

1 this predefined level. If it did not compromise the  
2 exclusion of the aneurysm, especially with the change  
3 of morphology over time and nothing was done about it,  
4 it was recorded as an adverse device-related event.  
5 But obviously, since nothing was done about it because  
6 there was no associated problems, then it became a  
7 minor event.

8 DR. JOHNSTON: Right. Renal  
9 insufficiency, for example, Table 21, page 62.

10 DR. MAKAROUN: The definition of renal  
11 insufficiency, maybe I should point you to Tab B in  
12 the briefing book. There is predefined categories for  
13 all the events that are classified with what is  
14 considered significant and nonsignificant.

15 To be significant, it had to be more than  
16 30 percent rise over the baseline creatinine and if  
17 it's more than 30 days, then it became renal failure.  
18 If it's less than 30 days, it's renal insufficiency.  
19 If it was a very minor transient rise of creatinine  
20 that went back to normal, it would have been  
21 classified as minor.

22 DR. JOHNSTON: Understand. Let me see if

1 there's any others. And the same would apply to nerve  
2 injury, Table 22?

3 DR. MAKAROUN: Correct.

4 DR. JOHNSTON: All right. I think you see  
5 where my concern is here. We're dealing with  
6 definitions, but we have a relatively small patient  
7 population and perhaps not perfect comparative data,  
8 and so I just want to make sure that --

9 DR. MAKAROUN: Correct.

10 DR. JOHNSTON: -- I understand the  
11 classifications. So the ones I have listed, you would  
12 all still count as minor and, I guess, I would agree  
13 with most of them.

14 DR. MAKAROUN: Actually some of the  
15 predefined limits to some of these complications, in  
16 the minds of many investigators, tend to favor the  
17 surgical control arm. For example, it was some, let's  
18 say, an ileus. If it was less than 96 hours, it was  
19 not counted as an ileus. If respiratory failure  
20 lasted less than 24 hours, it was not counted as a  
21 major adverse event. So when they became major  
22 adverse events, they were truly a major adverse event,

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1 and some consideration was given to the expected major  
2 adverse event that may happen with the surgical  
3 control arm.

4           Something came up a little bit earlier  
5 also regarding angina and, in this same line, I would  
6 like to indicate that if a preexisting condition, for  
7 example angina, was there and the patient had angina  
8 afterwards, that was not counted as a major adverse  
9 event. That is also indicated in the protocol. And  
10 for angina, per se, there was only one incidence of  
11 angina in the postoperative period and it was in a  
12 test patient and not in a control.

13           DR. JOHNSTON: I think you'll want to  
14 answer some more questions in a second. I want to be  
15 clear that I am not dealing with the comparative data.  
16 I'm simply dealing with some of the complications that  
17 I think I required clarification were minor, because  
18 that is now going to affect my view on what was major.

19           Would the patients, by the way, have  
20 regarded those as minor complications since you saw --

21           DR. MAKAROUN: By and all, yes.

22           DR. JOHNSTON: Okay.

1 DR. MAKAROUN: When you tell the patient  
2 that the device has moved down, but it's still sealing  
3 his aneurysm and there is no evidence that it's going  
4 to affect the treatment, they were pretty satisfied.

5 DR. JOHNSTON: All right. Now, my major  
6 concern relates to what was a major complication, not  
7 comparing it to open surgery, but what was a major  
8 complication and in how many patients? And I have  
9 gone through the table and I have listed major  
10 complications, such as bleeding with the procedure,  
11 that is clearly major, bleeding post-procedure,  
12 respiratory failure, renal failure, renal  
13 insufficiency, thrombosis, paraplegia, re-operation.  
14 I get a total of 33 major complications and we would  
15 all agree those are major. Now, is that in 33  
16 patients out of 140?

17 DR. MAKAROUN: No.

18 DR. JOHNSTON: Or would some have more  
19 than that?

20 DR. MAKAROUN: Several patients.

21 DR. JOHNSTON: More than one complication.

22 DR. MAKAROUN: Correct. Several patients

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1 had more than one complication.

2 DR. JOHNSTON: Right.

3 DR. MAKAROUN: More than one major adverse  
4 event and the definition is the time to the first  
5 major adverse event, but then some patients had more  
6 than one major adverse event.

7 DR. JOHNSTON: So how many patients out of  
8 the 140 had a major complication?

9 DR. MAKAROUN: In which group?

10 DR. JOHNSTON: Purely in the  
11 endoprosthesis group.

12 DR. MAKAROUN: In the TAG group?

13 DR. JOHNSTON: Correct.

14 DR. MAKAROUN: The major adverse events  
15 was 42 percent for the --

16 DR. JOHNSTON: That was total. I'm trying  
17 to eliminate some things like ileus and so on, because  
18 I'm coming from the fact that I am having trouble with  
19 the comparative groups and I think some of the  
20 statistical concerns have already been expressed.

21 So I'm trying to put myself in the  
22 position of evaluating the TAG group and understanding

1 what percentage of people had a complication. And it  
2 wasn't 33 out of 140. It was less than that.

3 DR. MAKAROUN: The numbers --

4 DR. JOHNSTON: Complications attributable  
5 to --

6 DR. MAKAROUN: The numbers that were shown  
7 are not the number of complications. It's the number  
8 of the proportion of patients who had at least one  
9 adverse event. So the 42 and the 77, and no matter  
10 how you drop it down, are the percentage of patients  
11 who had one or more adverse event.

12 DR. JOHNSTON: I'm not getting the sense  
13 that this is a fair description, however, of the  
14 device. If I were going to implant one of these  
15 devices in the future, if approved, I wouldn't tell a  
16 patient that would be their complication rate, because  
17 I don't believe it's that high.

18 Do you understand where I'm coming from?  
19 I'm making myself clear? I'm having trouble with the  
20 comparative study and I'm trying to understand the  
21 complication rate.

22 DR. MAKAROUN: Collecting prospective data

1 with a predefined set of events that you're going to  
2 track is typically what generates event rates that are  
3 higher than we typically would associate with certain  
4 procedures that we do all the time, and these are the  
5 numbers that came out from the prospective collection  
6 of the TAG data over two years.

7 ACTING CHAIR MAISEL: Dr. Johnston, are  
8 you saying that there are some events that are defined  
9 as major that you don't consider major?

10 DR. JOHNSTON: Correct, correct, and I  
11 don't believe that any of the consultants here would  
12 quote a 42 percent complication rate to a patient  
13 having this procedure, and I'm trying to get down to  
14 the fact of what is the complication rate from this  
15 procedure?

16 DR. MAKAROUN: Well, as a surgeon, I would  
17 quote them the rate of mortality and the rate of  
18 paraplegia and the rate of stroke that they may be  
19 liable to, plus an additional significant percentage  
20 of patients who will have other complications that may  
21 require treatment. That is probably less problematic  
22 to the patient. Transient elevation of the creatinine

1 that remains present for a certain period of time as  
2 "major" might not be of particular importance  
3 initially to quote, I guess.

4 ACTING CHAIR MAISEL: So I think the best  
5 we can say is as major adverse events are defined in  
6 this study, there were 42 percent of patients who had  
7 one or more major adverse event.

8 DR. JOHNSTON: Thank you. I have more  
9 questions, but I'll --

10 ACTING CHAIR MAISEL: Oh, please, go  
11 ahead. Continue.

12 DR. JOHNSTON: Can I clarify then the  
13 explants? I understand that there were three with  
14 complaints and you have one pending. Is it still  
15 pending or do we have information on it?

16 MR. NILSON: The complaint we have that is  
17 under investigation is currently being -- the tissue  
18 is being digested off of it, so we have not analyzed  
19 it.

20 DR. JOHNSTON: What about the other 10  
21 that you have received? You indicated you had no  
22 information on that.

1 MR. NILSON: The three that we have were  
2 associated with a complaint. The other explants we  
3 received were anecdotal. The physicians are very  
4 supportive of us wanting to understand what happens to  
5 these devices long-term.

6 DR. JOHNSTON: And what information can  
7 you give us about those 10 explants? I mean, you have  
8 heard questions related to the histology, related to  
9 its structure.

10 MR. NILSON: The information we have on  
11 those 10 explants is that they were not associated  
12 with complaint. They were not associated with a major  
13 device event. The patients died of other causes given  
14 the high morbidity of the patient population.

15 DR. JOHNSTON: Would you agree there could  
16 be abnormalities in those grafts?

17 MR. NILSON: Would you repeat the  
18 question, please?

19 DR. JOHNSTON: Would you agree that there  
20 might be abnormalities in those 10 grafts?

21 MR. NILSON: We have not identified any  
22 abnormalities in those 10 grafts.

1 DR. JOHNSTON: Okay. Can I ask about one  
2 of the cases of paraplegia and its relation to the  
3 graft? One case of paraplegia occurred very late,  
4 page 61, Table 20. Page 61, Table 20. That's unusual  
5 in my experience to have a paraplegia occur late, and  
6 I wondered if you had an explanation or if it was  
7 perhaps due to graft migration.

8 MR. NILSON: The patient did not have an  
9 associated device event, and I will bring up Dr.  
10 Makaroun to give the clinical opinion on late  
11 paraplegia.

12 DR. MAKAROUN: There were no late  
13 paraplegias. The case that is listed under that  
14 table, these are cases that are carried through,  
15 because this table is through two years that are  
16 present at that time. These are not new cases.

17 DR. JOHNSTON: But it's not listed in the  
18 second period of time. It's only listed in the third  
19 period of time.

20 DR. MAKAROUN: He may not have had a  
21 follow-up at that period of time. He may not have  
22 shown up for the follow-up, so he would not be listed.

1 But there were no clinical late paraplegia at any time  
2 that I am aware of at least.

3 MR. NILSON: Dr. Mitchell would like to  
4 add a clinical perspective.

5 DR. MITCHELL: All these events were  
6 independently adjudicated by the Clinical Events  
7 Committee, which, to the extent possible, was blinded.  
8 This particular instance, there was no definitive  
9 evidence. This is a control patient. There was no  
10 definitive evidence because of prolonged  
11 hospitalization through the first follow-up periods.

12 And finally, when we had an independent  
13 neurologic assessment, we then adjudicated that, in  
14 fact, there was paraplegic/paraparesis, and then that  
15 just got back-loaded, but it doesn't get captured in  
16 the first one month, one-year data.

17 DR. JOHNSTON: I understand. My final  
18 question relates to the strong bonding with the  
19 bonding tape that is now present in the graft and  
20 presumably is, therefore, restraining the stents. We  
21 all, I think, recognize that aortas dilate with time  
22 and what do you anticipate is going to happen when the

1 aorta dilates and the stents are constrained by the  
2 bonding tape?

3 MR. NILSON: The devices are manufactured  
4 to a consistent diameter that will not dilatate over  
5 time. Our data does not indicate that the aortas will  
6 grow over time. We are not familiar with that data.  
7 I would like to add that our migration rates are low  
8 and that would be one of the concerns if the aorta was  
9 dilatating and the device was not staying the same  
10 diameter.

11 DR. JOHNSTON: So if my hypothesis were  
12 accepted, that would warrant very careful follow-up of  
13 these patients?

14 MR. NILSON: Migration is a concern,  
15 especially in long-term, and we are evaluating all  
16 patients for migration.

17 DR. JOHNSTON: Thank you. Thanks, Mr.  
18 Chairman.

19 ACTING CHAIR MAISEL: Dr. Normand?

20 DR. NORMAND: Thank you. I am,  
21 unfortunately, going to revisit the control group.  
22 I'm going to begin with a statement that I think it's

1 going to be very difficult to include as a comparator  
2 a group of individuals who would never be eligible for  
3 the device. And so to me that fundamentally is a big  
4 flaw.

5 MR. NILSON: Could I request you to speak  
6 up, please?

7 DR. NORMAND: Oh, you can't hear me?

8 MR. NILSON: Yes.

9 DR. NORMAND: Okay. I'm sorry about that.  
10 I can speak louder. So I will restate it. What I had  
11 said was that I'm going to make a comment that I find  
12 the control group very difficult, as I think we're  
13 hearing, and I think it's going to be very difficult.

14 Most people, when you're conducting a  
15 trial, even if you're randomizing, the effect that you  
16 estimate has to be on comparable patients. And so the  
17 inclusion of patients in this study in the control  
18 group that are not eligible for the TAG device, to me,  
19 is a fundamental flaw.

20 And you have already reported that you do  
21 not know, it's my understanding, I may be mistaken,  
22 but my understanding of how you answered earlier was

1 that you do not know how many of the control patients  
2 were TAG eligible and how many were not. And so I  
3 don't think it's 100 percent, but I don't know what  
4 the number is, and so I have great difficulty from a  
5 philosophical point of view assessing the data.

6 So that is where I'm coming from. Now,  
7 with those comments in place without knowing the  
8 percent of the control group that are TAG ineligible,  
9 I'm struggling, but nevertheless I have questions  
10 about suppose we go forward, I do have a few questions  
11 regarding some other characteristics of the control  
12 group.

13 So the first question relates to the fact,  
14 at least from my count, five sites had no concurrent  
15 controls, and I was wondering why these patients were  
16 included, because I had thought I had read that you  
17 had to have some, at least there was a minimum number  
18 of, concurrent controls at each study site. I may  
19 have miscounted, but if you look at page 35 in the  
20 pivotal study, I think I highlighted a number of sites  
21 that had no concurrent controls. So why were they  
22 included?

1 MR. NILSON: The protocol stated that we  
2 strive to have no more than a five patient difference  
3 between controls and test subjects within a site.

4 DR. NORMAND: But there are some sites  
5 that have no control patients.

6 MR. NILSON: Again, we just strived to not  
7 have a more than five-patient delta. Some hospitals  
8 could enroll smaller numbers of each of the arms.

9 DR. NORMAND: Okay. 18 percent of the  
10 control patients were treated in the year before  
11 enrolling the TAG patients, and I'm wondering what the  
12 estimate of the safety endpoint and the effectiveness  
13 endpoint is when you exclude these patients given that  
14 it's confounded with time completely.

15 MR. NILSON: We did do that analysis and  
16 Dr. Verter can describe the analysis specifically.

17 DR. VERTER: If I may, I would like to go  
18 back to your first question. We actually did an  
19 analysis that only included those sites that had both  
20 control and test patients in it, and I don't have --

21 DR. NORMAND: Concurrent controls or it  
22 didn't matter?

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1 DR. VERTER: We actually did that also and  
2 the results are very similar.

3 DR. NORMAND: But we don't have those  
4 data, right?

5 DR. VERTER: I will try to find those  
6 numbers for you during the session. You wanted to  
7 know about whether the rates varied for the MAEs over  
8 the course of the recruitment period?

9 DR. NORMAND: I wanted to know what the  
10 estimate is when you eliminate 18 percent of the  
11 control patients who were treated in the year before  
12 enrolling the first TAG patient.

13 DR. VERTER: Right. They are getting that  
14 slide, but I can tell you that if you look at the  
15 slide when it goes up, it will show the major adverse  
16 events and mortality from 1993 to 2001. And what I  
17 think you will see is that when you eliminate those  
18 control patients from earlier, the results are still  
19 the same.

20 DR. NORMAND: And I'm wondering will you  
21 have enough power to see a difference if we have  
22 eliminated 18 percent?

1 DR. VERTER: Well, no, not that one. It's  
2 the one that has the major adverse events by year.

3 DR. NORMAND: Well, how about I go on and  
4 when the slide pops up --

5 DR. VERTER: Okay, sure.

6 DR. NORMAND: I believe you.

7 DR. VERTER: Okay. No, you want to see,  
8 right.

9 DR. NORMAND: So that when the slide pops  
10 up, I can see the number. And I'm going to ask this  
11 question again. I know I asked it earlier, but I am  
12 a little confused about the timing of the measurement.  
13 So I'm going to make two statements and you can  
14 correct me if I'm wrong.

15 My understanding is the timing of the  
16 measurements for the patient assessments, for example,  
17 12 months or 31 months, is after the hospital  
18 discharge.

19 MR. NILSON: I need to clarify my previous  
20 statement. That is one day post-treatment on both  
21 arms.

22 DR. NORMAND: Okay. So it's not post-

1 discharge

2 MR. NILSON: Correct.

3 DR. NORMAND: So it's post-procedure?

4 MR. NILSON: One day post-procedure is the  
5 start of the follow-up interval.

6 DR. NORMAND: Okay. And so that's also  
7 similar for the definition of your primary, your  
8 safety endpoints and your effectiveness endpoint?

9 MR. NILSON: Consistent through both  
10 definitions.

11 DR. NORMAND: Okay. That's good, because  
12 you did show a substantial difference in length of  
13 stay between the two groups. So I guess given this is  
14 a combination control group, remember the comment I  
15 made earlier about this, I'm wondering how the sponsor  
16 -- if you could give me some description of how you  
17 ensured comparable data collection for the two groups.  
18 By two groups I mean the TAG group and the control  
19 group, given one was historical and one was  
20 concurrent, and I guess the other two were concurrent.

21 How did you ensure that the information  
22 you were collecting meant the same thing? In an

1 observational study, we usually do several things to  
2 ensure the comparability or the ascertainment of the  
3 data. Can you just tell me how you actually collected  
4 the data?

5 MR. NILSON: We had CRFs, clinical report  
6 forms, and we did specific training at each site. We  
7 also had each site monitored to ensure the data was  
8 accurate and up to date, and we had all the events  
9 adjudicated by a CEC committee.

10 DR. NORMAND: So when you went back into  
11 the chart and looked at the baseline characteristics  
12 of the patients, for example, I'm saying charts, maybe  
13 I shouldn't say that, but when you went back and  
14 collected the information on the baseline  
15 characteristics of the study participants,  
16 particularly those that were enrolled one year before  
17 the study, the first TAG patient, that information was  
18 collected reading some information and that was  
19 measured in the same way that you would for the  
20 prospectively collected data?

21 MR. NILSON: All measurement aneurysm  
22 morphology data was collected in exactly the same way

1 independent of a subgroup of historical control, TAG  
2 device 99-01, TAG device 03-03. We kept everything  
3 exactly the same.

4 DR. NORMAND: And obviously, it wasn't  
5 blinded. Should I say that? Obviously, it wasn't  
6 blinded?

7 MR. NILSON: It was not blinded.

8 DR. NORMAND: Okay. I just have a few  
9 more questions, and I think it's because you have  
10 obviously a retrospective cohort for your control  
11 group. You have, it seems to me, a lot of differences  
12 in missed visits. For example, between the control  
13 group, I have a number here, 9 percent at one month  
14 for the TAG group and 20 percent at one month for the  
15 control groups.

16 Did you examine differences between those  
17 who had and did not have a visit? No?

18 MR. NILSON: We do not have that  
19 information available.

20 DR. NORMAND: Okay. So --

21 MR. NILSON: There would be no results if  
22 they missed the visit.

1 DR. NORMAND: But nevertheless, could you  
2 not compare characteristics of the individuals for  
3 whom showed up for a visit, so either age, you know,  
4 their baseline measurements? Often one would do this  
5 to see if there are differences in patients who show  
6 up for visits and don't show up for visits.

7 MR. NILSON: We did include those patients  
8 in worst case analysis, so they would be counted as a  
9 major adverse event or major device event.

10 DR. NORMAND: Okay. I think you answered  
11 my question. You did not examine whether or not you  
12 have problems in the missing data for those  
13 individuals who showed up for a visit and those who  
14 did not.

15 So the reason why I'm asking this, I think  
16 it's probably obvious, but when you're looking at your  
17 analyses when you reported some of your summaries, and  
18 I believe, unless I'm mistaken, the sponsor did do a  
19 propensity score analysis, at least it was in the  
20 appendix and I read it and I looked at it and it was  
21 exciting, but when I looked at that I thought gee, how  
22 did you include that information when you have missing

1 data?

2 So either did you do a complete case  
3 analysis for the patients for whom you're missing  
4 baseline data? Did you impute? If you imputed, you  
5 had to assume that there were similarities. Hence,  
6 could someone answer the question about how you  
7 treated the missing data in your analyses?

8 MR. NILSON: Dr. Joel Verter will answer  
9 how we did the propensity analysis.

10 DR. VERTER: Actually, I think I have to  
11 answer about six questions that you asked.

12 DR. NORMAND: I remember them all.

13 DR. VERTER: All right. Let's see how  
14 many I remember. Let me go back to the very first one  
15 about the trend over time. Okay.

16 DR. NORMAND: You found it?

17 DR. VERTER: Okay. Yes, we did find it.  
18 What you will see is that if you eliminate -- there  
19 were 23 subjects. Right. Please, show this slide.  
20 If you go through 1998, there were 23 subjects that  
21 had 14, at least one major adverse event, and after  
22 that there were 71 subjects who had 58. In fact, that

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1 incidence is higher in the more recent cases, about 80  
2 percent, versus the "historical" ones of 60.

3 DR. NORMAND: Does that alert you to  
4 collection? I mean, why would that happen?

5 DR. VERTER: I haven't done any tests of  
6 whether they were different or not. I mean, we have  
7 not looked at the individual characteristics to answer  
8 that.

9 DR. NORMAND: Okay.

10 DR. VERTER: I would also like to look at  
11 the historical, the concurrent versus the --

12 DR. NORMAND: Yes, I have looked at the  
13 historical versus the --

14 DR. VERTER: You saw that?

15 DR. NORMAND: In the appendix, I read  
16 these.

17 DR. VERTER: You saw the concurrent versus  
18 the --

19 DR. NORMAND: Yes, I did.

20 DR. VERTER: Okay. You don't have to show  
21 that one. Okay.

22 DR. NORMAND: I shouldn't say no. I mean,

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1 I saw it. I don't know if everybody else wants to see  
2 it.

3 DR. VERTER: Why don't we put it up for a  
4 sec. Not this one, the concurrent versus the test.  
5 We did an analysis that compared the concurrent  
6 surgical controls with the TAG device cases and saw an  
7 identical reduction in risk of major adverse events  
8 through one year, 42 percent versus 77 percent. Okay.  
9 Thank you for letting me show it.

10 DR. NORMAND: Do you want to go now to the  
11 missing data?

12 DR. VERTER: Yes.

13 DR. NORMAND: So did you look at the  
14 differences between those, forget about the treatment  
15 group right now, but those who did show up for a visit  
16 and those who did not?

17 DR. VERTER: Missing data at baseline or  
18 missing data at follow-up?

19 DR. NORMAND: At follow-up, and you have  
20 got problems in both places.

21 DR. VERTER: Right. We did look at some  
22 of the data at the baseline. We have not looked at

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1 patients who missed follow-up visits although, as Mr.  
2 Nilson expressed, we did include those in worst case  
3 analyses.

4 DR. NORMAND: Okay. I'm not going to beat  
5 it to death. I'll just ask one more question. In  
6 your propensity score analysis, did you only include  
7 those variables that were completely observed or what  
8 did you do?

9 DR. VERTER: If you're asking specifically  
10 the ones like the morphology.

11 DR. NORMAND: Yes.

12 DR. VERTER: Clearly, we could not include  
13 those. We couldn't.

14 DR. NORMAND: So you didn't include the  
15 variable or you didn't include the patients?

16 DR. VERTER: We didn't include the  
17 variable.

18 DR. NORMAND: Okay.

19 DR. VERTER: The patients were --

20 DR. NORMAND: So you just had then a much  
21 smaller subset of baseline characteristics to estimate  
22 the propensity score and model on, because you were

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1 missing the data on the other covariates that you  
2 needed?

3 DR. VERTER: In the control group. If it  
4 helps you at all, what we did do is an assessment.  
5 The morphology variables were available for virtually  
6 all of the test subjects and we did do a risk analysis  
7 within the test group and found that aneurysm diameter  
8 was related, but the others were not statistically  
9 related to the outcome.

10 DR. NORMAND: I think the bigger concern  
11 is, and I think it's your design, it's not a  
12 criticism, but your design is one such that if you go,  
13 you have more missing data for your control group, so  
14 you have got differential missing data and the concern  
15 is whether or not there is a problem with that.

16 I only have a few more questions. So we  
17 talked about the missed visits and there really wasn't  
18 an examination of who showed up and who didn't show  
19 up. I guess the question I think I want to ask is  
20 about the slide in the sponsor's presentation about  
21 blood loss and things such as that. I don't know if  
22 we need to go to it again, but it was page 69 of your

1 slide and page 78.

2 You have a number that says 94, but I  
3 don't think that's correct, right? In other words,  
4 when you represented the means for those particular  
5 variables, it was obviously for those patients for  
6 whom a measurement was available.

7 MR. NILSON: The secondary outcomes have  
8 different ns for each measured --

9 DR. NORMAND: Yes. I just want to sort of  
10 point out that when we were looking at that, I think  
11 it said 140, 94 but, indeed, I don't think it is.

12 MR. NILSON: The number you're referring  
13 to referred to the patients enrolled in each arm.

14 DR. NORMAND: Yes, but obviously that's  
15 not how you calculated the mean differences.

16 MR. NILSON: Again, could you show the  
17 slide?

18 DR. NORMAND: Go to page 69 of your --

19 MR. NILSON: Could you guys show the  
20 slide, please?

21 DR. NORMAND: That's 97.

22 MR. NILSON: So this is secondary

1 outcomes.

2 DR. NORMAND: No, that's 97. If you went  
3 to Slide 69. You may not be understanding my  
4 question, but I think it was Slide 69 of what you  
5 displayed.

6 MR. NILSON: The secondary outcomes were--  
7 could you, please, show the slide?

8 DR. NORMAND: Okay. All I'm asking is  
9 that 94 is, obviously, the people that were enrolled  
10 in the control group, but that's not the number on  
11 which those mean differences are based, right?

12 MR. NILSON: The mean differences are  
13 different. The denominator for the mean differences  
14 is dependent on which attribute you're referring to.

15 DR. NORMAND: Yes, because I don't think  
16 any of them are based on 94 in the control group.

17 MR. NILSON: The first one, aneurysm  
18 diameter, which is, in the sponsor's opinion, the most  
19 important attribute on the page, it has a complete  
20 data set.

21 DR. NORMAND: It does?

22 MR. NILSON: Yes.

1 DR. NORMAND: Okay. I now want to go to  
2 the confirmatory trial. I did have a question, I  
3 guess, for the FDA on this one, and that is the --

4 ACTING CHAIR MAISEL: Could the sponsor,  
5 please, take a seat and allow the FDA to approach the  
6 podium?

7 DR. NORMAND: I guess the question I have  
8 is they are using the sponsor and you're using the  
9 same control group twice. Some people have a concern  
10 about that. Were there any adjustments made for the  
11 fact that you're using the same control group twice?  
12 And also, I wanted to know if there was concerns about  
13 confounding by time?

14 MR. KAMER: Are you talking about the fact  
15 of multiplicity using --

16 DR. NORMAND: Yes.

17 MR. KAMER: You're asking us if --

18 DR. NORMAND: Do you have a concern about  
19 using the same control group twice?

20 MR. KAMER: I actually haven't thought  
21 about it.

22 DR. NORMAND: Okay.

1 MR. KAMER: But I had to go past some  
2 other issues.

3 DR. NORMAND: Okay.

4 MR. KAMER: So that was not at the top of  
5 my list, but I could see where you might look at that  
6 and consider that multiplicity or that it is highly  
7 correlated, very highly correlated with itself. What  
8 was the second part of your question though?

9 DR. NORMAND: I was also wondering whether  
10 or not there was any problems with time. I may not  
11 have understood this clearly, but in the confirmatory  
12 study, forgive me if I forget the sample size, I don't  
13 know if it's 51.

14 MR. KAMER: 51.

15 DR. NORMAND: Oh, good.

16 MR. KAMER: Yes.

17 DR. NORMAND: 51 in the TAG group, I'm  
18 wondering is there confounding by time with that one  
19 or the 51 at a completely different -- you know, is it  
20 two months after the control group, so that all the 51  
21 are treated, obviously, at a different point in time  
22 than the control group? That is my question. I'm

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1       sorry. I'm having a hard time getting it out.

2               MS. ABEL: Yes, the confirmatory study was  
3 conducted years later after the enrollment of the  
4 controls.

5               DR. NORMAND: And how far apart in time?

6               MS. ABEL: That was in the FDA  
7 presentation. In the review summary, there is a slide  
8 that shows the enrollment periods.

9               DR. NORMAND: Oh, okay. I will just look  
10 back at it.

11               MS. ABEL: Yes.

12               DR. NORMAND: Okay.

13               MS. ABEL: And it's probably in the  
14 sponsor's somewhere also. The first question had to  
15 do with?

16               DR. NORMAND: It has to do with the fact  
17 that you're using the same control group twice.

18               MS. ABEL: And I just wanted to throw out,  
19 I'm sorry, that it is very common for us, when we do  
20 have a modification, for the initial control group for  
21 their study that the sponsor uses the control over  
22 again. I can understand that there are some problems

1 with that from a statistical standpoint, but it is a  
2 common practice.

3 DR. NORMAND: Okay. I'm a statistician,  
4 so I have to tell you that there's a problem with  
5 that.

6 MS. ABEL: Right, exactly.

7 DR. NORMAND: But I'm going to stop now.

8 ACTING CHAIR MAISEL: All right. Sharon,  
9 Sponsor Slide 102.

10 DR. LINDENFELD: It's not just a  
11 statistical problem. It's a clinical problem as well.  
12 It's not just statistical. It's clinical when you  
13 have a time separation.

14 DR. NORMAND: Yes.

15 DR. LINDENFELD: So it's both.

16 ACTING CHAIR MAISEL: Sharon, Sponsor  
17 Slide 102, I think, answers your question about the  
18 timing.

19 DR. NORMAND: Oh, okay.

20 ACTING CHAIR MAISEL: Dr. Kato?

21 DR. KATO: I just have a couple questions,  
22 so I will defer a lot of the technical, statistical

1 things to my other colleagues, who are more  
2 appropriate and better trained than I, to ask those  
3 questions. One question for the sponsor and then I  
4 have two questions for the FDA.

5 I notice that you have specified  
6 indication or inclusion/exclusion criteria. Can you  
7 comment about the impact of those criteria, vis-a-vis,  
8 your product label?

9 MR. NILSON: The sponsor intends to  
10 include all appropriate anatomical references in the  
11 labeling and it is included in our worldwide IFU that  
12 is in circulation today, specifically aneurysm  
13 diameters that are needed for the device to be placed  
14 in appropriate anatomy, proper warnings about access  
15 vessel, significant thrombus or calcification. The  
16 sponsor is going to ensure that the proper labeling is  
17 included.

18 DR. KATO: I guess I'm concerned that in  
19 light of recent events not only, you know, within the  
20 drug community, but also within the device community  
21 that there needs to be a little bit more or a lot more  
22 disclosure about how devices and/or drugs should be

1 used, and I think it's up to the sponsor to very  
2 explicitly state these, specifically when this is a  
3 new device in the United States and then you have  
4 specific inclusion and exclusion criteria, which are  
5 not explicitly duplicated in your label. So that is  
6 just a comment.

7 Two questions for the FDA, I guess. I'm  
8 curious why the sponsor was allowed to not present  
9 their 2,000 European cases and the follow-up for that,  
10 and also why the sponsor was not asked to present  
11 their five-year follow-up data, which they clearly  
12 stated that they had?

13 MS. ABEL: We actually did request any  
14 additional data that the sponsor had from OUS studies  
15 in addition to the sponsor-investigator studies that  
16 were ongoing at this time. So we did request that  
17 information. The sponsor didn't have the information  
18 readily available. I think the reason that they  
19 weren't able to provide it probably has to do with the  
20 fact that this is an expedited PMA and we were working  
21 in a very short time frame.

22 DR. KATO: I'm sorry. You said what?

1 MS. ABEL: This was an expedited PMA, so  
2 we have been working in a very short time frame. The  
3 sponsor had, approximately, a month to prepare for  
4 this Panel meeting and answer all of our various  
5 questions. So I think that probably the lack of data  
6 from the OUS and the sponsor-investigator studies has  
7 to do with that.

8 DR. KATO: Well, Sponsor, could I then  
9 throw that question back to you? The FDA is saying  
10 that they asked for it, but you didn't provide it  
11 because of the expedited nature of this PMA.

12 MR. NILSON: The five-year data and the  
13 97-01 feasibility study was presented in the early  
14 portion of Dr. Makaroun's presentation. Again, that  
15 was a feasibility study with limited patients.

16 The device has been commercially available  
17 overseas, which means it wasn't associated with a  
18 clinical trial, so the follow-up data is limited. We  
19 do follow all of our complaints and vigilance reports  
20 and are very active in our communication with the FDA  
21 regarding any events that we deem are significant and  
22 should be reported.

1 DR. KATO: Well, you know, as you are  
2 probably aware, the number of reported incidents of  
3 device malfunction or device problems is probably a  
4 tenth of all the problems that probably do occur. You  
5 know, if you look at your own experience with getting,  
6 you know, retrieving devices that were explanted is  
7 difficult. How do you propose then if the Panel were  
8 to say we would like to have some long-term follow-up  
9 of devices implanted in the United States. How do you  
10 propose you're going to do that if you haven't even  
11 done that for your 2000 cases in Europe?

12 MR. NILSON: I would like to add that no  
13 information has been collected or reported that  
14 contradicts any of the conclusions that was made from  
15 the U.S. clinical studies. And we have proposed a  
16 post-market study that will include up to 350 patients  
17 in the U.S. that will have long-term follow-up past  
18 two years.

19 DR. KATO: Okay. But yet you have not  
20 done that for the other 2000 cases in Europe?

21 MR. NILSON: We have limited registry  
22 studies and there are some standard EUROSTAR national

1 registries in Europe that our device has been a part  
2 of, but those are voluntary registries that the  
3 physician decides to contribute the data to.

4 DR. KATO: Do you know how many cases have  
5 been reported to the registry in Europe?

6 MR. NILSON: I believe it's around the  
7 number of 300.

8 DR. KATO: 300. Do you know that for a  
9 fact or is that just a guess?

10 MR. NILSON: I have the information  
11 available, just not in front of me. There is a  
12 combination of registry studies. We did, in fact,  
13 start our own registry study with -- last March and  
14 there is, approximately, 114 patients enrolled in that  
15 registry study. The EUROSTAR registry has 199  
16 thoracic patients. I will have to qualify, but that  
17 is a combination of all commercially available  
18 thoracic devices in Europe, of which there are  
19 approximately seven, and that is a variable depending  
20 on which country you are referring to.

21 DR. KATO: Okay. The FDA mentioned that  
22 you wanted this done as an expedited PMA and,

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1 therefore, you didn't have time to produce additional  
2 data. Can you give me the rationale behind that,  
3 please?

4 MR. NILSON: The data that we are asking  
5 for approval on, again, is the primary endpoint of the  
6 99-01 Study, which is the one-year follow-up. We do  
7 have three-year data available on those patients in  
8 the U.S. That is the control clinical study that we  
9 are asking for approval. The confirmatory study again  
10 was done to ensure that the deployment characteristics  
11 of the modified device were not adversely impacted by  
12 its modification.

13 DR. KATO: Okay. Thank you.

14 MR. NILSON: Would you show the slide,  
15 please?

16 DR. KATO: All right.

17 MR. NILSON: This is a Kaplan-Meier  
18 freedom from major adverse events through three years  
19 in our pivotal 99-01 Study. I will have to qualify  
20 that this three-year data is relatively recent and has  
21 just come to our attention.

22 ACTING CHAIR MAISEL: Any additional

1 questions?

2 DR. KATO: No, thank you.

3 ACTING CHAIR MAISEL: Okay. Dr. Somberg?

4 DR. SOMBERG: I'll just make a very brief  
5 comment. First is, I agree with you Dr. Kato about  
6 the inclusion/exclusion criteria is very important for  
7 labeling and I hope we keep that under consideration  
8 as time progresses today in other deliberations.  
9 Number one is once again referring back, this is to  
10 the sponsor, but referring back to the FDA's comments  
11 in the briefing on page 10 where they point to  
12 differences in the TAG 1 Pivotal Trial and between the  
13 control and the treatment and the device group, and  
14 they point to differences in Class II, III and also  
15 symptomatology.

16 And I just wondered, because of everything  
17 we have heard about all the multiple endpoint,  
18 etcetera, I look towards mortality as being a, you  
19 know, very hard and very important thing to look at.  
20 Was an adjustment attempted to be made there for these  
21 differences that have been pointed out, in which I  
22 believe the sponsor was aware of as well?

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1 MR. NILSON: Dr. Makaroun can comment on  
2 that.

3 DR. MAKAROUN: Let me make sure I  
4 understand the question correctly. Are you asking  
5 about the numbers or whether there was an adjustment  
6 made?

7 DR. SOMBERG: A statistical adjustment.  
8 Well, you can't change the numbers.

9 DR. MAKAROUN: Right.

10 DR. SOMBERG: The numbers are the way they  
11 are. But since the two groups are not necessarily  
12 comparable with two key movers of the mortality issue,  
13 one could attempt to make an adjustment. Now, they  
14 pointed out there is also a lot of missing data there,  
15 so it may be very difficult to do that. But I just  
16 wondered if any attempt was made. I thought maybe a  
17 statistical person would be better at answering this  
18 than an expert clinician.

19 DR. MAKAROUN: Well, I don't believe there  
20 was any statistical attempt made to correct the  
21 mortality. Was there? No.

22 DR. SOMBERG: Okay.

1 DR. MAKAROUN: But maybe it's not bad for  
2 me to interject here and say that we don't believe the  
3 two groups are not comfortable. Those two groups have  
4 been assessed with all known variables that we know of  
5 that affect the outcomes of interventions and surgery.  
6 And except for the New York Heart Association  
7 classification and the symptomatic aneurysms at  
8 baseline, there was really no other difference.

9 And in the specific risk classification,  
10 which we used typically in most procedures, which is  
11 the ASA classification and the SVS risk scores, those  
12 two are very comparable in terms of the risk that will  
13 predict the major adverse events. And the only other  
14 parameter that is known from other studies and from  
15 this study through the Cox Regression Model to affect  
16 outcomes, which the size of the aneurysm was  
17 essentially identical between the two groups.

18 DR. SOMBERG: Okay. And the other  
19 question I had, I actually have two more. To be  
20 quick, my review of the mortality data, which is the  
21 ones you included in narrative-design, there was a CVA  
22 difference, 2 to 1, for -- with an increment in the

1 device group. And while I don't know if I have all  
2 the data and I'm not going to say I'm making a  
3 secondary study here or not, has that been looked  
4 into? Is this correct?

5 Because I just counted the number of cases  
6 where CVA is noted in a mortality case and the  
7 narrative section went through each and every case.  
8 And there was a 2 to 1. Am I doing something wrong or  
9 is that correct? I didn't note it noted other places.

10 MR. NILSON: Dr. Makaroun?

11 DR. MAKAROUN: By our count, the incidence  
12 is 4 percent through one year through 30 days in both  
13 groups and 5 versus 7 percent at one year.

14 DR. SOMBERG: But that's overall CVA.

15 DR. MAKAROUN: Right.

16 DR. SOMBERG: I'm talking about if you had  
17 a mortality and there was a CVA in those patients.

18 DR. MAKAROUN: Oh.

19 DR. SOMBERG: Which I couldn't tell you if  
20 it contributed to the mortality or not, but I'm  
21 talking about in the narrative. You know, it would  
22 say in the bottom death and it's treatment versus

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1 control and then you would see CVA mentioned.

2 DR. MAKAROUN: I see exactly what you  
3 mean. You're talking about the cause of mortality  
4 that's listed at the bottom of the narrative. This  
5 usually was taken from the --

6 DR. SOMBERG: No, I'm saying the  
7 mortality. It was a mortality.

8 DR. MAKAROUN: Correct.

9 DR. SOMBERG: Is treatment versus control  
10 and then in the narrative you would see CVA mentioned.  
11 I mean, you know, we all know that, you know, you  
12 never can say causal relationship. But I'm just  
13 saying it struck me as there was a lot of CVAs and  
14 then when I counted them up, there were more in a 2 to  
15 1 fashion mentioned in the treatment group versus the  
16 control group.

17 DR. MAKAROUN: There were five strokes in  
18 the treatment group. One of them was fatal in the  
19 perioperative period and that accounts for one of the  
20 two deaths that occurred in the first 30 days. The  
21 other strokes occurred later on and are unrelated to  
22 the periprocedural period. And it's difficult to

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1 attribute exactly the sequence of events that start  
2 from CVA to death and attribute the exact cause of  
3 death into one item versus the other, since some of  
4 these patients have multiple complications. But one  
5 of the death in the treatment group in the first 30  
6 days was due to complications of stroke.

7 DR. SOMBERG: Okay. My last question was  
8 concomitant therapy. And this is something I'm always  
9 very interested in. But I didn't notice anything  
10 mentioned about the use of anticoagulants, the use of  
11 antiplatelet drugs, etcetera. There people have  
12 coronary disease. At some points in the course of use  
13 of the device it may be beneficial and other times it  
14 may be very deadly. Has that been looked at in any  
15 way? Let's say if it is approved, how are we going to  
16 handle this in the labeling?

17 DR. MAKAROUN: This was not mandated by  
18 the protocol. It was left to the particular sites to  
19 make their own practices, both for anticoagulation and  
20 for antiplatelet therapy. I'm not aware that we  
21 performed a particular data analysis or a subgroup  
22 analysis backward into investigating the effects of

1 those on the outcomes. All patients were  
2 anticoagulated during the procedure. The vast  
3 majority anticoagulated during the procedure. I am  
4 not aware of an analysis done for the antiplatelet  
5 regimen.

6 DR. SOMBERG: But I would just hope then  
7 at some point someone would try to harvest that data,  
8 because it's important in this day and age. I mean,  
9 two issues. What about the use of Coumadin in these  
10 patients? What about the use of Plavix in these  
11 patients?

12 MR. NILSON: The sponsor is committed to  
13 working with the Agency to ensure appropriate labeling  
14 is indicated on the device.

15 ACTING CHAIR MAISEL: Dr. Bridges?

16 DR. BRIDGES: I have a question addressed  
17 to the FDA. This has to do with the design of the  
18 confirmatory study. In one of your slides you stated  
19 that the rationale for the 30 day confirmatory study  
20 of the modified device design was that "Risk analysis  
21 demonstrated that only device delivery and not long-  
22 term efficacy would be affected by the modifications."

1 I was wondering if you could elaborate on what you  
2 mean precisely by risk analysis? And then I have a  
3 follow-up question for the sponsor.

4 MS. ABEL: Terry, do you want to take it?  
5 Terry Woods, Dr. Terry Woods was our engineer reviewer  
6 on this application, and she has been involved in the  
7 evaluation of the majority of these devices over time  
8 and was involved in this decision, so I think I'll  
9 turn it over to her.

10 DR. WOODS: The company did an FMEA,  
11 Failure Mode and Effect Analysis, to determine what  
12 they felt the possible failure modes were that could  
13 have been produced by the removal of the longitudinal  
14 wire. And after doing that analysis, they came up  
15 with a list of the bench tests that they thought would  
16 address that and these effects were only seen during  
17 the deployment in the first 30 days after deployment.  
18 So that was felt that their analysis addressed  
19 adequately the issues that were affected by the  
20 changes in the device.

21 DR. BRIDGES: Yes, I mean, this is just  
22 kind of a -- were you going to say something?

1 MS. ABEL: Yes.

2 DR. BRIDGES: Go ahead.

3 MS. ABEL: I just wanted to say that when  
4 they do the Failure Mode and Effects Analysis, they  
5 look at the various components of the device and what  
6 they contribute to the function of the device. So,  
7 for example, if you would modify the ends of the  
8 graft, which are the portions that are keeping the  
9 device in place, you would assume that there could be  
10 effect on migration over time, endoleak. You know,  
11 you look at what each part of the graft is intended to  
12 do and then you figure out if you change that part,  
13 obviously, what it could have an affect on.

14 And the reason that the deployment wire  
15 was there was to make sure that, because you say the  
16 way that the device is deployed, it springs open from  
17 the middle going to the ends. And so if you didn't  
18 have that stiffness there, there is the potential that  
19 it could end up within the aneurysm, because you need  
20 to make sure that it stays along the catheter length  
21 while it is deploying. So you need to then if you  
22 remove that wire, figure out whether you have managed

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1 to continue to do that.

2 After deployment, there is no effect of  
3 that wire and that was further demonstrated by the  
4 fact that when the wire broke in 40 some patients, we  
5 didn't see migrations associate with that, so the wire  
6 wasn't holding the device in place. It wasn't doing  
7 anything else in terms of contributing to the function  
8 of the graft. So that's the sort of thing that we  
9 looked at.

10 DR. BRIDGES: Yes, just as a general -- I  
11 mean, obviously, this comes up with devices. I mean,  
12 people modify them and you can't do, you know, a full  
13 blown clinical study for every modification. So is  
14 this a process that occurs? I mean, there is  
15 obviously a well-established precedent for this  
16 approach of doing a risk, what do you call it here, a  
17 risk analysis.

18 MS. ABEL: Risk analysis.

19 DR. BRIDGES: And then determining what  
20 you need to study to determine whether a device can be  
21 approved with a limited amount of clinical data.  
22 Because a number of the questions that have been asked

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1 here relate to the confirmatory study and concerns  
2 about the size, the relatively small size, the  
3 relatively short follow-up, the applicability of this  
4 other control group, which is historically removed  
5 from this more recent study.

6 Can you just give us some very brief  
7 insight on what the FDA's approach to this issue is in  
8 general?

9 MS. ABEL: It looks like Bram wants to do  
10 it, but I was going to say that it certainly is  
11 something that we do all the time. After a device is  
12 approved through a PMA process, I can't remember the  
13 time frame before the first supplement arrives to  
14 introduce the modified device. I mean, it's very  
15 common. These devices like, say, go through iterative  
16 development over time. And for each of the  
17 modifications, we do this sort of assessment.

18 So, for example, if the delivery catheter  
19 is modified for a stent, we look at do we need  
20 clinical data at all or, you know, are you able to  
21 evaluate the modifications on the benchtop? And we do  
22 that again through an evaluation of the potential

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1 changes to the product and their effect on  
2 performance. But, Bram, did you want to say  
3 something?

4 DR. ZUCKERMAN: Yes, thank you, Dorothy.  
5 I would like to make a few general comments in reply  
6 to Dr. Bridges' excellent question. Dr. Bridges, I  
7 think you have hit upon the heart of the device  
8 paradigm, you know.

9 DR. BRIDGES: No pun intended.

10 DR. ZUCKERMAN: Excuse me?

11 DR. BRIDGES: Nothing. I'm sorry.

12 DR. ZUCKERMAN: But you're a heart  
13 surgeon, so you did a good job. You know, I think  
14 it's, obvious, that we try to extrapolate as many of  
15 the good clinical trial principles from drug  
16 development over the last 50 years to this device  
17 clinical trials arena. But there are certain  
18 differences, as you've noted. The total product  
19 lifecycle is much shorter. The ability to work with  
20 very fine engineers is available. Sometimes we do  
21 understand mechanisms of action.

22 And here is an example where the Agency

1 and sponsor try to utilize what are called "least  
2 burdensome principles," where the process involves  
3 both an engineering analysis and clinical analysis,  
4 and this is not unusual, because the least burdensome  
5 paradigm is part of the way that the device center  
6 operates.

7 DR. BRIDGES: One other quick question  
8 along that line. One of the modifications of the  
9 device did include strengthening the graft material by  
10 adding stronger, less permeable PTFE material. And I  
11 was wondering if perhaps the sponsor could comment on,  
12 you know, obviously, in your initial device you  
13 decided what the porosity was going to be. In the  
14 modified device you strengthened it by decreasing the  
15 porosity. There must be some consequences, some  
16 engineering consequences.

17 One would think that that might alter the  
18 hemodynamics of the endoleaks which can occur on the  
19 basis of porosity. I mean, it would seem that less  
20 porosity is a good idea anyway if we think that some  
21 endoleaks come from lower porosity. Is there any  
22 downside to that? And what was the thinking that led

1 to those, the engineering considerations initially and  
2 then in the modified design?

3 MR. NILSON: Lou Smith will answer that  
4 question.

5 MR. SMITH: Hello, my name is Lou Smith.  
6 I'm working with W.L. Gore and Associates. In the  
7 developing of the thoracic graft, in the beginning we  
8 chose a graft material that had 20 to 25 years of  
9 experience in use in normal vascular grafting, its  
10 strength and porosity, and that is part of what was  
11 incorporated into the original design. In developing  
12 the modifications through the process of the risk  
13 assessment that was described to you by the FDA, we  
14 determined that in order to strengthen and stiffen the  
15 graft, that an additional layer of ePTFE film would be  
16 appropriate.

17 To do that it had to reduce permeability.  
18 What that can lead to is a reduction in any transmural  
19 fluid leakage that may pass through the wall, which is  
20 a known complication in some vascular grafts as well,  
21 normal surgical vascular grafts. To address your  
22 specific question about endoleaks, our device, the

1 original and modified, were using a material that  
2 would not normally leak blood under normal  
3 physiological conditions, hold blood.

4 So we don't experience in our particular  
5 graft design any endoleaks associated with overall  
6 porosity and they were listed in the presentation as  
7 Type IV endoleaks. Those are generally more seen by  
8 grafts made out of textile type components. So our  
9 expectation is that there would be minimal if non-  
10 deleterious effects by reducing the permeability and  
11 an added advantage of reducing any transmural fluid  
12 leakage across the wall.

13 In addition, some of the testing showed  
14 that with that stronger material we were able to  
15 actually have a more conformable, uniformly  
16 conformable graft as opposed to the device that had  
17 the longitudinal spines in it, which somewhat is  
18 conformable in one orientation, but not in the other.  
19 So to summarize, we wouldn't expect any deleterious  
20 effects from reduction of permeability. We expect the  
21 advantage of reducing any potential transmural fluid  
22 leakage.

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1 In terms of histology, we did study it in  
2 animals. We saw no real significant difference  
3 between the two types of materials. The explants that  
4 we have looked at have shown us very little graft  
5 healing. It's known in the literature that stent  
6 grafts don't necessarily heal like conventional  
7 vascular grafts do. We see some tissue deposit at the  
8 entrance and exit sites of the graft. But, in  
9 general, histological reaction is minimal.

10 DR. BRIDGES: Thank you.

11 ACTING CHAIR MAISEL: Dr. Nicholas?

12 DR. NICHOLAS: Thank you. I have two  
13 comments that were questions, but Dr. Yancy has  
14 covered them very well. And that's this issue of the  
15 control group, which really has, I think we've all  
16 discussed now, major shortcomings in terms of the  
17 heart association classifications, the symptomatic  
18 patients, the temporal relationship of when the  
19 entered, the fact that they were rejected as potential  
20 candidates for the TAG graft.

21 In addition to which, this issue of major  
22 adverse events really seem to be, in some cases, part

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1 and parcel of open surgery. 24 hours on a ventilator  
2 is classified as a major adverse event and called  
3 respiratory failure. Whereas, I consider that a  
4 pretty good post-op course if it was limited to that.  
5 And the same for creatinine of going up 30 percent,  
6 which we take that from 2 to 2.6, that's again a  
7 question of is that a major or a not so major adverse  
8 event?

9 The second comment I have is related to  
10 the 03 Study and the duration. I'm reassured by the  
11 comments of the FDA regarding the structural analysis  
12 and the risk, but the fact remains that although 75  
13 percent of the major adverse events occurred in the  
14 first 30 days, 28 percent of them occurred between day  
15 31 and day 365 and another 14 percent in the 366<sup>th</sup> day  
16 to the 730<sup>th</sup> day. So are we looking at a progression  
17 or is this really going to level off as your last  
18 Kaplan-Meier suggested?

19 So any comments on either of those two  
20 issues? Because I have one more then after that.

21 MR. NILSON: Dr. Makaroun will speak to  
22 those.

1 DR. FERGUSON: Yes, I think one of the  
2 clarification points were that those events that  
3 you're talking about really want to focus on the  
4 device-related events, as opposed to the major adverse  
5 events and those leveled off.

6 DR. NICHOLAS: They did? Okay. Thank  
7 you.

8 DR. MAKAROUN: Let me start with the last  
9 question, I guess, first, which is the device-related  
10 events. I think you may have gotten already an answer  
11 to it.

12 DR. NICHOLAS: Yes.

13 DR. MAKAROUN: If you want me to show you  
14 the --

15 DR. NICHOLAS: That's fine.

16 DR. MAKAROUN: There are really no major  
17 device-related events after the first six months.

18 DR. NICHOLAS: Okay.

19 DR. MAKAROUN: And they remain completely  
20 flat through two years.

21 DR. NICHOLAS: And you, as an  
22 investigator, are comfortable that between day 30 and

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1 the six month interval, the newly designed graft will  
2 meet those expectations?

3 DR. MAKAROUN: I'm very comfortable that  
4 this device will meet the expectations of the previous  
5 device.

6 DR. NICHOLAS: Okay.

7 DR. MAKAROUN: Now, which other item do  
8 you want me to address?

9 DR. NICHOLAS: Nothing, the control group.  
10 I think that the control --

11 DR. MAKAROUN: Do you want me to address  
12 the New York Heart since this seems to be coming up  
13 several times?

14 DR. NICHOLAS: Sure.

15 DR. MAKAROUN: I did mention during my  
16 presentation, and maybe it has not been made again  
17 entirely clear, that we use the New York Heart  
18 classification on the CRFs, specifically to exclude  
19 patients who are in Class IV, because that we  
20 predetermined as an exclusion criteria from the study.

21 DR. NICHOLAS: Okay.

22 DR. MAKAROUN: There is no missing data.

1 There has been a lot of confusion about the large  
2 number of so-called missing data in the New York  
3 Heart. They are not missing in the New York Heart.  
4 There was a choice on the CRF as nonapplicable, and we  
5 believe that a lot of these patients may not have had  
6 heart disease or may not have been considered to have  
7 congestive heart failure for which the New York Heart  
8 Association classification would be appropriate, and  
9 the nonapplicable box could have been checked.

10 Please, show us the slide, if you don't  
11 mind. In addition to this, the rate of major adverse  
12 events as it happened during the study does not seem  
13 to have prejudiced the results against the surgical  
14 control. Although the numbers are small and it's very  
15 hard to derive any conclusions, the rate of major  
16 adverse events in the higher classifications of the  
17 New York Heart in the surgical control group are  
18 actually lower than they were in the lower  
19 classifications. So we do not believe that this  
20 resulted in any bias against the surgical group.

21 ACTING CHAIR MAISEL: Okay. Thank you.  
22 Dr. Nicholas, did you have any additional?

1 DR. NICHOLAS: Yes, I do. This is an  
2 observation from the data. Your inclusion criteria  
3 indicate that you require a 2 centimeter proximal neck  
4 and 2 centimeter distal neck. The data on Table 14,  
5 page 50, indicates that the average length of a  
6 proximal neck was 6.3 and the 25<sup>th</sup> percentile was 3  
7 centimeters. The distal neck average was 8  
8 centimeters and the 25<sup>th</sup> percentile was 3.7. Yet, in  
9 your inclusion you were down at 2 centimeters and in  
10 your labeling, you're recommending the device for a  
11 neck of 2 centimeters.

12 Are you comfortable that this is going to  
13 seat and seal at 2 centimeters? There is no data in  
14 the tables that indicates 2 centimeters works.

15 DR. MAKAROUN: The longer numbers you are  
16 referring to are the length of actual neck to the  
17 neck's vessel, so this is not what was necessarily  
18 actually used to cover during the procedure. There  
19 were several patients that had 2 centimeter ceiling  
20 zone beyond the subclavian or above the celiac, and  
21 there was no association between the device-related  
22 events and the length of the neck that was covered.

1            Obviously, when more neck is available, we  
2            did tend to securely place it a little bit more than  
3            2 centimeter, but 2 centimeter was enough to enter the  
4            patient into the trial and there were several patients  
5            who did have it with 2 centimeter.

6            DR. NICHOLAS: That was my next question.  
7            Were there patients who had, indeed, a 2 centimeter  
8            neck, because they are not listed? Your minimum neck  
9            length -- well, the 25<sup>th</sup> percentile was 3,  
10           approximately, and 3.7 distally.

11           DR. MAKAROUN: This is the 25<sup>th</sup> percentile  
12           of the anatomic measurement from the end of the  
13           aneurysm to the neck's vessel. This is not the 25<sup>th</sup>  
14           percentile of what was actually covered.

15           DR. NICHOLAS: Of what was available.

16           DR. MAKAROUN: Exactly. We don't  
17           necessarily always go and cover all the neck that is  
18           available.

19           DR. NICHOLAS: Okay.

20           ACTING CHAIR MAISEL: Okay. Dr. Krucoff?

21           DR. KRUCOFF: Just a clarification  
22           question to start. Dr. Mitchell mentioned that your

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1 CEC was blinded. Can you help me understand how your  
2 CEC was blinded?

3 DR. MITCHELL: To the extent possible, and  
4 clearly that has some obvious limitations, but when we  
5 reviewed events, patients, treatment arm and sites  
6 were kept blinded to the extent possible. There were  
7 obviously some variables that were quite obvious for  
8 stent versus control groups.

9 DR. KRUCOFF: I would assume to adjudicate  
10 almost any major adverse event that knowing whether or  
11 not a patient had an operation was -- did you try and  
12 bind them to the actual procedure of origin?

13 DR. MITCHELL: Yes. They all had an  
14 operation or a procedure, depending on how you want to  
15 consider it, and if the patient had a stroke, then  
16 there might not be any other defining variables, which  
17 would unblind that situation.

18 DR. KRUCOFF: So they were just going for  
19 a CT scan or whatever?

20 DR. MITCHELL: Obviously, many things  
21 precluded that blinding.

22 DR. KRUCOFF: Okay.

1 DR. MITCHELL: But to the extent possible,  
2 we tried to keep the committee blinded.

3 DR. KRUCOFF: Thank you. I also would  
4 just like to make sure that I understand the timing of  
5 follow-up as we have got, at least what I think is,  
6 two different versions. The definitive timing of  
7 follow-up was 24 hours after the procedure, begins 24  
8 hours after the procedure?

9 MR. NILSON: The follow-up was treatment  
10 plus one day, yes.

11 DR. KRUCOFF: So we still must know were  
12 there any deaths before 24 hours in the TAG group that  
13 do not appear in these data or strokes or other major  
14 events that are before that 24<sup>th</sup> hour?

15 MR. NILSON: Could you clarify the  
16 question? Was there deaths and major adverse events  
17 or both?

18 DR. KRUCOFF: Either/or.

19 MR. NILSON: Either/or. Dr. Verter will  
20 respond to that comment.

21 DR. VERTER: I just want to clarify the  
22 first question you asked. When we did the time to

1 major adverse events analysis, day zero was the day of  
2 the procedure. So patients who had an event on day  
3 zero were counted.

4 DR. KRUCOFF: For the time axis?

5 DR. VERTER: Yes.

6 DR. KRUCOFF: Great. Okay. So that  
7 helps, but it doesn't help me if a patient had a  
8 procedure and 10 hours later died.

9 DR. VERTER: He was counted.

10 DR. KRUCOFF: It was captured?

11 DR. VERTER: Yes.

12 DR. KRUCOFF: Okay. Because to me,  
13 follow-up begins when follow-up begins and to say that  
14 follow-up begins 24 hours after the procedure to me  
15 would imply that if somebody died before 24 hours,  
16 that that's not in their follow-up.

17 DR. VERTER: No.

18 DR. KRUCOFF: So is that --

19 DR. VERTER: They were captured.

20 DR. KRUCOFF: That's captured. Okay.  
21 Because obviously, your vascular complications, I  
22 assume, come from the angiographic images during the

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1 procedure.

2 MR. NILSON: Yes.

3 DR. KRUCOFF: And by and large, so the  
4 information that we have been reviewing is -- I will  
5 say this as a statement but, please, correct this if  
6 this is wrong. My understanding is that the  
7 information for complications that we have been  
8 looking at all day long would include from the time a  
9 procedure was done. Is that --

10 MR. NILSON: All adverse events were  
11 captured from the time the procedure started until the  
12 latest follow-up period.

13 DR. KRUCOFF: Great.

14 DR. NILSON: And the patient you are  
15 referring to, who would die within 24 hours, would be  
16 considered an aneurysm-related death.

17 DR. KRUCOFF: So a device-related death?

18 MR. NILSON: Yes.

19 DR. KRUCOFF: Okay. Thank you. To me,  
20 out of all the comments, which are many, about the  
21 control group and obviously the different ways of  
22 viewing the comparability versus the potential

1 difference between the control group and the treatment  
2 group, to me the key missing link is still anatomy.

3 So I actually wonder, to the physicians  
4 who have used this thing, what do you guys consider  
5 your most important? Of all the imaging techniques  
6 available, which one really gives you the most  
7 information? I realize you use them in combination,  
8 but can you tell me when you approach these folks,  
9 which one piece of imaging information gives you the  
10 most information about whether this is a TAG kind of  
11 case or not?

12 MR. NILSON: Dr. Makaroun?

13 DR. MAKAROUN: The simplest way to answer  
14 this is a very good CT scan. The average CT scan that  
15 is obtained with reconstructions at the standard level  
16 of 5 to 7 millimeters will not be adequate to evaluate  
17 this. This is probably the test that gives you the  
18 most information about the quality of the neck and the  
19 diameters that you need for measurement.

20 However, for the length, it may not be  
21 very adequate and you may have a very hard time  
22 because of the curvatures to estimate the tortuosity.

1 So what modern day practice is we do a very fine 2 or  
2 2.5 millimeter reconstructions and do a 3-D  
3 reconstruction that you can evaluate for both  
4 angulations, tortuosity, presence of calcification and  
5 a variety of other parameters that are necessary to  
6 evaluate the patient for a TAG.

7 DR. KRUCOFF: Thank you. And along those  
8 lines, I'm also going to -- well, I'll leave it to you  
9 to decide who, but just from a clinical point of view,  
10 is it fair to actually say that it has no clinical  
11 prognostic impact as to whether there is a neck  
12 between the head and neck vessels and the proximal end  
13 of the aneurysm or whether the aneurysm is longer or  
14 larger than would qualify for this study or can you  
15 guys really say to me that the anatomic range outside  
16 of what is appropriate for TAG deployment has zero  
17 influence of prognosis?

18 MR. NILSON: Dr. Mitchell?

19 DR. MITCHELL: I don't think we're saying  
20 that. I think that for both the TAG surgical and the  
21 control group, proximity, involvement proximal to the  
22 subclavian does incur a higher risk of stroke both for

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1 the TAG device and for a surgical patient.

2 DR. KRUCOFF: Okay. I'm sorry, not  
3 proximal, because proximal and subclavian was excluded  
4 from the control group, as well, was it not?

5 DR. MITCHELL: No. The device could go up  
6 to the carotid.

7 DR. KRUCOFF: I'm just trying to  
8 understand of the patients who are included in these  
9 analyses, so we have the control group, which in part  
10 is made of patients who you couldn't put a TAG into.

11 DR. MITCHELL: No, not all the patients.  
12 It's an important point. Not all the patients who are  
13 in the control were not eligible for the TAG.

14 DR. KRUCOFF: Okay. All the concomitant  
15 patients?

16 DR. MITCHELL: Not even all the  
17 concomitants. Some of that was by patient election,  
18 so some patients chose not to have a stent graft  
19 placed.

20 DR. KRUCOFF: Okay. So some of the  
21 concomitant control population were patients who  
22 anatomically were not suitable for TAG?

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1 DR. MITCHELL: Yes, that's fair.

2 DR. KRUCOFF: Is that fair?

3 DR. MITCHELL: Yes.

4 DR. KRUCOFF: Okay. So in that patient  
5 group, what I'm asking is anatomically, does that have  
6 any prognostic implications from your clinical  
7 experience?

8 DR. MITCHELL: Correct me if I'm wrong,  
9 Dr. Verter.

10 DR. KRUCOFF: Works for better outcomes.

11 DR. MITCHELL: But our process did not  
12 show proximity to the subclavian as an independent  
13 risk factor. I would say, however, that in our  
14 Stanford series that that proximity did confer an  
15 increased risk of stroke.

16 DR. KRUCOFF: Right. Okay. Now, my  
17 understanding from my clarification question this  
18 morning was that, in fact, we don't have the numbers,  
19 which means you don't have the numbers as to actually  
20 in the concomitant control group, some of whom are  
21 patients who are anatomically unsuitable for TAG, that  
22 we actually know how many there are.

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1           And my understanding is also that in the  
2           retrospective control group that was derived from the  
3           time prior to the beginning of the study backwards in  
4           time, that we also don't know how many of them would  
5           have been anatomically potentially suitable for the  
6           TAG if the study had been running at that time. Now,  
7           is that wrong? Do we actually have those numbers?

8           DR. MITCHELL: I don't believe we have  
9           those numbers. You are correct.

10          DR. KRUCOFF: Okay. Was any kind of core  
11          laboratory used for imaging analysis of CAT scans,  
12          angiograms? As you look at migration, we're recording  
13          a lot of vascular complications. Can you help me  
14          understand how many of these descriptors and/or  
15          endpoints were independently generated from a core  
16          laboratory or are these, basically, site readings?

17          MR. NILSON: We did have a core lab for  
18          both the 99-01 Study and the 03-03 Study, and did use  
19          the site data as the primary analysis. Dr. Matsumura  
20          can comment on any. Do you have any specific  
21          questions regarding the core lab?

22          DR. KRUCOFF: I would love to know whether

1 you had concordance or discordance with the core lab.  
2 I would love to know if there are core laboratories  
3 measurements, in what fraction of deployments the  
4 sizing of the device was appropriate or inappropriate.  
5 I'm going to stop there.

6 DR. MATSUMURA: Sure. Thank you. I'm  
7 John Matsumura and contrary to my previous  
8 introduction, I'm not a professor of surgery. I am an  
9 Associate Professor in North Western and I do have  
10 research and consulting arrangements with the sponsor  
11 and several research arrangements with other sponsors  
12 who make thoracic devices.

13 One of my roles here was the core lab  
14 director, and so I can comment on questions related to  
15 that. Your specific question, if I recall, the first  
16 one was correlation.

17 DR. KRUCOFF: I'm sorry, can you tell me  
18 what kind of core lab?

19 DR. MATSUMURA: Oh, okay.

20 DR. KRUCOFF: Is this CT scan?

21 DR. MATSUMURA: Yes, the imaging core lab.

22 The purpose was to do independent over-read of CT and

1 chest X-ray images that were performed post-procedure  
2 on the test group. So we received the images from  
3 sites and in the Panel pack there is an indicator of  
4 the precise numbers we did for each of those levels,  
5 and it was over 90 percent of those that were read by  
6 the site.

7 You asked about correlation between the  
8 two and I would reference you to page 77 in the Panel  
9 pack, Table 31. The biggest difference, in my mind,  
10 and you can ask further questions if you would like,  
11 is that in endoleak where the sites identified a total  
12 of 22 endoleaks in the first year and the core lab  
13 identified 12 in the scans that we received.

14 And if you think first about the major  
15 endoleaks, there were four that have been mentioned,  
16 again, in the first year. There was 100 percent  
17 concordance in those. We identified all four of those  
18 endoleaks that the sites felt needed to be intervened.  
19 There were an additional 14 that were identified by  
20 the sites that were not identified by the core lab, so  
21 I'll try to walk you through this.

22 There were eight that we agreed on, four

1 were the majors. The 14 that we did not agree on were  
2 all minors. Of those 14, 12 of the endoleaks were  
3 identified or diagnosed by the site on day zero or  
4 one, the day of the procedure, I didn't read the  
5 sites, so I don't know how, I presume that's on the  
6 angiogram done during the procedure. 12 of those 14  
7 were no longer present when we received the CT image  
8 from the site.

9 So I think the vast majority of that lack  
10 of concordance is the fact that we did not review  
11 imaging that the site had available. The other two,  
12 I stand by my reads. I think they did not have  
13 endoleaks. The sites did. All I can tell you about  
14 that is that the size of those aneurysms did not  
15 enlarge. In fact, one of them decreased over the next  
16 three years by 9 millimeters. They haven't performed  
17 any intervention. I don't know why they read them as  
18 endoleak, but I don't think there is one there.

19 DR. KRUCOFF: Okay. So thanks. I think  
20 you answered one of my key questions, which is that,  
21 did I hear you right, every single vascular post-  
22 procedural observation that was acted on, that was

1 treated further, was concordantly read?

2 DR. MATSUMURA: Yes.

3 DR. KRUCOFF: Between the core lab and the  
4 site?

5 DR. MATSUMURA: Yes.

6 DR. KRUCOFF: Okay.

7 DR. MATSUMURA: All four that were -- and  
8 if I can just follow-up on your question before in the  
9 morning. You asked if an endoleak was categorized as  
10 minor and later had an intervention, how is it  
11 treated. In fact, that was referenced all the way  
12 back to its initial diagnosis and changed to major.  
13 So there is actually one case of that.

14 DR. KRUCOFF: Okay. And you guys don't  
15 look at angiograms?

16 DR. MATSUMURA: No, we did not.

17 DR. KRUCOFF: Thank you. Was there an  
18 angiographic core lab?

19 DR. MATSUMURA: No, we did not review  
20 angiograms.

21 DR. KRUCOFF: The definition of vascular  
22 complications that have been mentioned a number of

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1 times, higher in this group, it's a vascular  
2 procedure, and did that come from your core lab?

3 DR. MATSUMURA: No, the vascular  
4 complications is a site-determined or a clinical event  
5 that they recorded. We did record extrusion, erosion,  
6 rupture, prosthesis material fatigue and those are in  
7 this table, I've sent you, it's on page 77.

8 DR. KRUCOFF: Okay. Thanks. Well,  
9 obviously, there is not going to be data, but I would  
10 encourage the sponsor. One thing for the size French  
11 and insertion of this device and range of even  
12 remediable vascular complications associated with it,  
13 I would sure hope that you would gather these  
14 angiograms and try and systematically give  
15 interventionalists, surgical, etcetera, some clues  
16 about what to look out for or some characterization  
17 and some possible predictors of what would predict  
18 trauma when you use the device.

19 Okay. Let me quickly try and wrap up  
20 here. Endoleaks. Non-progressive endoleaks. What  
21 does a patient get told? Does the patient get told to  
22 take it easy, normal activity? What do you guys tell

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1 the patient when a small endoleak is observed?

2 MR. NILSON: Dr. Makaroun?

3 DR. MAKAROUN: I guess what we have done  
4 is extrapolate the knowledge that has been acquired in  
5 the abdominal aorta and try to apply it to the  
6 thoracic aorta since, obviously, we do not have as  
7 much clinical knowledge in the thoracic aorta.

8 What we have learned over the last eight  
9 to nine years of experience with the abdominal aorta  
10 is our initial level of concern about the endoleaks  
11 may not be warranted in all types of endoleaks. It  
12 may be warranted in Type I and Type III endoleaks,  
13 which by and large usually we try to address, while  
14 the Type II endoleak or the indeterminate endoleak,  
15 especially if they are associated with a stable  
16 aneurysm or a shrinking aneurysm, seem to behave in a  
17 very benign fashion over a prolonged period of time.

18 We try to provide this information to the  
19 patient and indicate that the type of endoleak that  
20 they have seems to behave in a rather benign fashion  
21 over time and does not affect the risk of rupture.  
22 There are very, very few ruptures reported in the

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1 literature of a prolonged period of time in patients  
2 with Type II endoleaks and a stable aneurysm.

3 DR. KRUCOFF: So I'm sorry, do you  
4 restrict their activity for a period of time? Is that  
5 what you do?

6 DR. MAKAROUN: No, there is absolutely no  
7 indication --

8 DR. KRUCOFF: No restriction?

9 DR. MAKAROUN: -- that the activity level  
10 is related to the worsening of the endoleak.

11 DR. KRUCOFF: Okay. We heard one  
12 testimony before the formal presentations today on the  
13 potential impact on a human being's quality of life  
14 from an individual who, I guess, had been through  
15 this, and I think the spirit of an opportunity to not  
16 get sliced in the sternum and go through the surgical  
17 version of repairing these things has been made very  
18 clear.

19 And I know this is looking backwards, but  
20 it would have helped me a lot to have some quality of  
21 life or other data to really help understand how much  
22 of an impact, in addition to all of the fuzziness that

1 we have to do deal with with non-randomized trials,  
2 this device is capable of and if future work is done  
3 in this area, I would certainly encourage you. That  
4 ought to be a slam dunk in terms of really helping  
5 quantify the qualitative impact on people's lives of  
6 the device. So I assume no quality of life. I didn't  
7 come across any quality of life data. Is that --

8 MR. NILSON: Given the ambiguity of  
9 quality of life, we tried to capture that in our  
10 secondary outcomes specific to ICU stay, hospital  
11 stays.

12 DR. KRUCOFF: Yes, yes.

13 MR. NILSON: And time to return to normal  
14 activities.

15 DR. KRUCOFF: Right. Okay.

16 ACTING CHAIR MAISEL: Mitch, in the  
17 interest of time, if you could try to wrap up.

18 DR. KRUCOFF: Okay. Well, I'll keep it to  
19 two quick clarifications and stop. You guys described  
20 sensitivity analysis where the 10 missing 12 month  
21 follow-ups in the TAG group were all replaced with bad  
22 events and your data still looks pretty good in the

1 format it was presented.

2 I guess what I learned as the real worst  
3 case approach to a sensitivity analysis is to not only  
4 assign the bad events to the treatment group, but to  
5 take the missing 12 month in the control group and  
6 assign them good events. Has that been done?

7 MR. NILSON: We did. That's exactly what  
8 we did in our worst case analysis.

9 DR. KRUCOFF: Okay. I'm sorry. I only  
10 heard that we assigned the bad events. So you  
11 assigned nought to one and one to the other? Okay.  
12 I will take your word for it.

13 MR. NILSON: We applied worst case in both  
14 directions depending on which group it was related to.

15 DR. KRUCOFF: No.

16 MR. NILSON: Specifically test groups.

17 DR. KRUCOFF: I'm talking about best case.  
18 I'm talking about the mostest worst is really a best  
19 case in the control arm, worst case in the treatment  
20 arm.

21 DR. VERTER: Yes. In the test arm, we  
22 assigned all those that were missing as if they had

1 had an event.

2 DR. KRUCOFF: Yes.

3 DR. VERTER: In the control arm, we  
4 assigned all that were missing as if they didn't have  
5 an event, and that was the results I gave you, that  
6 Dr. Makaroun gave you and I apologize.

7 DR. KRUCOFF: I'm sorry. I just  
8 misunderstood your method. Okay. Thank you. And the  
9 last question, in Slide 118 of Dr. Makaroun's  
10 presentation, which is the freedom from an MAE though  
11 that 30 days where you showed the curves for 99-01 and  
12 03-03 and your control.

13 It looks to me like there is virtually a  
14 complete separation between 99-01 and 03-03 and, in  
15 fact, of all the non-randomized patient cohorts that  
16 we have to talk about, these two cohorts are enrolled  
17 with identical inclusion/exclusion criteria. They are  
18 all treated with the device. They are missing anatomy  
19 that we don't have on any of these patients as  
20 missing, and the outcomes and the data collection were  
21 identical. And it looks to me like these two curves  
22 separate. Can you help me understand that?

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1 MR. NILSON: Dr. Makaroun?

2 DR. MAKAROUN: I guess it's not customary  
3 to look very hard at 30 day curves. It may look a  
4 little bit more separated than it is. Can you,  
5 please, show us the slide? There is a difference  
6 that, obviously, numerically is clear between 12  
7 percent major adverse events in the 03-03 and 28  
8 percent in the 99-01 at 30 days and the confidence  
9 interval. I'm sorry?

10 DR. KRUCOFF: I'm sorry, I was talking  
11 about in your set, it's 118.

12 DR. MAKAROUN: This is an additional  
13 slide. Can you show us the 118? This is just the  
14 explanation of this. This is the one you mean?

15 DR. KRUCOFF: Yes. Thank you.

16 DR. MAKAROUN: All right. Let's go back  
17 to the other slide, please. The explanation is that  
18 there is a difference and, as you know, then the 95  
19 percent confidence interval for the risk difference,  
20 the 16 percent difference of the confidence interval  
21 is from 3 to 29. Most of that difference is  
22 attributable to bleeding, which is procedural bleeding

1 that most likely has progressed over time. We have  
2 learnt how to deal with the sheath, which actually  
3 have changed from the 99-01 to 2001. We have better  
4 sheaths today than we did four years ago.

5 DR. KRUCOFF: Thank you.

6 ACTING CHAIR MAISEL: Dr. Lindenfeld?

7 DR. LINDENFELD: Okay. Thank you. Again,  
8 this is really a nice device and the presentations  
9 have been straightforward today. I just have a couple  
10 of questions and let me just start off by saying one  
11 of my questions we're going to address now is my  
12 concern that, at least, when you look at the one and  
13 two-year data that mortality is not different. One  
14 would have hoped that by saving all this operative  
15 intervention that you would see a difference in  
16 mortality.

17 So now, what my question is, now I become  
18 more concerned about the lack of comparability of the  
19 control group compared to the device group, because we  
20 have seen that, if anything, it appears there is a  
21 trend towards things we think might be associated with  
22 a higher mortality in our control group and yet, our

1 mortalities, which are high at one and two years, are  
2 not different.

3 So we have been through all that. I'm not  
4 going to go back through the differences again, but it  
5 is a concern, because at the end of the day no  
6 patient, I think, would want to have surgery if they  
7 could have this for the same mortality. But some  
8 patients might ask me Doctor, are you sure that the  
9 mortality here is the same? And I'm not certain.

10 I mean, I don't have a reason to believe  
11 that this increases mortality, but I'm concerned that  
12 it doesn't appear to decrease it and I'm concerned  
13 that there is no correction for what appear to be some  
14 differences in the baseline characteristics that would  
15 lead to a higher mortality.

16 So again, I'm sympathetic to that, but  
17 that is my basic clinical concern, whether I can sit  
18 down with Mr. Jones and say, of course, I don't want  
19 to have bleeding and I don't want to have  
20 postoperative complications, but are my long-term  
21 complications less and is my mortality the same? And  
22 I'm not certain of that here. I believe because of

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1 these differences that we have talked about, that  
2 that's a problem.

3 Now, let me just get back to that with one  
4 more question. Do we know? Do all of the surgical  
5 patients, the '94 surgical patients, have follow-up at  
6 one year? Do we know whether they are alive or dead?  
7 And I have the same question for the TAG patients or  
8 are there 10 TAG patients missing and no surgical  
9 patients missing at one year?

10 MR. NILSON: We do have follow-up  
11 compliance. Could you, please, project the slide and  
12 I will ask Dr. Makaroun to comment on the subject  
13 status.

14 DR. LINDENFELD: Okay. Well, let me just  
15 ask my question, because I think if -- my question is  
16 I know you have added the worst case scenario for  
17 major adverse events, but if we have all the follow-up  
18 on the surgical patients and we're missing 10 in the  
19 TAG group and we don't know whether they are alive or  
20 dead, we could have a major mortality difference here.  
21 I mean, we could. So I mean, do we not just even know  
22 that those 10 patients are alive or dead? It's

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1 important to me to know that, again getting back to  
2 this major question.

3 MR. NILSON: Dr. Makaroun?

4 DR. MAKAROUN: Let me start by responding  
5 to the last one, which is the missing data at a  
6 particular time interval of observation for the  
7 calculation of certain numbers. The fact that 10  
8 patients may not be available at the 12 month follow-  
9 up visit for the calculation of the 12 month or the  
10 one-year data does not mean that they are not  
11 available for follow-up and they did not show up  
12 outside the window.

13 DR. LINDENFELD: No, no, I understand  
14 that. Excuse me, I just don't want to prolong it. If  
15 you know that those 10 patients are alive --

16 DR. MAKAROUN: We know.

17 DR. LINDENFELD: -- because you followed  
18 them up later, then I'm happy with that. What I want  
19 to know is at one year, do we know?

20 DR. MAKAROUN: These are not lost to  
21 follow-up. These did not show up for that visit.

22 DR. LINDENFELD: Okay. But do we know all

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1 10 of those were alive, because they showed up a month  
2 later or two months later? That's what I want to  
3 know.

4 DR. MAKAROUN: I cannot tell you 100  
5 percent --

6 DR. LINDENFELD: Okay.

7 DR. MAKAROUN: -- that all 10 of them are  
8 alive.

9 DR. LINDENFELD: This is a concern. I  
10 have to know.

11 DR. MAKAROUN: But these are not lost to  
12 follow up.

13 DR. LINDENFELD: Okay.

14 DR. MAKAROUN: So if they are not lost to  
15 follow-up, then we know.

16 DR. LINDENFELD: Well, dead is pretty lost  
17 to follow-up.

18 DR. MAKAROUN: Excuse me?

19 DR. LINDENFELD: I mean, dead is pretty  
20 lost to follow-up, I mean.

21 DR. MAKAROUN: Then they would have been  
22 counted in the lost to follow-up, not in the did not

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1 show up for the one-year follow-up.

2 DR. LINDENFELD: Okay. Yes, I don't want  
3 to give you a hard time. I just want to know that you  
4 know that those 10 people that didn't come for their  
5 12 month visit, since we have a one-year mortality to  
6 look at, that they are actually alive, that somebody  
7 saw them sometime later or how many of those do we  
8 know that for, because we have exactly equal mortality  
9 and a high mortality here.

10 And you know, again, what we're saving  
11 now, we're not saving people strokes or MIs, I will  
12 come back to paraplegia, or death. What we're saving  
13 them is the hospitalization, so it becomes really  
14 important to know if there is a mortality difference  
15 here.

16 DR. MAKAROUN: Well, the study was not  
17 designed to show a reduction in all-cause mortality.  
18 We are not trying to reduce mortality over the  
19 effective treatment, which is surgery. Both treatment  
20 arms -- can you, please, show us the slide?

21 DR. LINDENFELD: No, I totally understand  
22 that and I know you don't have enough numbers, but 10

1 is a big difference when you're looking at the numbers  
2 of deaths that you have here. All I want to know is  
3 do we know that those 10 people that didn't show up at  
4 one year, since we do have one-year mortality data, do  
5 we know whether they are alive or do we just not know?  
6 Did any of them show up later?

7 DR. MAKAROUN: I do not have narrative  
8 summaries in front of me to tell you all 10 of them  
9 showed up, but all these patients are now at least  
10 three years past and if they have died, they would be  
11 either in the lost to follow-up or in the death  
12 column. They will not be in the did not show up for  
13 the one-year follow-up.

14 So at one year when they are lost, when  
15 they did not show up, those 10 are just did not show  
16 up, so those are alive during follow-up and they will  
17 show up either in the death column later or in the  
18 lost to follow-up.

19 DR. LINDENFELD: Okay. But then I guess  
20 maybe --

21 DR. MAKAROUN: So those 10 are alive.

22 DR. LINDENFELD: So you know everyone in

1 the study, whether they are alive or not? In other  
2 words, there were none lost to follow-up, but you  
3 don't know whether they are alive or dead?

4 DR. MAKAROUN: They will be either  
5 classified under lost to follow-up and that we don't  
6 know anything about them or they will be classified  
7 under death.

8 DR. LINDENFELD: Okay. Then how many of  
9 those are there at one year that we just don't know?

10 DR. MAKAROUN: They are lost to follow-up.  
11 Can you, please, show us the lost to follow-up slide.

12 DR. LINDENFELD: I mean, I'm sorry, but I  
13 think it's important, you know, how many do we know  
14 whether or not -- that were missing, whether or not  
15 they are alive or dead.

16 DR. MAKAROUN: We did show a slide before.  
17 Please, show the slide. As you can tell, like with  
18 any other study, some patients decide to withdraw,  
19 refuse to follow-up or die and these do not count.  
20 Obviously, they don't show up for their visits. The  
21 missed visits are a separate category. The withdrew  
22 or lost to follow-up are a separate category and the

1 expired are a separate category.

2 DR. LINDENFELD: Okay. Yes.

3 DR. MAKAROUN: Can you go to the other  
4 slide that you had earlier? Now, we have, as somebody  
5 else asked earlier for a longer term follow-up, these  
6 two, the all-cause mortality, essentially, remains  
7 identical between both groups. As both, essentially,  
8 have been treated for their basic aneurysm-related  
9 disease, they are expected to succumb to the general  
10 mortality of their age and comorbidities.

11 There is an early numerical advantage that  
12 does not really gain significance and is not expected  
13 to gain significance necessarily in the first few  
14 months to the TAG device and over a three year period,  
15 the all-cause mortality is equivalent, which is what  
16 would have been expected from this trial.

17 DR. LINDENFELD: Okay. Okay. And then a  
18 quick question about the major adverse events. Was  
19 the paraplegia documented permanent or transient? The  
20 definitions in the B Appendix don't specify.

21 DR. MAKAROUN: All paraparesis/paraplegia  
22 with a permanent or deficit were counted as major

1 events. All four happened in the early phase. One of  
2 them completely resolved, one partially improved, two  
3 are permanent.

4 DR. LINDENFELD: Okay. So but there are  
5 quite a few more than that, I think, aren't there?  
6 I'll come back to that. I think there's more  
7 paraplegia than that. Okay. I would just make a  
8 quick comment in the interest of time that as we said  
9 earlier, I'm sort of concerned, too, about this  
10 difference in major adverse events. Again, no one  
11 denied no one wants to be cut open and have these  
12 operative things, but I'm just concerned that some of  
13 these things that are considered major adverse events  
14 sort of defuses the data bed and we have a 30 percent  
15 increase in creatinine. I don't think most of us  
16 would consider a major adverse event.

17 DR. MAKAROUN: A 30 percent increase in  
18 creatinine was used as a definition before it gets  
19 classified. That was not what made it major. What  
20 made it major if they went to dialysis, if that caused  
21 them heart failure, if that increased, so less than 30  
22 percent was not even considered.

1 DR. LINDENFELD: No, I'm sorry, but in  
2 your major adverse events table, Table 15, you have  
3 renal failure and renal insufficiency and the  
4 definition of renal insufficiency -- and the big  
5 difference comes in renal insufficiency and the  
6 definition of renal insufficiency in the appendix is  
7 a 30 percent increase in creatinine.

8 DR. MAKAROUN: Correct. That's the  
9 definition of failure. It's not the definition of  
10 major renal insufficiency or major --

11 DR. LINDENFELD: But that's what's in your  
12 table. That's Table 15. There is quite a difference  
13 there in the two groups.

14 UNIDENTIFIED SPEAKER: What page is that?

15 DR. LINDENFELD: 52.

16 UNIDENTIFIED SPEAKER: Page 52?

17 DR. LINDENFELD: 52. I mean, that's  
18 what's in the table and that's where the difference  
19 lies between the two groups. Let me give you a second  
20 to look at that, because again, just very quickly I'll  
21 go through these. I think that some of these things  
22 have changed.

1 DR. MAKAROUN: The page is 52?

2 DR. LINDENFELD: Right, page 52 of that  
3 pivotal study.

4 DR. MAKAROUN: Correct. This is the  
5 incidence of the major events.

6 DR. LINDENFELD: Right.

7 DR. MAKAROUN: These are not 3 percent or  
8 30 percent increase over baseline. The 30 percent  
9 increase over baseline is the definition of what makes  
10 or what makes it an event to start being counted.  
11 That does not necessarily classify it as major or  
12 minor. What classifies it as major and minor is what  
13 we defined earlier on which is death, permanent  
14 sequelae, long hospitalization necessary for  
15 treatment, a variety of other criteria that are  
16 derived with other criteria available in 1997.

17 But if anything was less than 30 percent  
18 of baseline, that was not even a question to discuss.  
19 If it was over 30 percent, that made it renal  
20 insufficiency. It had to go way beyond that before it  
21 was called major and make this stable.

22 DR. LINDENFELD: Okay. Well, then I'll

1 have to look at that again. And then I'm confused  
2 about that one. Sorry. Okay. And then the final  
3 thing, the baseline characteristics that we usually  
4 think are important to people in vascular disease,  
5 such as creatinine and the presence of diabetes, were  
6 those different between the surgical groups?

7 DR. MAKAROUN: Between the TAG device  
8 group?

9 DR. LINDENFELD: Between the surgical  
10 groups and the TAG group.

11 DR. MAKAROUN: They were -- essentially,  
12 all the analysis of every single item was identical  
13 except for -- no, I'm sorry, not identical, but that  
14 was fairly similar except for the symptomatic  
15 aneurysms.

16 DR. LINDENFELD: Okay. Because we didn't  
17 see the creatinine or the presence of diabetes in any  
18 of the tables.

19 DR. MAKAROUN: All of these patients had  
20 creatinines lower than 2, so it was very hard to  
21 classify them further.

22 DR. LINDENFELD: Well, actually, it isn't,

1 because I think in a lot of cardiac data now it has  
2 been shown that even a .1 increase in creatinine  
3 confers a substantial mortality and the difference  
4 between 1.4 and 1.7 would be substantial. But again,  
5 there is a substantial difference there. Okay.

6 ACTING CHAIR MAISEL: Dr. Ferguson?

7 DR. FERGUSON: Well, I, too, would like to  
8 add my congratulations to the sponsors and to the FDA  
9 for both for very lucid presentations to me. I have  
10 three questions. One is about this hot potato we have  
11 been talking about, the major adverse event sheet.  
12 And my only question is is this protocol that we have  
13 defined for us that covers just about everything in  
14 the medical pharmacopeia is was that defined before  
15 1997 and carried through unaltered for the whole time?

16 MR. NILSON: Dr. Matsumura would like to  
17 address that question.

18 DR. MATSUMURA: The short answer is yes.

19 DR. FERGUSON: Thank you.

20 DR. MATSUMURA: With these criteria we're  
21 defined a priori.

22 DR. FERGUSON: A short answer is good for

1 me. Thank you.

2 MR. NILSON: I could have done that.

3 DR. FERGUSON: Surgical question. We've  
4 talked a lot and what I've gotten from the length of  
5 the neck and those sorts of things is that Dr.  
6 Mitchell, in a very surgical way, has said if you can  
7 put a surgical clamp on, if you're doing a surgical  
8 resection, then you've got enough room between the  
9 subclavian and the beginning of the aneurysm. Did I  
10 quote you correctly?

11 MR. NILSON: Dr. Mitchell?

12 DR. MITCHELL: No, not exactly.

13 DR. FERGUSON: Okay.

14 DR. MITCHELL: But criteria for inclusion  
15 in a surgical group was that the aorta had to be  
16 clampable, whereas an inclusion criteria for the TAG  
17 group was there had to be 2 centimeters of defined  
18 neck. There's a slight difference.

19 DR. FERGUSON: Okay. Well, that's what I  
20 wanted to outline. In other words, 2 centimeters for  
21 the TAG and a centimeter?

22 DR. MITCHELL: Clampable.

1 DR. FERGUSON: Clampable. Centimeter? I  
2 mean, 2 centimeters is what I would call clampable, as  
3 a surgeon. But I just --

4 DR. MITCHELL: I think you need for than  
5 a centimeter.

6 DR. FERGUSON: Yes.

7 DR. MITCHELL: I don't know.

8 DR. FERGUSON: I do, too.

9 DR. MITCHELL: Yes. I would be  
10 uncomfortable with just a centimeter.

11 DR. FERGUSON: The only reason I'm  
12 bringing this up is to try to compare the surgical and  
13 the medical group. And it sounds to me like that at  
14 least talking about the proximal, which is the  
15 important definer of what you're going to do, both of  
16 those would be the same for both treatment arms.

17 DR. MITCHELL: We think they are  
18 comparable.

19 DR. FERGUSON: Okay.

20 DR. MITCHELL: And the only descriptor  
21 really that predicts mortality is size and that we  
22 know is comparable.

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1 DR. FERGUSON: Right. The third and last  
2 question. We're going to be asked when we talk about  
3 the questions and this goes back to some that have  
4 been asked before. I apologize for that. But in the  
5 draft for the indications and questions for the Panel,  
6 in our book, the question proposed to us was, and I  
7 think this is correct, because I couldn't find any  
8 differences as I went through the material, the  
9 proposed Indication For Use, this gets to the  
10 labeling, proposed Indication For Use of this device  
11 is as follows:

12 "Endovascular repair of aneurysm of a  
13 descending thoracic aorta." Clearly, nobody on your  
14 side or this side wants that to be the total criterion  
15 for the use of the device. My question is where are  
16 all of the defining limiters that we have been talking  
17 about? Are those going to be put on the label? Are  
18 they going to be put in an appendix? You know, what  
19 is the plan for those? Because I didn't see them in  
20 here.

21 MR. NILSON: The indication of  
22 endovascular repair of aneurysms is of the descending

1 thoracic aorta is the indication we are implying for  
2 that will be qualified with appropriate anatomical  
3 limitations to ensure proper device function as were  
4 captured in the studies.

5 DR. FERGUSON: See that needs to be  
6 clarified for me, because I've been on panels before  
7 and they are very sticky about and we're sticky about  
8 being sure that all of the material that is important  
9 in the Indication For Use is right up in the front.  
10 And so I don't understand what you mean by that.

11 MR. NILSON: The IFU in the back of your  
12 briefing book is our current worldwide IFU and that's  
13 where we're going to start. And that has again the  
14 appropriate anatomical requirements for this device to  
15 function properly in that application.

16 DR. FERGUSON: Okay. Thank you. Let me  
17 talk about that.

18 DR. EDMUNDS: And the exclusions?

19 MR. NILSON: And the exclusions.

20 DR. EDMUNDS: All right.

21 DR. YANCY: Bill?

22 ACTING CHAIR MAISEL: Thank you very much.

1 Dr. Yancy?

2 DR. YANCY: I'm sorry to go back.

3 ACTING CHAIR MAISEL: Go ahead.

4 DR. YANCY: If I can just ask one question  
5 that hopefully will at least clarify something in my  
6 mind? I'm looking specifically at Table 15 on page  
7 52, entitled "Primary Safety Endpoint Major Adverse  
8 Events Through 365 Days Post-Treatment." Then I'm  
9 looking at Table 20, which is a two page table on  
10 pages 60 and 61, which is "Major Adverse Events By  
11 Follow-Up Period."

12 And as I look at the line items that are  
13 portrayed here, there are different numbers. And so  
14 there is a real problem with definition, because on  
15 Table 15, we're capturing a number of things that are  
16 described as major adverse events and on Table 20,  
17 we're capturing the same line items, but with  
18 different assessments. So I think that part of what  
19 is troublesome for us is that we have a large group of  
20 candidate major adverse events which are portrayed on  
21 15 and then using the same nomenclature, there appears  
22 to be redefinition.

1           Can somebody in the study cohort, one of  
2           the lead investigators, help me understand the  
3           difference, your intended difference, between 15 and  
4           20, Tables 15 and 20?

5           MR. NILSON: Dr. Verter can address your  
6           question.

7           DR. VERTER: Okay. I think has come up  
8           before, so I'm glad you reasked it again. On the  
9           first table, a patient is captioned in the top line  
10          only once, any single, any one or more major adverse  
11          event in the first 365 days after the procedure. That  
12          could have appeared multiple times below and that's  
13          why if you add up all those numbers, you're going to  
14          get a lot more than the top line.

15          In the second table you mentioned, a  
16          person could appear more than once on a line and more  
17          than once in each of the intervals. So someone who,  
18          for example, had atelectasis in zero to 30 days and  
19          had the same event between 31 days and 365 would  
20          appear in both of those columns.

21          DR. YANCY: So if I can pressure just one  
22          second, so I can understand this.