

1 course of their follow-up. Subsequently the
2 endoleak was not demonstrated but their aneurysm
3 enlarged. The patient was converted at a time in
4 the future and at the time of conversion no
5 endoleak was demonstrated and there was some
6 serosanguinous fluid in the aneurysm sac, but it
7 certainly wasn't blood in the sac. So, my take on
8 that was that the endoleak sealed. There was no
9 further bleeding but there was progression of
10 enlargement of the aneurysm.

11 DR. MATSUMURA: These cases all generate a
12 lot of interest and perhaps I can refresh Dr.
13 Brewster's memory. I believe that patient did have
14 a type II endoleak by CT. Subsequent CT did not
15 have it identified. So, perhaps you are referring
16 to core lab review of that patient's assessment of
17 endoleak. The site performed an MR with and
18 without gadolinium and did determine there was a
19 type II endoleak there. Based on that information,
20 the site felt there was a type II endoleak. The
21 patient declined intervention, catheter based, and
22 did have a conversion. But perhaps, David, you
23 have more.

24 DR. BREWSTER: Well, I think it is quite
25 possible, Dr. Comerota, that this represents the

1 vexing problem of type II endoleaks that may, in
2 fact, come and go perhaps because they are sealed
3 temporarily by thrombus. Then, of course, there is
4 this clinical entity of endotension where an
5 investigator simply cannot, by whatever modality
6 they choose, identify an endoleak but there is
7 aneurysm growth. Presumably, the aneurysm remains
8 pressurized in some fashion. Even at surgery, with
9 the aneurysm sac open and thrombus evacuated, you
10 may not identify leak but, yet, the aneurysm has
11 enlarged. I think we are still trying to determine
12 what causes these limited or unusual instances and,
13 more importantly, what the proper clinical response
14 is. Sometimes the treatment may be worse than the
15 problem.

16 DR. MATSUMURA: I do want to get to the
17 meat of that question though, which is the other
18 two patients who didn't have the endoleak in the
19 pivotal study. One was a Washington Hospital case.
20 That patient did not have any endoleak identified
21 before study but during the procedure they did
22 measurements of the proximal neck dilatation so
23 they were no longer oversizing the device, and it
24 was felt that the enlargement may be due not to a
25 visible endoleak but the fact that the aortic lumen

1 and its pressure is in direct contact with thrombus
2 of the aneurysm sac. That patient, therefore, did
3 not have an endoleak but had aneurysm growth.

4 So, that leaves us with the third pivotal
5 patient and the feasibility patient who had growth
6 without endoleak. I personally requested that the
7 physicians explant these devices and look very
8 carefully for what perhaps you are alluding to,
9 that perhaps there is an ultrafiltration or
10 transgraft flow or weeping that causes the clear
11 fluid as opposed to blood. They both videotaped
12 these. I reviewed both videotapes. I have spoken
13 to both of them. With the clamps off, the aneurysm
14 sac opened, directly inspecting the graft looking
15 for weeping, they didn't see it. Of course,
16 vascular surgeons are very familiar with this
17 phenomenon where you see it coming through and that
18 does not appear to be the etiology in this case.

19 For a lot of us I think it is a vexing
20 thing, these leaks that can be seen on some films
21 but not others. Is it positional? Is it coming at
22 some time points but not all? I don't really have
23 the answer to that.

24 DR. COMEROTA: Has that been observed in
25 either your experience or Dr. Brewster's experience

1 in any other of the endoprostheses?

2 DR. BREWSTER: Certainly, the phenomenon
3 of endotension has. That is, aneurysm sac
4 enlargement without identifiable endoleak. Out of
5 interest, I have observed in several cases of
6 clinically open repair aneurysms that years later,
7 after the shell of the aneurysm had been closed
8 around the graft, subsequent aneurysm sac
9 enlargement occurs. Aspiration and even operation
10 has revealed a similar clear fluid in a couple of
11 cases that I am personally aware of.

12 DR. COMEROTA: So, it has.

13 DR. BREWSTER: Yes.

14 DR. COMEROTA: With the Dacron type.

15 DR. BREWSTER: With the standard Dacron
16 prosthesis.

17 DR. COMEROTA: Right, thank you.

18 DR. LASKEY: Is that it, Tony?

19 DR. COMEROTA: Yes.

20 DR. LASKEY: Before we move on to the next
21 discussant, I have one quick question. Endoleak
22 was associated with size at 24 months but not at 12
23 months. Could you tease that out a little bit
24 better and what the implications are for follow-up,
25 number one, and safety assessment, number two?

1 DR. MATSUMURA: I will take that one I
2 guess. The Chair points out that in your panel
3 package, 225, we did an analysis looking at
4 relationship between aneurysm shrinkage or growth
5 using a 5 mm threshold and the presence of an
6 endoleak at the time point at the end of that
7 interval at which size was determined.

8 I would just digress for a moment and say
9 I have had a strong interest academically in
10 endoleaks and aneurysm size change, and I think
11 that with adequate power you can show statistical
12 relationships between the two. That is
13 demonstrated with data. At one year the p value on
14 that relationship is 0.12, a non-statistically
15 significant trend, but at two years, with further
16 observations, it is a statistical trend. About
17 half the patients who have enlargement have an
18 endoleak which is higher than the rate of patients
19 who do not have enlargement or shrinkage, which is
20 about 9 or 14 percent.

21 Now, your question was how does this
22 impact on patient safety. I think all of us are
23 sensitive to monitoring for endoleaks because we
24 believe that there may be that relationship, that
25 this radiographic surrogate could predict adverse

sgg

1 events. In particular, we are worried about the
2 type I and type III endoleaks which seem analogous
3 to never having put the endograft in.

4 Unfortunately, because it is not entirely
5 predictive and many of the patients with endoleaks
6 still have stable aneurysm size or aneurysm
7 shrinkage, and because our own analysis shows in
8 this pivotal trial that endoleak does not predict
9 increased mortality, I cannot say that it is a very
10 useful clinical predictor. We pay attention to it.
11 We look at it and sometimes we even reintervene,
12 especially if it is a type I or III. We also get
13 more "intervening-ish" if the aneurysm is
14 enlarging.

15 So, we recommend in this trial, and I
16 think subsequently, that patients be monitored for
17 endoleaks with a CT scan at baseline, 6 months, 12
18 months and annually, and that the physicians review
19 that and if they have these surrogate findings,
20 like endoleak, that they consider the patient for
21 reintervention, particularly if it is a type I or
22 type III.

23 DR. LASKEY: Thank you. Dr. Najarian?

24 DR. NAJARIAN: Thank you, Dr. Comerota,
25 for your elegant summary and I will not duplicate

1 that. This is a difficult problem, primarily I
2 think in this patient population that is older and
3 has multiple medical problems. So, obviously,
4 there is a lot of interest in these devices.

5 I do have a question. I think the safety
6 of the device has been well demonstrated. As far
7 as the efficacy, I guess the bottom line would be
8 how many patients are free of rupture. Of course,
9 you have followed your patients out to one and two
10 years and I guess one question is the precursor to
11 rupture, we would assume, is increase in aneurysm
12 size, and you have addressed that a little bit just
13 now. But at one year you had 13 patients or 8
14 percent demonstrating an increase in aneurysm size,
15 and at two years 21 patients or 14 percent. So,
16 you have demonstrated an increase at two years. I
17 don't know if one can extrapolate, but do you see
18 any kind of trend there? I know you are going to
19 be doing a follow-up study and you are going to
20 continue following these patients, but at what
21 point are we concerned or at what point have we
22 answered the question of have we decreased the rate
23 of aneurysm rupture?

24 DR. NAFTEL: As far as aneurysm growth
25 across time in the entire group of patients, we

1 have closely looked at the aneurysm size and on the
2 average--and that is the important part--on the
3 average there has been no increase from 1 month to
4 6 months to 12 months or to 24 months. So, just
5 speaking as average growth, nothing is happening.

6 That is very different from what you are
7 asking, what about the proportion of patients that
8 are having a growth of 5 mm or more? That
9 proportion is increasing, as you noted. But
10 interestingly enough, the other end of the spectrum
11 is happening too in that the proportion of patients
12 with shrinkage below 5 mm is increasing with time.
13 What that would lead you to realize is that the
14 variability is increasing in aneurysm growth across
15 time. So, that is just to give you an overview but
16 Jon can answer the clinical part.

17 DR. MATSUMURA: I am not sure that the
18 assumption or the hypothesis that aneurysm
19 enlargement is predictive of rupture after
20 endovascular repair is proven in this study. I
21 think it is a concern that we have and, hence, the
22 management guidelines that the PIs formulated.

23 I would point out that the majority of
24 patients in the study do not have aneurysm
25 enlargement. I think 93 percent have stable or

1 shrinking aneurysms at one year and 86 percent at
2 two years. And, the growth rate is relatively slow
3 so that these enlargements can be detected, can be
4 reintervened when appropriate. We haven't had any
5 ruptures in the pivotal study following those
6 guidelines and that follow-up. We did also look at
7 aneurysm enlargement similar to endoleak, is it a
8 predictor for mortality, and it is not.

9 DR. NAJARIAN: Let me ask you just as a
10 clinician, at what point do you intervene in an
11 aneurysm that is increasing in size?

12 DR. MATSUMURA: It is very much an
13 independent physician judgment. There are some
14 very respected endovascular specialists who have
15 said publicly they want to see a very high
16 threshold, like 10 mm or 15 mm, before they are
17 sure that it is an enlarger; it is not just a
18 variability of that one episode. But when it gets
19 to 5 mm growth, I generally start evaluating that
20 individual patient, and a lot of it depends on what
21 type reintervention I am contemplating, the
22 patients themselves and the risk factors. So, the
23 answer to your question for me, personally, is
24 about a 5 mm threshold of growth when I start to
25 consider reintervention.

1 DR. BREWSTER: I would simply emphasize
2 Dr. Matsumura's points that this remains an area of
3 really individual clinical and patient judgment and
4 preference. Obviously, it depends quite a bit on
5 the starting point, the starting diameter of the
6 aneurysm. If you treated a 5 cm aneurysm and it
7 increases to 5.5 cm in maximal size, that will be
8 perhaps much less of an impetus than if you started
9 with a larger aneurysm that now gets over 6 cm.

10 But then, as Dr. Matsumura emphasized,
11 each patient has to be assessed and a very elderly
12 patient with a lot of co-morbidities if they
13 require open conversion, you may have to seriously
14 think about that before embarking on that. So, I
15 don't think we can really neatly categorize or give
16 very specific guidelines for those sorts of
17 decisions.

18 DR. NAJARIAN: You do understand my
19 concern though that the number of increasing
20 aneurysms increases with time.

21 DR. BREWSTER: Absolutely.

22 DR. LASKEY: Any other comments related to
23 that question from the panel?

24 DR. ROBERTS: I would ask a question, and
25 that is that if you see an increasing size and an

1 endoleak, does that change your threshold for being
2 concerned and thinking about reintervening? If so,
3 what kind of reintervention are you doing?

4 DR. BREWSTER: I think that is a valuable
5 point and one of the factors of clinical judgment
6 that help you make that decision. For instance, if
7 you see an enlarging aneurysm in the presence of a
8 proximal attachment endoleak, I think virtually
9 every vascular surgeon would respond that
10 reintervention is indicated, and likely conversion
11 unless you can replace a cuff more proximally and
12 so forth. The more difficult decision may relate
13 to type II endoleaks that are not only a little bit
14 harder to treat but the clinical significance is
15 often murkier really. But I think you are right,
16 an endoleak, particularly of a type I or type III
17 variety, would be much more compelling to treat.

18 DR. NAJARIAN: I have another question,
19 and maybe this will be covered in the questions to
20 the panel, but it has to do with I guess labeling
21 and sizing.

22 DR. LASKEY: We can certainly fold that
23 into our recommendations to the FDA, if you want to
24 hold it. Do you want to articulate it now?

25 DR. NAJARIAN: Well, it is actually

1 informational. You know, your graft is made in
2 sizes and the only recommendation--well not the
3 only one but one of the recommendations is that the
4 iliac limb be greater than 10 mm. The iliac limbs,
5 the manufactured iliac limbs come in 12 mm and 14.5
6 mm diameters and you recommend that it be 10-20
7 percent increase in size over the native vessel.
8 How about implanting it in smaller vessels? Are
9 there any recommendations from the manufacturer?
10 If you have a 12 mm iliac limb, can that be placed
11 in a 6 mm vessel? I mean, at what point have you
12 constricted the graft too much, and what is your
13 recommendation?

14 MR. WILLIAMS: I will start with the
15 answer on that and I will probably ask for some
16 clinical perspective from the responders here as
17 well. Currently, in addition to the two iliac limb
18 device sizes that you mentioned, the 12 and the
19 14.5, we also have an iliac extender which goes
20 down to a 10 mm diameter. So, there is the
21 possibility within the oversizing range that you
22 mentioned. And, I think you mentioned 10-21
23 percent, that range is really specific to the
24 aortic end of the endoprosthesis and there is a
25 slightly broader range of oversizing for the iliac

1 components. So, including both common iliac and
2 external iliac anatomy or smaller common iliac
3 anatomy, effectively we have a treatment range of
4 approximately 8 mm to 13.5 mm. You may be
5 constrained in terms of overall treatment length as
6 to whether or not you can use an ipsolateral leg
7 component, contralateral leg component versus
8 extenders or some combination of extenders. But
9 the oversizing is a very specific recommendation as
10 I think the good clinical results reflect working
11 within those indications. It also helps ensure
12 that based on our testing of the device, based on
13 the way the device was designed, it can promote
14 longer-term device durability when operating within
15 those constraints.

16 DR. MATSUMURA: I guess the only clinical
17 perspective I would add to that is that within this
18 trial we didn't have any reduced limb flow, any
19 limb occlusions. The AVIs were stable and there
20 weren't any clinical adverse events referable to a
21 graft limb occlusion. So, I think within the
22 context of this trial, the patency is excellent.
23 What happens if you try to put a 14 in a 6--I am
24 sure there is some border that you can't push but
25 we don't know what it is.

1 DR. NAJARIAN: And the same question
2 regarding the delivery device. It goes through an
3 18 French sheath. Does the company have a
4 recommendation as to the minimal size femoral
5 artery access that can be allowed? I mean, we
6 measure the femoral artery access and the external
7 iliac artery access and a contraindication would
8 be, you know, a small vessel. So, I assume it
9 would be 6 mm. But does the company formally
10 recommend that?

11 MR. WILLIAMS: Yes, we are making formal
12 recommendations within the context of our existing
13 IFU as well as the draft IFU that has been provided
14 in the panel pack. That recommendation is that the
15 patient's vascular anatomy, both in terms of
16 diameter as well as disease state and tortuosity,
17 can effectively accommodate the 18 French delivery
18 profile, and that includes the 18 French vascular
19 introducer sheath which, in fact, has a slightly
20 larger outer diameter profile.

21 So, when we are training physicians and
22 assisting them through an initial learning curve on
23 this, we really try to reinforce all of these
24 different aspects of what it means to have
25 acceptable ilio-femoral access anatomy. Any time

1 currently we see a diameter where we are doing film
2 reading and advisement, technical advisement that
3 drops below those formal diameters of the 18 French
4 introducer sheath we certainly call this to the
5 attention of the physician, and go so far as to say
6 that if someone chooses to move forward in treating
7 a patient, realizing that there are constraints in
8 that anatomy, that there is a potential additional
9 level of risk for ilio-femoral vascular access
10 damage associated with that.

11 Clearly, people are treating patients with
12 ilio-femoral access vessels smaller than
13 effectively the 6.5 mm to 6.7 mm of a French
14 sheath, and the vast majority of the time with
15 careful technique and good case planning it can
16 work out to be a very effective treatment. But
17 that is one of those areas where we are taking a
18 very consistent approach in terms of our training
19 and advisement for physicians.

20 DR. NAJARIAN: So, you obviously address
21 that in your training.

22 MR. WILLIAMS: Yes, the labeling in terms
23 of the IFU but also the physician training
24 materials.

25 DR. NAJARIAN: Thank you.

1 DR. LASKEY: Let's go around the table.

2 Dr. Aziz?

3 DR. AZIZ: I too would like to echo that I
4 very much enjoyed the presentation and I think I
5 learned a few things as well.

6 I will try not to repeat the questions
7 that were asked previously. One of the questions
8 is in the control group you did a CT scan at one
9 year. What was the reason for that? As a part of
10 the study?

11 DR. MATSUMURA: Well, when we were
12 designing the study I thought it was very important
13 that we try to capture events that might be
14 happening in the control group which would be
15 similar to the endo group, specifically things such
16 as ventral hernias, pseudo aneurysms, and not so
17 much at one year but the long-term data from the
18 Canadian study has shown that a lot of patients,
19 after open repair, if you do a CT scan and
20 follow-up, I believe they showed 65 percent of
21 their surviving patients had some type or aortic
22 dilatation and about 14 percent of those actually
23 had an aneurysm in the aorta or iliac areas that
24 were large enough to indicate a repeat procedure.
25 So, it was really for the long term so we would be

1 able to assess some of these findings.

2 I think it is quite possible we might have
3 unexpected findings in terms of renal mass, or
4 something, and we need the data in the control
5 group to make a valid comparison.

6 DR. AZIZ: The operative time, I think the
7 mean was probably 144 minutes, obviously from all
8 centers. Did you find that the time decreased with
9 experience and in the busiest centers as the
10 operators got better they were taking a shorter
11 period of time to do it?

12 DR. MATSUMURA: I see the statistician
13 saying we don't have that formal analysis, but I
14 see a clinician saying that he either wants to
15 respond or he knows.

16 DR. BREWSTER: I don't have detailed facts
17 for you, but I can assure you there is a learning
18 curve obviously. Just becoming familiar with the
19 device definitely would shorten the time. So, I
20 think the answer to your question is yes.

21 DR. AZIZ: I mean, I think obviously this
22 is for elective cases but in the future, obviously,
23 more patients who have leaking aneurysms--I imagine
24 that this technology would be particularly adept to
25 using in those patients if the time, you know, were

1 shorter.

2 DR. BREWSTER: I think your point is very
3 well taken. Indeed, some feel that the greatest
4 benefit from endovascular repair may, indeed, come
5 from urgent treatment of patients with leaking or
6 ruptured aneurysms. Obviously, that is a much more
7 difficult area in terms of accurate device
8 selection. Perhaps this device might not be the
9 best but a one size fits all concept may be applied
10 and, of course, the center has to have inventory.
11 But I think your point is a very valid one because
12 I think, as was mentioned earlier today perhaps by
13 Dr. White, there really hasn't been improvement
14 despite all of our anesthesia and intensive care
15 improvements over the past one or two decades. The
16 results or outcome of ruptured aneurysm repair
17 really have not improved.

18 DR. AZIZ: I think another group, as this
19 becomes more available, is the patient who has
20 coronary disease and AAA. We, ourselves, have
21 patients where we have done the CABG and the AAA
22 ruptures and, currently, the only option is to do
23 them as a combined procedure. But I think
24 something like this would be to do it and then wait
25 maybe a week or two and do the CABG. This would be

1 another nice group.

2 DR. BREWSTER: Those sorts of
3 circumstances come up really quite often in
4 clinical practice.

5 DR. AZIZ: Again, I think one of the
6 conclusions is that patients with smaller body mass
7 had associated increased risk of complications.
8 Can you just expand on that a little bit?

9 DR. MATSUMURA: As you pointed out, that
10 was a predictor in the Cox model. We brought that
11 up at an investigator meeting, the last one in New
12 York, and I think the DSMB also considered that
13 data. The thought was that perhaps it is
14 reflective of patients who have malignancy because
15 it is in the survival one. It is not the same as
16 gender. Gender is not a risk factor. Perhaps we
17 could get into that more later.

18 DR. BAILEY: I will just jump in here
19 briefly. I was not understanding the magnitude of
20 the effect either. What scale is body mass index
21 measured in? Is it kilograms per meter squared?

22 DR. MATSUMURA: Yes.

23 DR. BAILEY: So like 25, 26, 27?

24 DR. NAFTEL: Right, where greater than 30
25 is obese.

1 DR. BAILEY: That is an astonishingly high
2 hazard ratio or odds ratio, 0.2 or something, 0.3,
3 i.e., if you go from 25 to 26 you have a four-fold
4 lower risk. I didn't see how that could possibly
5 hold.

6 DR. NAFTEL: Right. Recall that in the
7 stratified actuarials it was just amazing. It was
8 a very large effect. I do recall that, as you were
9 mentioning, it did look like it was very possibly
10 the cancer patients but I don't know that for sure.
11 I don't have that data.

12 DR. BAILEY: What was the distribution of
13 body mass index?

14 DR. NAFTEL: I don't recall. I remember
15 those break points of cachectic and obese, and we
16 certainly were in either side of those. So, I
17 couldn't give you the exact distribution--or maybe
18 I could.

19 [Laughter]

20 For body mass index, in the EBE group it
21 ranged from 16.6 all the way up to 41. That is
22 huge. In control, from 10.9 to 56.6. So, it is an
23 incredibly wide range.

24 DR. BAILEY: I mean, if you haven't
25 rescaled it then your odds or hazard ratio,

1 whatever it is, implies every unit change in this
2 index confers a reduction of risk by a factor of
3 four or so.

4 DR. NAFTEL: Yes, this is for survival.
5 Right, Jon? This is relative. As you know better
6 than any of us, when you get to these low risk
7 areas, you know, if you cut it to a fourth that is
8 still going from maybe one percent to one-fourth
9 percent. So it is relative within that death rate.
10 So, it looks bigger than it is.

11 DR. AZIZ: A couple of other questions. I
12 think there was a comment made that low platelet
13 counts were associated with increased
14 complications. Is there a cut-off or is it a
15 continuum? What do you mean by low platelet
16 counts?

17 DR. NAFTEL: A lot of this is philosophy I
18 guess. In all the analysis that I do, I enter
19 everything as a continuous variable and I don't
20 look for cut points unless they just absolutely
21 exist. So, it was entered as a continuous
22 variable.

23 DR. AZIZ: And where was the biggest
24 gradient seen? Was it less than 100,000? Is that
25 something people should look out for? If there is

1 a very low platelet count, I mean, is it something
2 that should raise a red flag?

3 DR. NAFTEL: I don't know that for sure.
4 We have done all the stratified actuarials and we
5 can come up with those, but in what we have
6 presented to you we don't have cut points. All we
7 can say for sure is a lower platelet count is
8 associated with higher risk.

9 DR. LASKEY: But it was one of these
10 highly statistically significant things without
11 being necessarily clinically. You have it out to
12 four digits and it is 0.98. It is awfully close to
13 1.0 in terms of the point estimate. So, it is hard
14 to take some clinical sense away from that.

15 DR. NAFTEL: That is true. Again, that
16 0.998 is generally dependent on how you have scaled
17 the platelet counts. So, just to be totally
18 honest, a good statistician can make it anything he
19 or she wanted by the scaling but the p value, of
20 course, would not change. It would stay the same.
21 But my job would be to make it clinically relevant
22 for you, to give it some units that are more
23 helpful.

24 DR. AZIZ: This is a surgically related
25 question. In the three patients who had to be

1 converted for a variety of reasons from EBE to
2 surgical, were there any technical issues? When
3 you put your clamp you would probably put it higher
4 up. When you open it, can you cut across the
5 graft? When you put stents in for coronary
6 bypasses it is a real problem. You cut it open?
7 You slit it open, you put the graft in; you have to
8 take it out? I mean, how do you handle that?

9 DR. BREWSTER: Well, I can't speak from my
10 experience since none of my patients have to be
11 converted--I am just kidding!

12 [Laughter]

13 It obviously generally implies a more
14 technically challenging procedure because very
15 often, as you indicated, I think suprarenal
16 clamping temporarily will be required. Then you
17 have the additional problem of dislodging the
18 device without shredding the aorta. That may in
19 many cases not be too difficult, particularly if
20 you are operating for, say, a proximal attachment
21 leak. But it depends and it is variable. I think
22 many surgeons will have different approaches. Ours
23 is usually to gain temporary suprarenal control,
24 open the sac, remove the device because most of
25 these are purposely deployed as close to the renal

1 arteries as you can get them. So, I think you
2 pretty often have to have a suprarenal clamp to
3 safely dislodge and remove the device. That is
4 generally a somewhat bigger undertaking than a
5 standard repair.

6 DR. AZIZ: But you could open it, do the
7 proximal anastomosis, lay it like a trouser, within
8 a trouser and not take it out? Could you do it
9 that way?

10 DR. BREWSTER: It could be a strategy I
11 suppose. I think in this particular device, should
12 you want to cut across it, you can.

13 DR. AZIZ: This is again my cardiac aspect
14 coming out, if you needed to put an intra-aortic
15 balloon in somebody who had this device in, you
16 don't see any reasons why one couldn't do that?
17 Right? Later down the road?

18 DR. BREWSTER: No problem.

19 DR. MATSUMURA: I would probably think
20 that if it was done very early after the procedure
21 I would want to do that under fluoroscopy to make
22 sure that you could watch the passage.

23 DR. LASKEY: It is interesting you say no
24 problem, but for the cardiologist coming in at
25 midnight to do that, that is an adventure.

1 DR. MATSUMURA: I think what David might
2 be referring to is that after implantation there is
3 not just the anchors but there is some fixation. I
4 would just add to his comments on explantation that
5 I have had discussions with agency physicians too.
6 We do have a series of things we recommend to
7 physicians who are doing elective explantation that
8 they may want to try not based on evidence but just
9 common sense. If you cool the device, it may
10 become less rigid and you would be able to remove
11 it. And, in the proximal neck you may want to try
12 to really constrain it, as opposed to just trying
13 to pull it down against the force of the anchors.
14 Those things seem to enhance the ability to remove
15 the device.

16 DR. AZIZ: Some of the patients, when they
17 had blood loss, up to 4 L--I am sure it doesn't
18 happen in most of them, is that due to--I mean, is
19 there anything that can be done to reduce that loss
20 because that seems excessive?

21 DR. MATSUMURA: In a specific patient or
22 all the patients on average?

23 DR. AZIZ: Well, there were one or two
24 patients who had a 4 L loss and it is classified as
25 periprocedural. Are there any tricks or does that

1 get better with time?

2 DR. MATSUMURA: I think most of the blood
3 loss that I have encountered in endovascular
4 aneurysm repair has been problems with the sheath.
5 Usually the issue with the 18 French sheath, people
6 aren't paying attention, looking at the fluoro
7 screen, working on the other side and the 18 French
8 sheath is out so you now have an arteriotomy to
9 control. I suspect that most of the issues are in
10 that area when there is blood loss associated with
11 endovascular repair. There weren't any conversions
12 in this series so I don't think it was the
13 operative procedure.

14 DR. AZIZ: When you took the grafts out,
15 you talked about the wires, and all, but there is
16 no endothelial lining, no fiber deposition?

17 MR. WILLIAMS: Based on the few number of
18 explants that we have had the opportunity to
19 analyze, the endothelialization is very minimal.
20 Dr. Matsumura did mention some amount of tissue
21 attachment. That is also variable. It really
22 depends on how much "healthy" neck or iliac vessel
23 the device is exposed to and how much time it has
24 had, that length of exposure. Fundamentally, and I
25 think this is well published in the literature,

1 across these endovascular devices, specifically
2 aortic devices, the amount of ingrowth and
3 incorporation is certainly limited. Again, in our
4 very small number of explants and conversions that
5 we participated in, the device removal itself has
6 not posed any significant technical or clinical
7 challenges for the physician.

8 DR. LASKEY: Dr. Pentecost?

9 DR. PENTECOST: A question for Dr.
10 Matsumura, in the patients that were treated for
11 embolization, it says in your data there were 14.
12 I assume that is 14 patients not 14 interventions?
13 Yet, you said later that only 12 patients at one
14 year had type II endoleaks. Could you explain
15 that?

16 DR. MATSUMURA: Yes. The slide you are
17 referring to is 82. At the one-year time point
18 there were 15 patients who had reintervention for
19 endoleak or aneurysm enlargement. Of those 15
20 patients, one had both reintervention for
21 enlargement and endoleak, and that was the
22 ligation. The other 14 were the catheter-based
23 embolizations, and all those were done for
24 endoleak. I think what you are asking me to
25 explain is were still some endoleaks later, were

1 those effective.

2 DR. PENTECOST: No, I am asking you why
3 there were 12 patients with type II endoleaks but
4 14 patients treated.

5 DR. MATSUMURA: Oh, embolization was
6 determined by the sites upon the site data. It
7 doesn't mean that 14 patients were treated at the
8 12-month point. Many of those patients were
9 treated during the first year and so we can't
10 directly correlate a 12-month assessment by the
11 core lab of CTs to the number of procedures done
12 throughout that year.

13 DR. PENTECOST: I still don't understand.
14 You have post-procedure to 12 months, 14 patients
15 treated with embolization--

16 DR. MATSUMURA: Right, so if a patient had
17 a coil embolization at 3 months that sealed the
18 endoleak, there would not be an endoleak visible in
19 the core lab when they got the scan at 12 months.

20 DR. PENTECOST: Okay. The other question
21 I have is why you chose not to include the raw data
22 about aneurysm expansion, i.e., 5 mm step-wise.
23 That means that patients with aneurysms from 5-5.8
24 cm, for example, could have a 4 mm growth, which
25 would be almost 10 percent and would be called no

1 growth by your study. Certainly, 1 mm would easily
2 be within the range of measuring errors so you
3 could have a lot of patients with some growth in
4 their aneurysms that would be called no growth by
5 your analysis. So, basically it is sort of an
6 expectation from the agency as well as the sponsor
7 that I think everybody could understand raw data
8 very clearly and it would seem to be more valuable.

9 DR. MATSUMURA: Perhaps you could pull up
10 BU24.

11 [Slide]

12 The 5 mm threshold I think is widely
13 accepted by clinicians and is defined in many
14 protocols as the threshold of about two standard
15 deviations. So, less than that would be considered
16 measurement error. In fact, as I mentioned in my
17 response to the question of what threshold I would
18 use, some people use even a higher threshold than
19 5, but this is a scatter plot that does demonstrate
20 the actual data at the 12 and 24-month time points.

21 I believe the corollary of yours is also
22 true, that there are some patients who might cross
23 that threshold of 5 but at a subsequent scan--I
24 don't just believe this, I know this--don't have
25 the growth that was determined at that time point.

1 So, it is an observation like any other that has
2 variability and the 5 mm threshold has been widely
3 accepted by many.

4 DR. BAILEY: Just sort of a follow-up on
5 that, that is not to say though that a 3 mm group
6 mean difference wouldn't be important to know
7 about. So, I think his point is that even though
8 on an individual patient basis 5 mm might be the
9 threshold, when you are presenting group data it
10 might be well to include the more continuous data.

11 DR. PENTECOST: That is all I have.

12 DR. LASKEY: Kent, do you have anything
13 left?

14 DR. BAILEY: I have a few points or
15 questions. First of all, I guess as a
16 biostatistician it is my job to say shame on you
17 for not randomizing, although others have done
18 that, and that is facetious.

19 But I do want to ask a serious question,
20 how extensively it was piloted or tried. Did you
21 discuss this with patients and find out that nobody
22 was interested, or how hard did you work at it?
23 Sometimes this can depend on how it is presented to
24 the patient.

25 DR. MATSUMURA: I, myself, have had

1 experience in trying to do it before and the issue
2 is if you have endografts available that the
3 patient can get to if they are randomized to a
4 control and they have suitable anatomy, that is
5 where they go. I personally surveyed all the 19
6 site investigators and asked them about a
7 randomized trial because we would be able to do a
8 lot of other things with that as well. Only two
9 reported to me that they thought they would be able
10 to meet the enrollment goals at the sites where
11 they practice, and all of them are fairly
12 experienced clinicians, radiologists and surgeons
13 who have been taking care of patients for some
14 time.

15 DR. BAILEY: So, basically patients who
16 are eligible for the endograft are not interested
17 in having the possibility of undergoing surgery?

18 DR. MATSUMURA: A significant portion. I
19 even brought up the idea use as, I believe, in some
20 cancer trials where you randomize after they are
21 asleep but nobody felt that that was appropriate,
22 zero of the 19 investigators.

23 DR. BAILEY: I do want to echo that you
24 have presented some nice data and a well-conducted
25 study. Since the study isn't randomized, then

1 obviously the question really becomes how
2 comparable are the groups and you have presented a
3 lot of data, and there was other data in the pack,
4 that suggested that, surprisingly actually to me,
5 these groups were fairly evenly balanced, with a
6 couple of exceptions which have been noted--sex,
7 there was about twice as high a percentage of
8 women, and then the symptomatic status.

9 So, it would be nice to think that maybe
10 these really are comparable. The obvious
11 difference is the inclusion criteria in terms of
12 anatomy. Obviously, it is completely confounded
13 with treatment assignment so you can't answer
14 anything about that in this study. But can you go
15 to any external data, such as surgical databases,
16 to look at the impact of anatomy on outcomes? It
17 would seem to behoove us to do that if we want to
18 make this claim. I don't really get much
19 confidence from the fact that surgeons don't
20 consider anatomy a risk factor to say that on a
21 large group basis there might not be some important
22 differences in outcome. That wouldn't negate the
23 fact that it is not considered an issue as far as
24 surgery. So, I wonder if there is any data out
25 there or that could be gleaned from surgical

1 databases to compare outcomes in these different
2 anatomic subsets.

3 DR. BREWSTER: I think your points are
4 very valid. I think, unfortunately, that data
5 isn't readily available in the literature. It is a
6 field perhaps ripe for investigation but I don't
7 think we are aware of any valid data in that
8 regard.

9 DR. MATSUMURA: At the time of the design
10 of the study and also at the time of the original
11 clinical submission we did do a literature search.
12 People have studied surgical outcomes with open
13 aneurysm repair extensively. I think there might
14 even be a summary list of these in the executive
15 summary. Clearly, many clinical variables have
16 been found--renal failure, COPD, recent heart
17 disease, but we could not find a single one that
18 showed that for patients where if there was a
19 planned infrarenal procedure--and, again, I would
20 emphasize that is what we had in the protocol, that
21 there were anatomic predictors of outcome. We
22 thought there might be and that is why we recorded
23 them in detail and are analyzing them, and hope to
24 publish them, but at the time we designed it we
25 weren't aware of anything that would tell us that

1 is something to look for. We do know it is a
2 predictor in endovascular repair, and I think that
3 is why we had to have anatomic constraints. We
4 didn't want to treat patients who we didn't think
5 were suitable anatomically for endovascular repair.

6 I would like to jut go back to one
7 assumption that you may or may not have made about
8 gender difference when you pointed out that we have
9 more women in our control group than our test
10 group. I am sure you have seen the analysis in the
11 panel pack. Within this study, in the EBE group
12 female gender was not a risk factor for adverse
13 events. In fact, we looked at it in comparison to
14 survival. We looked in terms of major adverse
15 events, and actually the only statistically
16 different thing between men and women was that in
17 the EBE group women had fewer cumulative adverse
18 events than men. So, if anything, it actually
19 favors the control group.

20 DR. BAILEY: Just sticking on that point
21 for a minute, did you analyze just overall
22 mortality differences in just men?

23 DR. NAFTEL: Yes, I did exactly that. I
24 am not, you know, real big on subsetting but,
25 still, we have to learn what we can. So, yes, I

1 looked in just the men and compared the mortality.
2 I looked in men and just compared adverse events.
3 In the men the differences between the control and
4 EBE were just like the entire group. In the
5 females, as Jon was saying, there still were
6 consistent differences although we are certainly
7 running short of numbers, but I was comforted by
8 those subgroup analyses.

9 DR. BAILEY: I think I saw something on
10 the subgroups in the packet that suggested that
11 women--maybe it was at one year--had a higher
12 mortality in the surgical arm than in the EBE arm.
13 It looked pretty substantial. Obviously, you might
14 not have power to see a difference between men and
15 women, but it might be helpful. You know, there
16 are different ways to adjust for differences. You
17 never are quite sure what the right thing to do is
18 and, of course, that is the advantage of
19 randomization.

20 DR. MATSUMURA: Your recollection is
21 correct in that in the surgical control group there
22 was a trend but it wasn't significant. With
23 respect to the literature, there is only one of
24 those seven or eight studies quoted that showed a
25 difference in gender for open surgical control.

1 So, the vast majority of the studies in the
2 literature don't show that gender difference, but
3 it was a fairly large one that I think some of the
4 panel members may be familiar with.

5 DR. BAILEY: You can quibble or make a
6 valid criticism about randomization, nevertheless,
7 I don't think it changes the impact in terms of
8 safety. In other words, I think you have convinced
9 me that the non-surgical option has a lower
10 surgical complication rate in terms of bleeding and
11 so forth. That probably isn't going to depend on
12 your choice of randomization or non-randomization.
13 However, I think it does speak to what is the
14 quantitative effect. So, the question would be
15 whether the complication rates are all the same in
16 surgery or whether they do vary.

17 Turning to the effectiveness, I read Gary
18 Kamer's point and I can certainly agree with him
19 that if it was specified a priori that the goal was
20 to demonstrate an 80 percent effectiveness rate at
21 one year, as defined by your particular measure,
22 then the lower confidence interval certainly
23 wouldn't allow you to make that claim.

24 I am not sure what that 80 percent means
25 exactly, but if it is a labeling issue there are a

1 number of other reasons why I wouldn't be
2 comfortable talking about an 80 percent
3 effectiveness rate. You know, the denominator for
4 the measurement of effectiveness was 195 as opposed
5 to 230, and I guess my question is what do you know
6 about the people who weren't studied, and was there
7 any evidence--I mean, if you did a worst-case
8 analysis, obviously, you would be in bad shape. I
9 am not saying you should do that, but what did you
10 do to accommodate all that missing information?

11 The other question I have is about leaks
12 and the like. You take these snapshots at
13 different points in time, but what about the
14 cumulative incidence of leaks? I think maybe you
15 have an analysis in which you count every person
16 who ever had a leak. I am not sure if that is
17 true. What if somebody dies? Are they still in
18 the analysis? So, I have a lot of questions about
19 how you come up with a cumulative estimate of the
20 proportion of patients at one year who have had a
21 leak? Then, the issue of the missing data. So,
22 maybe you could address that.

23 DR. NAFTEL: There are several questions
24 here. Let me just go through them and you tell me
25 when I didn't hear them. Would you mind if I

1 talked about efficacy for a second at 80 percent?
2 Because we certainly have thoughts and I know it is
3 a concern, given that the statistician raised the
4 concern.

5 [Slide]

6 This is a little bit complex but it
7 doesn't have to be. This slide is straight out of
8 the protocol. Now, I have spent the last two years
9 working incredibly closely with the people at Gore,
10 but I will have to say this was done before I came
11 on board. So, this is something that Gore and FDA
12 agreed to originally.

13 You are right, it was 80 percent that they
14 went for, and please excuse the jargon but there is
15 no way around it. So, the way it is presented in
16 the original PMA is that the null hypothesis is
17 that the efficacy proportion is less than 0.8, and
18 the alternate hypothesis is that it is equal to
19 0.8. Now, in order to reject that null, we will
20 have to statistically prove that we are above 0.8
21 or above 80 percent or it would take a confidence
22 limit that is about 80 percent.

23 One reason this is all fascinating is
24 these words still are straight out of the protocol
25 and it says while it is difficult to estimate the

1 success rate, if one assumes that the success rate
2 will be 80 percent, a sample size of 156 will
3 provide a lower 95 confidence bound of
4 approximately 73 percent. See, I really don't know
5 why that was in here because if they are going
6 strictly by the way it is stated, that is
7 irrelevant; we have to be above 80. So, I don't
8 quite understand that.

9 I would have expected a couple of things.
10 First of all, I am extremely familiar with FDA
11 using objective performance criteria for heart
12 valves, OPCs. I was in on some of that work in the
13 early '90s. In that, when there was a standard the
14 FDA has taken the approach that you have to prove
15 that your rate of thrombus, or whatever, was less
16 than twice this objective level. If we went that
17 way, all we would have to do is prove that we are
18 above 60 percent. So, it is taking a little
19 different tack than the usual FDA approach. So,
20 that is a little strange.

21 [Slide]

22 Perhaps a lot of us would be more used to
23 seeing something where we have a null hypothesis
24 that p is equal to 0.8 and the alternative is the
25 other, that we are less. You would have to worry

1 about power, but as long as your 95 percent
2 confidence limit included 0.8 you would be okay.
3 So, what does all this mean? I am not sure but I
4 have some thoughts.

5 [Slide]

6 So, here is a plot of the whole thing.
7 The dotted line, of course, is the 0.8 magic level.
8 In the protocol, the way it was written, they said
9 if we get 156 evaluable patients at one year, and
10 that was specified; that was part of the answer, it
11 would take 125 to hit 80 percent and there is the
12 95 percent confidence limit. So, that is what is
13 in the protocol; I am not sure why.

14 Now, one thing the statistician said is
15 why did you use site data? Well, in fact,
16 everything now is core lab. So, here is the core
17 lab efficacy. We had 196 patients with a CT scan
18 read at the core lab at one year, and 158 are
19 successful. So, that gives us 80.6 percent
20 efficacy rate but, in fact, the 95 percent
21 confidence limits are below 0.8. So, I certainly
22 agree with the FDA statistician, Mr. Kamer, that we
23 didn't meet it. But if you are perhaps a little
24 bit more pragmatic and say, well, is 80.6
25 consistent with 80, well, it absolutely is. There

1 is no evidence that we are below 80 and that is
2 what we were worried about. There is plenty of
3 evidence that we are consistent with 80 or even
4 above it. We are also encouraged by the fact that
5 by doing the same analysis of the site data we come
6 up with incredibly similar results.

7 DR. BAILEY: I would have a slightly
8 different spin on that. I mean, there is about a
9 50 percent chance that you are below 80.

10 DR. NAFTEL: Exactly right. Yes, a little
11 less than 50 but, yes, I agree.

12 DR. WHITE: I am sorry to interrupt. Can
13 you justify the 196 at the core lab? We are told
14 in the FDA review that I believe there were only
15 151 evaluable CT scans by the core lab.

16 DR. NAFTEL: Right, that has been updated.
17 I think they didn't mean to tell you that number,
18 but it is 196 at the core lab. It is in the panel
19 pack. That is at one year. So, that is the number
20 of CT scans that they have read.

21 DR. BAILEY: What was the reason for
22 missing--

23 DR. NAFTEL: Okay, let's discuss that.
24 So, it is 196 out of 235. The ones that don't have
25 scans, and I won't give you the exact numbers but

1 we can find them but we are missing 39 patients.
2 We have had several deaths, several withdrawn, a
3 few that did not come back for a visit, a very few,
4 and then there is a small number that didn't have a
5 one-year CT scan. So, 196 out of 235 strikes me as
6 extremely good given all those things.

7 The original protocol does specifically
8 say that this efficacy would be based on the
9 patients available at one year. But I had the same
10 nervousness that I think you have. So, we looked
11 very carefully at those patients that are not in
12 the 196 and I said, well, just tell me anything you
13 know. Was there a leak at six months? Were they
14 alive at 24 months and you found a leak? What do
15 you know?

16 Looking only at endoleak, of those 39, 20
17 percent had an endoleak identified at some time.
18 So, I felt like that was pretty good, that the
19 patients not represented here seemed to be similar.

20 DR. BAILEY: You mean they were identified
21 at other time points?

22 DR. NAFTEL: Right, they had a CT scan at
23 six months, one month or even 24 months. So, I
24 thought that was the best I could do.

25 Now, I will say that for everything else

1 we did, you know, we employed Kaplan-Meier where,
2 you know, you use the patient. They are in the
3 denominators as long as you have follow-up. It is
4 just a slice of time where we only have that CT
5 scan, right there.

6 DR. BAILEY: But I guess it is your
7 one-year calculation--I am still not clear, that
8 one-year 80 percent figure is just based on that
9 snapshot? Right?

10 DR. NAFTEL: Yes, that is correct.

11 DR. BAILEY: Did you ever try to get the
12 cumulative--I mean, do leaks go away?

13 DR. NAFTEL: Well, they do. That would be
14 a clinical question but from my perspective, I
15 still was interested in that and we did do the best
16 Kaplan-Meier or life table that we could do, time
17 to first endoleak. So, we looked at that the best
18 we could and found, as we have said, that they tend
19 to appear, the majority appear in the first month.
20 But, to me, the Kaplan-Meier, or whatever, of the
21 time to endoleak, if you looked at the cumulative
22 proportion at one year, that would be the figure I
23 would think would be more--maybe it wasn't in the
24 protocol but that, to me, sort of captures what is
25 the efficacy.

1 DR. MATSUMURA: I think I disagree with
2 that just a little bit in terms of the clinical
3 importance. Kaplan-Meier, as you are very well
4 aware, once you get an endoleak, you are in there.
5 So, if a patient had an endoleak that was
6 identified on the discharge, say, CT scan and that
7 wasn't there at one, six or 12 months and the
8 patient, you know, wasn't going to be treated, we
9 would normally consider those not an endoleak at 12
10 months. In fact, the protocol specifically said
11 that. It said if we have an endoleak that resolves
12 by one month, that will not be--I forget the
13 term--treatment failure or whatever. So, I think
14 that clinicians have an impression about those
15 early endoleaks.

16 What I think the Kaplan-Meier is useful
17 for, and I don't know if you are looking for it, is
18 that it helps you determine are there many new
19 endoleaks that are occurring later, and most of
20 those occur in the one to three month range and
21 then it flattens out.

22 DR. BAILEY: I think I am almost done. In
23 terms of mortality, obviously you don't have power
24 to really look at this although it is obviously of
25 great interest. If you just look at the two-year

1 curves there was about 13 percent mortality in the
2 EBE group versus seven percent in the control
3 group, so a hazard ratio of about two. Obviously,
4 you wouldn't have much of an idea how much of that
5 could possibly be due to anything but I think it is
6 concerning. Although I think you want to try to
7 predict it and understand it with multivariate
8 models, I think you only have about 40 events and
9 the model you have in there for adjustment, to me,
10 is just way over-parameterized. I believe, in
11 fact, that that body mass index effect is
12 essentially infinity; it might as well be infinite.

13 So, I think it gives us the important
14 lesson that there are many other variables that are
15 important for mortality, other than the aneurysm,
16 but I don't necessarily think that the point
17 estimate you get after adjustment is any more
18 reliable than the unadjusted one just because the
19 model is way too busy. You know, you throw a lot
20 of noise into there as well when you do Cox
21 regression on about seven variables with about 40
22 events. I guess I am concerned about that.

23 You know, I think it does tell us that
24 there are a lot of other things going on as far as
25 mortality is concerned but I am not sure it

1 improves our understanding and doesn't give us any
2 insight. I mean, the groups were comparable to
3 begin with. You said that and you showed that.
4 So, why do we have to adjust?

5 DR. NAFTEL: If I may, I just absolutely
6 agree with you totally. My friends in the clinical
7 statistical group at Duke have a rule that they
8 will only put one variable in the model for every
9 five events. So, that leaves us with very little.
10 And, I actually agree.

11 In this setting, I was just so interested
12 in getting a good comparison of the two groups for
13 mortality, and just looking to see if there could
14 possibly be anything else that was causing me to be
15 misled when I said there was no difference. So, I
16 admit we overstepped, and certainly I do get a
17 little nervous as I hear the clinicians trying to
18 make a whole lot out of this when our only point
19 was to see if an adjustment made any difference in
20 the comparison of the two groups.

21 DR. BAILEY: Did you try many different
22 adjustment models, or just tried to fit as many
23 variables as the data seemed to ask for?

24 DR. NAFTEL: My general approach is
25 usually to go forward, if that is what you are

1 asking. So, in this case I went forward, ignoring
2 the group variable just to see what was going on,
3 but for the final analysis I brought them in one
4 variable at a time and always kept checking the p
5 value of the group variable to see what was
6 happening. But, you are right, there is just not
7 power here to do much.

8 DR. BAILEY: I think that is the bottom
9 line. This is not exact, or even a science. You
10 just don't know what to adjust for. Sometimes you
11 can over-adjust, and I will just leave it at that.
12 I think that exhausts my questions.

13 No, one other thing, efficacy. Again, I
14 don't claim that you can capture efficacy in one
15 single parameter, but given that that is the stated
16 measure of efficacy, the other reason I think it is
17 hard to make a claim about the percent being 80
18 percent is you have not looked at, or at least I
19 haven't seen any analysis of heterogeneity of
20 efficacy. In other words, if you had some patients
21 where there is a much higher rate of leaks, then
22 you wouldn't want to just make a blanket statement
23 of 20 percent. Did you look for heterogeneity of
24 the rate of leaks?

25 DR. NAFTEL: We looked for risk factors

1 for leaks, certainly, just to see if some groups
2 were at higher risk. Do you remember right off
3 hand, Jon? I know there were only, like, two
4 variables and I have to admit I don't remember what
5 they were, but it wasn't very impressive as I
6 recall. We did examine that but didn't find any
7 apparent predictors. Given that, then every
8 patient coming in is the same and you say, okay, we
9 think you will have a 20 percent risk of a leak.

10 DR. MATSUMURA: Or we don't have the power
11 to detect a relationship. I am sure there are
12 predictors but we didn't find them in a study of
13 this size.

14 DR. BAILEY: Thank you.

15 DR. LASKEY: Did you want to introduce
16 Gerry Gray to the group?

17 DR. ZUCKERMAN: Yes, as I mentioned
18 previously, due to unforeseen circumstances Mr.
19 Kamer is unable to join us this afternoon, but his
20 supervisor, Dr. Gerry Gray, team leader in stats,
21 would like to make a few comments and discuss some
22 of the issues with Dr. Bailey.

23 I want to remind the panel that the
24 opportunity is here for discussion with both FDA
25 reviewers and the sponsor, and some questions have

1 been raised about what our interpretation of the
2 primary efficacy hypothesis was two years ago, etc.

3 DR. GRAY: Good afternoon. My name is
4 Gerry Gray. I am the team leader for the
5 cardiovascular device statistics team.

6 What I am going to do now is review and
7 read into the record I guess the main comments that
8 the statistical reviewer, Gary Kamer, had regarding
9 the submission. His first comment and certainly
10 the strongest statistical criticism is that it is a
11 non-randomized trial. Maybe we have sort of beaten
12 this to death, but the patients were assigned by
13 either their anatomy or physician judgment into one
14 or the other treatment groups. The problem with
15 that is we can't separate out effects from being
16 due to treatment or being due to the selection of
17 the assignment process.

18 For example, if you looked at Table 4.4 in
19 the panel pack, you saw there were, indeed, a lot
20 of anatomical differences between the two groups,
21 as you would expect, because those were the
22 criteria that were used. If you look at Table
23 4.11, it shows that at least potentially the
24 proximal neck angle is a significant risk factor
25 for late serious adverse events. In fact, every

1 degree seemed to increase the odds of an event by
2 about one percent. I should note that the average
3 neck angle was 22 percent in the EBE arm versus 35
4 percent in the control arm. So, there is some
5 potential that at least some of the measured
6 covariates had an effect on the outcome.

7 You should note though that the odds ratio
8 for the early events was around 12 in favor of the
9 device, and for late events it was 1.3 in favor of
10 the device. That analysis was after adjustment for
11 the measured covariates. So, the question here
12 then is if there is potentially some other
13 non-measured covariate that can explain away that
14 entire effect, the 12 for early events and the 1.3
15 for late events. I haven't seen any formal
16 analysis of that, but it is unlikely in my opinion
17 that that would be the case, that there was some
18 unmeasured covariate that was enough to explain
19 away that entire effect for the serious adverse
20 events. But, again, we haven't seen any formal
21 sensitivity analysis that could have been done.

22 The second main point of the statistical
23 review was regarding the mortality. As has been
24 discussed here, there was some slight increase in
25 mortality in the EBE group but it was not

1 statistically significant. That could be entirely
2 due to power, that there were not enough
3 observations, or it could just be that there is
4 nothing really there. So, the statistician just
5 recommended that clinicians carefully review all of
6 the mortality events to see what their judgment was
7 on that.

8 The final main point of the statistical
9 review was regarding the effectiveness endpoint.
10 The prior null hypothesis was that the success rate
11 would be less than 80 percent. So, in order to be
12 successful the device would have to successfully
13 reject that null hypothesis and have an observed
14 success rate that is somewhat higher than 80
15 percent. If you want to translate that into
16 confidence intervals, it means that the lower bound
17 of the confidence interval has to be above 80
18 percent.

19 Now, we can debate about whether the
20 denominator was 196 or 201, or whether the success
21 rate was 80.6 percent, 82 or 83, but all of that is
22 sort of irrelevant because none of those rates and
23 none of the confidence intervals you would form
24 using those rates would result in a lower
25 confidence bound that is above 80 percent.

1 So, I think the bottom line is that the
2 null hypothesis that was specified in the protocol
3 was not rejected. In that statistical sense the
4 device didn't meet the prior specified
5 effectiveness goal. That is not to say that 80
6 percent isn't clinically meaningful, but it didn't
7 meet the goal that was in the clinical protocol.

8 So, that is pretty much my summary of the
9 statistical review. If anyone has any questions, I
10 would be glad to try to entertain them. Thank you
11 very much.

12 DR. LASKEY: Thank you, Gerry. Don't
13 interpret our quiescence as lack of interest. We
14 have been beat over the head here for the last 45
15 minutes. But thank you for your addition. Moving
16 on, Dr. Sidawy?

17 DR. SIDAWY: Two questions, one is on
18 erectile dysfunction. Some of these patients that
19 you have treated are pretty young and this,
20 obviously, is pretty important. You had in the
21 pre-procedure numbers 14 and 16 percent, but I did
22 not see an analysis post-procedure. Is endograft
23 protective from that point of view because we do
24 know that the open technique usually leads to
25 erectile dysfunction in men? That is the first

1 question. Go ahead and answer it and then I will
2 ask you the next one.

3 DR. MATSUMURA: If erectile dysfunction
4 was identified in the patients in either group that
5 was permanent, lasting that met the criteria, that
6 C level, for permanent adverse sequelae and that
7 would have been captured as a major adverse event,
8 and I assume you are talking about permanent
9 erectile dysfunction, not a transient one.

10 DR. SIDAWY: What I am saying is did you
11 ask for it postoperatively? Because it sounds like
12 from your pre-procedure analysis you did actually
13 have solid numbers, 14 and 16 percent, but I did
14 not see in the post-procedure results that you had
15 any numbers on that.

16 DR. MATSUMURA: If you look at the CRFs,
17 erectile dysfunction I believe is one of the things
18 that is asked. But I have subsequently learned
19 that you really need a professional interview to
20 get at that appropriately, and having a research
21 nurse inquire of an older patient about that
22 function is not the most reliable method. So, of
23 the ones that we did capture, there did not seem to
24 be a difference. I think it was one or three
25 percent, not a big difference. Many of the

1 patients had it at baseline.

2 DR. SIDAWY: Dr. Freischlag, on my left
3 here, said you should ask their wives.

4 [Laughter]

5 DR. BREWSTER: She is a stickler for those
6 performance standards.

7 [Laughter]

8 DR. SIDAWY: The next question, I go back
9 to what Dr. Comerota was asking about, that serous
10 fluid around the graft. Is that the same as
11 weeping of the PTFE graft that we see in AV access
12 that has been reported as very difficult to take
13 care of and when you operate on these patients you
14 see actual weeping of the graft? I presume that
15 the thickness of the PTFE material in the endograft
16 is less than the thickness of the thin wall graft
17 that is usually used in AV access. So, would that
18 contribute to that?

19 DR. MATSUMURA: I will just reiterate that
20 we did ask the physicians and I looked at the
21 videotapes. We didn't see the weeping that I have
22 seen with AV access.

23 MR. WILLIAMS: Your statement or
24 assumption about the graft material being thinner
25 than that of standard graft materials is correct.

1 It is an ultra thin tube graft. However, there are
2 some uniqueness in the graft design and
3 construction which would potentially counteract a
4 thinner membrane. The microstructure of this
5 particular PTFE is really not different or
6 significantly different from PTFE vascular grafts
7 that you are all familiar with. But, because of
8 the unique fluoropolymer binding of the stent to
9 the graft, much of the graft is rendered
10 impermeable.

11 So, again, I will go back to some general
12 statements here, if I may, which is that
13 ultrafiltration or what may be termed in some cases
14 perigraft seroma is a relatively rare vascular
15 complication. It has been reported in virtually
16 all types of synthetic grafts and even some
17 biological graft materials and applications. This
18 phenomenon is possible with PTFE vascular grafts,
19 including the EBE. However, to date we don't have
20 any direct clinical evidence or findings that show
21 that this is specifically occurring with this
22 device.

23 DR. SIDAWY: Thank you, Mr. Chair.

24 DR. FREISCHLAG: I had a question about
25 the number of KUBs that were performed in these

1 patients. It seemed that it was a very low number.
2 Could you say why they were able to get a CT scan
3 and not a KUB?

4 DR. BREWSTER: To answer your specific
5 question first of why did they get a CT scan and
6 not a KUB, I think that many of the clinicians who
7 are involved in the research study also take care
8 of patients outside the study and many of them have
9 come to regard the KUB in those non-research
10 patients as really not very useful, and many times
11 they don't use it in clinical practice in their own
12 non-research patients.

13 But one thing I did want to point out is
14 that even though we have as high a compliance rate
15 in abdominal film, we did have a very high clinical
16 compliance rate where we would be able to capture
17 clinical adverse events if there were some related,
18 and we also had a very high rate on the CT scan so
19 we would be able to capture those radiographic
20 surrogate markers that might be of interest, such
21 as type I, type III endoleaks and aneurysm
22 enlargement.

23 In addition, even though at a given time
24 point the abdominal x-ray compliance was not as
25 high as CT or clinical, I can say that 229 of the

1 235 patients had an abdominal film at some point
2 seen in the core lab, and I believe there are three
3 other patients who have an abdominal film at the
4 site which is either in transit or is going to be
5 read. Of the three remaining patients who might
6 have never had an x-ray, one has died already and
7 the two, we are going to lasso them I suppose.

8 DR. FREISCHLAG: As you know, we added
9 that to one of the studies we did and I just wanted
10 to know if there was a trick to getting the KUB
11 done on a patient versus a CT scan. You can get a
12 CT scan any time you walk into a hospital now.

13 The other question I had about the patient
14 group was that there were quite a few with
15 symptoms, as you put it; the aneurysm was
16 symptomatic. There were 11 in the EBE group and 15
17 in the control group. Could you define what
18 symptom meant and what was the delay for surgery in
19 those two groups? Was it longer in the EBE group
20 to get the graft versus in the control group?

21 DR. BREWSTER: As I am sure you are aware,
22 determination of true symptoms in an aneurysm
23 patient is often difficult because in patients with
24 chronic back pain it is very hard to sort out that
25 sort of symptom from a patient with back pain truly

1 caused by an aneurysm. So, I think much of this
2 was in the eye of the beholder. It was up to the
3 individual investigator at each site to determine
4 if that judgment applied.

5 I think even if you had a similar number
6 of patients, it is almost certain that for the
7 endograft patients there would be a fewer number
8 perhaps treated in that fashion because clinically
9 the surgeon is much more uncomfortable waiting for
10 the time to enroll the patient, obtain the device,
11 and so forth which, especially in a research
12 protocol, can be a somewhat lengthy process. So, I
13 think that clearly explains the difference in
14 frequency within the study.

15 DR. FREISCHLAG: They weren't contained
16 ruptures though, they were just symptoms from the
17 patient?

18 DR. BREWSTER: They were patients with
19 either back pain, flank pain or perhaps were felt
20 to have a tender aneurysm that were judged to have
21 a so-called symptomatic aneurysm. I don't know if
22 Dr. Matsumura has any additional comments.

23 DR. MATSUMURA: No, when you look at how
24 they individually listed in the CRFs, they were
25 chronic back pain, flank pain, a couple with

1 abdominal pain. There were no ruptures. That was
2 a specific exclusion criterion.

3 DR. FREISCHLAG: I had a question about
4 the patient that was listed on page 176 who had an
5 EBE placed and then went down while he was watching
6 TV at home, and was brought into the ER. It was
7 deemed, when you talked to the ER physician, that
8 they didn't think it was a rupture even though the
9 patient did not get an autopsy. My concern is the
10 sudden nature of that patient's death and whether
11 or not there was a hematocrit drawn? It also seems
12 that the patient had had an endoleak that hadn't
13 been--it was just at the one-month time; it was at
14 the time of discharge.

15 So, my question is it is listed as a
16 myocardial infarction and you have another doctor
17 saying it sure didn't look like a ruptured aneurysm
18 by physical exam, but there were some things in the
19 history that would make you worry, and I am sure
20 you worried. So, I wanted to know about
21 hematocrits and any of your thoughts about that
22 patient as to whether or not it could have been a
23 rupture.

24 DR. MATSUMURA: For this specific patient
25 I would like to address your questions and then

1 also try to answer one of the questions that came
2 from the right side here.

3 This particular patient, to my knowledge,
4 did not have a hematocrit. We did, on our
5 committee, review the source documents available to
6 us, such as the paramedic run sheet, etc. The site
7 investigator had done an extensive analysis, not
8 just interview the ER doc but the family and got
9 quite a bit of information, and he came to this
10 assessment which is detailed in a long letter to
11 his IRB.

12 But I have the concern that has been
13 raised that many of these sudden deaths could be
14 aneurysm ruptures, or that they could be missed and
15 I am sure in many of the large aneurysm trials that
16 has been substantiated. I think it is important to
17 note that those sudden deaths occur in control
18 groups and endograft groups equally, and we
19 wouldn't expect to see a lot of aneurysm rupture
20 after open repair within the first two years.

21 What we did in terms of that in the
22 clinical events committee is we tried to adjudicate
23 causes of death--and now I am going to the general
24 level--as best we could from the available
25 information, but we found it very difficult to

1 reverse or change a site investigator's comment if
2 we didn't have some kind of compelling evidence
3 that it was something else.

4 [Slide]

5 Nevertheless, when we go to
6 aneurysm-related survival, I felt that it is very
7 important to have a cautious approach or a general
8 approach for what is aneurysm related. So, we had
9 that definition of anything within 30 days, the
10 usual surgeon's definition, if it happened within
11 30 days it is related. And, I caught a lot of
12 flack around the sponsor where we included a
13 patient who had a gunshot wound within 30 days of
14 an embolization procedure.

15 [Slide]

16 We also counted if they were, as Dr.
17 Comerota pointed out, within the same
18 hospitalization. So, there were two control
19 patients, one who never left the ICU and one who
20 never left the hospital, who died.

21 [Slide]

22 Of those aneurysm-related deaths that you
23 saw in our comparison of aneurysm-related survival,
24 only one of those four were determined by the
25 investigators to be procedure related but, because

1 they were within 30 days, we felt that they would
2 be categorized that way. So, my best approach to
3 it is just to apply a very broad category for what
4 we call aneurysm related using that time point,
5 which I think is the surgical tradition.

6 DR. FREISCHLAG: So, your committee really
7 was fairly well convinced that that patient did
8 have some sort of cardiac event from all the
9 information you had?

10 DR. MATSUMURA: Yes.

11 DR. FREISCHLAG: On page 214 there was
12 some information that you so nicely gave us from
13 Europe, and there were two episodes where there was
14 an issue of getting the device out of a patient and
15 there was some injury to some arteries from two
16 different countries. Were there any issues in
17 removing the device in this country in those groups
18 of patients, or was this something just at the
19 beginning that made it difficult for those two to
20 be reported?

21 DR. MATSUMURA: In answer to your
22 question, there are no issues in this country in
23 all those studies, in the U.S., and the details are
24 provided there. I do remember hearing about one of
25 those, and I don't want to go through all the

1 details because we want to get to some more
2 questions, but one of them was a specific
3 manufacturing issue where they couldn't get it out,
4 and that is not expected ever to occur with the
5 subsequent manufacturing changes that the sponsor
6 initiated and that went through the agency.

7 DR. FREISCHLAG: That was my follow-up
8 question, was there something identified that
9 subsequently has been corrected so that wouldn't be
10 an issue?

11 MR. WILLIAMS: Yes, in the one patient
12 that Dr. Matsumura refers to where the delivery
13 catheter was, in fact, stuck relative to the
14 completely deployed device, that was identified as
15 a manufacturing process error. It has only
16 occurred that one time and there were immediate
17 steps taken relative to the process and
18 instructions to ensure that that was remedied.

19 DR. FREISCHLAG: We were talking about the
20 control group when Dr. Brewster was discussing how
21 many patients ended up in the experimental group
22 versus control. The indications for these patients
23 for this trial were anatomy, which gauged whether
24 or not they were going to be in the experimental
25 group. Then, if they did not meet the anatomy

1 criteria they went into the control group.

2 My question is were there patients that
3 did not fit the anatomy and, therefore, would not
4 be an EBE candidate that went on to not get any
5 surgery at all? That ended up not getting an open
6 operation because perhaps the local investigator
7 felt that aneurysm was too small; they were too
8 sick; or there were some other issues. Did you
9 have a group of patients out there that didn't get
10 operations? I know in other groups sometimes some
11 information comes from a group that doesn't get the
12 procedure during the period of time, and I wanted
13 to know if there was a small number of patients, a
14 large number of patients, or if you know of any
15 patients that started off and then didn't get any
16 procedure whatsoever.

17 DR. MATSUMURA: We don't have data on
18 patients except for those that were consented for
19 the study. I think that breakdown is in there.
20 None of those patients, to our knowledge, did not
21 get a procedure or had aneurysm rupture. I didn't
22 show it in the presentation but we do have the
23 deployment success in the control group and 100
24 percent of those patients, all 99, had their
25 surgical graft placed. There were no aborted

1 procedures due to MI during induction or something.

2 DR. BREWSTER: I think if a patient wasn't
3 enrolled in the study there is no available data.

4 DR. FREISCHLAG: Certainly, when you start
5 assessing a patient for a study you would get their
6 anatomy first. Certainly, for the VA study that we
7 are going to do, we have to consent them the minute
8 we say hello. Then we go do the CT scan and start
9 the anatomy. So, I guess my question was whether
10 or not a lot of anatomy evaluation was done prior
11 to consenting into the procedure, and were there
12 patients concurrently that were being followed that
13 didn't get surgery. It sounds like you don't know
14 the answer because they are out there but we don't
15 know them.

16 My last comment was a comment about the
17 brochure to the patient, which is very nicely done.
18 However, on page 65 I think there is a misleading
19 piece to the part where you talk about what are
20 some of the symptoms of abdominal aortic aneurysm.
21 The first sentence is the most common symptom of an
22 abdominal aortic aneurysm is pain. That is true,
23 that that is going to be the most common symptom,
24 but as we know, 90 percent of people that come to
25 see us with an aneurysm don't have symptoms. And,

1 I think this is sort of scary, saying that the most
2 common symptom of this is going to be pain when
3 most of them don't have any symptoms.

4 So, I would recommend that that be
5 rewritten for the patient. If you get a symptom,
6 it is going to be pain but most patients don't get
7 any symptom at all. If I was a patient reading
8 that, I think I would run to your office with all
9 the chronic back pain, knee pain, headache,
10 whatever pain I could come up with to tell you my
11 aneurysm is in trouble. So, I just didn't like the
12 way that read.

13 MR. WILLIAMS: The sponsor very much
14 appreciates that. It is a good thing we labeled it
15 "rough draft" when we put it in here.

16 DR. FREISCHLAG: I am done. Thanks.

17 DR. LASKEY: I know that our schedule
18 calls for a break but I would prefer if we just
19 finished the FDA questions and then we can have a
20 short break. So, Dr. Roberts?

21 DR. ROBERTS: Thank you. First of all, I
22 would like to thank and congratulate the FDA for
23 putting together a nice panel pack which didn't
24 break my back when I was bringing it here, to
25 Washington. I thank you for all your hard work in

1 doing that.

2 I have a number of questions. The first
3 one has to do with the control CTs. It looked like
4 you got a fair number of patients who were in the
5 control group and who got CTs and, yet, you didn't
6 give us any information about the aneurysm
7 shrinking in there. I assume that everyone shrank?

8 DR. MATSUMURA: We haven't analyzed that
9 but I think your assumption is correct.

10 DR. ROBERTS: It just seems to me you put
11 all of these patients through CT scans and, yet,
12 you didn't give us any data on the follow-up on
13 them. So, I mean, it was kind of why bother if you
14 are not going to use the information, which I think
15 actually is valuable information because if, in
16 fact, it turned out that not all of the aneurysms
17 shrank after the surgical repair you would like to
18 know that. So, I would encourage you to look at
19 that information.

20 The next question that I have goes to the
21 patients in terms of their selection. In the panel
22 pack it reads that it was the patients who ended up
23 in the control group who had proximal neck greater
24 than 15, proximal neck angulation greater than 60
25 or, presumably, thrombus at the arterial

1 implantation site. By arterial implantation site,
2 do you mean the aorta or do you mean anywhere?

3 DR. MATSUMURA: We mean the infrarenal
4 aortic neck in that context.

5 DR. ROBERTS: Well, I mean, I am assuming
6 that those weren't the only criteria because when I
7 look at the group of measurements that you have
8 here, on page 105, in the control group you have I
9 don't know how many but certainly some patients who
10 have a zero common iliac diameter, which I assume
11 means that they were, in fact, occluded and the
12 left common iliac is 1 mm, which I assume means
13 that it was essentially occluded. So, I am
14 assuming that at least some of these patients were
15 patients who had iliac artery occlusions or had
16 very small iliac arteries, which might explain
17 where some of the women who were in your control
18 group came from because perhaps they had small
19 iliac arteries.

20 I also notice that you don't have anyone
21 in the graft group that had iliac arteries less
22 than 6. So, I am just wondering was that an
23 inclusion criterion that they had to have an iliac
24 artery of at least 6 in order to have a graft
25 placed.

1 DR. MATSUMURA: To answer your last
2 question, the inclusion criteria which were applied
3 to both groups was that they had to have an
4 ilio-femoral access with the 18 French one side, 12
5 French on the other side. I think you are right in
6 your assumption that that was probably an occlusion
7 of that common iliac artery.

8 DR. ROBERTS: I mean, certainly that would
9 be fair enough. I mean, you wouldn't be able to
10 put an endoluminal graft in someone who had an
11 occlusion. But it does just sort of bring up the
12 question of perhaps some of the women--you know,
13 perhaps the excess of women in the control group
14 was because maybe some of them had small iliacs
15 that you couldn't get up. Is that possible?

16 DR. BREWSTER: Yes.

17 DR. ROBERTS: One of the other questions
18 that I had was you just showed the mortality and
19 you had three deaths in the EBE group and two in
20 the control group. Were any of those
21 intraoperative mortality?

22 DR. MATSUMURA: No. You are referring to
23 aneurysm-related mortality when you mention two in
24 the control and four [sic] EBE group.

25 DR. ROBERTS: Well, they were within the

1 30 days, right? Or, within the hospital time?

2 That slide you just showed?

3 DR. MATSUMURA: The two in the control
4 group were not within 30 days but those patients
5 never went home after their initial procedure. The
6 three in the EBE all went home and came back within
7 30 days and died. The secondary procedure death
8 was a patient with a gunshot wound within 30 days
9 of a coil procedure. So, there were no
10 intraoperative deaths in this group. There were
11 also no intraoperative deaths in the previous group
12 because they would have been included here within
13 30 days.

14 DR. ROBERTS: So, that brings me to my
15 next question, which is that I noticed that in the
16 new trial that is going on--I mean, I know we are
17 not looking at that device, but from what you said
18 earlier that device isn't very different and, yet,
19 there have been two deaths, intraoperative deaths
20 putting that device in. Since I am assuming that
21 that device is being put in in the same sites where
22 you were putting in the other device and that these
23 are experienced operators who have done a lot of
24 these devices now, my question is, is there a
25 change? I mean, both of them were iliac artery

1 ruptures or lacerations that couldn't be repaired
2 in time and the patient died on the table.

3 My question is, is there enough of a
4 change in the device that it would explain the
5 deaths? Or, has there been a change in the
6 criteria that are being used? In other words, that
7 the iliac arteries may be smaller than they were
8 and that we are, you know, stretching the limits.
9 And, does this say anything about our concern?
10 Because what I am really concerned about is you
11 don't say anything in your labeling about how large
12 the iliac arteries ought to be to put this device
13 in. You leave it very nebulous, like, well, as
14 long as it is suitable morphology. And, I am
15 really concerned that as people start to try and
16 push the limits on this because they are going to
17 see this device and they are going to say, gee,
18 this is a little device; this is a lot easier to
19 put in, and if they start stretching the
20 indications if we are going to run into these iliac
21 artery ruptures that end in death. So, I would
22 like to kind of get a feeling about this.

23 MR. WILLIAMS: The two events that you are
24 referring to did, in fact, occur in our ongoing IDE
25 study for the second generation device. That

1 device only has very minimal changes. Certainly
2 these changes do not affect the delivery size
3 profile, flexibility, fundamental behavior
4 characteristics as part of the delivery into the
5 patient.

6 The two deaths, closely related here were
7 a very unfortunate coincidence in terms of timing.
8 We had viewed at the company the images on these
9 patients and had been in close consultation with
10 these experienced endograft physicians, if you
11 will, and both the physicians and the sponsor had
12 identified that there was potentially an increased
13 risk for ilio-femoral access complications in these
14 patients.

15 The diameters were small but nothing
16 smaller than what we had previously consulted on in
17 many patients prior to this. In addition to small
18 diameter, as you are well aware, there are various
19 disease states in these vessels and both of these
20 patients had a combination of calcific plaque and
21 tortuosity. One patient did that ruptured in the
22 iliac area did, in fact, make it into a surgical
23 conversion OR scenario but did not survive the
24 actual conversion. One patient did, in fact,
25 immediately expire on the table of the endovascular

1 suite.

2 We have not changed our criteria. We
3 have, as a result of these two particular
4 situations, strengthened warnings,
5 contraindications and our training materials. We
6 have also added an additional line in our
7 contraindications. It is not as specific as you
8 just recommended. We don't go as far as to say
9 specific size or diameter relationships. However,
10 in the training materials the outer diameter of an
11 18 French sheath and the outer diameter of a 12
12 French sheath is clearly delineated to physicians
13 as part of the training. This is where we get into
14 an area of clinical judgment. From a sponsor
15 standpoint we have not necessarily changed our
16 behavior in terms of what we are encouraging or
17 what we are doing in terms of training, and we are
18 trying to point out potential increased risk to
19 physicians who are choosing to treat patients who
20 may have some of these increased risk scenarios. I
21 would ask Dr. Brewster to add some additional
22 clinical perspective to this.

23 DR. BREWSTER: Dr. Roberts, I think your
24 point is a very important one. I can speak with
25 first-hand knowledge about one of these patients

1 because it was a patient that I treated. I
2 certainly acknowledge that I was pushing the limits
3 in an elderly, very high risk woman with
4 recognizably small vessels, who probably could not
5 be treated in a standard endovascular fashion with
6 any other device. Access went all right with the
7 sheath but the injury occurred, as often is the
8 case and as Mr. Williams pointed out, in a patient
9 with somewhat tortuous and calcified vessels in
10 addition to small caliber. Injury occurred with
11 withdrawal of the sheath and evulsion of the
12 external iliac artery from its bifurcation at the
13 common iliac artery. Conversion was carried out
14 but, as is often the case with these high risk
15 patients, the patient did not survive.

16 I think it is a matter of poor patient
17 selection or inappropriate judgment and, you are
18 quite right, I think it is critical that training
19 and so forth emphasize this.

20 DR. ROBERTS: Yes, and I might go just a
21 little further and suggest that perhaps it is
22 something that ought to be considered for the
23 labeling, that in fact one might want to consider
24 adding some language to the effect of, you know,
25 what a reasonably sized--certainly know what the

1 size of an 18 French sheath which
2 is--what?--probably more like a 21 French sheath on
3 the outer diameter, something like that so that,
4 you know, you could say that perhaps--I don't know,
5 but certainly since at least in your study you
6 didn't have anyone that had less than 6 mm and,
7 granted, that is a common iliac so I don't know
8 what the externals look like and that actually
9 might be important information, to know what the
10 external iliac artery diameters were. But,
11 certainly, you might put something to the effect
12 that with a smaller caliber vessel, or something
13 about it being heavily calcified or tortuous that
14 this might not be the best thing to do because I am
15 concerned that, you know, there is going to be a
16 tendency to try and stretch the limitations and I
17 would hate to see us in a situation where we had
18 deaths because people weren't being as careful as
19 they should be about that.

20 Now, let me just ask a question because, I
21 must admit I am sure I am just dense, but I have a
22 little bit of confusion about the endoleak
23 business. That is, at 12 months you have, at least
24 on this one table, 6.8 which is on page 136, 27
25 patients, 27 total patients with an endoleak,

1 whatever kind they are. Then, at 24 months you
2 have 24 patients. Now, I am assuming that the 24
3 patients in the second 12 months, 12-24 months are
4 separate patients. Is that correct?

5 DR. MATSUMURA: You are asking how much do
6 they overlap. This is the core lab data and you
7 are correct, it is 27 of 156 at 12 months and 24 of
8 119. Eleven of those patients overlap of the 24.

9 DR. ROBERTS: So, in fact, you have 13 new
10 patients that developed endoleaks. Is that
11 correct?

12 DR. MATSUMURA: Thirteen patients who did
13 not have a 12-month CT at the core lab that showed
14 an endoleak. So, if they missed that interval,
15 they are new patients in that regard from the core
16 lab perspective.

17 DR. ROBERTS: So, how many of the patients
18 then didn't you have CT scans on, and so you don't
19 know whether it is new or not? Let me rephrase
20 that. Let me make sure that I am clear. You had
21 27 patients--

22 DR. MATSUMURA: All the 11 had 12 months.

23 DR. ROBERTS: Had 12-month CTs. So, there
24 are 11 patients that did not have endoleaks at 12
25 months but at 24 months did have endoleaks. Is

1 that correct?

2 DR. MATSUMURA: Thirteen.

3 DR. ROBERTS: Excuse me, 13. There are 11
4 overlaps. There are 13 new patients. Just out of
5 curiosity, you have patients that ended up getting
6 some type of therapy for their endoleak. What was
7 the success rate for getting rid of the endoleaks
8 in those patients?

9 DR. MATSUMURA: You are walking through
10 the process and don't apologize because I have done
11 this many times, and I just again want to point out
12 that it is difficult to correlate the core lab
13 findings with site actions through a whole year
14 because they don't exactly match.

15 But I can answer your question about what
16 happened with the interventions. There were 15
17 subjects in the first year who had 17
18 interventions. I have already many times mentioned
19 the ligation for aneurysm size increase. So, there
20 are 14 subjects who had 16 coils. Let's
21 concentrate on those.

22 The initial investigator report on the CRF
23 was that 88 percent of those were successful, of
24 the 17 interventions, 15. But I just want to point
25 out that is the initial investigator's impression

1 of success. When we look at the one-year
2 interventions, we do have some good data from the
3 two years to say was it really successful, which I
4 think is what you want to know. Five patients were
5 confirmed by subsequent CT, and all subsequent CTs
6 in those patients ended up being endoleak free and
7 I would consider those successful. Two of the
8 patients died of other causes, the gunshot wound we
9 have mentioned and a lung cancer. It is debatable
10 whether you want to call that success but they
11 died. There are five that clearly were not
12 successful. They had recurrent endoleaks after
13 initially appearing to cease. Of those five, two
14 were the two reintervened in the first year and
15 another one of those patients had another
16 embolization the second year. Then, two of the
17 patients clearly did not have success. They
18 continued to have endoleak as identified by the
19 investigator at the time of the initial procedure.

20 We have some data on those seven who have
21 endoleaks in terms of size change, and five of them
22 have not had any subsequent aneurysm size change.
23 Two continue to have aneurysm enlargement. So, I
24 would say definitely there are two failures;
25 definitely there are five successes. How you want

1 to categorize those other ones depends on how you
2 want to categorize them.

3 DR. ROBERTS: So, basically all of them
4 that are failures and still with endoleaks are just
5 being followed at this point.

6 DR. MATSUMURA: No, of the seven patients
7 who either had an initial seal and the endoleak
8 came back or had persisted, three have had
9 retreatment, two during the first year and one
10 during the second year.

11 DR. ROBERTS: And the retreatments we
12 think are successful on those?

13 DR. MATSUMURA: I don't have the data on
14 what happens during the second year because I need
15 the third year data to know.

16 DR. ROBERTS: Yes.

17 DR. MATSUMURA: I can tell you that when
18 the physicians filled out the case report form on
19 what their initial impression was during the second
20 year, I think 80 or 90 percent thought they were
21 successful at the time of the procedure, similar to
22 the first year, and perhaps that would predict that
23 the ultimate outcome when we get three-year data
24 will be similar to what the two-year data says
25 about first year interventions.

1 DR. ROBERTS: We tend to be optimistic.
2 The other thing, and this goes a little bit into
3 labeling but I guess I will just do it while I am
4 here now, is that my feeling is that you have Table
5 3 on the labeling which indicates that there have
6 been no conversions. Now, I agree because you are
7 doing it in 12-month data points but you do say
8 below that that three conversions have occurred
9 greater than 24 months after that.

10 My recommendation is to say that there
11 have been three conversions. Then, if you want to
12 asterisk them, you can say it was after 24 months,
13 fine. But I think that when people look at that
14 table the first thing that they see is zero and
15 whether or not their eye tends to go below that and
16 notice that, in fact, there were three that
17 happened later--I think it is a little misleading
18 and it would be nice to not be misleading.

19 I have one other--actually I have a couple
20 of other questions but maybe I should let somebody
21 else have a chance, except that I do want to say
22 one thing, and that is again with regards to your
23 patient brochure and, as Dr. Freischlag said, I
24 would really very much congratulate you on; it
25 really is quite nice. However, my feeling is that

1 page 77 is very misleading. This is something that
2 I would say to the FDA in general. I don't
3 honestly know what the patient instructions are on
4 the other devices. I didn't stop to look at that.
5 But I think it is very important that these
6 patients understand that these have to be very
7 carefully followed.

8 I mean, I just was involved with a lady
9 who came in, had an endograft placed two years ago,
10 has never had any follow-up. Her aneurysm had
11 grown from 6 cm to 9 cm. She was symptomatic and
12 it was rupturing. And, the patient and her family
13 said no one ever told us that we needed any
14 follow-up on this. I will say that the family was
15 a good family that, you know, I think was very
16 committed to this woman and I think it may have
17 slipped through. But I think we need to be very
18 clear with the patients and their families that
19 these mandate follow-up, mandate it.

20 I mean, there isn't anything in here about
21 making sure that you follow up with your imaging,
22 which I think is very important. I think the other
23 thing is that you probably need--and, again, this
24 is for the FDA and all of the manufacturers--to put
25 in the brochure that this procedure may not be the

1 end of things for you; that you have something on
2 the order of a 20 percent risk of developing an
3 endoleak. By the way, you should put in the
4 glossary endoleak and explain what that is. And,
5 that you may in fact need further procedures to be
6 done to try and control those endoleaks. I think
7 we really need to make sure that patients
8 understand this because it is not at all laid out
9 and, quite frankly, it makes it look like it is,
10 you know, a wonderful procedure. You know, I am
11 going to go and sit with my grandchild and never
12 have to worry about this again, and we know that is
13 not true. We really need to make sure that we are
14 honest with the patients that this is not the end
15 of the line; may not be the end of the line for
16 this aneurysm and that you may need something else
17 done about it. I will stop with that. Thank you.

18 DR. LASKEY: Bruce?

19 DR. PERLER: Thank you. I too want to
20 thank the agency for putting this data together in
21 a very reader-friendly fashion, and congratulate
22 the sponsor for what I think was a very well
23 conducted study and data that is very clearly
24 presented, and also for long-term follow-up,
25 greater than 90 percent clinical follow-up which I

1 think is laudable. I must say, I use the term
2 long-term somewhat begrudgingly because I think 12
3 months or 24 months in a life cycle of a stent
4 graft is still a bit of a snapshot, pursuant to
5 what Dr. Roberts was just talking about.

6 Fortunately, most of my questions have
7 already been answered so I just have a couple of
8 brief points. There was one comment in the
9 submission where you said type I endoleaks at one
10 year were reclassified by site as type II, and
11 related to Table 4.16. I didn't quite understand
12 how many and what that was all about. It was
13 always my impression that the core lab
14 interpretation is much more sensitive in terms of
15 these sorts of complications.

16 DR. MATSUMURA: In the presentation, and
17 we did stick with the core lab data, I think while
18 we find that page--

19 DR. PERLER: It was page 116.

20 DR. MATSUMURA: Was it type III endoleaks
21 reclassified as type II?

22 DR. PERLER: It was just a sentence. In
23 the text it says type I endoleaks at one year were
24 reclassified by the site as type II, and it didn't
25 say how many. I was hoping you could elaborate on

1 that sentence.

2 DR. MATSUMURA: I know that there were two
3 patients who had type I or type III endoleaks that
4 the site reported at the one-year time point. This
5 is my site so I know how this went. On the CT scan
6 they believed they were type III endoleaks. Those
7 patients were brought back for an arteriogram at a
8 subsequent visit and in the interim visit, or
9 whatever time that was, they were reclassified as
10 type II endoleaks following arteriography. It is
11 the policy not to go back and change what your
12 impression was at 12 months because of the new
13 data. It theoretically is possible that that was a
14 type III endoleak that sealed. So, reclassified is
15 probably the wrong word. It is probably that with
16 additional evaluation it was now classified as a
17 type II.

18 DR. PERLER: Based on angio.

19 DR. MATSUMURA: Based on subsequent
20 imaging, more definitive imaging.

21 DR. PERLER: The second point related to,
22 I guess, the seven percent of patients who had
23 aortic extenders and about a quarter of the
24 patients who had iliac extenders. Have you looked
25 at that group as part of your multivariate analysis

1 for long-term adverse events? One would think that
2 is a subpopulation in whom one might want to have
3 more heightened long-term surveillance. Have you
4 looked at that group individually or as part of the
5 multivariate analysis for long-term outcomes?

6 DR. NAFTEL: Yes. We incorporated the
7 extender, both aortic and iliac extender as
8 separate variables in all of the analysis for the
9 EBE group, of course. We found that there was no
10 additional risk for either adverse events or
11 mortality with the use of either extender.

12 DR. PERLER: The incidence of either renal
13 insufficiency or renal failure was quite low but I
14 know that in every case the conclusion was drawn
15 that it was not device or procedure related, even
16 in one patient who I think had documented
17 cholesterol embolization. It just strikes me that
18 if you have a patient with an aneurysm and an
19 atherosclerotic aorta and you are manipulating
20 wires and catheters and sheaths that it is
21 certainly conceivable that there could have been
22 intraoperative and even long-term
23 arteroembolization, compromise to the renal
24 arteries or dire related injury. I was just
25 wondering how one concludes that none of these

1 complications were related to the device or the
2 procedure.

3 DR. MATSUMURA: As I mentioned, in the
4 determination of aneurysm I am really uncomfortable
5 with the way the investigators will categorize
6 device or procedure related just because of the
7 characteristics you mentioned. So, when we did the
8 analysis and we did the presentation today we
9 didn't try to differentiate those. We looked at
10 all the adverse events related to them and then
11 just used the 30-day time point to say early and
12 late.

13 I think for many of these, as you read the
14 narratives or if you look at the primary source
15 documents and case report forms knowledgeable,
16 experienced physicians will come up with different
17 impressions of those in terms of relationship
18 particularly.

19 DR. PERLER: The creatinine of over 2.5
20 was an exclusion criterion I guess for the study.
21 Should that be an absolute contraindication to this
22 procedure in the labeling, or relative
23 contraindication, do you think?

24 DR. MATSUMURA: It is difficult to say
25 that since we don't have the patients above 2.5.

1 The reason why we chose the creatinine cut-off of
2 2.5 was so that we could get contrast-enhanced CT.
3 In previous experience, patients who are above
4 that--physicians and clinicians--patients become
5 reluctant to get a contrast-enhanced CT and
6 follow-up when their creatinine is that high. So,
7 that was the rationale.

8 We did look at pretreatment BUN and
9 creatinine levels in both groups and, in fact, the
10 EBE group had a significantly higher BUN and a
11 significantly higher creatinine pretreatment. But
12 I think the low rate of renal complications, both
13 early and late, attest that both treatments seem to
14 have few renal complications. There are some but
15 they are relatively low.

16 DR. PERLER: Just two other quick labeling
17 issues, I know significant thrombus was an
18 exclusion criterion. I just wonder if that is one
19 of those issues that you know it when you see it
20 but it is pretty hard to define. I mean, could you
21 more objectively or explicitly define significant
22 thrombus in the labeling for the clinician? Is it
23 circumferential? Is it based on the thickness of
24 the thrombus?

25 DR. MATSUMURA: The way we defined it in

1 the investigator group was the site where you
2 intended to deploy the prosthesis, you know, that
3 15 mm, it was too much thrombus if it was more than
4 25 percent of the circumference and greater than 2
5 mm in thickness for that 25 percent. It is
6 extremely arbitrary. At the time, in 1998 or '97,
7 whenever we did it, we didn't have any data but
8 that is what we came up with as the threshold as
9 something more objective.

10 DR. PERLER: So, for the label in 2002
11 should it be that specific in terms of a
12 contraindication to attempting this procedure? Or,
13 should we stick with significant thrombus?

14 DR. MATSUMURA: Again, since we didn't
15 include patients with significant thrombus I can't
16 say, but I think if you want to use something more
17 specific in the labeling, that is what I would use
18 because that is how we applied it.

19 DR. PERLER: I assume no patient in this
20 study had both internal iliacs occluded. Is that
21 correct? I know this is somewhat of a controversy
22 among people who work in this area in terms of the
23 benign nature of that happening, and most of us try
24 to avoid it.

25 DR. MATSUMURA: Yes, there were some of

1 those in our investigator group. The consensus was
2 that you had to preserve flow to one hypogastric
3 artery. So, either due to preexisting disease or
4 your planned treatment algorithm, there had to be
5 one hypergastric artery left open.

6 DR. PERLER: I guess my last question just
7 relates to physician training. As I read it, there
8 is going to be kind of a rank order algorithm that
9 the sponsor has to identify initial sites for
10 distribution of this device. Really my question
11 relates to the point Dr. Roberts raised about
12 long-term surveillance, and there is no question in
13 my mind that Gore is going to follow these study
14 patients compulsively and completely and report
15 accurately on their outcomes, but it is the
16 thousands of individuals out there already with
17 commercially available devices who come downtown,
18 they get a procedure. They may see the
19 practitioner once and go back to the family
20 practitioner, the nurse practitioner internist, and
21 we are already seeing in our practice patients who
22 have had devices placed and, as she said, have
23 never had a follow-up.

24 I don't know if there is any way that you
25 can address that in terms of physician training and

1 selection of physicians and sites to begin to place
2 these devices, but I would just be interested in
3 your comments on that and how you might address
4 what I think is a potential risk to patients long
5 term.

6 MR. WILLIAMS: I appreciate your concern
7 and your comments. We certainly share those
8 concerns. We have constantly emphasized in our
9 physician training, and obviously with the benefit
10 of a rigorous clinical trial it is much easier to
11 emphasize, but because we are taking this
12 clinically proven training program out into a
13 commercial environment, and even based on what I am
14 hearing you say today based on your clinical
15 experiences, there is a need to reinforce the
16 surveillance on these patients and impress upon the
17 patients that this is a very important part of the
18 continuing success of their therapy. I think it
19 behooves us to make sure that we do everything we
20 can in the context of the labeling and physician
21 training.

22 DR. PERLER: The problem is that the
23 person putting it in is not going to be the person
24 seeing the patient at three years and five years,
25 and so forth. That is the real conundrum.

1 MR. WILLIAMS: Right.

2 DR. PERLER: Thank you.

3 DR. LASKEY: Chris and then Ileana, and we
4 will take a ten-minute break at that point. Dr.
5 White?

6 DR. WHITE: Thank you very much. I would
7 like to just give you another chance to tell me the
8 denominator that you used to figure out the primary
9 efficacy. You still think that is 196?

10 DR. NAFTEL: I do, yes.

11 DR. WHITE: The reason that I am asking
12 that is because if you look at Table 4.16, on page
13 532, it actually says at the bottom of the table
14 that 40 of the scans were non-interpretable. So, I
15 am wondering how you can use 196 if you couldn't
16 interpret 40 of the scans.

17 DR. NAFTEL: The 196 is the number of CT
18 scans, that is true. At the core site some were
19 not interpretable. We are looking at the efficacy
20 measure, looking for both aneurysm growth and
21 endoleak. So, we took all the information we had
22 for either one of those, plus also the
23 device-related complications. You are certainly
24 right, some were not interpretable.

25 The only other thing I can say is that in

1 the site CTs where we came up with the same
2 efficacy rate, the sites obviously are treating
3 patients and none of their CTs were uninterpretable
4 and we came up with essentially the same
5 percentage.

6 DR. WHITE: There is a reason why you
7 chose a core lab to report your data? Was there a
8 reason to choose a core lab to report the data?

9 MR. WILLIAMS: Yes, the core lab provides
10 an independent review of the radiographic imaging.

11 DR. WHITE: So, I don't think it is
12 adequate to use the site reading as an explanation
13 for lack of data on the core lab side. I think
14 that is disingenuous. I think there were not a few
15 scans that were not interpretable; there were 40.
16 I think that brings the number down to 156, not
17 196. Do you disagree with that?

18 DR. NAFTEL: It would be a little bit
19 higher than that because non-interpretable for
20 aneurysm growth didn't correlate exactly with
21 non-interpretable for endoleak.

22 DR. WHITE: We were told by the FDA
23 reviewer that there were 155 pairs of CTs used. Do
24 you disagree with that?

25 DR. NAFTEL: That number is 186.

1 DR. WHITE: Can I have the FDA reviewer
2 respond to that? Paul?

3 DR. CHANDEYSSON: Paul Chandeysson. Not
4 having counted these, all I can do report what was
5 in the submission. There does seem to be a
6 question of how many is in the denominator. But,
7 as Dr. Grey pointed out, it doesn't really matter
8 what the denominator is. It is pretty clear that
9 the 95 percent lower confidence limit does not meet
10 the 80 percent.

11 DR. WHITE: Well, my point is not that so
12 much, although I am very troubled that you didn't
13 meet your own criteria for success, but I am even
14 more troubled by the fact that your primary
15 endpoint is determined by only 70 percent data.
16 You are only looking at about 70-72 percent of
17 these patients. Three out of ten are not even
18 being examined for the primary efficacy endpoint.
19 If 156 was the number for endoleak, for example,
20 that is 72 percent of the 215 that were eligible at
21 one year for follow-up. So, three out of the ten
22 people aren't even being looked at. I find that to
23 be a big number, a worrisome number, and it gives
24 me pause and lack of confidence in your ability to
25 assess the outcome if the primary endpoint is an

1 endoleak.

2 DR. MATSUMURA: I think what you are
3 asking is how do you select this denominator versus
4 other ones--

5 DR. WHITE: No, that is not what I asked.
6 You tell me in Table 4.16 that you had 156 CT scans
7 that were to be evaluated at 12 months, and I am
8 telling you that 156 of 215 is about 72 percent. I
9 find that to be extraordinarily low for a primary
10 efficacy endpoint. Whether or not it reaches 80
11 percent--I am unhappy that it is less than 80
12 percent but I am even more unhappy that we are not
13 counting very many of the patients. It is not a
14 very thorough evaluation of the primary efficacy
15 endpoint. I mean, I am not sure that you need 97
16 percent but 72 seems to be awfully low. If you
17 choose that as your primary endpoint, how can you
18 not have better data collection?

19 DR. MATSUMURA: Can I just ask for
20 clarification to that question? You are saying
21 that 156 of the patients of the 215 have an
22 endoleak?

23 DR. WHITE: No, only 156 patients were
24 evaluated for an endoleak.

25 DR. MATSUMURA: By the core lab at 12

1 months had an evaluable CT scan.

2 DR. WHITE: Well, is that another way to
3 say they were evaluated for endoleak?

4 DR. MATSUMURA: Yes.

5 DR. WHITE: And that was your primary
6 endpoint of efficacy that you chose?

7 DR. MATSUMURA: One of three, yes.

8 DR. WHITE: Well, we will get to the
9 enlargement in a minute but you are not doing that
10 good on the first one. You know, are you telling
11 me that 72 percent is adequate?

12 DR. MATSUMURA: If I can just finish, what
13 we wanted to do when we chose the denominator is to
14 pick something that seemed to represent an adequate
15 denominator. You have three components. As you
16 are pointing out, you have endoleak; there is
17 aneurysm enlargement which, as you are going to
18 point out, there are fewer pairs of core lab CTs to
19 evaluate; and then there is device-related
20 complications where the denominator is 235. So, we
21 had this calculation to make. We have three
22 separate denominators and which one do you choose
23 because you might have a patient with a
24 device-related complication that never makes it to
25 12 months. Okay?

1 The selection was based on what we thought
2 was a fair approximation of what the available
3 information is. When we made the extrapolation
4 from site-reported data that paralleled findings
5 at core lab we felt it was appropriate to pick that
6 denominator.

7 I agree with what I think you are getting
8 to in your comments, that you could make a strong
9 case to choose a different denominator.

10 DR. WHITE: Well, the question is whether
11 you are being disingenuous in your slides. I mean,
12 you showed us a slide where you said 196 is the
13 denominator, this morning, and you told me that it
14 was 196 and that is just not true.

15 DR. MATSUMURA: Which one would you prefer
16 to use if the DRC, say, denominator is 235--

17 DR. WHITE: Well, the incidence of DRC was
18 only three percent so we are not going to miss a
19 whole bunch there. But we are talking about a 20
20 percent endoleak rate.

21 DR. LASKEY: I am going to intervene here.
22 I think Dr. White has a valid point. The panel
23 remains concerned about choice of the unit of
24 analysis here and the denominator for that
25 particular endpoint. I suggest, in the interest of

1 time, we move on. You have made your point. The
2 panel is certainly as concerned as you are. Go
3 ahead, Chris.

4 DR. WHITE: No, that is okay.

5 DR. LASKEY: You had some others about
6 enlargement?

7 DR. WHITE: It is all the same issue. I
8 believe that you have under-reported. I believe
9 that you haven't been as forthright as you could be
10 about the data. I think you made me work hard to
11 find that, and I would have appreciated it if you
12 had just told me up front.

13 DR. LASKEY: Ileana?

14 DR. PINA: Several more points. I want to
15 clarify that when I asked about sudden death I did
16 not mean aneurysm-related sudden death. The most
17 common cause for sudden death is cardiac and it is
18 ventricular arrhythmias. So, when I say sudden
19 death I don't think that any of these deaths were
20 necessarily ruptured aneurysms. But I think it
21 underscores the morbidity of this population and in
22 this population about 30 percent of patients do die
23 suddenly.

24 I will jump immediately to the patient
25 education brochure. There is nothing in there that

1 relates that the most common cause of demise in
2 these patients may not be the aneurysm itself but
3 may be one of the co-morbidities, and the
4 importance of following with their cardiologist,
5 and the importance of continuing taking their
6 cardiac medications--just because the aneurysm has
7 been fixed, that doesn't mean that the
8 co-morbidities have gone away. I mean, we know
9 from the cardiac literature that over 70 percent of
10 patients who have any kind of peripheral vascular
11 disease have very significant coronary disease
12 whether proven or not.

13 Dr. Matsumura, you were saying that there
14 was more than one sudden death in the control
15 group. So, they were occurring in both groups. I
16 only counted only one episode that I could define
17 as sudden death in the control group. Again, I am
18 not saying you are under-reporting; I am just
19 saying that I think deaths have been classified as
20 other than what they really are.

21 I have one question about a patient on
22 page 5106. It is of particular interest to me
23 because it is a patient who had a transplant in
24 1992. It indicates that a CT scan showed
25 significant mural thrombus and clots throughout the

1 upper portion in both limbs, with left greater than
2 right. Does that mean inside the graft?

3 DR. MATSUMURA: Yes.

4 DR. PINA: Again, this sort of concerns me
5 because it sounds like a lot of this patient's
6 symptoms were due to that and not having anything
7 to do with rejection. So, again, I go back to the
8 anticoagulation issue which I think also has to be
9 included in your packet. If patients are on
10 aspirin, they need to continue on aspirin. If they
11 are on warfarin for some other reason, like atrial
12 fibrillation, they need to be continued.

13 So, those are more points of comments that
14 still concern me. One question about the fracture,
15 the FDA had a pretty excellent review about the
16 fracture. There were two fractures. One was
17 identified by the core lab but it was not
18 identified by the investigator or not seen in the
19 investigator CT scan or x-ray. What is the
20 sensitivity of the CT scans in picking up
21 fractures? Is there another, more sensitive way of
22 doing this? I may be a little bit mixed up but I
23 think that the fracture, obviously, is a very
24 important issue and the FDA spent a lot of time
25 going over that. It seems low but, still, can it

1 really be identified clinically by the center that
2 is doing it?

3 DR. MATSUMURA: The question of how good
4 is CT scan in evaluating fractures, I think not
5 very good. The abdominal films--I think you meant
6 to ask what was used to identify those two
7 fractures by the core lab. We can bring the core
8 lab director up here, but we really don't know how
9 good it is when there are two events and we don't
10 have explants, which I think would be a definitive
11 assessment of how many fractures there are. I can
12 say that we feel that abdominal x-rays are our best
13 available test. We think that there are certain
14 improvements that can be made to abdominal x-rays
15 within this study. I think in February a
16 supplement was applied to expand it to four views
17 with centering on the device. I am not a
18 radiologist, but techniques to optimize
19 visualization of the wire fracture so we can use
20 the best available tests, short of explantation, to
21 try to identify the fractures. But we only two
22 episodes, I don't know that we can tell you how
23 sensitive or specific it is.

24 DR. PINA: Will that be in your physician
25 education packet? I don't remember seeing it.