SMITH: It depends what you're
9 testing. If you're testing a device, then a Type II
10 endoleak may be completely divorced. But the animal
11 study could be very important because you might want
12 to study the behavior of the endoleak. For example,
13 if you take Type II endoleak, it may be associated
14 with low-grade infections, and the production of
15 thrombolytics inside the thrombus. And that may
16 progress to the coating of a graft or a device with a
17 drug that fights the infection. So it's the behavior
18 of the endoleak, not the behavior of the device. So
19 an animal study may be very important, but it depends
20 what you're looking at.

21 MS. ABEL: And that might get back to what
22 I mentioned, that that would be important to research,

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1 that may be more related to, like you say, studying
2 endoleaks and figuring out better ways to address that
3 issue, as opposed to trying to qualify your device.
4 You know, is it prepared to go into clinical.

5 MR. SMITH: Unless the device is
6 associated with a drug that's attached which fights
7 infection. So it's a different purpose.

8 MS. ABEL: Right. So depending on the
9 design of your device, you may have to do some
10 different studies to evaluate particular issues. Is
11 that fair?

12 DR. WHITE: I think we've got a false
13 assumption that the modeling correlates to a clinical
14 situation. And the perfect example of this is if you
15 read, there's a book written by McDonald on
16 hemodynamics. It goes through all of this stuff very
17 carefully. You make bigger connections, smaller
18 connections. You've got a lot of formulas that go
19 with that. And the whole theory of hemodynamics,
20 which is what we're talking about, does not translate
21 to a clinical model in a patient that's complex.

22 And that's the piece we're missing. You

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1 can't somehow dial that into an animal and say the
2 relevance of anything, particularly an endoleak if it
3 has any significance. It's two issues. It either
4 affects the healing, or it affects the hemodynamics.
5 And those are the only two issues related to it.
6 Whether it's there or not otherwise doesn't make any
7 difference, and we're confused in this correlation of
8 does a hemodynamic model have a clinical effect in an
9 animal. The answer to that is you don't know. You
10 can study it and quantify it, but you don't know the
11 effect.

12 MS. ABEL: Tom?

13 DR. FOGARTY: Well, you do know.
14 Greyhounds have higher blood pressures than any other
15 dog. Sheep have different pulse pressures than pigs.
16 The hemodynamics that relates to dislodgement because
17 of linear shear, and widening the pulse pressure
18 increases the width of the aorta. You know, I'd
19 suggest that we ought to do less animals, and take
20 that money, and contribute it to animal shelters.

21 MS. ABEL: So noted.

22 (Laughter.)

1 MS. DECKER: Maria Decker. For the
2 aneurysm model, there are different advantages of
3 having one with collaterals or one without. If it's
4 an animal aneurysm model without collateral, one can
5 study the sealing effect at the ends of the endograft.

6 DR. VIRMANI: I think there are advantages
7 and disadvantages to animal models. There's no
8 question none of them really truly simulate human
9 disease, and we all agree to that. It's not that
10 we're saying that -- but I think there is something
11 extra learned from an aneurysm itself as compared to
12 when you do it within a normal vessel wall.
13 Therefore, I think it is worth considering that if
14 somebody has tested the device in an aneurysm model,
15 I think would make a little more difference in terms
16 of whether it applies -- it will apply more likely to
17 human than would a normal aorta. Normal aorta is not
18 even worth looking at in some ways. But, I would
19 qualify that and say if you're going to do a normal
20 aorta, you should do a few animals to at least learn,
21 at a month's pace at least, to know what happens in an
22 aneurysm.

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1 MS. ABEL: And I think what we're trying
2 to get at by breaking all this down is figuring out
3 exactly what it is that you would get. I think it's
4 one thing to say intuitively I would be interested in
5 seeing how this thing works in an aneurysm model, but
6 exactly what information do we get out of it is harder
7 to nail down. So that's what we're trying to go
8 through this exercise for.

9 And I think we also haven't really gotten
10 to the column of Data Analysis Challenges. And that's
11 where, if you put it in this aneurysm model, and you
12 are looking for endoleak, what if you see endoleak?
13 What does that mean? How do we deal with that issue?

14 MR. BIGGERSTAFF: We built an aneurysm
15 model in sheep. And we had one Type I endoleak. And
16 the reason for the Type I endoleak was because we had
17 a short leg, and it was possibly undersized.

18 And the point I really wanted to make is
19 that also the sheep's vessels are really elastic. So
20 the whole sizing and oversizing rationale is different
21 in that kind of animal. And I think the take-home
22 message was that we couldn't learn too much about the

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1 propensity to endoleak in the device. And actually I
2 was trying to get the model better and more accurate,
3 and to get the imaging better so we got the right neck
4 length and so on. So yes, it tells you something, but
5 all of these things are rather approximate analogues
6 to the clinical situation.

7 MR. SMITH: I'd like to just add, I'm not
8 sure that we would be settled on what type of
9 aneurismal model would be appropriate. We're
10 presented with several different options here. I
11 think a lot of manufacturers have attempted to create
12 aneurismal models. I think there is animal survival
13 issues just at the aneurysm creation stage. So to me,
14 there's as much research necessary for a good aneurysm
15 model as there is to figure out how to evaluate the
16 graft in it. And so I caution combining two research
17 things together while you're trying to come up with a
18 device to be evaluated clinically.

19 MS. ABEL: But if we could, let's just
20 pretend that we could come up with a good aneurysm
21 model. Let's just pretend. If we did have it, what
22 could you learn. And if the only thing that you've

1 introduced is an aneurysm, as opposed to maybe there's
2 some various ways that you can do it where you can
3 impart some additional changes that would be a little
4 more mimicking human anatomy. What additional level
5 of information do you get.

6 And so like you say, even if you figure
7 out how to do it, there's a cost issue with respect to
8 it, there is additional animals, there is data
9 interpretation. And is that all worth the information
10 you get out of it.

11 EDWARDS LIFESCIENCE: I wanted to say
12 aneurysm endoleak is a result of many factors that do
13 not exist in animal model. So let's assume you do
14 make an aneurysm in an animal model, and then you
15 evaluate your tests, lack of/presence of, as Mark
16 explained the tortuosity. Lack of/presence of
17 calcification. Many other factors, the drag force
18 that Rod was talking about. A lot of these things are
19 missing. Those are the factors that cause endoleak,
20 and if it's going to -- it's not going to teach you
21 much if these factors are missing. And if it does.

22 MS. ABEL: So what you're saying is that

1 there are overriding factors that are missing, that
2 even if you put in the aneurysm itself, that you're

3 DR. CRIADO: But it seems, you know,
4 listening to this conversation, that it is bound to
5 generate more questions than answers. And that it
6 really doesn't make a lot of sense even to create an
7 aneurysm model and test these devices, provided, as
8 Rod was saying, that we are talking about conventional
9 materials. And that would make sense, perhaps, to run
10 an acute study on a normal animal with a normal aorta,
11 perhaps to look at the deployment delivery
12 characteristics and things like that. But the
13 aneurysm model. And you said let's assume that
14 there's a good, and how do you define good? And
15 apparently there isn't such a thing, even conceivably.
16 So it just sounds to me like it would generate, and it
17 does generate, more questions and doubt than answers.

18 MS. ABEL: Which kind of goes back to
19 Lou's comments. If a model is truly developed, and
20 everyone agrees that that's a reasonable model, then
21 maybe it's time to start thinking about looking at
22 that more closely in terms of the requirements.

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1 Stuart?

2 MR. RODGER: Yes, Stuart Rodger. Even if
3 you make one of these analytic models, what are you
4 going to put in it? Are you going to put in a
5 straight graft, or are you going to put in a
6 bifurcated graft? And going back to one of the issues
7 that Dr. Hallisey raised, is that it's very difficult
8 to try to evaluate a bifurcate model in a larger
9 animal. So I think there's a lot of these things,
10 whether it's endoleak or migration. Are we trying to
11 look for failure modes using a straight graft when the
12 majority of the clinical uses are going to be in a
13 bifurcate model which are of themselves limited in
14 their application in animals.

15 I think I agree with Frank that the more
16 complicated we make the animal testing, then I think
17 the more erroneous information we may actually end up
18 with. I'm not saying we shouldn't do it, but I think
19 by creating more and more difficult animal studies,
20 and animal models, I wonder what the clinical
21 implication for that and trying to assess the results
22 of that is.

1 MR. YU: I think endoleaks obviously is
2 quite complex. I mean, there's Type I, Type II. I
3 think in terms of discussing creating animal models,
4 maybe you should divide it into just looking at purely
5 Type I, either to keep attachment on endoleak issue.
6 And in Type II, that's certainly a very different
7 physiological condition. Maybe you have quite a
8 different environment rather than trying to combine
9 two together. And in relation to Type I, obviously if
10 you have endoleak that's a loss of sealing. And
11 invariably, sealing within the graft, you're talking
12 about the actual graft material, the loss of contact
13 between the graft to the vessel wall. And obviously
14 in that situation maybe once you look at how well is
15 the graft attaching to it. What's the contact
16 situation.

17 And along with that, the reliance in Roy's
18 clinical paper pointed out, if you oversize
19 excessively, potentially you can increase the endoleak
20 rate over time. And the question there is that if you
21 oversize too much, are you getting additional grafting
22 folding. And given that a lot of the other

1 conventional Dacron grafts. When you have graft
2 folding, is the stent material actually strong enough
3 to sufficiently compress those folded regions. And
4 are you creating gaps or what have you under those
5 situations. So I think it's -- even just looking at
6 a Type I endoleak, then there's already a lot of
7 mechanical factors that's in place and might be worth
8 trying to focus on some of those in animal model
9 development.

10 DR. CRIADO: I think we need to be careful
11 to separate the discussion here, because I believe
12 some people are perhaps beginning to think that some
13 of us are saying that animal models are not valuable.
14 That's not what we're saying. I believe we are
15 talking about the regulatory process, and whether the
16 agency will ever allow a new device with conventional
17 materials to move forward without extensive animal
18 work. I think -- isn't that the point?

19 MS. ABEL: At our next table, we're going
20 to get more into exactly what testing should you be
21 doing for a new device and that sort of thing. I
22 don't want to think of it as a regulatory issue --

1 DR. CRIADO: But isn't that the issue,
2 though, Dorothy? As to how much this contributes to
3 the process?

4 MS. ABEL: But we want it to be
5 scientifically valid. And when you talk about
6 regulatory, it's like what does Dorothy want, which
7 isn't scientifically valid in any way, shape, or form.

8 (Laughter.)

9 MR. BATY: That's been recorded.

10 MS. ABEL: That's in the minutes. That'll
11 be quoted more than once, I'm sure. But you know, and
12 like I say, we're trying to break it down so that we
13 can say specifically, and I think it's a good point,
14 if we look at Type I endoleak. But what I keep
15 hearing is that we get back to, it's the contact
16 information, it's the healing information. I think
17 certainly you're going to look at conformity, those
18 sorts of things, where again, if you get an endoleak,
19 it would be something you would know. You wouldn't
20 say, okay, I'm going to go to a clinical study soon.
21 I need to figure out if I'm going to have endoleaks
22 with this device. I'm going to test it in an animal

1 and make sure I don't have endoleaks. I just, I see
2 that as two, and I keep saying it, two different.

3 DR. CRIADO: Isn't that what we're saying,
4 that you would never be able to say that, on the basis
5 of an animal experiment. You just can't imagine how
6 that would be possible.

7 MS. ABEL: And if you incorporate an
8 aneurysm model, would you then be able to say that?

9 DR. CRIADO: No, you would -- without
10 question.

11 DR. VIRMANI: I think one of the things
12 the aneurysm models could tell you is in a situation
13 where you have very poor healing in an animal at 28
14 days to three months. You have very poor healing. It
15 will tell you that in humans it's going to be worse.
16 If in one situation you have a stent graft which
17 actually healed very well at one month, and another
18 one which heals very poorly at one month, you will be
19 able to evaluate those things, and therefore you can
20 say if the healing is poor, likely in humans it's
21 going to be a bigger problem. It's the healing that
22 is important at the interface between the stent graft

1 and the normal vessel wall.

2 DR. CRIADO: And this healing in the stent
3 graft of this qualifier?

4 DR. VIRMANI: I want to --

5 DR. CRIADO: Wait, I'm talking about the
6 aortic stent graft.

7 DR. VIRMANI: I agree with you that it
8 will make a difference. And I can tell you for one,
9 if the healing is not there at one month, there is no
10 granulation tissue even at one month, I can guarantee
11 you in humans is going to be worse.

12 DR. FILLINGER: But humans don't heal. I
13 mean, the reason we use -- when we do an open repair,
14 the reason we use permanent sutures is because we
15 found out a long time ago if we don't use permanent
16 sutures, if they dissolve 15 years later, the
17 anastomosis falls apart 15 years later. Humans don't
18 heal. There is no -- I mean, we need acute fixation
19 and acute sealing that works in the absence of healing
20 because there won't be any in humans.

21 DR. VIRMANI: That's not true. If you put
22 stents in an aorta which is atherosclerotic, and you

1 get no -- just pure stent, not a graft, I'm saying.
2 When you're sealing at the site. Over the stent,
3 there is new intimal formation.

4 DR. CRIADO: You can depend on that. I
5 mean, I didn't want to be abrupt, but in clinical
6 vascular surgery, we essentially don't care about
7 healing, vis-à-vis AAA repair.

8 DR. VIRMANI: I wouldn't say that, that
9 you don't care about healing, at all. I mean I think
10 that's a statement that shouldn't be made, that there
11 is no healing and you're happy with it. DR. MATSUMURA:
12 Well, I think it's really a matter of designing. And
13 there is always going to be a percentage of people who
14 do not heal. So from at least a development point of
15 view, you have to design and think of the absence of
16 healing permanent sutures, stent fixation. Because
17 you can't assume that everyone's going to heal.

18 So healing, I think, is a finer screen.
19 It's a finer mesh. It's a way to differentiate in a
20 fine way between devices or materials. But in terms
21 of the ultimate goal of providing a safe and effective
22 AAA exclusion device, I don't think any can count on

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1 healing.

2 DR. VIRMANI: I don't see the point of
3 doing any experiments whatsoever. According to you,
4 it seems that you shouldn't do any animal experiments.

5 MS. ABEL: I think when you're talking
6 about healing here, I think it's valid to say that you
7 may be comparing it to what you know how other devices
8 function. And if you see a difference, again that
9 would lead you to try to figure out why. I don't know
10 that you would be able to say, when you've got another
11 Dacron graft with another nitinol stent, that if
12 things look a little different, if they did look
13 different, you would say is the radial force
14 different. Is the configuration different? And see,
15 and go into it, and possibly try to figure more out.
16 So I mean, I don't think anyone's saying don't do
17 animal studies. It's just trying to figure out
18 exactly what it is you're getting out of it. And to
19 say it heals in an animal, and therefore it is good
20 and it will heal in a person is -- that's the only
21 thing people here are saying that we have seen with
22 vascular grafts. With endovascular grafts, it's just

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1 not reality in all patients.

2 MR. SMITH: I was just going to say that
3 it's important to use the right terms so you think
4 properly. And what we're talking about is
5 incorporation. We know that with woven Dacron, and
6 that's what we're talking about and I'm hearing. With
7 woven Dacron you can pull it out after 15 years. It's
8 woven Dacron that doesn't incorporate and heals. So
9 it's really how we use the terminology. It's not that
10 humans don't heal.

11 MS. ABEL: That's a good point. And
12 certainly it's more appropriate to say the tissue
13 reaction, the host reaction to the graft, and what
14 have you.

15 MR. WANINGER: Just -- this is Matt. One
16 other thought is you don't want to underestimate the
17 importance of your oversizing when it comes to this,
18 evaluating endoleaks in animal models. Because you
19 don't always have the opportunity to do pre-procedure
20 imaging, and then have a device made for the animal,
21 and then actually do the implant. You're going to make
22 a specific size ahead of time, and very likely you're

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1 going to have suboptimal sizing. Some may be
2 undersized, some may be oversized. So you may be
3 predisposed to an endoleak simply because of the
4 sizing of the devices as they go in.

5 And then if you've got an animal that
6 continues to grow, that vessel may continue to grow,
7 and so your sizing's going to be suboptimal at the
8 later time points, which may also predispose you to
9 endoleak.

10 DR. WHIRLEY: I would assume that at the
11 end of the day when we get through these 12 items,
12 we'll try to find out what the primary endpoints would
13 be for doing an animal study. And I think we're
14 making this kind of complicated because while we're at
15 it, certainly we'll look at all these items. I mean,
16 you're not going to do a study and not look and see if
17 it's patent, or not look and see if it's migrated.
18 But I think the point you're trying to make is that
19 those aren't individually the reasons why you do an
20 animal study. So maybe we just need to cut to a
21 chase, find out if we need to do an animal study and
22 why, and then look at what are the secondary things

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1 that you're going try to work on on the way.

2 MS. ABEL: You can be on the steering
3 committee next year.

4 (Laughter.)

5 MS. ABEL: We're playing our game today.
6 We're going to make this agonizingly painful to look
7 at the individual failure modes, because we do get
8 people saying, you know, our device is great and grand
9 because we did not see this in an animal model. And
10 we get people saying we should do more animals, we
11 should do less animals, we should do whatever. And
12 what we're trying to get to is the bottom absolutely
13 rationale as to if you can only document negative
14 findings, then that may mean that you're in the realm
15 of doing a less rigorous animal model where you don't
16 have to do a GLP study out to seven years. So we have
17 to -- that's our goal, and our next table after the
18 break, which what time are we supposed to break? So
19 we'll get to that. I'm sorry, there was a hand over
20 here somewhere.

21 DR. FOGARTY: No, I'm going to refrain.

22 (Laughter.)

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1 MS. ABEL: Okay. So we will move along,
2 and I think we're going to try not to have redundant
3 conversations and blast through this so we can have
4 our break.

5 So deployment and delivery, I think
6 everyone agrees that it is something that you can look
7 at in the animal model. It's something that you
8 attempt to evaluate, but once again, you don't have
9 the tortuosity, you don't have the anatomical
10 limitations in the animals that you do in the clinic.
11 But it's certainly -- it's something to look for.

12 Is there any reason to believe that if you
13 incorporate an aneurysm in your animal model that you
14 would have a more challenging evaluation in delivery
15 and deployment.

16 AUDIENCE MEMBER: Say that again? What
17 was that?

18 MS. ABEL: Is there reason to believe that
19 if you incorporate an aneurismal model in your animal
20 study that you would have a greater, better challenge
21 to evaluate delivery and deployment.

22 DR. HALLISEY: Dorothy, I would say you

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1 don't need that more complex model for delivery and
2 deployment. I'm including in that the device that's
3 used to deliver, the delivery catheter. The only
4 caveat I would say is that the infra-renal neck maybe.
5 You'd be testing how close you can get to the infra-
6 renal neck with your delivery device. But it's
7 probably not necessary. You're trying to see if you
8 can land your jet on an aircraft carrier, basically.
9 You don't need to have an aneurysm or a big gaping
10 hole in your runway to know that you're doing it in
11 the correct way. So you don't need the more complex
12 aneurysm there.

13 DR. CRIADO: But on the other hand, the
14 anatomy has to be semi-similar, such as remote entry
15 site, trans-femoral or trans-iliac as opposed to
16 direct, et cetera. The anatomy has to be more or less
17 comparable, it seems to me.

18 MS. ABEL: But there isn't anything
19 necessarily that you could change in the animals?

20 DR. CRIADO: Right, right.

21 MS. ABEL: At this point, to make them a
22 more appropriate challenge to delivery and deployment.

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1 Is there any agreement?

2 MR. YU: I think where you were talking
3 about saving our animal costs and so forth. I think
4 testing of delivery systems really is one key area
5 that you can really say, and not avoid animal testing.
6 Because certainly animal -- doubtless what animal
7 you're going to, the amount of tortuosity -- so you're
8 not very close to what you see clinically. Yet again,
9 those extreme conditions can much better be tested in
10 a bench top model where you can force that, and you
11 can apply the blood pressure. And certainly for
12 delivery systems there is no long-term issue that you
13 need to leave it in there. And it's very much acute
14 study, talking about seal, talking about its ability
15 to function properly in a tortuous environment.

16 MS. ABEL: I think that's very --

17 DR. VIRMANI: I think casting is a very
18 good idea of doing it. Make human casts. And I think
19 on the bench-top testing would be a very good thing to
20 do, because we can never simulate that in animals. So
21 the delivery aspects should be tested in a model which
22 simulates human disease, and on a bench-top.

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1 MS. ABEL: Okay. So it kind of gets along
2 the same status as our other things. It's something
3 that you're certainly going to look at. If you find
4 negative findings, you would try to figure out why.

5 DR. VIRMANI: I think most companies do it
6 anyway. In today, at least.

7 MS. ABEL: Okay. And so you wouldn't
8 necessarily get more information using an aneurysm
9 model with delivery and deployment.

10 Biological response, which is probably the
11 biggest issue that people are still focusing on with
12 respect to animal studies. And I just -- we've
13 already talked about the limitations of the various
14 animal models with respect to how they compared to
15 humans, so I don't think we have to spend more time on
16 that. And I think we all agree that you look at the
17 biological response.

18 Is there anything that you could do to
19 make the model more complicated to get additional
20 information? I mean, I think even if we aren't
21 talking about putting an aneurysm in, I've heard a lot
22 of discussion about controls. And so maybe that would

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1 be something to put in here as just, it's important to
2 have a concept of what to expect, and the only way to
3 do that currently is controls. Is that fair?

4 DR. VIRMANI: What are you going to use as
5 a control?

6 MS. ABEL: Well, I think you'd have to
7 justify it. You would have to come up with, just like
8 any other aspect of the study. Mark?

9 DR. FILLINGER: In terms of additional
10 information, just like with endoleaks, we talked about
11 the degree of oversizing I think is really important
12 in that, whether the graft is oversized, undersized,
13 and how much it's oversized or undersized may affect
14 whether you have a -- what type of biological response
15 you have. So paying attention to that during that
16 testing, if you're going to do that sort of a thing,
17 it should be documented.

18 MS. ABEL: Okay. Any other thoughts with
19 respect to biological response? I think we talked
20 about it quite a bit during our other discussions
21 here. Yes?

22 DR. VIRMANI: What time period are you

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1 going to look at biological response? Is it
2 immediate? Is it three months? Is it ten months? Is
3 it one year? What is considered as a biological
4 response for what time period?

5 MS. ABEL: I think that's a good question.
6 I was trying to figure out if that's something that
7 we'll be touching on a little bit later, or if it's
8 something that we need to talk about over break
9 because it's a big issue with respect to what should
10 animal models look like in the future. And certainly
11 time frame would be important. So I just want to
12 table that so everybody can have a little coffee and
13 they don't fall asleep on us. That's a very good
14 point.

15 Adverse events due to excessive radial
16 force. And that is somewhat linked to the biological
17 response. And it has to do with what you had
18 mentioned previously. So it would be nice if we could
19 evaluate it. I don't know that it's actually -- have
20 there been animal models that have shown the problem
21 before it got into the clinic?

22 MR. RODGER: No.

1 MS. ABEL: Would you like to share with
2 the audience?

3 MR. RODGER: Yes, we had one device where
4 we did animal models, and we didn't see any adverse
5 events due to radial force at all. But when we moved
6 into clinicals, we had a real issue with it. And we
7 had significant neck dilatation in a number of
8 patients. And we had to go back and, well, David had
9 to go back and spend a year trying to see what caused
10 it. But we certainly didn't identify it in -- and
11 that was using different animal models. We used cows,
12 sheep. We did the whole McDonald's Farm thing, you
13 know, we had everything going.

14 (Laughter.)

15 MR. RODGER: And we still didn't see the
16 source. The thought of having to then create new,
17 more complicated animal models just scares the living
18 daylights out of me.

19 VASUTEK: Can I just respond to Stuart
20 there.

21 (Laughter.)

22 MR. STEVENSON: It's only fair. Sorry,

1 David. One thing that we did learn was about
2 excessive oversizing. And I think that was what we
3 learned. So I would conclude with Mark that
4 oversizing is certainly something that has to be
5 considered.

6 In a greater perspective, maybe we need to
7 consider our worst case for everything, what we're
8 looking for. Companies trying to develop devices, is
9 to prove that the device in its worst case is
10 acceptable, and goes back to biological response. We
11 may see healing in some cases. I'm hearing that we
12 probably don't see it very often, but we may. But the
13 worst case is that we don't see healing. So
14 therefore, we need to design a device that copes with
15 no healing whatsoever.

16 We may deploy devices at the correct size,
17 and they'll be fine, but we may deploy devices
18 oversize. So we need to, if we're going to use
19 models, we need to consider using them at their worst
20 case so that we see the envelope, the design envelope,
21 stretched.

22 DR. GREENBERG: Something they said

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1 sparked another thought. When you are doing an animal
2 study, we've talked about scaling down devices for the
3 proper species. Part of that scaling down becomes
4 difficult if you don't have the same mechanical
5 properties, for example, radial force, as you would
6 have in your normal device. And so then you go
7 through a whole engineering effort, not just to scale
8 it down, but to make sure that it's at per-unit area
9 of some sort, the same radial force. And it becomes
10 quite a complicated issue.

11 MS. ABEL: All right. Sounds like we've
12 had enough discussion on radial force then. We're
13 going to group together loss of integrity. And we can
14 include in that corrosion. It's interesting, there
15 wasn't anyone that thought they needed to look for
16 corrosion in their animal models, at least that were
17 reported to us. And so I would just be interested in
18 -- I would say that you should certainly note any
19 negative findings. Not that you are necessarily 100
20 percent evaluating for corrosion, again, but it seems
21 like something that you'd be paying attention to.

22 And probably with the integrity of both

1 the graft component and the metallic components, is
2 there an animal model that you could possibly design
3 that would have the adequate forces that you'd be able
4 to evaluate integrity.

5 DR. WHIRLEY: This is Robert. I think the
6 loads on devices in animal models are often far
7 smaller than they are clinically. And you're only
8 getting cycles at physiologic rates. So from a
9 fatigue standpoint, they're not so good. So given
10 that the loads are generally smaller, and you're
11 getting few cycles, I'm not sure you'd really learn
12 much about integrity from animal models.

13 MS. ABEL: And what about graft, and
14 sutures, and those sorts of things?

15 DR. WHIRLEY: Well, certainly if you
16 sought observation in your animal models, that would
17 be something you'd want to look into. But I think in
18 vitro testing might be a better challenge.

19 DR. VIRMANI: I think some of it you can
20 learn from the animal models, the integrity of the
21 various components. For example, I give you if you
22 have a coronary stent and it fractures in the animal,

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1 you know you're going to have problems in the human.
2 So therefore I would say that you should at least look
3 up to one year. If the integrity of the material is
4 maintained up to one year, then I think at least you
5 know up to that one year in a human should be
6 relatively safe. It's not to say that it will be.
7 I'm not saying that it will be, but at least you have
8 to strengthen your hands to say that it will work in
9 humans.

10 MS. ABEL: Okay. Well, we'll get back to
11 the timing issue a little bit later.

12 DR. GREENBERG: Can I just respond? I
13 agree, although I think that the timing and the
14 benefit of each test has to be juxtaposed. So if we
15 have a failure that may possibly occur in an animal,
16 but we know that if we have a more rigorous test that
17 is going to produce a failure, we should at least
18 economically go to the more rigorous test immediately.
19 I think that looking at failures in animals for long-
20 term integrity issues is a very nebulous and difficult
21 thing, especially when we get to large-diameter
22 devices.

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1 DR. VIRMANI: I agree, but supposing it
2 does fracture, in such a situation then I think it
3 does tell you that this is not likely to work. That's
4 your minimum standard, in a sense.

5 DR. GREENBERG: I'm just trying to stay
6 away from the subjunctive.

7 MS. ABEL: Okay. I think we should
8 probably move on to the next. I think we'll get into
9 this in the afternoon, or after the break.

10 MR. KING: I would just reiterate what's
11 being said here in the sense that you make these
12 secondary observations, and if you do see the fabric
13 has distorted, then obviously you make those
14 observations. But you don't design an experiment in
15 an animal to look for that type of failure mode,
16 clearly.

17 MS. ABEL: Okay, good. Thank you. Size
18 increase and rupture. Again, you had, Dr. Hallisey,
19 had talked about actually designing animal studies to
20 evaluate rupture. And that was interesting to me.
21 Are there any other thoughts with respect to that from
22 other folks?

1 DR. MATSUMURA: It relates to nothing. I
2 thought that's what clinical trials did.

3 MS. ABEL: You don't do clinical trials to
4 evaluate rupture.

5 DR. MATSUMURA: Well, you're evaluating
6 eventual rupture. Trying to exclude.

7 MS. ABEL: But you don't design a clinical
8 study to actually determine your rate of rupture. You
9 can't design a study. It would be too big, and too
10 long, and all that sort of thing. So if you are able
11 to prevent rupture in a pig, do you have a great
12 device for treatment of pig aneurysms, or does it tell
13 you something about the potential for avoiding rupture
14 in the clinic? And is that something that -- getting
15 back to one of Lou's earlier comments -- if eventually
16 people do come up with an aneurysm model that is
17 reproduce-able, that's validated, that incorporates
18 some of the various characteristics, then is it time
19 to talk about whether there's added benefit?

20 I guess in your model and your example, I
21 thought there are certainly some devices where you
22 would be pretty sure that your pig's still going to

1 rupture because the wall of the graft is more
2 permeable. Well, you can figure out the permeability
3 of the graft wall on the bench-top. You can compare
4 it to other devices. Do you need to do an animal
5 model to show, yes, you would get a rupture if you've
6 got something that's expanding at the rate where it's
7 expected to blow in two weeks.

8 DR. HALLISEY: I'd like to add, I knew
9 this was going to be a controversial one, but when it
10 comes down to it, those are the two big questions that
11 patients want to know. First of all, is my aneurysm
12 going to rupture six months from now, two weeks from
13 now, whatever.

14 AUDIENCE MEMBER: As though your pig
15 patients, or your dog patients, or your sheep
16 patients.

17 DR. HALLISEY: I know, exactly. But if
18 you can test it, you can validate that model. And
19 that's why I had in that slide that that model
20 described by Maynar needs to be validated. And if in
21 then using that model you demonstrate the stent graft
22 does exclude the aneurysm, it doesn't rupture, and

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1 statistically significant, you have a point with your
2 model. It's a little bit -- your stent graft is a
3 little bit different than the other stent graft.

4 Now, the other thing, we did talk earlier
5 about endoleaks. That's the second biggest thing that
6 patients ask about is they don't like coming back for
7 other interventions for endoleaks. So I'm taking it
8 from a clinical perspective. Is there something from
9 animal modeling that we can do to help our patients,
10 because that's what it's all about. In the long run,
11 you can put in all the stent grafts you want, but if
12 the aneurysms rupture, or the patients keep coming
13 back for more interventions, or endoleaks, it's going
14 to end up being far more costly to patients, to the
15 health care system.

16 So I would propose that you can test this
17 new stent graft, or a stent graft, in a rupturing
18 model, and say that it might be more beneficial than
19 another stent graft. Now, can you apply it to humans?
20 Yes, I agree, you're going to have a hard time testing
21 that, and you're going to have a hard time getting
22 people to volunteer to test that in humans. But I'd

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1 like to see it in animals.

2 MS. ABEL: I guess I can get back to Roy's
3 previous comment about what do you gain. You know
4 what you're putting into it, you're developing a whole
5 new model, you're going to have to deal with whatever
6 results you get. And what is the true gain? And I
7 think for your patients what they really need is the
8 results of a good clinical study so that you can go
9 tell them this is what you can expect to see.

10 I find it very difficult -- I'm certain
11 that we at the agency never say, oh, if you've shown
12 that it adequately protects a pig from rupturing you
13 can claim that it's, you know.

14 DR. CRIADO: Yes. I can't imagine talking
15 to my patients and making them feel reassured out of
16 the outcome in pigs and sheep, you know? I can't
17 imagine that that would work. I agree with what you
18 just said, yes. Clinical data, clinical trials and so
19 forth would be powerful. Not animal experiments.

20 MS. ABEL: Yes, you would have to put the
21 qualifier in when you're talking to your patients that
22 that is where you get the information from. You can't

1 just say, oh, this one's not going to rupture, or you
2 won't rupture with this device.

3 MR. BORDEAU: This is Bill. I think we're
4 not only talking about in this case, if we were to
5 proceed with a model like that, validating the
6 aneurysm and its ability to rupture, but you're also
7 validating your neck, and you're validating the sizing
8 protocol you have. These things are also critical in
9 whether this model's going to be reproduce-able. And
10 so it's actually much more complex than just coming up
11 with an aneurysm, whether it be a peritoneal patch or
12 a Dacron graft. We don't have consensus on that yet.

13 MS. ABEL: That's a good point. Again,
14 just in terms of what -- you still have all the other
15 limitations, and with respect to what Matt was saying
16 previously in terms of sizing and other issue with the
17 animal models, that complicate issues. Stuart?

18 MR. RODGER: In this kind of somewhat
19 esoteric arena of trying to create aneurysms in
20 animals, how predictable are those models? I mean,
21 can you accurately say I expect this one to rupture in
22 two weeks, or this one in four weeks? And how sound

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1 are the judgments that you'll make from those
2 experiments?

3 MS. ABEL: Well, we already said that the
4 model needs to be validated. So I think we can all
5 agree at this point in time there's no model that
6 anyone has agreed upon as the best situation with
7 respect to trying to create an aneurysm. There isn't
8 a validated model.

9 And we're trying to figure out how much
10 energy should be put into trying to come up with that
11 model. What additional information would we get out
12 of it. And so let's again go to the utopia. Let's
13 assume the model exists where you can create an
14 aneurysm, and it's reliable, and you know that -- in
15 the rupture one it will rupture at 2.7 weeks. You
16 know, what will you learn by putting your device in
17 there? Will you learn something from a developmental
18 standpoint, or is it something that you need to test
19 your device, and that's sort of a model in order to be
20 prepared to go into a clinical? You know, so I think
21 that's another aspect.

22 MR. YU: I think what to look at is, if

1 you're going to have a rupture, invariably there's
2 going to be some physical hemodynamic forces, whether
3 it's through a type of endoleak, or some sort of
4 trans-graft seepage of what's under pressure acting on
5 the sac. So one way to look at it in terms of helping
6 you approve a process, or add a plus sign, is to say
7 look at artificially created aneurysm sac model, at
8 the end of the animal sacrifice you just put a knife
9 into that, and if not a drop of blood comes through,
10 then I think there is a level of confidence. Whereas
11 one where you cut into it and you see drips and drips
12 of blood coming out, then you have to ask where does
13 that blood come from. And there may be -- that could
14 be a definite point.

15 MS. ABEL: But you may also be able to,
16 again, look at the permeability of the device in the
17 first place without even going into an animal model.

18 MR. YU: Right.

19 MS. ABEL: To figure out if you've got a
20 trans-graft. Well, I think we should take a break,
21 you'll all be glad to know. And we had planned on
22 having a nice long break so you could all talk amongst

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1 yourselves, but we're now going to cut that down. So
2 if we could get together at five after. Thank you.

3 (Whereupon, the foregoing matter went off
4 the record at 10:53 a.m. and went back on the record
5 at 11:23 a.m.)

6 MS. ABEL: So, I'm assuming that you have
7 been taking copious notes, and you're completely up to
8 speed with respect to what we just discussed. But
9 I'll still go over it just in terms of if you look at
10 Table 1.4, which Angie has on the screen and you have
11 in your packets. In the packet we actually put in
12 what people thought they were evaluating in the animal
13 model. And again, this is -- the way I interpret it
14 is they thought that they would set out to look for
15 patency. But I'm sure that a lot of is just they
16 documented patency. So that's what people are
17 actually looking for, and that appears on my screen.
18 And then Angie has the blank table that we'll be
19 filling out.

20 So now we're into the process of getting
21 into the downright for a new endovascular graft,
22 should we be doing an animal study to evaluate this

1 particular attribute or failure mode. Now we all
2 agree up front, we don't have to say it again, that if
3 you would observe any of these things in your animal
4 model, that you would have to write it down, figure
5 out what happened and why, and figure out if it's
6 really a problem or if it's an incidental finding of
7 your animal model.

8 So what we're looking for now is just do
9 you need to, for example -- we'll get into time frames
10 later too -- but let's just say 20 weeks because
11 that's what's in the ISO standard. Do you need a 20-
12 week GLP study to look at patency in order to have
13 enough information to go into a clinical study. In a
14 new endovascular graft. And if at this point in time
15 we could consider it to be kind of the standard
16 endovascular graft as opposed to -- obviously if you
17 come up with new materials, unique designs, you're
18 going to have to do additional testing specific to
19 those differences. So we're just talking run-of-the-
20 mill, someone has an endovascular graft for AAA
21 treatment. Do you need to design an animal study to
22 look for patency?

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1 All those in favor of no? Okay. So you
2 will document patency, but you don't necessarily have
3 to design the study to look at patency.

4 Now, if you've modified your current
5 endovascular graft. Let's say you're already legally
6 marketed in the U.S., and you're going through those
7 evolutions that Donna Bea was talking about this
8 morning. And the change that you've made could
9 potentially change sealing and fixation effectiveness.
10 Is there any reason, again, that you would be looking
11 at patency necessarily?

12 (Chorus of Nos.)

13 MS. ABEL: And now you've made a
14 modification that could affect your ability. Again,
15 patency not an issue though. So this is just going to
16 go much quicker. Now, are controls necessary? I
17 don't think we have to talk about that column unless
18 we actually have a 'Yes' somewhere else in the row.

19 Now, we can go across, like we've just
20 done in our little example, or we could go down the
21 column. Any preferences?

22 (Laughter.)

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