

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

5950 01 JUL 30 10:14

+ + +

CIRCULATORY SYSTEM DEVICES PANEL

+ + +

MEETING

+ + +

MONDAY,

JULY 9, 2001

+ + +

**This transcript has not  
been edited and FDA  
makes no representation  
regarding its accuracy**

The Panel met at 10:00 a.m., in Salon A-C,  
Gaithersburg Marriott Washingtonian Center, 9751  
Washingtonian Boulevard, Gaithersburg, Maryland, Dr.  
Cynthia Tracy, Chairperson, presiding.

PRESENT:

CYNTHIA M. TRACY, M.D., Chairperson

JEFFREY BORER, M.D.

MICHAEL DOMANSKI, M.D.

THOMAS FERGUSON, M.D.

TED KAPTCHUK, O.M.D.

FRANCIS KLOCKE, M.D.

**NEAL R. GROSS**  
COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

## PRESENT (Continued):

MITCHELL KRUCOFF, M.D.

WARREN K. LASKEY, M.D.

MICHAEL C. MORTON

ILEANA PINA, M.D.

JANET T. WITTES, Ph.D.

MEGAN MOYNAHAN, Executive Secretary

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

C O N T E N T S

|  | <u>PAGE</u> |
|--|-------------|
| Conflict of Interest Statement . . . . . | 5           |
| Introductions . . . . .                  | 7           |
| <u>Endovascular Grafts:</u>              |             |
| FDA Presentation:                        |             |
| James E. Dillard . . . . .               | 10          |
| Dr. Larry Kessler . . . . .              | 21          |
| Public Comment:                          |             |
| Beverly Huss . . . . .                   | 29          |
| Dr. Don Schwarten . . . . .              | 36          |
| Tom Wilder . . . . .                     | 41, 56      |
| Dr. Christopher K. Zarins . . . . .      | 41          |
| Dr. Rodney White . . . . .               | 64          |
| Dr. Kim Hodgson . . . . .                | 68          |
| <u>Eclipse PMR Holmium Laser System:</u> |             |
| Sponsor's Presentation:                  |             |
| Richard Lanigan . . . . .                | 76          |
| Dr. Patrick Whitlow . . . . .            | 80          |
| Dr. William W. O'Neill . . . . .         | 110         |
| FDA Presentation:                        |             |
| Dr. Michael R. Berman . . . . .          | 125         |

C O N T E N T S (Continued)

|  | <u>PAGE</u> |
|--|-------------|
| FDA Presentation (Continued)                                   |             |
| Dr. Lesley Ewing . . . . .                                     | 131         |
| Questions to the Panel, Dr. Michael R. Berman                  | 142         |
| Review by Dr. Thomas Ferguson . . . . .                        | 147         |
| Commission Discussion, Recommendations and<br>Voting . . . . . | 153         |

P R O C E E D I N G S

(10:06 a.m.)

1  
2  
3 CHAIRPERSON TRACY: Good morning. I'd  
4 like to call to order this meeting of the Circulatory  
5 Systems Device Panel.

6 This morning's topic is update to the  
7 panel on recent issues with endovascular grafting  
8 systems.

9 MS. MOYNAHAN: And I'd like to begin by  
10 reading the conflict of interest statement for this  
11 morning.

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

16 To determine if any conflict existed, the  
17 agency reviewed the submitted agenda for this meeting  
18 and all financial interests reported by the committee  
19 participants. The conflict of interest statutes  
20 prohibit special government employees from  
21 participating in matters that could affect their or  
22 their employer's financial interests.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealgross.com](http://www.nealgross.com)

1           The agency has determined, however, that  
2           the participation of certain members and consultants  
3           the need for whose services outweigh the potential  
4           conflict of interest involved is in the best interest  
5           of the government. Therefore, waivers have been  
6           granted for Dr. Janet Wittes, Jeffrey Borer for their  
7           interest in firms that could potentially be affected  
8           by the panel's recommendations.

9           Copies of these waivers may be obtained  
10          from the agency's Freedom of Information Office, Room  
11          12A15 of the Parklawn Building.

12          We would like to note for the record that  
13          the agency took into consideration other matters  
14          regarding Dr. Wittes, Borer, Cynthia Tracy, Warren  
15          Laskey, Francis Klocke, Ileana Pina, and Mitchell  
16          Krucoff. Each of these panelists reported interest in  
17          firms at issue, but in matters that were concluded are  
18          not related to today's agenda. The agency has  
19          determined, therefore, that they may participate fully  
20          in all discussions.

21          In the event that the discussions involve  
22          any other products or firms not already on the agenda

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 for which an FDA participant has a financial interest,  
2 the participants should excuse him or herself in such  
3 involvement, and the exclusion will be noted for the  
4 record.

5 With respect to all other participants, we  
6 ask in the interest of fairness that all persons  
7 making statements or presentations disclose any  
8 current or previous financial involvement with any  
9 firm whose products they may wish to comment upon.

10 CHAIRPERSON TRACY: Can I ask the panel  
11 members to introduce themselves? Mr. Dacey.

12 MR. DACEY: Robert Dacey from Longmont,  
13 Colorado, the consumer representative.

14 MR. MORTON: Michael Morton. I'm an  
15 employee of W.L. Gore & Associates. I'm the industry  
16 representative.

17 DR. KAPTCHUK: Ted Kaptchuk. I'm  
18 Assistant Professor of Medicine at Harvard Medical  
19 School.

20 DR. BORER: I'm Jeff Borer. I'm a  
21 Harriman Professor of Cardiovascular Medicine at  
22 Cornell and a new chairman of the Cardio-Renal Drugs

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Advisory Committee of the FDA.

2 DR. WITTES: I'm Janet Wittes from  
3 Statistics Collaborative, and I'm a regular panel, the  
4 statistician on this panel.

5 CHAIRPERSON TRACY: I'm Cynthia Tracy.  
6 I'm an electrophysiologist at Georgetown University  
7 Hospital.

8 MS. MOYNAHAN: I'm Megan Moynahan. I'm  
9 the Executive Secretary of the Circulatory System  
10 Devices Panel.

11 DR. LASKEY: Warren Laskey, an  
12 interventional cardiologist at the University of  
13 Maryland.

14 DR. FERGUSON: Tom Ferguson, cardio-  
15 thoracic surgery, Washington University, St. Louis.

16 DR. PINA: Ileana Pina. I'm the Director  
17 of Heart Failure Transplantation at Case Western and  
18 a member of the Cardio-Renal Advisory Committee.

19 DR. KLOCKE: I'm Fran Klocke. I'm a  
20 cardiologist and Director of the Feinberg  
21 Cardiovascular Research Institute at Northwestern  
22 University Medical School.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. KRUCOFF: I'm Mitch Krucoff. I'm an  
2 interventional cardiologist at Duke University Medical  
3 Center and the Director of Interventional Devices  
4 Clinical Trials at the Duke Clinical Research  
5 Institute.

6 MR. DILLARD: Jim Dillard. I'm the  
7 Director of the Division of Cardiovascular and  
8 Respiratory Devices at the Food and Drug  
9 Administration, Center for Devices and Radiological  
10 Health.

11 MS. MOYNAHAN: I'd like to read the  
12 appointment of temporary voting status for today.

13 Pursuant to the authority granted under  
14 the Medical Devices Advisory Committee charter, dated  
15 October 27th, 1990, and as amended August 18th, 1999,  
16 I appoint the following individuals as voting members  
17 of the Circulatory System Devices Panel for this  
18 meeting on July 9th, 2001: Mitchell Krucoff, Michael  
19 Domanski, Thomas Ferguson, Francis Klocke, Ted  
20 Kaptchuk, and Ileana Pina.

21 For the record, Dr. Pina is a consultant  
22 to the Cardiovascular and Renal Drugs Advisory

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Committee of the Center for Drug Evaluation and  
2 Research, and the other individual are consultants to  
3 this panel. They are all special government employees  
4 and have undergone the customary conflict of interest  
5 review and have reviewed the material to be considered  
6 at this meeting. Signed by David W. Feigal, Director  
7 of the Centers for Devices and Radiological Health.

8 CHAIRPERSON TRACY: At this point we'll  
9 have the FDA presentation.

10 MR. DILLARD: Well, good morning. Thank  
11 you.

12 First of all, I'd like to welcome all of  
13 our Advisory Panel members to two very fun filled days  
14 of the Cardiovascular Panel meeting. We have  
15 certainly four very topical areas to discuss, and as  
16 we all realize cardiovascular medicine continues to be  
17 something that's a very hot topic, and so one of the  
18 things we'd like to do this morning is give you an  
19 update on endovascular graphs and abdominal aortic  
20 aneurysms.

21 Next slide, please.

22 First of all, why do we think that this

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 update is not only timely, but appropriate? And what  
2 is it by way of an update? Because this is something  
3 that's probably a little bit new for this particular  
4 panel, although not completely new. Some of our  
5 colleagues here from Cardio-Renal, I think, get these  
6 updates on a regular basis, and I think we'd like to  
7 start making these regular for this particular  
8 advisory panel, too, and then talk a little bit about  
9 the process.

10 So, first off, why are we doing this? I  
11 think it's been a known fact for quite some time that  
12 you as the Advisory Panel come, sit, give us a  
13 recommendation on a particular product type, and never  
14 really get to hear what happens with that product as  
15 the development continues and as the life cycle  
16 continues for the product.

17 And I think technological evolution has a  
18 lot to do with that, and just your need and desire to  
19 hear about the particular products that we ask you to  
20 come and advise us on.

21 We're also doing this to really increase  
22 the agency openness. As we all know, with FDAMA of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 1997, the agency was really designated by our board of  
2 directors, Congress, to provide more information to  
3 the public, provide more information to you as  
4 Advisory Panel members, and to increase the  
5 interactions that we have with outside experts as well  
6 as industry, and additionally to reduce some of the  
7 misperceptions that may be going on and to really give  
8 an open and frank discussion about where our  
9 technology currently resides.

10           What I'd like to do is just quickly  
11 introduce the pre-market background. Some of you  
12 might have served on that particular advisory panel.  
13 Many of you did not, and to talk a little bit about  
14 the recent developments, and then I'm going to sit  
15 down and Dr. Larry Kessler, who is our Director of our  
16 Office of Surveillance and Biometrics, will give you  
17 a little bit of a post market perspective about this  
18 particular technology, and then I think you will also  
19 hear from the industry and give you an update about  
20 where they currently stand with their own  
21 technologies.

22           The process today will include an update

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 because that's predominantly what we're here to do  
2 today, and we're not going to be asking your for any  
3 formal Advisory Panel recommendations, but if you do  
4 have some questions, I think there will be a number of  
5 individuals here with particular areas of expertise  
6 that will be able to answer some questions.

7 Next, please.

8 There are two currently approved  
9 endovascular graft pre-market approval applications:  
10 the Guidant Endovascular Solutions Ancure Endograft  
11 System and the Medtronic AVE AneurRx Stent Graft. Both  
12 of these products went to an advisory panel on June  
13 23rd, 1999, and both of the products were recommended  
14 for approval with conditions.

15 And the two main conditions that I think  
16 really resided from that particular Advisory Panel  
17 meeting was that there was a need, since this was a  
18 permanent implant, to have a five-year post approval  
19 follow-up of the IDE cohort patients, as well as to  
20 look at subsequent training programs that would  
21 include not only physician training, but any of the  
22 other support personnel that may be necessary for the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 particular intravascular procedure.

2 Both of the applications were approved on  
3 the same day, September 28th, 1999, and the  
4 predominant patient population that we're talking  
5 about is abdominal aortic aneurysm patients.

6 Next slide.

7 The recent developments I think we've  
8 heard a lot about not only from the clinical  
9 literature, but I think at most professional society  
10 meetings this has been a very hot topic about what  
11 some of the medium term results are showing, and that  
12 some of the outcomes have changed somewhat, although  
13 not dramatically in terms of the percentages, but have  
14 changed from what the Advisory Panel saw back when  
15 they met.

16 And there are a couple of themes that I  
17 think continue to come out. The patient selection  
18 continues to be one of the clinical issues of  
19 predominant importance, and who are the right types of  
20 patients that should be receiving the endovascular  
21 grafts?

22 Training and proper deployment for both

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 systems, as well as other systems under development,  
2 remains a very topical area and one that we have been  
3 spending a lot of time working with the manufacturers  
4 on.

5 And another theme that's coming out  
6 certainly clinically is that the follow-up is a  
7 crucial piece to it, and the types of imaging  
8 procedures that are used, and there may be a more  
9 frequent need for patient monitoring and follow-up.

10 We've heard about some device integrity  
11 issues. They certainly were not completely  
12 understood at the time of approval. Many products  
13 that are permanent implants we don't have the full  
14 picture on at time of approval, and leaks and  
15 fractures have been some things that have been  
16 reported in the medical literature.

17 And you probably remember, at least those  
18 of you who were at that meeting, that the products are  
19 very difficult to manufacture. Many of them are  
20 handmade. They're hand sewn in some case, and they're  
21 quite difficult. I think the large scale production,  
22 as well as just the intricacies with the device is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 something that the manufacturers have been working on  
2 and we've been working closely with them.

3 Next slide.

4 There have been a number of very public  
5 announcements by both of the companies, as well as  
6 FDA, about the status of endovascular grafting.  
7 Medtronic on January 24th, 2001 -- you'll probably  
8 hear some more about these -- but sent a performance  
9 update on their particular technology. They talked  
10 about optimizing patient treatment and selection, the  
11 need for regular follow-up, that they had started an  
12 explant program to look at the explanted devices.

13 They had also mentioned the fact that they  
14 had some stent fatigue fractures and some suture  
15 breaks, but that they certainly felt that the product  
16 remained safe and effective.

17 Guidance most recently had a voluntary  
18 halt and recall, March 16th through 19th, in that time  
19 period. There were a number of things that came out,  
20 a number that were put out by the particular sponsor,  
21 and that their conclusions were it does not affect the  
22 impacted patients, and that based on regulatory

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 deficiencies, that was the primary reason for their  
2 voluntary recall, and that their long-term results  
3 certainly indicate that the product is still safe and  
4 that this does not impact patients who are currently  
5 implanted, and that you should continue normal follow-  
6 up.

7           And under both of these circumstances, the  
8 companies have been very interactive with the agency,  
9 have met with us frequently on their individual  
10 issues, and they remain committed to continuing to  
11 work on their products and work very closely with us  
12 in order to make sure that the optimal product is on  
13 the market.

14           Next slide, please.

15           I think in this particular case, we've all  
16 recognized that there's a need for longer term follow-  
17 up, and sometimes when we're looking at new  
18 technologies, while it's very interesting for us to  
19 continue to monitor the product because it's very  
20 important, I think in this case these particular  
21 products, it's been crucial for us to be focused on  
22 the long-term follow-up.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   And I think to that end, continuing the  
2 post approval follow-up certainly to the five years  
3 may result in some labeling changes, and I think that  
4 we believe that that will happen and certainly could  
5 happen on almost a yearly basis as we learn more about  
6 these products at each year of the follow-up.

7                   The literature has been very helpful to  
8 us. There's been a lot of information that has been  
9 provided at the society meetings, as well as the  
10 literature, and the FDA looks at that very closely  
11 also, and I think that that's another good source of  
12 information that generally results in some labeling  
13 changes.

14                   And optimizing patient selection continues  
15 to be one of the foremost issues that we're working  
16 with the sponsors on because I think we're still  
17 learning a lot about the patient populations. We're  
18 learning about those patients that are optimal for the  
19 different types of technologies, and it very well may  
20 be in the future that not every device is optimal for  
21 every patient, and I think that's something that we  
22 take very seriously in terms of our responsibilities.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   There will continue to be with all  
2 technologies generational product changes, and I think  
3 that that's something that's fairly standard for us,  
4 but for the manufacturers to continue to focus on  
5 because, as they will tell you and I think you'll  
6 hear, we're talking about first generation products.  
7 And we have seen certainly in our history at FDA that  
8 as subsequent generations become available, many times  
9 you can optimize the therapy and optimize which  
10 patients get it.

11                   And in terms of post market surveillance,  
12 there are other large efforts to take a look at other  
13 patients as well that are beyond the IDE patient  
14 cohort, but somewhat focused on the IDE cohort, and  
15 hopefully we can also learn something from that that  
16 will be factored into subsequent generations of the  
17 product.

18                   Next slide, please.

19                   So really in conclusion we will continue  
20 to work with the manufacturers. It's not only  
21 something that we have to do, but it's something in  
22 this particular case that is absolutely mandatory for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 us. We've been meeting with not only these  
2 manufacturers, but other developers of endovascular  
3 grafts to try to really get to the point where we have  
4 the optimal products for the patient population and  
5 continue to be focused on not only the short term in  
6 this case, but the longer term clinical data.

7 It will help us factor in the clinical  
8 needs as well as what we learn from device experience,  
9 and really just my final point here, just to say this  
10 is really the way that the agency is moving, trying to  
11 optimize the total product life cycle so that we have  
12 an understanding not only at the time that we approve  
13 the product, but through the subsequent generational  
14 changes and post market data. How do we get to the  
15 point where we're saying the right types of things in  
16 the labeling and we have the right type of training?

17 So with that I think I will conclude, and  
18 if there's any questions, I'd be happy to answer them  
19 now or I can get Larry up here, and you can ask us  
20 both at the end.

21 Dr. Tracy.

22 Again, I'll just introduce you, Larry.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Larry is the Director of our Office of  
2 Surveillance and Biometrics, and he's going to talk to  
3 you about post marketing information.

4 DR. KESSLER: Thanks, Jim.

5 And I want to thank Megan for facilitating  
6 this.

7 And this slide show is going to come up.  
8 So for about five minutes I'm going to talk to you a  
9 little bit about the medical device reporting system,  
10 some of the information we have, and some of the  
11 directions we're taking with this product, and I'll do  
12 it as swiftly as I can.

13 Next slide.

14 The medical device reporting program since  
15 1984 has been mandatory for manufacturers and more  
16 recently mandatory for user facilities. These are  
17 reports that come from the industry to the FDA.

18 Next slide, please.

19 Beginning about 1992, we received over  
20 100,000 medical device adverse event reports per year.  
21 It includes a wide variety of information, including  
22 device specifics, event description, et cetera.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   But the third bullet is among the most  
2                   important.       Reports often have very limited  
3                   information.    They provide critical signals to the  
4                   FDA, but they are often limited.   So it makes some of  
5                   their investigation hampered.

6                   The next slide shows you some of the  
7                   recent data frozen at about the end of May in terms of  
8                   the number of adverse event reports we've had on both  
9                   the AneuRx and the Ancure product.   You see among the  
10                  AneuRx product 13 deaths, 95 serious injuries, and 24  
11                  malfunctions.   You see a much larger number of MDR  
12                  reportable events for the Ancure product.

13                  And that little footnote is kind of  
14                  important.   The 2,037 reports are what we call summary  
15                  reports.     When Guidant discovered some of the  
16                  regulatory problems it had, it came to the FDA and  
17                  said, "We had a large number of very, very similar  
18                  problems in instructions for use.   Can we send them to  
19                  you in a batch instead of individual reports?"

20                  So that's what the 2,000 reports entail,  
21                  and the Guidant manufacturing folks can tell you more  
22                  about it if you wish.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                    Nevertheless, their death, serious injury  
2                    and malfunction reports were relatively astonishing in  
3                    terms of size.

4                    I'm going to detail the serious injury  
5                    reports for the two companies and just give you a  
6                    picture that the problems we're seeing are somewhat  
7                    different for each product.

8                    Next slide.

9                    These are percentages of the 95 MDR  
10                    reports, reports of serious injuries from the AneuRx  
11                    product. You see 36 percent, the modal group, are  
12                    leaks, some removal difficulties, and some positioning  
13                    difficulties, and then the fourth group is migration.

14                    Both the leaks and migration are reports  
15                    that tend to happen after the device is implanted, not  
16                    at the time of implant, but tend to happen upon  
17                    further follow-up.

18                    A contrast, which is the next slide for  
19                    the Ancure product where you'll see a large number of  
20                    problems reported that are associated with deployment,  
21                    the removal difficulties, sticking, resistance. Those  
22                    three problems, which are a large number of reports,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 have to do with deployment, and that was the chief  
2 type of problem.

3 So at the time when we looked at these  
4 number of reports, we started getting concerned, and  
5 the FDA put out a public health advisory to the  
6 clinical community and hospitals detailing what we  
7 knew about the reports and the problems at that time.

8 Many of the clinicians were probably aware  
9 of some of these problems. We felt it was important  
10 for FDA to make a public statement about the nature of  
11 these problems and our understanding of them.

12 One of the things you don't see with these  
13 reports are denominators. So you might want to ask,  
14 "Gee, you got 530 reports out of how many?"

15 We almost never try to compare things like  
16 the MDR reports with, say, number of sales. Medical  
17 device reports are notoriously under reported by a  
18 factor of from one percent to ten percent. So there  
19 could be tenfold as many reports or 100-fold as many  
20 reports.

21 Typically MDRs are under reported by the  
22 clinical community in general. In fact, it's one of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the problems that we have with medical device reports.

2 Next page, next slide. Oops, that was  
3 two.

4 We have two authorities. Jim has already  
5 mentioned one that can help us in the post market  
6 period once a device comes to market. One of these  
7 authorities is called Section 522, originally mandated  
8 in 1990 under the Safe Medical Devices Act and changed  
9 under FDAMA in 1987.

10 Post approval studies refer to PMA  
11 products, and Jim mentioned the condition of approval  
12 studies for both of these products had to do with  
13 long-term follow-up of the IDE cohort. Both of these  
14 authorities are seen as complements to the pre-market  
15 program.

16 We tend to use Section 522 in a few  
17 different cases than condition of approval. We tend  
18 to use them with 510(k) products where condition of  
19 approval does not apply, but we also tend to use it in  
20 situations where follow-up of an IDE cohort, for  
21 example, would not be appropriate.

22 Our questions of some of the products in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 this case have to do more with long-term follow-up of  
2 what's going on with community patients.

3 So the next slide and last one refers to  
4 a post market study order that was just issued  
5 recently, June 13th, to Medtronic on the AneuRx  
6 product, and our biggest concerns are comparison of  
7 post market to pre-market patient populations, and  
8 then in italics on purpose, comparison of post market  
9 to pre-market types and rates of adverse events.

10 As I said, the medical device reporting  
11 program just gives us signals. It doesn't give us  
12 rates, and you don't want to try and create rates from  
13 MDR. You'll get false pictures, but you need some  
14 sort of a population look so that we can find out  
15 whether, in fact, the problems that we've seen in the  
16 IDE cohort translate similarly or are different in  
17 community patients.

18 We are under the impression that these are  
19 devices that can be difficult to implant, that can be  
20 quit tricky. The vasculature of patients can be  
21 sometimes torturous leading to problems, and if  
22 community physicians are not as skilled as those in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the trials, we may be seeing more problems in the post  
2 market period or perhaps there's been a learning curve  
3 and we're seeing fewer.

4 But we don't know the answer, and that's  
5 why we've asked Medtronic to immediately conduct a  
6 post market study on community patients.

7 Finally, we're looking in this study for  
8 compliance rates with follow-up and the types of  
9 imaging that are done principally with community  
10 patients. Again, the recommendations that are coming  
11 out about these products require complex imaging and  
12 not everybody may have access to or understand the  
13 imaging that needs to happen. So this is our post  
14 market study order.

15 I'd like to comment that a few weeks ago  
16 the American College of Cardiology, the Society for  
17 Thoracic Surgery, the Duke Centers for Education  
18 Research on Therapeutics, and FDA co-sponsored a  
19 meeting at Heart House about post market follow-up for  
20 cardiovascular products. Mitch Krucoff was in  
21 attendance, and maybe some of the audience was as  
22 well.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   At that meeting we tried to find out what  
2                   are the right kind of models to follow these kinds of  
3                   cardiovascular products in the post market period to  
4                   give us adequate information to make not only good  
5                   regulatory, but sound public health decisions?

6                   One of the models you'll see later today  
7                   or hear from is the Lifeline Registry, and it's that  
8                   kind of mechanism that exists, a shared public health  
9                   and industry cooperative that can help us collect  
10                  data, such as the post market data we're talking  
11                  about, which we think is vital to understanding the  
12                  nature and use of these products.

13                  Thank you for your time. If you have any  
14                  questions, Jim and I are here at your service.

15                  CHAIRPERSON TRACY: Any questions form the  
16                  panel?

17                  MR. DILLARD: It's a quiet group this  
18                  morning.

19                  CHAIRPERSON TRACY: We're just getting  
20                  warmed up.

21                  At this point we'll open our public  
22                  hearing, and I understand there are a number of people

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 who would like to speak today, and I believe first is  
2 Beverly Huss.

3 MS. HUSS: Good morning. I'm Beverly  
4 Huss, President of Guidant Endovascular Solutions.

5 I would like to thank FDA and the Panel  
6 for the opportunity to discuss the current situation  
7 with the Ancure system. As you know, the Ancure  
8 device is for the treatment of abdominal aortic  
9 aneurysms, the endovascular treatment of AAAs, and has  
10 been on the market since the end of September of 1999.

11 This product has been used to treat more  
12 than 7,000 patients worldwide with excellent long-term  
13 clinical results. At three years, there are zero  
14 ruptures in bifurcated implants, and only two ruptures  
15 in tube implant patients. Ninety-six percent of  
16 patients treated with these implants that have  
17 received a bifurcated device have aneurysms that are  
18 controlled or shrinking in size during the three-year  
19 follow-up period.

20 There was only one migration in a patient  
21 treated with a bifurcated device with no clinical  
22 sequelae. All of the long-term clinical data from the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 original PMA clinical study in the post market period  
2 with the over 6,000 cases we have in our database  
3 remains consistent with excellent long-term clinical  
4 results.

5 Earlier this year, as Mr. Dillard  
6 mentioned, internal audits of our regulatory and  
7 quality systems created some findings that caused us  
8 to voluntarily stop shipment and production of the  
9 Ancure product line. The issues were found as a  
10 result of an internal audit and fit into four main  
11 categories.

12 First, we made certain changes to improve  
13 the delivery system and did not submit those to FDA.  
14 We did not update our instructions for use to include  
15 delivery system deployment techniques recommended to  
16 resolve deployment difficulties.

17 We found issues with the integrity of our  
18 packaging, and we also did not report some field  
19 observations regarding deployment issues with the  
20 Ancure system to FDA.

21 We brought forward our findings to FDA and  
22 submitted a corrective action plan that outlined our

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 steps to resolve these issues. We've updated FDA  
2 monthly as to our progress on this plan, and we have  
3 completed all items on the plan either on time or  
4 early.

5 I'd like to thank FDA for their  
6 cooperation and professionalism in working with us to  
7 resolve these issues.

8 Now, we've made enormous progress in all  
9 of the four areas I mentioned. All of the pre-market  
10 approval supplements for changes to the delivery  
11 system have been filed with FDA and are currently  
12 under review. I'd like to again recognize and thank  
13 FDA for their commitment to working with us to return  
14 and cure the patients and physicians in a timely  
15 manner.

16 The instructions for use have been updated  
17 to include delivery system techniques recommended to  
18 resolve the deployment difficulties that could occur  
19 during the procedure. The updated instructions for  
20 use were also part of the PMA supplements that have  
21 already been filed with the agency and are under  
22 review.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Internally, we have rewritten all of our  
2 regulatory and quality systems and trained our  
3 employees on these new procedures. We have  
4 successfully completed testing of a new packaging  
5 design, and we expect to be treating patients in the  
6 next week in a controlled manner.

7 Medical device reports have been filed  
8 with FDA for the field observations I mentioned  
9 previously. I'd like to discuss our approach to these  
10 reports and give you a little bit more detail there.

11 As Dr. Kessler said, the vast majority of  
12 the medical device reports for Ancure relate to the  
13 acute delivery system issues and not the long-term  
14 endograft. It's important to note that leaks  
15 discussed are primarily acute Type I endoleaks  
16 resolved interoperatively.

17 We have taken a very strict and  
18 appropriate interpretation, we believe, of the medical  
19 device reporting guidelines and regulations. If the  
20 device cannot be absolutely ruled out as the cause of  
21 death, conversion to open surgery or injury to the  
22 patient, or an additional step in the procedure, or a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 malfunction, we report it to the FDA.

2 Now, our field sales and clinical team  
3 provide an important clinical support service to  
4 physicians performing endovascular repair of AAAs by  
5 attending nearly every case performed. These  
6 specialists provide important information on device  
7 use and also record important implant information on  
8 device performance interoperatively.

9 Consequently, we have a great deal of  
10 information on over 6,000 cases performed during the  
11 post market period. This information was reviewed and  
12 medical device reports were filed based on the  
13 conservative standards I outlined.

14 Approximately 88 percent of the total MDRs  
15 filed for the Ancure relate to delivery system  
16 deployment techniques that were not part of the  
17 original instructions for use. These reports were  
18 outlined by Mr. Kessler under the injury section and  
19 the summary sections of his presentation.

20 Of the 530 reports described under injury,  
21 70 percent, or 365 cases, required an additional step  
22 in the procedure to deploy the device and resulted in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 no real patient injury.

2 This means additional steps were utilized  
3 to deploy the device with no injury to the patient,  
4 but because the techniques were not described in the  
5 instructions for use, they were reported as an  
6 additional intervention.

7 These new delivery system deployment  
8 techniques have been incorporated into the new  
9 instructions for use currently being reviewed by the  
10 agency.

11 The remaining medical device reports filed  
12 can be broken out into the categories of death,  
13 serious injury, and malfunction. Again, conservative  
14 reporting guidelines were used, and if the device  
15 could not absolutely be ruled out as a cause of an  
16 event, it was filed with FDA.

17 We would like to respectfully request that  
18 FDA hold all manufacturers to the same medical device  
19 reporting standards.

20 One of the most important messages that  
21 I'd like to leave you with today is that the clinical  
22 data has not changed throughout the pre- and post

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 market period of use of the Ancure device. The  
2 delivery system deployment issues and techniques do  
3 not impact the long-term safety of the endograft.

4 The clinical data from the PMA and the  
5 6,000 cases in our post market database remain the  
6 same in terms of technical procedure success, death  
7 within 30 days, and conversion to open surgery within  
8 30 days.

9 Ancure has a consistent clinical  
10 performance history throughout the time pre- and post  
11 market it has been on the market. The majority of the  
12 deployment issues have been addressed by the delivery  
13 system deployment techniques in the new instructions  
14 for use, and the clinical data from the Ancure IDE  
15 study shows excellent long-term endograft performance.

16 In particular, there are three hook  
17 breaks, one in each of three different devices seen at  
18 three years in the clinical study, none of which have  
19 results in any adverse clinical sequelae for the  
20 patients.

21 There are zero hook breaks reported in the  
22 7,000 bifurcated implants that were completed post

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 market. Ninety-six percent of bifurcated devices show  
2 aneurysms controlled or decreasing in diameter at  
3 three years, with 74 percent decreasing at three  
4 years.

5 There are zero ruptures in the over 7,000  
6 bifurcated implants, with only two tube ruptures and  
7 one migration seen in a bifurcated device, again, with  
8 no clinical sequelae to the patient.

9 At this point, I would like to ask our  
10 Chief Medical Officer, Dr. Don Schwarten to come up  
11 and talk further about the long-term Ancure clinical  
12 data, and then Don and I would be happy to take your  
13 question.

14 DR. SCHWARTEN: Thank you very much.

15 I will try to elaborate a little bit on  
16 what Bev has already mentioned though on the clinical  
17 data, although she's done a fairly thorough job of it.  
18 The material I'm going to present to you will be, by  
19 and large, new material compared to what you have seen  
20 before. Some of it will be data relevant to the IDE  
21 trial.

22 When we as physicians make a decision to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 intervene on a patient with an abdominal aortic  
2 aneurysm, our goal is to prevent rupture. I think  
3 that the essence of abdominal aortic aneurysm therapy  
4 is survival rupture free, and if we look at what Bev  
5 has already mentioned with the Ancure bifurcated  
6 implant, and over 7,500 implants from December of 1995  
7 until February of 2001, there have been no ruptures  
8 reported with Guidant with the bifurcated implant.

9 The two ruptures that occurred with the  
10 tube graft I'd like to address for a moment. The  
11 first was a patient who was implanted, was seen at  
12 one-year follow-up, doing well, no endoleak, was lost  
13 to follow-up and presented after his two-year follow-  
14 up emergently with a contained rupture, and was  
15 treated. We did not receive that graft back at  
16 Guidant, but we were told that the graft was intact  
17 and there were no hook fractures.

18 The second patient was a patient who was  
19 implanted in January of 2000 and ruptured in July of  
20 2000. We had the opportunity to review the films for  
21 that patient, and the patient was implanted with a  
22 tube graft against Guidant's recommendation.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I think some additional encouraging data  
2 comes from the IDE study as it relates to the midterm.  
3 I emphasize I do believe this is midterm data, and Bev  
4 has already outlined that at three years, 74 percent  
5 of patients have had a decrease of greater than five  
6 millimeters in the size of the diameter of the  
7 aneurysm. An additional 22 and a half percent have an  
8 aneurysm that is unchanged in size, for a total of 96  
9 percent controlled or no changes in size or a decrease  
10 in size in the abdominal aortic aneurysms.

11 Bev also mentioned that we've had several  
12 migrations. One migration in a bifurcated system was  
13 discovered by the core lab. It was a relatively minor  
14 migration, again with no clinical sequelae.

15 The four migrations noted in patients with  
16 tube implants, one of them was a proximal attachment  
17 system migration. The other three were distal  
18 attachment system migrations. None of the patients  
19 have developed endoleaks and none of them have been  
20 converted.

21 This is a graft intended to let you see  
22 what has happened in terms of operative mortality and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 conversion rates in the PMA trial versus what has  
2 happened since commercialization in October of 1999.  
3 As you can see, during the PMA trial, the conversion  
4 rate was 5.2 percent and the death rate was one  
5 percent.

6 If you look at this slide and I'll ask you  
7 to compare and contrast it with the next slide, which  
8 will cover the trial studies and the control release  
9 study, but it's easy to see that the conversion rate  
10 has dropped precipitously from 5.2 percent, and the  
11 death rate has consistently been below the one  
12 percent.

13 And, again, this is in light of the fact  
14 that this population is being treated by a variety of  
15 physicians, not the controlled study physicians in  
16 special hospitals who have perhaps somewhat superior  
17 skills and training. So this represents the general  
18 population therapy as we know it.

19 As Bev has mentioned, the consistency of  
20 the performance of the Ancure implant, looking at the  
21 first three columns, all of them prospective  
22 controlled studies. Particularly note the controlled

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 use period in March to April of this year in which 352  
2 patients were treated with a technical success rate  
3 equivalent to or slightly better than those in the PMA  
4 and the complete Ancure trials, with a 30-day  
5 mortality of less than .3 of a percent and a  
6 conversion rate, again, consistent with what was going  
7 on during the other two PMA trials.

8 In summary and conclusion, I think the  
9 Ancure device has exhibited consistent clinical  
10 performance relative to the history of the device.  
11 The majority of the deployment issues have been  
12 addressed by the troubleshooting techniques added to  
13 the IFU, and data from the IDE shows long or midterm  
14 endograft performance to be superb.

15 Thank you.

16 CHAIRPERSON TRACY: Thank you.

17 Are there any brief questions from the  
18 panel for clarification purposes?

19 (No response.)

20 CHAIRPERSON TRACY: We really are quiet  
21 today.

22 Thank you very much.

1 We'll move on to Dr. Zarens.

2 MR. WILDER: Good morning. My name is Tom  
3 Wilder. I'm the Vice President and General Manager of  
4 Medtronic AVE's Endovascular Stent Grafts Division.

5 I'm delighted to have with me Dr. Chris  
6 Zarins from Stanford University.

7 For the sake of time, the majority of our  
8 presentation today will be an update on the entire  
9 clinical experience of the AneurRx device, and to Mr.  
10 Dillard's and Mr. Kessler's points and emphasis on the  
11 long-term outcomes that we've seen.

12 Time permitting, I will then follow up  
13 with a summary of various Medtronic activities,  
14 including the post market surveillance efforts that  
15 Medtronic has undertaken on the AneurRx device.

16 And with that, I'd like to turn it over to  
17 Dr. Zarins.

18 DR. ZARINS: My name is Chris Zarins. I'm  
19 here on behalf of Medtronic as a consultant. My hotel  
20 and travel is paid for by Medtronic, and as part of my  
21 overall investment strategy, I am a stock owner in  
22 both Medtronic and Guidant.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           Before you, you should have a packet with  
2           some published information on the outcome of the  
3           AneuRx stent graft. I think as we think about this  
4           technology, we need to keep it in the perspective of  
5           the overall treatment of aortic aneurysms.

6           As a vascular surgeon, I have been doing  
7           open aneurysm repair for 25 years, and in my practice  
8           today, I continue to do more open aneurysm repairs  
9           than endovascular repairs.

10           There's been a variety of publications  
11           that have come out of the clinical trials for the  
12           AneuRx stent graft, including results of the Phase 1  
13           and Phase 2 results; a detailed analysis of the  
14           aneurysm rupture issue; the importance of endoleaks,  
15           and the four-year results, which was published in the  
16           February issue of the Journal of Vascular Surgery,  
17           which you should have in your packet, and I will  
18           provide you with some updated information because that  
19           publication, the data cutoff was a year ago June.

20           I've also provided you with three  
21           abstracts to address some of the issues. Two years  
22           ago the Advisory Panel requested information on how

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the device performs in women, and there's an abstract  
2 dealing with this issue, and I'll touch on that  
3 briefly.

4 Also, we'll have some information on how  
5 this compares with open surgery and also how this  
6 device has performed in the introduction into  
7 community practice.

8 As we think about the overall issue, we  
9 should keep in mind why we treat aneurysms to begin  
10 with, and there's really only one reason to treat  
11 aneurysms, and that is to prevent aneurysm rupture and  
12 death from rupture. And ideally we should be able to  
13 do this without morbidity and mortality, but  
14 unfortunately that's not the case, and the standard  
15 treatment, open surgery, is certainly prone to a  
16 relatively significant incidence of morbidity and  
17 mortality, and the relative effectiveness of  
18 endovascular and open repair in avoiding these  
19 problems needs to be better understood.

20 So what I would like to propose to you is  
21 a mechanism to really define the primary outcome  
22 measure of treating aortic aneurysms, and that is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 preventing aneurysm related death. You don't want to  
2 die of a ruptured aneurysm. You also don't want to  
3 die of the treatment of that aneurysm.

4 So that we should define death due to the  
5 rupture of the aneurysm; death within 30 days of the  
6 primary treatment, whether it be open or endovascular;  
7 and death within 30 days of any secondary treatment  
8 related to that aneurysm; and death for any graft  
9 related problems.

10 We have taken an approach of a broad view  
11 of looking at the data, that is, considering every  
12 single patient that has been treated with the AneuRx  
13 stent graph. So when we evaluate the clinical trial  
14 patients, we have looked at all patients in Phases 1,  
15 2, and 3, including emergency and compassionate use  
16 patients who are treated outside of the protocol  
17 guidelines during the clinical phase.

18 It includes the learning curve for every  
19 single treatment, and it includes device manufacture  
20 changes during the course of the treatment.

21 Two years ago when we presented this data  
22 at the Panel, we presented 416 stent patients versus

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 66 open surgery in the Phase 2 clinical trial. It's  
2 obvious that the 66 open patients are an inadequate  
3 surgical control group to really compare this  
4 technology because the number is so small. And I'll  
5 bring you some more information on the role of open  
6 surgery.

7 It's important to realize that there was  
8 a device manufacture change, and this occurred very  
9 early. The very first 174 patients in the clinical  
10 trial, 40 of them in Phase 1, received a stiff body  
11 design. This was modified to a segmented body design,  
12 which is a flexible design, and this is the one that  
13 is commercially available, and this is the one that  
14 has been used for the majority of the clinical trial  
15 and is the one that is commercially available now.

16 If we look at the problem of aneurysm  
17 rupture in comparing the stiff versus the flexible  
18 body design, using Kaplan-Meier analysis, you can see  
19 that the chance of rupturing with a stiff design is  
20 considerably higher. It's about five times higher  
21 with a stiff design than with the flexible design and  
22 with a Kaplan-Meier analysis at three years, freedom

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE, N.W.  
WASHINGTON, D.C. 20005-3701

1 from rupture with a stiff is 96 percent and with the  
2 current clinically available device, it's 99.5  
3 percent.

4 If you look at the overall four-year  
5 results, 98 percent of patients have had successful  
6 implantation of the device. Procedure mortality in 30  
7 days is 1.8 percent. Surgical conversion, early and  
8 late, including conversion for ruptures, is 3.4  
9 percent.

10 The rupture rate, 1.1 percent; rupture  
11 related death, 0.5 percent; and aneurysm related death  
12 is 2.3 percent. I think these results are very good  
13 and remarkably good compared to what one might expect  
14 from open surgical repair.

15 If we look at now a four-year Kaplan-Meier  
16 outcome analysis, freedom from rupture, this is now  
17 considering all patients, including the emergent, off  
18 protocol use, and the stiff body patients; considering  
19 all patients, freedom from rupture, 98.2 percent at  
20 four years. Freedom from surgical conversion, 94  
21 percent, that is, only six percent of patients over  
22 four years ever need open surgery, and probability of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 survival is 82 percent.

2 Now, in April the FDA put out a public  
3 health notification and commented a significant  
4 concern, about 25 ruptures. However, the detail and  
5 the context of these ruptures was not presented, and  
6 I'd like to provide that to you today.

7 As of June there are actually 28 ruptures,  
8 and this is a worldwide experience. This is not an  
9 experience in a clinical trial. In the U.S. clinical  
10 trial, every single patient, there were 15, 1.3  
11 percent. In the U.S. commercial, that is, post  
12 market, there have been 9,100 patients with seven  
13 ruptures, 0.1 percent. In the worldwide international  
14 commercial trial, there have been six ruptures, 0.2  
15 percent. Thus, the total worldwide out of over 13,000  
16 implants, there have been 28 ruptures, 0.2 percent.

17 But this itself also doesn't tell the  
18 story because we need to know a little bit more about  
19 the detail of the ruptures. There have been ruptures  
20 prior to device insertion. There have been ruptures  
21 related to the procedure. There have been ruptures  
22 due to the stiff device, and there have been ruptures

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 due to the flexible device.

2 And if you can see on the right-hand  
3 column there, the post implant flexible, there have  
4 actually been 11 ruptures, and those are the ones that  
5 are really of significance in regard to the current  
6 clinical device that is on the market.

7 So really 11 ruptures that we need to  
8 focus on, and I'll provide some detail.

9 This, again, shows that the stiff device  
10 has about a fivefold greater risk of rupture than the  
11 current flexible device, and in the U.S. clinical  
12 trial, there have been six post implant ruptures with  
13 the flexible device, a prevalence of 0.6 percent.

14 If we look at the 19 patients with  
15 ruptures post implant, that's overall 0.1 percent. If  
16 we take out the stiff devices, then it's really 11  
17 ruptures out of 13,000 or 0.08 percent.

18 Now, let's look at the causes of the  
19 ruptures. As I said, there are a variety of causes.  
20 The first patient had a small iliac vein, and the  
21 procedure was abandoned. The device was never  
22 inserted. The patient subsequently ruptured. This is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 counted as a rupture.

2 The second patient is a 91 year old lady  
3 who was in the cafeteria of the hospital and ruptured  
4 her aneurysm, was brought to the emergency room, and  
5 the family refused to have open surgery because she  
6 was 91 years old, and they said, "Oh, we happen to  
7 have a stent graft." They took her up to the  
8 operating room, put her in a stent graft. She was in  
9 shock, and she died. That's a rupture. That was  
10 ruptured prior to the device insertion.

11 There are two ruptures of the iliac prior  
12 to device insertion.

13 There have been peri-procedural ruptures  
14 related to ballooning of the iliac artery or  
15 perforation of the aneurysm. So these are technical  
16 procedures that result in surgical conversion.

17 The post implant ruptures, the 19, are the  
18 ones that we really have to be very concerned about.  
19 Of note, only three of those patients had endoleaks,  
20 and 16 did not. So all the talk that we've heard  
21 about endoleaks does not seem to be a primary  
22 predictor or indicator of device failure or the risk

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 of rupture.

2 The vast majority, 18 out of 19 of the  
3 ruptures, were due to inadequate fixation due to poor  
4 patient selection or to low placement of the device in  
5 the neck. In one instance, the neck was too large, 29  
6 millimeters, with the device largest being 18  
7 millimeters.

8 So proximal and distal fixation of the  
9 device is really the etiology and causae of rupture.  
10 The important thing to note about this is that these  
11 evidences of poor device fixation are visible on  
12 imaging studies either immediately after implantation,  
13 and they may continue to be visible for up to three  
14 years prior to rupture. So there's a lot of time to  
15 fix it.

16 And in retrospective analysis, every  
17 single one of those 18 ruptures could have been fixed  
18 with placement of an extender cuff had the physicians  
19 involved done that. This was not done, and ultimately  
20 this led to aneurysm rupture. So I think that most of  
21 these are preventable.

22 Importantly, there was no evidence that

1 problems with device integrity, metal frame fractures,  
2 suture breaks or fabric tears led to any of the  
3 aneurysm ruptures in the U.S. clinical trial.

4 Endovascular repair in women. This was  
5 one of the stipulations two years ago from the panel.  
6 We have looked now at the commercial design and your  
7 stent graft, 117 women compared to 903 men. Women  
8 were older. These are statistically significant  
9 differences that are in the abstract that's before  
10 you. Women were older than men and had smaller iliac  
11 arteries and infrarenal necks and relatively larger  
12 aortic aneurysms. They experienced more technical  
13 difficulties and more deployment failures, iliac  
14 dissections, and inadvertent branch occlusions than  
15 men.

16 But nonetheless, the technical success  
17 rate was 95 percent in women, 99 percent in men, and  
18 this led to a higher rate of rupture in women than  
19 men, and a higher rate of surgical conversion in women  
20 than men.

21 In Kaplan-Meier analysis out to three  
22 years, freedom from rupture, there was 96 percent in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 women and 99 percent in men. Freedom from conversion,  
2 88 percent in women and 95 percent in men.

3 It's important to note that the women  
4 underwent surgical conversion, but they didn't die of  
5 it, and they didn't die of the ruptures.  
6 Consequently, the freedom from aneurysm related death  
7 was no different between women and men. Ninety-seven  
8 percent at three years in women, 98 percent in men.

9 So endovascular repair is equally  
10 effective in women and in men in achieving the primary  
11 objective of preventing aneurysm related death, which  
12 is why we do any treatment of aortic aneurysm, and at  
13 three years, 97 percent in women and 98 percent of  
14 men.

15 Well, how does it compare to open surgery?  
16 We can't tell from the clinical trial because there  
17 are only 66 patients in the surgical arm of the  
18 clinical trial. So to try to assess this, we looked  
19 at Stanford University's experience. 441 elected  
20 aneurysm repairs over a seven-year period. Forty-  
21 months before we started the AneuRx program, and 40  
22 months afterwards, there were 264 open aneurysm

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 repairs, and 177 endovascular, all of them with the  
2 Ancure stent graft.

3 There was no difference in the patient  
4 populations between open and endovascular, except that  
5 the follow-up period was a little bit longer in the  
6 open surgery because we started that earlier than the  
7 stent graft.

8 Importantly, the procedure mortality for  
9 open repair was 3.5 percent for 264 aortic aneurysms  
10 repairs. That's pretty good for open surgery. It  
11 was 0.5 percent for endovascular repairs,  
12 statistically significantly different.

13 What's more important is the secondary  
14 procedure rate, mortality for open surgery was 14  
15 percent, and the mortality rate for a secondary  
16 procedure for endovascular was zero percent.

17 Well, what were the secondary procedures?  
18 The rate of secondary procedures was the same between  
19 open and endovascular, 16 percent for open and 18  
20 percent for endovascular. No significant difference  
21 in the prevalence of the secondary procedures, but the  
22 magnitude of secondary procedures was very different.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 If you needed a secondary procedure for open aneurysm,  
2 you had an intra-abdominal procedure in ten percent,  
3 pseudo aneurysms, infected graft, aorta enteric  
4 fistula, and anastomotic hemorrhage. There was only  
5 one percent open abdominal procedure, one surgical  
6 conversion in the endovascular group. The vast  
7 majority of procedures in the endovascular is a groin  
8 procedure by placement of an extender cuff, a low risk  
9 procedure.

10 Consequently, if we look at aneurysm  
11 related death rate, 5.7 percent for open surgery, 0.5  
12 percent for endovascular. So if you don't want to die  
13 of your aneurysm, you should have endovascular  
14 procedure instead of open procedure.

15 So the risk of aneurysm related death was  
16 tenfold higher with open surgery than it is with  
17 endovascular repair. While the incidence of secondary  
18 procedures was similar, the magnitude and risk of  
19 secondary procedures are significantly higher  
20 following open procedure.

21 Not, this is true if we look at other  
22 large surgical series, 30-day mortality, and late

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 deaths. So for open surgery, between 5 and 12 percent  
2 is the aneurysm related death rate.

3 For the AneuRx clinical trial, 2.3  
4 percent. It will take a lot of long-term problems  
5 with endovascular to ever catch up with the problems  
6 that you get with open surgery.

7 So I think that the early results are very  
8 favorable in favor of endovascular compared to open  
9 surgery.

10 What about the community experience as  
11 this is rolled out into the community? We looked at  
12 the Northern California region, 20 hospitals, 294  
13 patients, every single patient treated in Northern  
14 California region over the past 20 months, since  
15 market approval. These were large and small  
16 hospitals, with a range of one case to 80 cases with  
17 a mean of 15 cases per hospital.

18 The overall success rate was 293 out of  
19 294, 99.7 percent. I think that this may be due to  
20 the training program and the proctoring and the  
21 information that we have learned during the clinical  
22 trial in term so how to place these devices properly.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           There was only one patient that had a  
2           surgical conversion due to misdeployment of the iliac  
3           limb, and that patient is alive and well. Thirty due  
4           to mortality, 0.7 percent; one due to stroke and one  
5           due to multiple system organ failure; six percent  
6           secondary procedure rate; 13 percent endoleak rate.  
7           No different from the clinical trial; no aneurysm  
8           ruptures.

9           So I think that the initial roll-out of  
10          this in the community has been very favorable, and no  
11          worse than; it's hard to say, but it actually looks a  
12          little bit better than the clinical trial in the early  
13          roll-out in the community experience.

14          So I think we can conclude that the  
15          endovascular pair is effective in preventing aneurysm  
16          rupture in 99.5 percent of patients at four years  
17          using the commercial device. It eliminates the need  
18          for open surgery in 94 percent of patients, and it  
19          greatly reduces the morbidity of aneurysm repair and  
20          significantly reduces the risk of aneurysm related  
21          death compared to open surgery.

22                 MR. WILDER: How many minutes do I have

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 left? I'll try to be very, very brief. One to two.  
2 Okay.

3 First slide.

4 This is a first generation therapy, and  
5 one can characterize most of the devices available in  
6 the U.S. and in Europe today as first generation in  
7 nature.

8 Medtronic is committed to partnering with  
9 physicians and regulatory agencies to responsibly  
10 develop this important therapeutic option for  
11 patients.

12 We are making a massive investment in  
13 training and education in the U.S. market. Our  
14 physician training program, which contains a didactic  
15 session, as well as proctor cases. The proctoring is  
16 done in part by independent physicians who are  
17 treating their own endovascular patients and their own  
18 practices and are dealing with the similar risk-  
19 benefit decisions that practitioners have to make, and  
20 we find that a valuable part of the training program.

21 We've also attempted to be as forthright  
22 as possible with product performance updates,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 educational symposia that reached over 700 physicians  
2 recently with discussion on patient selection, the  
3 importance of follow-up, the ruptures, as well as some  
4 summary findings from our explant program.

5 Next slide, Chris.

6 We are committed to monitoring the  
7 performance of our product. Primary is our continued  
8 follow-up of the valuable complete clinical history of  
9 the AneuRx device in the ID cohort.

10 Post market surveillance, we are committed  
11 to adverse event reporting and have been. That's an  
12 important aspect and one with complaint investigation.

13 We've commenced a Lifeline Registry as one  
14 part of what will be a multi-pronged effort at  
15 addressing some of the important questions that have  
16 been raised regarding practice of this therapy and  
17 outcomes of this therapy as it's rolled out to a large  
18 base of implanters, and we're working with FDA on a  
19 plan, as Dr. Kessler mentioned.

20 Next slide.

21 We will advance the technology, as was  
22 referred to earlier. The device iterations will occur

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 over a decade long period. Medtronic has done this  
2 before in other therapies, and we will do so in this  
3 therapy.

4 We're leaning on expert advice from a  
5 scientific advisory board. The explant program, which  
6 I'm sorry due to time I couldn't go into more detail  
7 with you, provides valuable insights to device  
8 durability and design.

9 We will leverage our collective AneuRx  
10 talent experience, which is approaching 30,000  
11 implants to date, and when you handle complaints and  
12 MDRs and investigate them seriously, you learn a lot,  
13 and we are incorporating those things into rapid  
14 product line iterations.

15 So with that I'd like to thank you for  
16 your time, and make ourselves available for questions.

17 CHAIRPERSON TRACY: Thank you.

18 Any questions from the panel for  
19 clarification?

20 DR. WITTES: I have a denominator  
21 question. On the slide that you showed the five-year  
22 experience, 28 ruptures, you had proportion rupture,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and in the light of Dr. Kessler's discussion about the  
2 problems with denominators and reporting, I wonder.  
3 What you have is basically 1.3 percent in the clinical  
4 trial and .1 percent commercially.

5 And I just wonder whether you believe that  
6 .1 percent.

7 DR. ZARINS: I have a great deal of  
8 confidence of the clinical trial. Those patients are  
9 followed extremely closely, and I don't think that we  
10 have missed any ruptures in the clinical trial.

11 Regarding the overall worldwide  
12 experience, it's very difficult to know, and I'm sure  
13 that there may be some events that are unreported, but  
14 even if we look at just the cohort of clinical trial,  
15 knowing that those are the oldest patients and with  
16 the least experience and, frankly, many of them were  
17 not positioned properly below the renal arteries as we  
18 should, the incidence is still very low with the  
19 flexible commercial design.

20 MR. WILDER: Dr. Wittes, if I might follow  
21 up, the incidence rate, I think, to Dr. Kessler's  
22 point, companies can find safety in large

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 denominators, and clearly there are issues with the  
2 MDR reporting regardless of how effectively companies  
3 are pursuing it. You will not find marketing  
4 materials from our company that quotes anything other  
5 than the clinical experience, and we feel a controlled  
6 cohort is the best way.

7 If we were promoting the device, the  
8 freedom from rupture statistics from the ID cohort are  
9 the effectiveness measures that we would position  
10 ourselves upon.

11 DR. WITTES: Okay. Thank you.

12 CHAIRPERSON TRACY: Thank you.

13 Dr. Krucoff.

14 DR. KRUCOFF: I just want to make sure  
15 that I understood a couple of the numbers that did  
16 flash by. With the four year and 84 percent survival  
17 rate, the implication there is that the vast majority  
18 of these deaths are not endovascular or aneurysmally  
19 related. Is that?

20 DR. ZARINS: That is correct. We actually  
21 did a comparison to an expected survival rate, and  
22 patients with aneurysms have a lower anticipated

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 survival compared to age match and sex match controls,  
2 and the survival we saw in this series is actually 20  
3 percent lower than expected survival for age and sex  
4 matched population in the United States, but it is  
5 reflective of the aneurysmal population.

6 DR. KRUCOFF: And, Dr. Zarins, relative to  
7 the open repair data that you presented, am I wrong or  
8 not? The open repair population likely to be a  
9 different vascular subset than the endovascular?

10 DR. ZARINS: Yeah, they probably tend to  
11 be a better risk population than the endovascular  
12 group. I think the endovascular group, even in the  
13 clinical trial, as the trial went on, patients kept  
14 coming in because they were, quote, not fit for open  
15 surgery, and the age raised higher. So that the age  
16 in the surgical control group was 69 and the age in  
17 the endovascular group was 73.

18 And so that there is a large cohort of  
19 patients who are clearly not candidates for any open  
20 surgery who come into the endovascular arm. So I  
21 think you're actually getting a sicker patient  
22 population in that group.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. KRUCOFF: So from your all's  
2 perspective, the post market study order takes you  
3 where?

4 MR. WILDER: You know, back to the MDR  
5 question, Medtronic -- any time an AneuRx device is  
6 used anywhere in the world, we own part of the  
7 outcome, and I think the post market order raises  
8 important questions about the rapidity with which this  
9 technology has been diffused throughout the American  
10 physician practice, and I think the question of short-  
11 term and long-term outcomes in a patient in a  
12 community patient population, given the steep learning  
13 curve with this therapy, are interesting questions.

14 I think we need data before we begin to  
15 draw conclusions and make policy, and I think that's  
16 what part of the post market order is focused on.

17 DR. ZARINS: And the informed consent  
18 process then to patients involved in this experience,  
19 do you see any unique comments that involve in the  
20 informed consents under this sort of circumstance?

21 DR. ZARINS: I think clearly, the informed  
22 consent always includes the admonition that this will

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 be long-term follow-up and very close follow-up that's  
2 going to be required since we do not know the real  
3 long-term outcome of this technology.

4 But at the same time, you cannot assume  
5 that it necessarily will require lifelong follow-up.  
6 We just don't have the data to know that yet, or that  
7 you will require three dimensional spiral CTs. Maybe  
8 ultrasound just like we have always followed  
9 aneurysms, plus a plain abdominal film, will be  
10 sufficient to follow these patients long term, but  
11 that clearly needs to be proved with further data and  
12 documentation.

13 CHAIRPERSON TRACY: Okay. Thank you.  
14 Thank you.

15 MR. WILDER: Thank you.

16 CHAIRPERSON TRACY: Dr. White.

17 DR. WHITE: Thank you very much.

18 I had petitioned the panel to make a short  
19 presentation regarding surveillance and the Lifeline  
20 Registry. My disclaimers related to this panel are  
21 that I was the principal investigator on the AneuRx  
22 clinical trial in the United States. I'm the PI on

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 several other endoluminal graft studies, been  
2 compensated for those activities, and related to this  
3 short presentation today, I'm the Chairman of the  
4 Society for Vascular Surgery and the American Society  
5 for Vascular Surgery, Clinical Trial Assessment  
6 Committee, which is responsible for the Lifeline  
7 Registry.

8 As you've heard and seen in many of these  
9 presentations, currently patients that have been  
10 evaluated with endoluminal grafts, we've looked at  
11 adverse outcomes and focused on those, and those are  
12 very valuable to highlight what the initial problems  
13 are with the technologies, but also at the same time,  
14 a database that would let us look at long-term  
15 outcomes is particularly important.

16 What has happened with regard to the  
17 Lifeline Registry is at the time of original PMA  
18 approvals, there was an agreement established between  
19 the manufacturers, the Society for Vascular Surgery,  
20 and as ex officio members on this Lifeline Registry,  
21 representatives of the FDA, HCFA, and NIH.

22 That collaborative group has been able to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 sit down and come up with a way to look at the  
2 patients that were approved in the IDE subset, how  
3 that translates to the five-year follow-up mandate,  
4 and there is an agreement then with each of the  
5 manufacturers that have submitted the PMA data and had  
6 approve, in this case Medtronic and Guidant, that  
7 those data for the five-year surveillance be part of  
8 the registry.

9 Now, what that's done currently is that it  
10 has established a database in the Lifeline Registry of  
11 about 1,650 patients. The average follow-up on those  
12 patients is three to five years, and because of the  
13 five-year mandate for follow-up, there's a very high  
14 compliance rate so that in comparison to other  
15 registries where it's very difficult to get data, this  
16 one is reliant upon the FDA mandate, makes the  
17 compliance rate very high, and in that regard, this  
18 database is now becoming a very mature data set to go  
19 back and analyze questions and ask whether or not  
20 there are relevant points we can glean from this  
21 information.

22 And if we get the slides, but I'll tell

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 you the registry has a Web site. It's  
2 lifelineregistry.com, and anyone who would like to  
3 propose questions related to how we query this  
4 database, we would like to receive those. This is an  
5 important way for us to look at not only this data set  
6 as it's followed up, but hopefully other  
7 manufacturers, once they've submitted their data set,  
8 will become part of the registry so that we can  
9 continue to mature this information.

10 The other piece that's recently been  
11 activated by the registry is a post market  
12 surveillance study, and it's an attempt to do, as has  
13 been suggested by Drs. Dillard and Kessler, that we  
14 look at each patient post and try to see how this  
15 information would relate particularly to being able to  
16 treat patients appropriately.

17 And the mechanism for this is as patients  
18 are entered into clinical practice, their CT data is  
19 transmitted to a central NERI site. We're able to  
20 collect those over time, and with information that  
21 looks not only at the length and appropriate fixation  
22 information, but also at the same time to be able to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 look at the morphology on the CT scans.

2 It gives us a data set that's automatic.  
3 This would be an on-line service available, and there  
4 are now five clinical sites being sponsored by a trial  
5 by combined Lifeline Registry, Medtronic, and this is  
6 available now actually with the FDA reviewing this to  
7 see how the surveillance issues develop.

8 I realize you're tight on time, and it  
9 doesn't look like the computer is going to work. So  
10 I can stop with that, but I would be happy to answer  
11 any questions.

12 CHAIRPERSON TRACY: Thank you.

13 Any questions?

14 (No response.)

15 CHAIRPERSON TRACY: Thank you very much.

16 Dr. Hodgson.

17 DR. HODGSON: Thank you.

18 In the interest of time and clarity, I  
19 have provided a transcript of my comments to the Panel  
20 members.

21 My name is Kim Hodgson, and I'm professor  
22 and Chairman of the Division of Vascular Surgery at

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Southern Illinois University, Chairman of the SESAAVS  
2 Endovascular Issues Committee, and President-elect of  
3 the Society for Clinical Vascular Surgery.

4 I've been performing endovascular  
5 intervention since 1990 and have made endovascular  
6 training of vascular surgeons the focus of my academic  
7 career.

8 I was one of the Phase 2 and 3 AneuRx  
9 investigators, enrolling the second highest number of  
10 patients in the Phase 2 trial.

11 I'm also an investigator for the Gore  
12 Excluder and Endologix devices and have a modest  
13 experience with the Talent and Ancure devices.

14 While the comments that follow do not  
15 necessarily reflect the official positions of any of  
16 the organizations I serve, they are commonly felt and  
17 expressed by those of us active in the endovascular  
18 technologies, and therefore, in my opinion, need to be  
19 shared with the agency for your consideration.

20 There will be those among you who will  
21 recognize that my comments and suggestions here today  
22 are self-serving. I will make no apologies for that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and hasten to point out that just because they are  
2 self serving does not mean that they are not valid,  
3 nor that they are not also in the best interest of the  
4 patients of America with aortic aneurysms, the group  
5 that both you and I need to consider foremost.

6 Like any first generation therapy, the  
7 AneurX endograft is good, but far from mature  
8 technology. It is but the first step in an  
9 evolutionary process that promises to revolutionize  
10 the way we treat aortic aneurysms, but still needs  
11 considerable study, refinement, and most of all,  
12 judicious oversight to insure that it does not harm  
13 the patients of today while we seek to perfect the  
14 device of tomorrow.

15 Applied correctly and appropriately  
16 monitored, I believe that this device is safe and  
17 effective in achieving the goal of preventing aneurism  
18 rupture in the overwhelming majority of patients.

19 However, when improperly utilized,  
20 patients can be directly harmed or left unprotected  
21 from rupture while thinking they have been effectively  
22 treated.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           That this, in fact, has been happening  
2           since commercialization of these devices is  
3           indisputable. While it might be arguable that this is  
4           more of an indictment of the training process than  
5           condemnation of the physicians involved, I am  
6           compelled to pose the following questions.

7           Have patients been better served by the  
8           widespread and largely unregulated application of the  
9           technology than they would have been if treated by  
10          physicians thoroughly experienced with not only the  
11          endografting procedure itself, but also with the  
12          proper patient selection and surveillance, CT scan  
13          interpretation, and endoleak management?

14          In its present state, is the learning  
15          curve of this technology simply too steep for  
16          widespread commercialization?

17          And lastly, I ask: why should we allow  
18          patients to pay the price for physicians whose sole  
19          interest in the technology lies in being competitive  
20          in their marketplace?

21          So how would I suggest we address the  
22          problems we've seen since commercialization? We need

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 to recognize that aortic endografts are not simply a  
2 new kind of stent, and an aneurysms is not just a  
3 variation of standard arterial occlusive disease.  
4 Aortic endografting regardless of the device is a  
5 revolutionary procedure requiring new evaluation and  
6 planning techniques, device implantation skills,  
7 experience with novel secondary interventions to  
8 address frequently encountered complications, and the  
9 existence of strict surveillance protocols and  
10 mechanisms.

11 At this time, few physicians who have not  
12 been one of the various endograft trial sites can be  
13 expected to have the requisite skills or support  
14 systems to successfully implant this technology. So  
15 labor intensive is the evaluation and follow-up of  
16 these patients that my office has a full-time person  
17 devoted to the management of a database of patient  
18 measurements, surveillance appointments, and outcomes.

19 Is this degree of diligence in following  
20 these patients likely or even possible with the  
21 majority of physicians desiring to offer this  
22 procedure? Most think not, and consequently, the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 present approach of training and then selling these  
2 endografts to virtually anyone who wants to be able to  
3 offer this therapy is, in the opinion of many, not a  
4 winning strategy for our patients.

5 With a learning curve felt by most  
6 experienced endografters to well exceed 25 patients  
7 and hundreds of physicians anxious to be trained, we  
8 are putting thousands of patients at risk by this  
9 approach both now from insertion related complications  
10 or failures and in the future from rupture or  
11 unnecessary secondary procedures.

12 Furthermore, industry under threat of  
13 litigation is forced to expend limited time and  
14 resources training all comers, whether more are needed  
15 in a region or not, resources that could be better  
16 spent on research and development into new endografts  
17 that address the endograft failure modes now coming to  
18 light.

19 At this point in the evolution of this  
20 technology, it is clearly prudent and logical to limit  
21 the distribution of these devices to a finite number  
22 of Centers of Excellence, perhaps 50 to 100, who have

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 demonstrated skills in patient selection,  
2 implantation, and post procedure management. The  
3 centers could be required to adhere to strict  
4 surveillance protocols and to report data on their  
5 patients for subsequent analysis.

6 This approach allows patients to continue  
7 to maximally benefit from this evolving technology  
8 while limiting its misapplication and potential harm.

9 Furthermore, it allows us to study the  
10 technology with an eye towards perfecting it while  
11 minimizing as much as possible the risk to the  
12 patients we treat today.

13 Accordingly, new endograft applications to  
14 the FDA for approval should, in my opinion, be  
15 subjected to similar limited commercialization until  
16 the evolutionary process is far further along than it  
17 is at the present time.

18 While it may be debated whether or not the  
19 cat was prematurely released from its bag in the first  
20 place, most would agree that it should not have been  
21 given a free reign of the house and that it is well  
22 past time to recapture and control it while we still

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 can.

2 While industry, physicians, and the FDA  
3 all recognize that this needs to be done, each points  
4 the finger at each other when asked who should  
5 shoulder the burden and take the heat. Our patients  
6 meanwhile assume that someone is looking out for them.  
7 It's well past time we stop letting them down.

8 Thank you.

9 CHAIRPERSON TRACY: Thank you.

10 Any questions for Dr. Hodgson?

11 (No response.)

12 CHAIRPERSON TRACY: Is there anybody else  
13 who would like to make some comments?

14 (No response.)

15 CHAIRPERSON TRACY: If not, we'll end the  
16 open public hearing and take a 15 minutes break, and  
17 I'd ask everybody to leave so that they can bring some  
18 more chairs into the room for us.

19 (Whereupon, the foregoing matter went off  
20 the record at 11:21 a.m. and went back on  
21 the record at 11:40 a.m.)

22 CHAIRPERSON TRACY: Thank you for your

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 cooperation during the break, and I hope it got a few  
2 more seats in here.

3 The second topic that we'll be covering  
4 today is the Eclipse PMR Holmium Laser System, and  
5 first we will have the open public hearing. Is there  
6 anybody here who would like to make some comments?

7 (No response.)

8 CHAIRPERSON TRACY: If not, we will close  
9 the open public hearing and move on to the sponsor's  
10 presentation.

11 I just remind everybody to introduce  
12 yourselves and to state any conflict of interest that  
13 you might have.

14 MR. LANIGAN: Good morning, Dr. Tracy,  
15 members of the panel. My name is Richard Lanigan.  
16 I'm the Vice President of Government Affairs for  
17 Eclipse. I'm an employee of the company, and I hold  
18 stock in the company.

19 On behalf of the company and the clinical  
20 investigators, we'd like to thank you for your time  
21 and attention this morning in considering the PMA  
22 supplement for the Eclipse percutaneous myocardial

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 revascularization or PMR system.

2 Next slide, please.

3 During the company's presentation, I will  
4 provide a brief background and device description.  
5 Dr. Patrick Whitlow will provide the study design and  
6 methodology, as well as the clinical results.

7 Dr. William O'Neill will provide a risk-  
8 benefit analysis.

9 Next slide.

10 Additionally, we have other medical  
11 experts in attendance today to answer any questions  
12 from the panel regarding this PMA supplement. They  
13 include Dr. William Knopf, Dr. Jan Eric Nordrehaug,  
14 Dr. Gary Schaer, all three of which have been involved  
15 as PMR investigators.

16 Additionally, we have an experienced TMR  
17 surgeon, Dr. Keith Allen.

18 Next slide.

19 TMR was first studied in the 1980s and  
20 clinically applied in the 1990s. The first approved  
21 surgical TMR system was in 1998, and the Eclipse TMR  
22 system was approved by the FDA in February of 1999.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   The surgical approach involves a  
2 transmural channel all the way through the heart  
3 muscle from the epicardial or outside-in approach.

4                   Based upon the early clinical results with  
5 the surgical approach, Eclipse utilized its flexible  
6 fiber optic technology to develop the percutaneous  
7 approach, the Eclipse PMR system under consideration  
8 today.

9                   In the percutaneous approach, it is an  
10 inside out channel from the endocardial surface that  
11 goes part way into the heart muscle.

12                   Next slide, please.

13                   The three major components of the Eclipse  
14 PMR system under consideration today include a Holmium  
15 YAG laser that generates the mid-infrared laser  
16 energy, an ECG monitor which synchronizes the delivery  
17 of that energy to the patient's heartbeat to beat when  
18 the heart is its thickest, and a coaxial catheter  
19 deliver system.

20                   Next slide.

21                   This illustration depicts the distal  
22 portion of that delivery system in the left ventricle.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Notice the blue aligning catheter and the white laser  
2 catheter which includes the laser fiber itself.

3 These three components can be manipulated  
4 to access all areas of the myocardium, maintain  
5 contact to the heart wall, and create perpendicular  
6 channels into the muscle.

7 Next slide, please.

8 The laser catheter is an advancing  
9 catheter and torque controlled. The extendable fiber  
10 has an assembly on the tip which includes a 1.8  
11 millimeter quartz lens assembly. You'll notice a gold  
12 radiopaque band for visualization under fluoroscopy,  
13 and four nitinol petals near the tip that are designed  
14 to prevent complete transmural penetration.

15 The system delivers with four pulses to  
16 each channel site a total of eight Joules of energy to  
17 consistently create a five millimeter channel in the  
18 heart wall.

19 Next slide.

20 Looking more closely at the tip of the  
21 assembly, you'll see here from the other perspective  
22 that laser catheter is a pre-form at 90 degrees, and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the laser fiber extending from it with this assembly  
2 of the quartz lens, and you can see these nitinol  
3 petals as well as the tip.

4 And with that I'd like to introduce Dr.  
5 Whitlow.

6 DR. WHITLOW: I have no financial interest  
7 in Eclipse. My only interaction in terms of finances  
8 was that they paid for my trip here to present the  
9 data.

10 Next slide.

11 It's my pleasure to have the opportunity  
12 to discuss with you the results of two very pertinent  
13 randomized clinical trials that I believe provide very  
14 firm support for the approval of PMR.

15 The first trial is the PACIFIC trial,  
16 which was a prospective, randomized, multi-center  
17 study in the United States sponsored by Eclipse that  
18 randomized PMR in patients with medically refractory  
19 angina against a control group that got continued  
20 medical therapy.

21 The second trial was a trial done in  
22 Norway, the BELIEF trial, which was also a prospective

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 randomized trial, but this trial was double blinded,  
2 had independent assessment of angina. The patients  
3 didn't know whether they got treated or whether they  
4 got a sham control. So it provides additional data  
5 that I think are very important in considering  
6 approval of this treatment.

7 Next slide.

8 The PACIFIC trial is an acronym for  
9 potential angina class improvement from  
10 intramyocardial channels, and as I said, it randomized  
11 PMR plus continued medical therapy to medical therapy  
12 alone in patients with medically refractory Class III  
13 to IV angina in patients who had been turned down for  
14 both surgery and percutaneous revascularization.

15 Next slide.

16 The control group it's important to know  
17 in this trial was unblinded or not blinded from the  
18 beginning. The patients after enrollment in the trial  
19 in randomization were followed at three, six, and 12  
20 months, and we'll present the 12-month data primarily  
21 today, and no crossover from control to treatment was  
22 allowed in the study design.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Next slide.

2 These are the 11 centers that enrolled  
3 patients. You can see that a lot of very well known  
4 centers for doing clinical trials were involved, and  
5 several of the investigators are here for this trial.

6 Next slide.

7 The outcome measures for effectiveness  
8 included a primary endpoints angina improvement  
9 greater than or equal to two functional classes by the  
10 Canadian classification system and changes in exercise  
11 tolerance on the Bruce protocol, the modified Bruce  
12 protocol stress test.

13 Secondary endpoints were improvement of  
14 quality of life as measured by the Seattle angina  
15 questionnaire.

16 Next slide.

17 For safety outcome, mortality obviously  
18 was collected, and the incidence of adverse events was  
19 also tabulated.

20 For inclusion criteria, I've already told  
21 you most of them. The patients did have to be on a  
22 dose, a maximum dose of at least two anti-anginal

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 medications. The ejection fraction had to be greater  
2 than 30 percent, in addition to the severe angina and  
3 not be a candidate for other revascularization  
4 procedures.

5 The patient also had to have objective  
6 evidence of a reversible area of ischemia from  
7 thallium or other nuclear scintigraphy.

8 Next.

9 There are a lot of exclusion criteria  
10 listed on this slide. The pertinent ones specific to  
11 PMR is that the patient -- since the primary endpoint  
12 was exercise time, the patient could not be enrolled  
13 unless he could perform an exercise tolerance test and  
14 manifest angina on that test. He had to have a  
15 myocardial wall thickness of at least eight  
16 millimeters in order to not have an increased  
17 incidence of perforation if a thinned area of the  
18 myocardium were treated. If he had a thrombus on echo  
19 cardiography or angiogram, he was excluded, and if the  
20 patient had severe aortic stenosis, then he was also  
21 excluded.

22 Next slide.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   So a total of 200 patients were randomized  
2                   in this trial, 100 in each group. Withdrawals, there  
3                   were nine withdrawals during the study in the PMR plus  
4                   medications group, and eight patients withdrew in the  
5                   medications alone. So a total withdrawal rate of 8.5  
6                   percent.

7                   There were seven deaths during the year in  
8                   the PMR plus medication groups, and two deaths in the  
9                   medication group. That left, once we got down to 12  
10                  month data endpoints, 84 patients evaluable for PMR  
11                  plus medication and 90 for the medications alone  
12                  group, and you can see from the endpoints, the primary  
13                  and secondary endpoints we had a very high  
14                  ascertainment rate in those patients surviving without  
15                  withdrawals at the end of 12 months.

16                  Next slide.

17                  The data was analyzed in three different  
18                  manners. Most of the data I'm going to present to you  
19                  was analyzed by the last observation carried forward  
20                  method. That's the patient were analyzed by intention  
21                  to treat with baseline compared to their data at  
22                  different time points.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Values for patients who had reintervention  
2 or who withdrew from the study was carried over from  
3 the point of data collection most closely related to  
4 their withdrawal or their reintervention.

5 And values for patients who died were  
6 imputed to be the worst case scenario with an exercise  
7 tolerance test of zero time and angia (phonetic)  
8 classification that was imputed to be class five in a  
9 Seattle angina questionnaire of a score of zero in all  
10 categories.

11 When PMR reinterventions were counted as  
12 failures, that is, those only in the PMR group who had  
13 reintervention were counted, imputed the same way as  
14 those that died, the results of the tests were not  
15 different. All the statistically significant  
16 improvements were still improved significantly.

17 Next slide.

18 The other two methods of analysis, all  
19 surviving patients and surviving patients without  
20 interventions, we won't be presenting that data, but  
21 once again, all of the significant conclusions were  
22 verified by these other two methods of analysis as

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 well.

2 Next slide.

3 You can see that the average patient age  
4 was 62 to 63 years. The ejection fraction wasn't  
5 normal, but was only mildly impaired, over 50 percent  
6 in both groups. The majority of patients were male.

7 The majority of these patients had been  
8 intervened either with angioplasty, prior surgery, or  
9 a combination of those two.

10 Next slide.

11 Baseline characteristics are listed on  
12 this slide. It's important to note that about two-  
13 thirds of the patients had had a previous myocardial  
14 infarctions, and that about one-half of patients were  
15 diabetic in this study.

16 There were baseline differences in family  
17 history of coronary disease and hyperlipidemia at  
18 baseline with the medical group having more of each of  
19 these characteristics, but in multivariable analysis  
20 even accounting for these factors, still treatment  
21 was the major multivariate predictor of improvement of  
22 angina.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Next slide.

2 This is, again, an artist's depiction of  
3 the left ventricle with a PMR catheter involved. One  
4 thing I wanted to point out was that when the laser  
5 catheter is extended up to the ventricular wall, then  
6 you can see that the laser catheter here, the white  
7 laser catheter, actually will be pushed away from the  
8 wall visually. You can see that the catheter becomes  
9 loaded with pressure against the ventricular wall  
10 before the laser is fired, and that's an important cue  
11 to the operator that then it's okay to go ahead and  
12 fire the laser.

13 And any portion of the ventricular wall  
14 can be adequately treated so that the laser, again, is  
15 very perpendicular to the wall before the laser is  
16 fired.

17 Next slide.

18 The number of channels placed was an  
19 average of 16 in 30 minutes of laser time from the  
20 first laser channel to the last laser channel, and the  
21 average length of hospital stay was 1.2 days.

22 Now we'll go on to the results. The

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 primary endpoints, again, angina improvement greater  
2 than or equal to two classes by investigator  
3 assessment and improvement in exercise tolerance time  
4 on the treadmill and also improvement in quality of  
5 life.

6 Next slide.

7 If you look at the baseline distribution  
8 of angina, you can see that the patients by  
9 investigator assessment were all Class III and Class  
10 IV. Thirty-two percent of each group -- I'm sorry --  
11 38 percent of each group were Class IV and the  
12 remainder Class III.

13 And if you look down at the lower panel,  
14 the 12-month data shows a shift to the left in angina  
15 in the PMR treated patients with the majority of PMR  
16 treated patients being less than or equal to function  
17 Class II at 12 months, while the majority of patients  
18 in the medical group remained in Class III or IV.

19 And this difference was highly  
20 statistically significant with a p value of .001.

21 Next slide.

22 If we look at the way our endpoint was

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 stated, greater than or equal to two functional class  
2 improvement, five times greater in the PMR group than  
3 that medically treated group, 42 percent versus eight  
4 percent, again, very highly statistically  
5 significantly different.

6 We also instituted during the course of  
7 the trial an independent assessment of angina. It  
8 became very clear that that would be an interesting  
9 thing to do, and we needed to corroborate whether or  
10 not the investigator assessment of angina was, indeed,  
11 correct.

12 So this independent assessment was talked  
13 about and then implemented for the last 69 patients  
14 enrolled in the study. So consecutive patients that  
15 were enrolled, but only a subgroup of the patients got  
16 independent assessment at baseline and at 12 months.

17 And what you can see, again, is that there  
18 was a significant shift toward the left side of the  
19 graft in those patients treated with PMR, and the  
20 distribution of angina was shifted compared to the  
21 control group, again, highly statistically  
22 significant, corroborating that the improvement in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 angina seen by the investigator was also seen by an  
2 independent assessed angina.

3 Next.

4 This slide shows the angina improvement  
5 greater than two classes in this small subgroup of  
6 patients, and since it's only 69 patients, we have to  
7 take this dichotomous variable with a grain of salt,  
8 but what it showed was that of all surviving patients  
9 with that analysis, 21 percent of the PMR treated  
10 patients improved greater than two classes versus six  
11 percent of the medication group, again, statistically  
12 favoring PMR.

13 And if we look at all surviving patients  
14 without intervention, we basically get a similar kind  
15 of spread. Neither one of these were quite  
16 statistically significant, that is, a p value of .05,  
17 but with the small patient numbers, certainly the  
18 trend is encouraging that the independent assessment  
19 agreed at least in quality with the investigator  
20 assessment.

21 Next slide.

22 Exercise tolerance was assessed by the

1 modified Bruce protocol. It was standardized by a  
2 core lab who taught all of the technicians how to  
3 perform the test with the same kind of stopping rules,  
4 and both the exercise technicians and the core lab  
5 that read the test and reported the test were blinded  
6 as to patient treatment.

7 The patient before entering the study had  
8 two qualifying exercise tests that had to have a total  
9 time of within 15 percent of each other to make sure  
10 that the baseline was actually very well solid and the  
11 patient had to have angina on these tests in order to  
12 be randomized.

13 Next slide.

14 The baseline exercise time by the modified  
15 Bruce protocol was 419 to 451 seconds in the two  
16 groups, very similar.

17 Next slide.

18 And if we look at ETT improvement at 12  
19 months, the group with PMR improved by 50.8 seconds,  
20 while the group of people in the medical group that  
21 had pair tests actually decreased by six seconds. So  
22 a 57 second differential between the two groups,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 again, statistically much in favor of PMR.

2 Next slide.

3 There is no complete consensus that we  
4 could find in the literature for how many seconds or  
5 what kind of improvement actually constitutes a  
6 clinically significant improvement in exercise time.  
7 So we dichotomized the response in three different  
8 ways: a greater than 40 second improvement, greater  
9 than 60 second improvement, or a greater than ten  
10 percent improvement from baseline, and each of these  
11 were statistically significant improvements in the PMR  
12 group no matter how you analyzed the data, no matter  
13 how you dichotomized it.

14 Next slide.

15 Next we used the Seattle angina  
16 questionnaire to quantify a quality of life  
17 assessment. This questionnaire has been validated for  
18 patients with coronary disease. It was designed for  
19 patients with coronary disease, and it addresses the  
20 full spectrum of responses of patients with coronary  
21 disease and has very little influence of other co-  
22 morbid conditions that go along with coronary disease.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Next slide.

2 There are five components to the Seattle  
3 angina questionnaire, and you can see on this slide  
4 that improvement from baseline is plotted, and  
5 improvement from baseline was dramatically improved by  
6 PMR compared to medical therapy and highly  
7 statistically significant for all five of these  
8 variables.

9 Next slide.

10 There is no one recognized number for  
11 improvement on the Seattle angina questionnaire that  
12 turns out to be clinically significant. The numbers  
13 mentioned are between five and ten point improvement.  
14 So we plotted on this slide the percentage of patients  
15 in each group who had greater than ten point  
16 improvement in these four scales of the Seattle angina  
17 questionnaire, and once again, for three of the four,  
18 they were highly statistically significantly in favor  
19 of PMR, and a trend in the fourth characteristic.

20 Next slide.

21 For the term of angina stability, a raw  
22 score of greater than 50 is said to be an improvement,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealgross.com](http://www.nealgross.com)

1 a clinically significant improvement in this  
2 particular parameter, and 48 percent of the PMR  
3 treated patients versus 19 percent of the medical  
4 group improved to this degree.

5 So, again, a change that's highly  
6 statistically in favor of PMR.

7 Next slide.

8 So we've shown from this data that there  
9 are significant improvements in clinical parameters in  
10 these patients treated with PMR in terms of angina  
11 class, exercise time and quality of life. Now we have  
12 to turn toward the safety data to assess whether or  
13 not this was really a worthwhile procedure.

14 Next slide.

15 First, the all cause mortality over one  
16 year. This is a Kaplan-Meier curve, and by log rank  
17 analysis there was no difference between the two  
18 groups. I showed you data earlier that seven patients  
19 died over the year in the PMR group. Two died in the  
20 medical group, and this was not statistically  
21 different between the two groups.

22 If we look at the other adverse event

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 parameters, angina requiring hospitalization occurred  
2 in three of the PMR patients within 30 days. So we're  
3 looking at peri-procedural kind of events. Angina  
4 requiring hospitalization in the medical group  
5 occurred in two patients.

6 If we look at myocardial infarction, one  
7 patient in the medical group had a myocardial  
8 infarction while two in the treated group, the PMR  
9 treated group, had an infarction.

10 If we look at access site complications,  
11 obviously that was limited to the patients who had  
12 PMR, and we had two complications, one pseudo aneurysm  
13 and one leg ischemia that both resolved with  
14 treatment.

15 And then I think all the other events  
16 listed here we should go through individually to give  
17 you an idea of how important those events were.

18 Next slide.

19 One of the things we learned from this  
20 data, there were three episodes of complete heart  
21 block that occurred during the procedure. All three  
22 of these patients had the high septum being treated.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 So we know now that the high septum has an increased  
2 incidence of complete heart block that occurred in  
3 three of 29 patients who had that area treated. It  
4 shouldn't have been very surprising, I think, but we  
5 proved it in this study.

6 One of those complete heart blocks was  
7 resolved by temporary pacing. One resolved with  
8 atropine treatment, and the third patient had  
9 temporary pacing that had to be followed by permanent  
10 pacing.

11 In addition, at 26 days after treatment,  
12 one patient developed bradycardia that was symptomatic  
13 and required a permanent pacemaker.

14 Next slide.

15 When we look at the 30-day death, one  
16 treated patient who had no acute complications with  
17 his procedure died suddenly 28 days after treatment.  
18 So he was included in this peri-procedural group. At  
19 autopsy there were no adverse findings, no tamponade,  
20 no perforation, nothing from the procedure itself.  
21 The patient had very advanced calcific coronary artery  
22 disease and died a sudden death without a new

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 infarction and without any adverse sequelae that we  
2 could see from the treatment.

3 Next slide.

4 There were two patients hospitalized for  
5 heart failure after treatment with PMR within the  
6 first 30 days. One occurred at 16 days and one 18  
7 days after treatment. Both patients had a previous  
8 history of congestive heart failure. By the  
9 investigator both of these incidents were estimated to  
10 be of moderate severity and resolved with treatment  
11 with a diuretic.

12 It's important to know also that when  
13 ejection fractions were looked at between baseline and  
14 three months in the PMR group, there was no change in  
15 ejection fraction in the group, in the mean ejection  
16 fraction.

17 Next slide.

18 Non-QA myocardial infarctions occurred in  
19 two patients, one at 16 days and one at 26 days after  
20 treatment, and in the medical control group, as I  
21 already mentioned, one of these patients had a non-QA  
22 infarction as well three days after he was enrolled in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 this study.

2 Next slide.

3 There were three post procedural effusions  
4 found on routine surveillance and protocol mandated  
5 echo cardiography. They were asymptomatic and ever  
6 caused any clinical problems, and they occurred in  
7 three patients.

8 In addition, there was one patient who had  
9 a frank perforation. This patient had the septum  
10 treated also, had 20 channels placed in the septum,  
11 and one of those channels caused a perforation. There  
12 was a one millimeter VSD that was seen on the  
13 angiogram, the left ventricular angiogram after the  
14 procedure, and that persisted at the one-year follow-  
15 up echo; didn't cause any clinical significance, and  
16 the patient never developed any problem, and on shunt  
17 series, there was no shunt that was found. So it was  
18 a very small hole that had no clinical sequelae, but  
19 it was a perforation.

20 Next slide.

21 There were three cases of intraprocedural  
22 neurologic events. The first patient had a posterior

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 circulation CVA, and he had a history of being treated  
2 with coumadin therapy prior to his hospitalization for  
3 PMR.

4 The second patient likewise had a history  
5 of CVA, and he had a left hemispheric TIA with  
6 symptoms completely resolving within 24 hours after  
7 treatment.

8 The third patient was a patient that  
9 developed complete heart block and hypotension. It  
10 took some time for his complete heart block and  
11 hypotension to be resolved, and that patient had a  
12 right hemispheric CVA. He did not have any previous  
13 history of a CVA, however.

14 So to summarize these events, of which  
15 there were quite a number and we've gone over what I  
16 think are clinically important, the adverse events are  
17 expected in this group of very sick patients who have  
18 a catheterization or any kind of procedure, and we  
19 have to take that into account how sick the patients  
20 were before being treated, but there's definitely a  
21 finite but significant risk involved with treatment  
22 with PMR.

1           We believe that the adverse events may be  
2 minimized by very rigorous physician training, by  
3 careful patient selection, and by appropriate labeling  
4 such as reminding the operators that treatment of high  
5 ventricular septum may be associated with a high  
6 chance with that ten percent or so risk of complete  
7 heart block.

8           Next slide.

9           The 12-month adverse events are listed on  
10 this slide. Angina requiring hospitalization is the  
11 first of these events that we had listed. That was an  
12 a priori, and the protocol was listed as a serious  
13 adverse event, and the data were collected carefully.

14           If you look at these patients, 60 percent  
15 of both groups, over 60 percent in the previous year  
16 prior to randomization had been hospitalized an  
17 average of two times each. So we believe that this is  
18 a profoundly important event in the patient's life and  
19 also a cost kind of analysis. So we believe that it  
20 really belongs in the serious adverse events, and as  
21 I said, it was defined a priori.

22           That was the only adverse event that was

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701