

1 electrode in position, and a couple of those have been  
2 confirmed by post operative CT scans.

3 So this is an issue that will require  
4 continuing addressing.

5 CHAIRMAN PATOW: Dr. Canady.

6 DR. CANADY: I'm a little uncomfortable  
7 with the concept of saying that the two deaths were  
8 totally unrelated only in the sense that I think  
9 they're perfectly related with this kind of surgery in  
10 this area, both the serratia meningitis as well as the  
11 brain stem infarct.

12 And so in a sense because it's being  
13 implanted at the time of the tumor resection, you  
14 could argue that they're unrelated. On the other  
15 hand, you could argue that if at some point someone  
16 wished to implant the device not at the time of the  
17 surgery, that those would, in fact, be related  
18 complications to the surgical procedure.

19 CHAIRMAN PATOW: Dr. Shelton.

20 DR. SHELTON: I guess just a follow-up on  
21 that. There wasn't much <sup>\*\*</sup> information on that second  
22 death in our packet, the case from Pittsburgh, but the

1 feeling was the brain stem stroke was from the tumor  
2 removal, not from the insertion of the implant; is  
3 that right?

4 DR. BRACKMANN: As I understand it, that's  
5 correct. I have spoken with the surgeons, and this  
6 was a very large tumor, and they felt that there was  
7 arterial involvement by the tumor, actually was  
8 involved by the tumor, and that the stroke occurred as  
9 a result of tumor removal and was unrelated to the ABI  
10 placement.

11 DR. SHELTON: So then, in fact, just by  
12 putting the implant in, they didn't increase the risk  
13 to these patients?

14 DR. BRACKMANN: That was their judgment.

15 DR. SHELTON: Right.

16 DR. CANADY: I guess I would have just one  
17 follow-up on that, which is I think that probably may  
18 be true, but if you look at all posterior fossa or  
19 approaches to lesions in this area, even if you look,  
20 for example, at microdecompression where no tumor is  
21 involved, you will see those complications.

22 So I think it's important if at some point

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1 down the road someone is going to implant the device  
2 without a tumor, not at the time of the tumor, that,  
3 in fact, becomes a device related complication.

4 CHAIRMAN PATOW: At this point what we  
5 should be asking is for clarification from the panel.

6 DR. CANADY: Okay.

7 CHAIRMAN PATOW: And then we can take on  
8 those discussions a little bit later.

9 Dr. Kileny.

10 DR. KILENY: Thank you.

11 I have several questions. I'm a little  
12 confused by some of the numbers because the numbers  
13 that you are reporting here today and the numbers  
14 reported in the submission, there are some  
15 discrepancies in terms of the number of patients who  
16 did not stimulate.

17 According to the submission, there were  
18 seven, as Dr. Brackmann mentioned, who failed to  
19 stimulate immediately postoperatively, and an  
20 additional nine who did not stimulate further down the  
21 line in whom it was considered to be the electrode  
22 migration.

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1 In Ms. Ebinger's presentation, the number  
2 of non-stimulable patients reported is 13. So is it  
3 16 total or 13?

4 Then there were two who were explanted,  
5 and I'm not sure whether those two are counted among  
6 these 16 or not.

7 DR. BRACKMANN: The total number of non-  
8 stimulations was 16. There were 14 actually that did  
9 not stimulate at first hook-up, and one of those  
10 subsequently had an implant on the other side and is  
11 included in the data because of performance on the  
12 other side, but counting the first implant, she was a  
13 non-stimulator. So that's a little bit of the  
14 confusion.

15 But there were 14 who did not stimulate at  
16 the time of first hook-up, two who had performance for  
17 a period of time and then became nonperformers for a  
18 total of 16.

19 DR. KILENY: Thank you.

20 Further, to clarify some of the number  
21 issues, there were 90 patients initially available for  
22 evaluation, subtracting the two patients who were

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1 deceased. Now, ten of these, if I understand  
2 correctly, were lost to follow-up. So they're really  
3 not in your pool anymore, correct? Or they were never  
4 in the pool because they never reached either the  
5 three or six month. They just didn't show up for a  
6 variety of reasons.

7 MS. ARNDT: Right. They are not generally  
8 lost to follow-up. I believe several of them are, and  
9 I can pull out those details if you need them, but  
10 they basically for some reason -- they couldn't  
11 travel, they were ill, something like that. They  
12 missed both the three and the six month evaluation,  
13 but we did catch up with them at the next eval.

14 DR. KILENY: So if we take those into  
15 consideration, plus four who did not reach the  
16 evaluation stage, I guess, at three months and two who  
17 were explanted, your total pool is really 74 patients  
18 in whom you can report safety and efficacy data  
19 because you really don't have information on the 16  
20 patients.

21 MS. ARNDT: Okay. My count is a little  
22 different. Maybe we can resolve this.

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1 We're reporting that ten subjects missed  
2 those evals. So we had missing data for ten subjects.  
3 Six patients rather than four were implanted less than  
4 three months at the time that we collected the data.  
5 So they weren't yet captured, and then we had one  
6 subject who, as Dr. Brackmann described, was explanted  
7 prior to the three month interval.

8 So our numbers, including the 13 patients  
9 who did not stimulate at activation, those add up to  
10 30, which gives us an effectiveness sample of 60  
11 patients.

12 DR. KILENY: However, you did have access  
13 to the patients who did not stimulate. So while it's  
14 clear that they did not stimulate, and it's --

15 MS. ARNDT: Oh, I see.

16 DR. KILENY: -- quite clear what are  
17 effectiveness results would have been --

18 MS. ARNDT: Okay.

19 DR. KILENY: -- they were, in fact,  
20 available to be included in the effectiveness data as  
21 non-performers or non-stimulable where you could have  
22 assigned scores of zero. Otherwise this is like

1 reporting a surgical series and really just focusing  
2 on results in those who were actually successful.

3 MS. ARNDT: Okay. I understand now.

4 Martyn addressed that a little bit in his  
5 talk, and I'll just have him expound on that.

6 DR. HITSELBERGER: I guess our philosophy  
7 is that it's probably not the most helpful thing to do  
8 to confound two different types of poor performance.  
9 So if you have no performance because you didn't have  
10 activation, is it helpful to aggregate those non-  
11 performers with people who did have stimulation, but  
12 who did poorly?

13 So it is, in my view, more productive to  
14 disaggregate those two parts of the cohort, and as  
15 long as you clearly describe and quantify the  
16 proportion of nonactivation as an outcome of the  
17 trial, I think that is more helpful to potential  
18 recipients than aggregating the whole thing and  
19 including those guys in the group that had no  
20 performance. That was the philosophy.

21 DR. KILENY: You think that it's  
22 statistically then acceptable if you take this

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1 approach, to look at the proportion of non-stimulable  
2 patients relative to 90 when, in fact, you really  
3 didn't have access to 90, and we don't know how many  
4 of the ten who didn't show up were perhaps non-  
5 stimulated?

6 You know it's just a concern of as much as  
7 possible, as you have mentioned in your presentations,  
8 to have accurate presentation of the data and not to  
9 be caught in any sort of data reporting bias  
10 situation.

11 CHAIRMAN PATOW: At this point if we could  
12 keep our questions for clarification, and then we'll  
13 save the discussion until later, that would be great.

14 MS. ARNDT: If I could say one more thing.

15 CHAIRMAN PATOW: Certainly.

16 MS. ARNDT: Our philosophy was to provide  
17 this information to potential recipients in the way  
18 that Martyn has described, but in a way that they  
19 could see, all right, I have this chance of receiving  
20 benefit from the device. There's an 18 percent change  
21 that I will not receive auditory precepts, but if I'm  
22 not in that group, if I do, in fact, stimulate, then

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1 here's the range of performance that I might expect to  
2 see.

3 CHAIRMAN PATOW: Thank you.

4 Dr. --

5 DR. KILENY: One last question, and this  
6 is really a question.

7 CHAIRMAN PATOW: Okay.

8 (Laughter.)

9 DR. KILENY: Do you, in fact, have any  
10 data on preoperative audiological data? I, of course,  
11 realize this was not an issue of implantation  
12 criteria, but do you have access to preoperative  
13 otologic information on these patients?

14 MS. ARNDT: We do have preoperative  
15 audiograms for most of the subjects.

16 CHAIRMAN PATOW: Dr. Francis.

17 DR. FRANCIS: I have a question to Dr.  
18 Brackmann.

19 Any change in just the baseline  
20 complication rate that's known to be associated with  
21 these resections in patients that have the implant?  
22 And I'm specifically asking about the CSF leak rate.

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1                   And I wonder in terms of packing that  
2 cavity with fat afterwards if there was any tendency  
3 not to pack as much as one would want, and whether  
4 there would, therefore, be an increase in CSF leak  
5 rate and that was related to one of the patients that  
6 died.

7                   DR. BRACKMANN: Of course, we have to seal  
8 the CSF.       Now, our routine techniques for  
9 translabyrinthine approach is to open the middle ear,  
10 pack the eustachian tube, pack the entire middle ear,  
11 and then fill the cavity with fat. We fill it to the  
12 level of the dura. We close the dura. We did not  
13 alter that technique for the ABI, and we did not  
14 identify an increased rate of CSF leak.

15                  CHAIRMAN PATOW: Thank you, Dr. Brackmann.

16                  Dr. Roeser.

17                  DR. ROESER: There were 90 subjects that  
18 received the eight channel electrode and 27 with the  
19 21 channel electrode. Could you clarify the 20 21-  
20 channel difference?

21                  And secondly, did you see performance  
22 differences between the two electrode arrays?

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1 MS. ARNDT: Those are very good questions.  
2 The device that was used in the European trial, the  
3 regulatory requirements, as you know, are quite  
4 different. They did a pilot study, I believe, with  
5 ten subjects, and the device that they used contained  
6 20 electrodes. So a 20 electrode device.

7 Once they started their clinical trial, so  
8 to speak, the device that they requested CE Mark for,  
9 they went to the 21 electrode platform I think  
10 primarily to be more consistent with our Cochlear  
11 implant where we've got 22 channels in our existing  
12 program systems.

13 With respect to differences in device  
14 effectiveness, it's very hard to evaluate given the  
15 way that the European data was collected and reported.  
16 There were six different languages represented, and  
17 the test measures there, sometimes they are labeled  
18 and are called open set measures, but they're not  
19 really very open set, those kinds of things.

20 I just think it's very difficult to know.  
21 Certainly theoretically the added channels going from  
22 eight to 21 provide a lot of redundancy, and maybe Dr.

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1 Brackmann can comment on this. You know, if the  
2 device is in place quite perfectly, you've got a lot  
3 more chance of getting a response.

4 DR. BRACKMANN: Yeah. We think it can  
5 only improve performance by allowing more possible  
6 sites of stimulation.

7 CHAIRMAN PATOW: Thank you, Dr. Brackmann.

8 MS. THORNTON: Dr. Shannon.

9 CHAIRMAN PATOW: Question, Dr. Woodson?  
10 Oh, I'm sorry.

11 DR. SHANNON: I have one thing to add to  
12 that question.

13 CHAIRMAN PATOW: Yes.

14 DR. SHANNON: I'm Robert Shannon.

15 The other factor that enters into the  
16 multiple electrodes going from eight to 21 is that one  
17 of the problems in programming a device is programming  
18 around non-auditory stimulation, and the 21 gives much  
19 more flexibility in being able to do that. It gives  
20 a lot more options not only in providing different  
21 channels of information for sound reception, but also  
22 for avoiding non-auditory.

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1 CHAIRMAN PATOW: Thank you.

2 I think, Dr. Woodson, did you have a  
3 question?

4 DR. WOODSON: Yes. On the questionnaire,  
5 it was noted that seven of the 44 patients indicated  
6 it was not the right decision, and I wondered if you  
7 had any information on why they thought that.

8 MS. ARNDT: I don't believe that we've  
9 looked specifically at that. We could certainly pull  
10 those outcomes out.

11 My guess is that they're just not scoring  
12 very well, getting a lot of speech perception benefit  
13 from the device.

14 And as Kiara just pointed out, they also  
15 may be patients with normal hearing in the  
16 contralateral ear.

17 CHAIRMAN PATOW: Thank you.

18 Dr. Duffell.

19 DR. DUFFELL: A question for Dr.  
20 Brackmann.

21 How long is this surgery typically? I  
22 know it probably varies from patient to patient.

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1                   And then how much additional OR time is  
2 added for the placement of this device?

3                   DR. BRACKMANN: The total surgery varies  
4 tremendously depending upon the size of the tumor and  
5 where it's performed. Typically at our institution,  
6 the surgery is about four to five hours. The  
7 additional time for setting up stimulation  
8 intraoperatively does not exceed one hour.

9                   DR. DUFFELL: Okay, and then one last  
10 design question. On the drawing of the device, what  
11 is that second lead there? I know what the first one  
12 is. Obviously that's the stimulation part.

13                   DR. BRACKMANN: That's a ground electrode  
14 which is placed under the temporalis muscle.

15                   DR. DUFFELL: Okay. Thank you.

16                   CHAIRMAN PATOW: Dr. Hood.

17                   DR. HOOD: I'm wondering relative to the  
18 electrode design and the differences between the eight  
19 and the 21, is there any weight difference between  
20 those two? And I'm just curious if there would be a  
21 difference in opportunity for migration.

22                   DR. BRACKMANN: Well, I can't answer

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1 specifically weight. I think that the total mass, the  
2 electrode surfaces are slightly smaller with the 21  
3 electrode, but the weight is insignificant.

4 The carrier, which is really the key to  
5 fixation is the same. This is designed to fit within  
6 the confines of the lateral recess. So I do not  
7 believe that there will be any differences in the way  
8 it's handled or fits.

9 DR. KAHN: And, Dr. Brackmann, this is Dr.  
10 Kahn.

11 The migration issue then is what, just the  
12 trough, the big space, or is it so many disk surfaces  
13 that are hard to place or technical competence?

14 DR. BRACKMANN: Well, no. Where we have  
15 been able to identify difficulty it has been in very  
16 large lateral recesses. There are some patients  
17 because of just their anatomy who have very large  
18 lateral recesses. The electrode was designed to fit  
19 in the average or normal lateral recess. We've  
20 identified some patients where this is very patchless.

21 Where the electrode is placed, we pack fat  
22 in the lateral recess to hold it in position, and it's

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1           apparently that that has been inadequate.

2                       CHAIRMAN PATOW:   Dr. Gulya.

3                       DR. GULYA:   I just had a question that the  
4           mention of the slightly smaller electrode reminded me  
5           of.  What's the charge density at the slightly smaller  
6           electrode?  Is that still within sort of the same  
7           range as you had with the larger one?

8                       DR.   SHANNON:       Yes.       We had many  
9           discussions of this.

10                      This is Robert Shannon again.

11                      We had many discussions of this in the  
12           design of the electrode in the initial design  
13           differences between the eight electrodes used in the  
14           U.S. and the 21 electrodes used in Europe.  The  
15           diameter, the charge density is primarily related to  
16           the area on the edges of the electrode, so the  
17           circumference of the electrode, and the diameter of  
18           the 21 electrode design is 70 percent of the diameter  
19           of the eight electrode design.

20                      And when we designed the eight electrode  
21           design, we took our most conservative estimate of the  
22           charge damage limits that were then available from

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1 animal experiments and went more than a factor of two  
2 beyond that as a safety margin, and the 70 percent  
3 reduction in size with the 21 electrodes still leaves  
4 a considerable margin of safety on top of that.

5 CHAIRMAN PATOW: Other questions from the  
6 panel? Dr. Shelton.

7 DR. SHELTON: Another question back on the  
8 claims area for this. In looking at the numbers in  
9 this area, was the number of non-stimulable patients  
10 included in these percentages? Because it doesn't  
11 look like it was stated independently like you'd  
12 mentioned.

13 MS. ARNDT: The presentation is a little  
14 bit skewed since you're not seeing the full document,  
15 but if you look at the package insert in its entirety,  
16 the results of clinical studies section begins with a  
17 description of the adverse effects. It lays out the  
18 non-stems first thing, and then it goes into the 60  
19 effectiveness subjects, and then there is a final  
20 section under clinical considerations that provides  
21 more detailed information about the non-stimulation  
22 rates.

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1 DR. SHELTON: And why was it decided to  
2 use the statistics rather than use many, most, few to  
3 describe the results?

4 MS. ARNDT: We just patterned this on the  
5 insert that we had developed for our Cochlear implants  
6 and a recent guidance document from FDA on how these  
7 inserts should be structured, and our feeling until we  
8 sat in with the panel yesterday was that FDA was  
9 moving toward a more quantitative way of describing  
10 these results as opposed to assigning the qualitative  
11 indicators of many, most, and so forth.

12 CHAIRMAN PATOW: Other questions from the  
13 panel? Dr. Francis.

14 DR. FRANCIS: To what extent might you be  
15 able to say that non-medical intervention, such as  
16 auditor rehab., lip training, things like this, played  
17 a role in your data? And you know, that may be  
18 important in passing it on to the patient, for  
19 example.

20 MS. ARNDT: Certainly I think  
21 rehabilitation is something that these patients need.  
22 They need a lot of support, a lot of visits to their

1 audiologists to make sure that they have the best  
2 possible device programming.

3           If you remember the slide that Kiara  
4 showed for the longitudinal lip reading enhancement  
5 data, what you saw was that the bar for audition plus  
6 lip reading improved, but the lip reading alone scores  
7 stayed fairly stable.

8           I think it's most audiologists' experience  
9 that certainly some lip reading training can be  
10 helpful, particularly for some individuals, but the  
11 ability to lip read is not something that's easily  
12 trained. You're kind of good at it or you're not.

13           So certainly for individuals,  
14 rehabilitation can certainly enhance the effects. I  
15 think it's helpful also to set the appropriate  
16 expectations for what the patient might get from the  
17 device, but I don't think you would expect that by  
18 requiring someone to attend a lot of lip reading  
19 rehabilitation sessions that they would improve their  
20 performance so much that the device wouldn't be  
21 indicated or that the outcome would look much  
22 different.

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1 DR. FRANCIS: How about auditory rehab.?

2 MS. ARNDT: That's certainly something  
3 that we would recommend. Learning how to listen with  
4 the device and what all of these sounds mean is  
5 absolutely critical.

6 CHAIRMAN PATOW: Dr. Kileny.

7 DR. KILENY: How standardized was the  
8 neurophysiologic monitoring across the centers  
9 participating in these trials in terms of which  
10 cranial nerves were monitored, criteria for response  
11 criteria, and so forth and so on?

12 MS. ARNDT: I'll get started, and then I'd  
13 like to ask Dr. Van den Honert to help me a bit or Bob  
14 Shannon also.

15 The EABR procedure was not a dependent  
16 measure, if you will, for the clinical trial. It's a  
17 helpful procedure that really was developed as we got  
18 going with this technology.

19 We attempted to provide centers with  
20 guidance as to what they should do, what cranial  
21 nerves should be monitored, what the response looked  
22 like. We depended a lot on the work of Mickey Waring

1 to show clinicians what the response did, in fact,  
2 look like, but there's a lot of variability across the  
3 centers in terms of the kind of equipment they used,  
4 stimulation patterns, recording montages, all of those  
5 things.

6 DR. KILENY: How about response criteria  
7 that may be derived from the stimulation of other  
8 cranial nerves that may be in the vicinity, especially  
9 since quite a bit of anatomical distortion may be  
10 extracted in these cases?

11 MS. ARNDT: Sure.

12 DR. KILENY: Were there any criteria for,  
13 let's say, when you stimulate with your electrode pad  
14 and you get some type of response with a certain  
15 latency? This is associated with such-and-such  
16 cranial nerve. This is what I'm after.

17 MS. ARNDT: Chris, can you help us out  
18 with that?

19 DR. VAN DEN HONERT: Yes. I'm not sure I  
20 understand the question, but yeah.

21 CHAIRMAN PATOW: Could you identify  
22 yourself, please? Thank you.

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1 DR. VAN DEN HONERT: Chris Van den Honert  
2 from Cochlear Corporation.

3 CHAIRMAN PATOW: Thank you.

4 DR. VAN DEN HONERT: There was, in the  
5 protocol, there was a recommendation for continuous  
6 cranial monitoring of, as I recall, five, seven, nine,  
7 five, seven, and nine, I believe, so that any evoked  
8 response not dependent on specific latencies related  
9 to the pulses, but any evidence of myogenic activity  
10 would be considered stimulus related. The stimulus  
11 was applied in bursts. So it was fairly readily  
12 identified as stimulus related.

13 Does that address the question?

14 DR. KILENY: In part, but what I was  
15 asking really is to what extent the various centers  
16 have the knowledge of the response characteristics  
17 that may be associated with a specific cranial nerve  
18 that is not the cochlear nucleus.

19 For instance, if you activate the  
20 electrode carrier and you get a response with a  
21 certain characteristic, this means that we're  
22 stimulating cranial nerve five, for instance. Was

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1 that sort of looked at?

2 DR. VAN DEN HONERT: I guess the short  
3 answer is yes, but it depends on which channel you're  
4 examining. The ABI channel is the one that was  
5 examined for specifics of weight for morphology  
6 (phonetic).

7 I was getting feedback before.

8 Okay. The ABI channel is the one that was  
9 examined for specifics of latency and weight for  
10 morphology, but that was used as a positive indicator  
11 to indicate an auditory response. It was not used  
12 specifically to examined for non-auditory responses  
13 because it's a fairly nonspecific recording with the  
14 electrodes along the midline.

15 Certainly any nonspecific myogenic  
16 activity that was identified, a long latency, for  
17 example, five milliseconds or longer, would be a  
18 suggestion that something was being stimulated other  
19 than auditory pathway, and that was regarded as such,  
20 but it wasn't specific in the sense that there was no  
21 identification of what trigeminal stimulation would  
22 look like in the ABR trace or facial stimulation would

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1 look like in the ABR trace. It was just sort of a  
2 general latency exclusion. Anything long and large  
3 would be considered myogenic.

4 DR. BRACKMANN: We monitored with separate  
5 monitors facial trigeminal, ninth nerve, and then far  
6 afield for the EABR. So if there were spread to the  
7 other nerves, that would be picked up on those  
8 specific monitors as ninth nerve stimulation or facial  
9 stimulation, not on the EABR machine.

10 We identified the extraneous activity on  
11 those specific monitors, those electrodes in the  
12 muscle, facial, palate, and so on.

13 CHAIRMAN PATOW: I'd like to take one last  
14 question then from Dr. Woodson if we could.

15 MS. ARNDT: Pardon me. We've got one more  
16 comment if we can.

17 CHAIRMAN PATOW: Oh, quickly.

18 DR. HITSELBERGER: I was just going to say  
19 that --

20 CHAIRMAN PATOW: You'll need to come to a  
21 microphone. This is Dr. Hitselberger.

22 DR. HITSELBERGER: The monitoring of the

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1 seventh nerve, the facial nerve, and the ninth nerve  
2 are critical to the placement of the electrode. This  
3 is, of course, the part that the neurosurgeon does,  
4 and even just a little bit of motion, maybe half a  
5 millimeter, will result in profound changes on the  
6 ABR.

7 So far from being a detriment, the  
8 evaluation of where the ninth and the seventh nerve  
9 especially are, that's kind of critical to ascertain  
10 exactly where the lateral recess is, and not so much  
11 the lateral recess, but the cochlear nucleus.

12 Okay? Does that answer you?

13 DR. KILENY: Yes.

14 CHAIRMAN PATOW: Thank you.

15 Last question then from Dr. Woodson.

16 DR. WOODSON: Yes. I wanted to clarify  
17 some of the labeling with regard to the magnet because  
18 you mentioned, Dr. Brackmann, that you usually don't  
19 leave the magnet in and they glue this.

20 But the package insert talks about, you  
21 know, leaving the magnet in, and then you take it out  
22 in case they need to have an MRI. Is that the way the

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1 package insert is intended to be or if it's different  
2 than what the usual application is

3 MS. ARNDT: That is the way that it's  
4 presently written, with the intent being that if you  
5 knew that a patient would require serial MRIs  
6 immediately as NF2 patients, you certainly would  
7 remove the magnet at the time of implant, but that  
8 does provide you still with the option of keeping the  
9 magnet in if an MRI is not indicated for some reason.

10 DR. WOODSON: Isn't the primary indication  
11 of this it's intended use is for MF2 patients?

12 MS. ARNDT: Yes.

13 DR. WOODSON: So you would think the  
14 labeling would be directed towards those patients.

15 MS. ARNDT: We certainly can do that.  
16 That makes a lot of sense.

17 CHAIRMAN PATOW: Is there any way to tell  
18 whether the magnet is in place or not once the  
19 incision is closed?

20 MS. ARNDT: Absolutely. I think you can  
21 do that by X-ray.

22 DR. BRACKMANN: Just a plain X-ray would

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1 show that. You insert a nonmetallic sylastic disk in  
2 the place of the electrode -- I mean in place of the  
3 magnet. So that would be readily identified by just  
4 a plain X-ray.

5 DR. STALLER: Steve Staller from Cochlear.

6 You can tell very easily by taking an  
7 external magnet on a coil and put it on the patient's  
8 head.

9 CHAIRMAN PATOW: Thank you.

10 DR. STALLER: But you can do an X-ray if  
11 you'd like.

12 (Laughter.)

13 CHAIRMAN PATOW: I'd like then to close  
14 this session of questions for the sponsor from the  
15 panel. Thank you very much for your attention.

16 Unless there's an objection, I would like  
17 at this time to have our lunch break. It's been a  
18 long morning, and if we could come back then at an  
19 hour from now, which would be a quarter of one.

20 MS. THORNTON: Twelve, forty-five.

21 CHAIRMAN PATOW: Twelve, forty-five.

22 Thank you.

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1 I'm still trying to figure out whether my  
2 watch is on Eastern standard or Central time.

3 And at that time we'll have the FDA  
4 presentation.

5 Thank you very much.

6 (Whereupon, at 11:41 p.m., the meeting was  
7 recessed for lunch, to reconvene at 12:45 p.m., the  
8 same day.)

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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (12:52 p.m.)

3 CHAIRMAN PATOW: This afternoon we'll  
4 start with the FDA presentation.

5 Dr. Waxler.

6 DR. WAXLER: Good afternoon. Sorry for  
7 the delay.

8 First we'll hear from Dr. Jaffee. You're  
9 going to introduce the PMA. Teri is going to  
10 introduce the PMA, and then Dr. Jaffee will give the  
11 clinical.

12 CHAIRMAN PATOW: Thank you.

13 MS. CYGNAROWICZ: Good afternoon, Mr.  
14 Chairperson, distinguished panel. I'm Teri  
15 Cygnarowicz, audiologist and scientific reviewer in  
16 the ENT Devices Branch and team leader of this PMA.

17 As you have already heard an overview of  
18 the regulatory history, the device description, and  
19 details concerning the trial, I will simply go right  
20 into introducing my review team.

21 I would like to<sup>\*\*</sup> thank these individuals  
22 for all of their review time and effort on this

1 project.

2 Dr. Jaffee, physician and clinical  
3 reviewer of the surgical and medical aspects of the  
4 ABI;

5 Dr. James Kane, audiologist and clinical  
6 reviewer of the audiological data;

7 George Koustenis, biostatistician;

8 Dr. Sandy Weininger, electrical engineer;

9 Dr. Loren Zaremba, physicist;

10 Dr. William Regnault, mechanical engineer;

11 Dr. Joseph Jorgens, biomedical engineer,  
12 reviewer of the device software;

13 DR. Vasant Malshet, toxicologist;

14 Karen Baker, sterilization;

15 Ronald Swann, Office of Compliance;

16 Robert Fish, bioresearch monitoring;

17 And Mary Ann Wollerton, patient labeling  
18 review.

19 At this time I would like to introduce Dr.  
20 Sid Jaffee, who will provide you with comments  
21 regarding the medical and surgical aspects of this  
22 device.

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1 DR. JAFFEE: Good afternoon. Much of what  
2 I'm going to be saying now has been spoken this  
3 morning, again, by Dr. Brackmann and Dr. Hitzelberger,  
4 and sometimes things pay to be repeated though.

5 So could I have the first slide? Next.  
6 Got to get it in its mode.

7 We've heard the history this morning of  
8 the development of the ABI. It may pay to be  
9 repeated. There has been interest in this device for  
10 more than 20 years.

11 Again, in 1993, the Cochlear Corporation  
12 began a clinical trial with the nucleus 22, the eight  
13 electrode ABI system. This PMA reviews only this  
14 device.

15 In 1998, the FDA approved the nucleus 24  
16 with the 21 electrode Cochlear implant. Immediately  
17 following that, the corporation then went to develop  
18 the ABI system using the 21 electrodes.

19 Next.

20 The components, as mentioned earlier, the  
21 current ones are 24 implants, the body worn SPrint  
22 speech processor, headset and cables, and two

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1 programming systems.

2 Next slide.

3 Animal studies were done. These were done  
4 with primates. No significant adverse reactions were  
5 noted in the cochlear nucleus brain tissue, and this  
6 suggested the feasibility of re-implantation if it  
7 became necessary.

8 Next.

9 Surgery, translabyrinthine approach is the  
10 preferred approach for acoustic tumor removal and  
11 identification of the cochlear nucleus. The ABI has  
12 been performed, usually performed at the time of the  
13 second acoustic tumor removal.

14 The investigational study, and this has  
15 been discussed many times, today consists of 92  
16 subjects. The major complications were the extrusion  
17 of the receiver stimulator in one patient which  
18 required repeat surgery, necrosis in the flap which  
19 required repeat surgery, one patient who developed  
20 dizziness, blurred vision and tinnitus which gradually  
21 resolved.

22 Next.

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1           The investigational study, again, was on  
2 these 92 patients. We heard these numbers expounded  
3 many times this morning. Dr. Brackmann corrected the  
4 13 individuals at the bottom to tell us that it was  
5 14, and otherwise we have seen these numbers before.

6           Next study or next slide.

7           I'm going to skip this because of  
8 information that I found out about this morning.

9           Next.

10          And in summary, again, there's no device  
11 related neurological complications occurred during the  
12 study. The medical surgical and the device related  
13 complications were characteristic of Cochlear  
14 implantation and/or acoustic tumor removal. All were  
15 closed or resolved.

16          Next slide.

17          And in conclusion, the majority of  
18 patients received benefit from the ABI. Therefore,  
19 there is potential benefit for patients without much  
20 additional risk.

21          Thank you.

22          CHAIRMAN PATOW: Thank you, Dr. Jaffee.

1 Dr. Kane.

2 DR. KANE: If I could just say while we're  
3 waiting for the slides to come up that individual test  
4 metrics were reviewed quite well this morning. So I'm  
5 not going to repeat each one of those, but my intent  
6 is to raise some issues to have the panel discuss or  
7 think about in terms of --

8 MS. THORNTON: Excuse me, Jim. Could you  
9 speak into the microphone a little more?

10 DR. KANE: I'm sorry. I thought I was.

11 MS. THORNTON: It's very -- yeah. It's  
12 very hard.

13 DR. KANE: Better?

14 MS. THORNTON: Yeah.

15 DR. KANE: Okay. -- to raise some issues  
16 of data reporting and how they relate to potential  
17 labeling claims.

18 Next slide. Next one. Go ahead.

19 I see two areas of limitation in the data  
20 that were presented, one having to do with the U.S.  
21 study and the second part having to do with the  
22 European study, and I'll address those separately.

1 Go ahead and put up those.

2 These are the subject reports that were  
3 presented this morning, and there's another line  
4 there. Okay.

5 Of the 90 subjects reported for efficacy  
6 -- I mean for safety -- only 60 were reported for  
7 efficacy purposes. However, one-third of these  
8 subjects there's no data on.

9 There was some discussion this morning  
10 whether or not the subjects that failed to stimulate  
11 or were explanted should be included in the efficacy  
12 data, and also there were 16 subjects that either  
13 missed the eval. or were implanted too early to have  
14 efficacy reports on.

15 It's my opinion, I guess, that the 14  
16 subjects who failed to stimulate should be included in  
17 the efficacy results simply because failure to  
18 stimulate is a potential outcome of the study, and  
19 that is something that's known a priori.

20 The other 16 subjects that we're talking  
21 about can be followed and<sup>\*\*</sup> data can be gathered for  
22 them.

1           The other issue in relation to these  
2 subjects, whether we include 74, 60 in the efficacy  
3 analysis, is that one of the statements in the  
4 protocol was that efficacy data will be based on the  
5 six months endpoint or the three month endpoint if the  
6 subject was not available in six months. I would like  
7 to see the percentage of the efficacy subjects that  
8 were evaluated at three months and the proportion that  
9 were evaluated at six months that contribute to the  
10 overall report statements.

11           Next slide.

12           The European protocols differed from the  
13 U.S. protocols in a number of ways, and you can go  
14 ahead and hit that.

15           First of all, test materials was presented  
16 in six different languages. Scoring methods, chance  
17 scores, testing methods were inconsistent across test  
18 sites, and various electrode systems were used for the  
19 27 subjects that were reported in the European study.

20           Now, it is true that all of these things  
21 contribute to variability. However, mean data is  
22 particularly important in this instance because the

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1 electrode array that the sponsor is asking approval  
2 for is the 21 electrode array, and the data from the  
3 European studies were either 20 or 21 electrodes,  
4 whereas the eight electrode array in the United  
5 States.

6 Intuitively one would expect better  
7 performance from a 21 electrode array in terms of  
8 speech processing ability than an eight electrode  
9 array, but there were no mean data to compare  
10 performance across electrode systems.

11 So I took the individuals scores that were  
12 published in graph form and tried to estimate what  
13 each individual had for three particular tests: the  
14 sound effects recognition test, the stress pattern  
15 perception test, and the closed set word  
16 identification test. That was common to both the  
17 European study and the U.S. study.

18 Next change.

19 The first test results are the  
20 environmental sound recognition test, and I should say  
21 that also in fairness to the sponsor and just as a  
22 matter of reference I also included a two channel

1 electrode system which was the precursor to the eight  
2 electrode array, and chance scores are reported in the  
3 middle column for each one of the tests, and the  
4 sample size as well that contributed to the mean score  
5 that's in the last column.

6 And on the bottom you'll see the number of  
7 subjects were seven that contributed to the European  
8 data for this particular test, two from England and  
9 eight or five from Germany.

10 And as pointed out by the sponsor, there's  
11 big differences in the data from sites, but, you know,  
12 a mean score still is a major central tendency of the  
13 data, and it's a number that can be used.

14 Unfortunately, the European studies did  
15 not report any variability data. There's no standard  
16 deviations for them, and the House study, which was  
17 published in the Journal of Rehabilitation Research  
18 and Development in 1987 by Eisenberger, et al., did  
19 not report standard deviation. So I left that  
20 information out from the American study.

21 And you will note that the House initial  
22 electrode system, the mean score for this particular

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1 test was 42 percent, whereas it was 54 percent in the  
2 U.S. study for this PMA, and if we recognize the  
3 limitations of mean scores and we combine England and  
4 Germany, we end up with 52 percent.

5 And surprisingly, given all of that  
6 variability, there's not that large a difference  
7 across electrode arrays or processors.

8 Next slide.

9 These are simply those data in graphic  
10 form with the House Ear Institute on the left, U.S.  
11 study in the middle, and the European study on the  
12 right.

13 Next slide.

14 This is the stress pattern perception  
15 test, and you can see from the differences in chance  
16 scores for each measure across the European study the  
17 inherent variability are there and also the number of  
18 subjects that came from various sites, most of them  
19 coming from Germany.

20 The mean score across those subjects is  
21 approximately 72 percent, <sup>\*\*</sup> which compares extremely  
22 well with the U.S. study and also the older electrode

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1 array system.

2 Next slide.

3 These are simply, again, the visualization  
4 of the data.

5 Next slide.

6 This is the closed set worth  
7 identification test, and again, you will note the  
8 differences in chance scores across the European  
9 sites. However, if you take those data and you  
10 average them, lo and behold, they come out very, very  
11 close to both the U.S. study as well as the House  
12 study.

13 Also, it's consistent. The data are  
14 consistent in that for the closed word identification,  
15 performance, absolute performance for the means was  
16 roughly 30 to 40 percent poorer than on the stress  
17 pattern perception test, and that was also consistent  
18 across electrode array.

19 So what this says is that even though the  
20 number of electrodes increased tenfold, it had no  
21 effect in terms of these three measures, at least,  
22 which were sound alone on performance.

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1 Next slide.

2 And that, again, is just simply graphic  
3 representation of the data.

4 Go ahead, Karen.

5 In summary then, even though we have these  
6 difference, and surprising and maybe unfortunate that  
7 frequency resolution did not improve across electrode  
8 array, all ABI systems, however, did provide acoustic  
9 information to the patient or subject via electrical  
10 stimulation.

11 And also increasing the number of  
12 electrodes provides other benefits aside from speech  
13 perception, such as being able to program out  
14 nonauditory effects.

15 Go ahead, Karen, and do it again.

16 And also allowing changes in method of  
17 stimulation, such as monopolar or bipolar.

18 Next slide.

19 So the questions to the panel from my  
20 perspective then, given that the request for approval  
21 is based on an eight electrode system and there are  
22 limited data from the 21 electrode system, do the

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1 efficacy data from the nucleus 22 ABI system with  
2 eight electrodes; support approval of the nucleus 24  
3 ABI system with 21 electrodes.

4 And the second question is: does the  
5 hearing benefit from this device for the NF2 patient  
6 exceed the risk of implantation?

7 Thank you.

8 CHAIRMAN PATOW: Thank you.

9 We'll now have an opportunity for the  
10 panel to ask questions of the FDA presenters. Are  
11 there questions from the panel?

12 Dr. Duffell.

13 DR. DUFFELL: You mentioned in your  
14 presentation you kind of disagreed with the sponsor  
15 about the way they were representing the efficacy data  
16 because it did include the no stim. patients. In  
17 their labeling as it exists now, because I can't  
18 recall having seen it, do they disclose fully, you  
19 know, what happened with those patients such that at  
20 least the reader of the material gets the information  
21 even though it may not have been factored in the  
22 overall analysis?

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1 DR. KANE: James Kane.

2 If my memory serves me correctly, they do  
3 I believe Patti mentioned this morning state initially  
4 that roughly 18 or 20 percent did not stimulate, and  
5 then they go on and report the rest of the results.

6 However, I don't know how meaningful that  
7 really is in terms of information to a patient,  
8 whether they hold onto that or whether it should be  
9 scaled. That's a question for the panel to discuss,  
10 I think.

11 CHAIRMAN PATOW: Other questions from the  
12 panel? Dr. Hood.

13 DR. HOOD: In comparing the U.S. and the  
14 European performance data, I'm wondering if there was  
15 opportunity in the data to look at performance above  
16 chance levels and if that would represent things any  
17 differently.

18 I just noticed that the chance levels were  
19 different. Were those your estimates on the European  
20 tests or --

21 DR. KANE: <sup>\*\*</sup>No, no. Those were the  
22 sponsor's report chance levels.

1 CHAIRMAN PATOW: Other questions from the  
2 panel?

3 (No response.)

4 CHAIRMAN PATOW: Okay. We now have an  
5 opportunity for 15 minutes of additional comments from  
6 the sponsor.

7 I want to thank the FDA panel members or  
8 presenters, and the sponsor has an opportunity now if  
9 they'd like to present some additional comments.

10 MS. ARNDT: We'd just like to make a  
11 couple of clarifications first. The numerical error  
12 that Linda pointed out this morning in the claim is a  
13 typo. The number was written nine out of 31 as 61  
14 percent. It is, in fact, 61 percent, but the number  
15 is 19. I'm sorry about that.

16 CHAIRMAN PATOW: Could you help me find  
17 that?

18 MS. ARNDT: It is in the environmental  
19 sounds recognition claim; is that right?

20 CHAIRMAN PATOW: Identification of  
21 environmental sounds? \*\*

22 MS. ARNDT: Yes. There should be a number

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1 that's written nine out of 31, and it's actually 19.

2 CHAIRMAN PATOW: I'm sorry. I'm not  
3 seeing it. Can you read the entire claim?

4 MS. ARNDT: All right. It is the slide  
5 that's labeled "Questionnaire Results" actually, the  
6 first claim in that slide.

7 CHAIRMAN PATOW: Questionnaire?

8 MS. ARNDT: Questionnaire Results. N  
9 equals 44. Sixty-one percent of subjects, nine out of  
10 31. It's going to be the very last set of claims in  
11 the last presentation this morning. Nine should be  
12 19. That does, in fact, come out to 61 percent.

13 CHAIRMAN PATOW: Thank you.

14 MS. ARNDT: Secondly, the last set of  
15 slides that I showed were labeled as required  
16 training. You may have noticed that, and I stated  
17 that we were recommending training, and the  
18 recommendation is, in fact, the case.

19 We very much want to train our teams in  
20 all of these procedures, but as a sponsor we don't  
21 feel that we can require training of certainly well  
22 qualified professionals. So I'd like to make that

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1 distinction.

2           And then lastly, coming back to the point  
3 that the non-stimulation cases should be included as  
4 an outcome and represented in the effectiveness data,  
5 we clearly want to communicate the fact that we've had  
6 a lot of non-stimulations. That is an expected  
7 outcome of this procedure. It's something that  
8 patients should be aware of, but again, it is our  
9 opinion that we can do that separately. We want  
10 patients to, first of all, know the chances of  
11 stimulating. So will this work for me? Yes/no. I've  
12 got a 20 percent chance that it may not work for me  
13 based on this subject, on this study. But if it does,  
14 in fact, work, then the results for patients who  
15 stimulated range from X to X.

16           But we don't believe that assigning chance  
17 or zero scores to non-stimulations really represents  
18 the outcomes for patients who did stimulate in a way  
19 that provides good information to the consumer.

20           CHAIRMAN PATOW: Thank you.

21           We now have committee deliberations, and  
22 I would first like to ask that the primary panel

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1 reviewers, Dr. Gayle Woodson and Dr. Paul Kileny,  
2 present a summary of their review findings.

3 Dr. Woodson.

4 DR. WOODSON: I really must say I've  
5 appreciated the presentations so far today. I think  
6 at first blush it sounds like deliberating on  
7 approving the first auditory brain stem implant is  
8 somewhat of a radical step, but we know that there  
9 have been people who have been implanted for more than  
10 20 years in investigational, and so we have a long  
11 history to look back on.

12 And so I think it seems fairly clear from  
13 that and then from the presentations we heard from two  
14 of the subjects today that this is something that  
15 provides a real opportunity to hear for people who  
16 would not otherwise be able to hear, but it's still  
17 our job on the panel just to make certain that we  
18 review everything and make sure that it's safe, and  
19 that the effectiveness is adequately represented in  
20 the packaging.

21 And I think one of the first questions  
22 that was asked is whether we can use the data that's

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1 presented to support an implant system which  
2 technically is not the same implant system that was  
3 tested. I think we have a long history of results  
4 from the Cochlear implant experience to kind of help  
5 us in this, and I think that the other argument that  
6 this is a very small population and it would take  
7 quite a long time to accrue a number of patients to  
8 test this specific system is very reasonable.

9 The major issue between the two systems  
10 that would relate to safety would have to do with the  
11 difference in the implant itself, and I think we've  
12 already heard that the major difference is the number  
13 of electrodes and the fact that the individual  
14 electrodes would be smaller in the new system, but the  
15 European experience suggests that there's no  
16 difference in safety, and there are some theoretical  
17 and mathematical calculations that tell us that the  
18 charge to current density should be safe.

19 So then the other question is to make  
20 certain that the packaging clearly is supported by the  
21 data so that patients can make a rational decision.

22 I must say that when I first went through

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1 the material, I had the same impression as others,  
2 that I couldn't quite understand why we were  
3 separating out the non-stimulable patients from the  
4 ones that could be stimulated, but I'm beginning to  
5 see the rationale of that.

6 The patient may be -- what chance is there  
7 that I will be helped? And then if I am going to get  
8 some benefit, I think if you have all of those zeros  
9 in there, the mean is going to be a lot lower than  
10 what it would be for those that are stimulated.

11 I heard one of the patients today present  
12 to us saying you want to know what does it sound like  
13 to me. Well, we can't really tell us what it sounds  
14 like to her, and so I think the best information we  
15 can get is from analyzing from some of the data from  
16 patients who have been stimulated, and I can see the  
17 rationale that if you include in that the patients who  
18 don't get any benefit at all, that perhaps the data  
19 that you'd get, although it might be statistically  
20 significant, might not have that much meaning for the  
21 patient.

22 Those are my comments.

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1 CHAIRMAN PATOW: Dr. Kileny.

2 Thank you.

3 DR. KILENY: Thank you.

4 I'm going to read my comments so that we  
5 can move along.

6 As we all know, this is a premarket  
7 approval supplement application for the Cochlear  
8 Corporation, nucleus 24 auditory brain stem implant.  
9 Studies in the United States have taken place on the  
10 nucleus 22 eight channel ABI system coupled to a  
11 spectra 22 speech processor.

12 A 21 electrode system has been  
13 investigated in Europe, and the sponsor requests  
14 approval for the nucleus 24 M ABI in which a 21  
15 electrode array is coupled to a SPrint processor.

16 There were a variety of adverse effects  
17 and complications associated with the ABI. Many of  
18 those were minor, such as the presence of non-auditory  
19 effects that could be resolved through programming.

20 Two complications resulted in the  
21 necessity to explant the ABI. These were receive  
22 stimulator extrusion and a flap necrosis. None of

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1 these are specific to the ABI. These complications  
2 could occur with standard Cochlear implant surgery.

3 The two patients were deceased of causes  
4 not directly associated with ABI surgery.

5 The main adverse outcome associated with  
6 the ABI was lack of auditory stimulation. This  
7 occurred in 16 patients of the total 74 available for  
8 investigation. It is significant to know in many of  
9 these patients there were not electrophysiological  
10 responses associated with cochlear nucleus stimulation  
11 obtained intraoperatively.

12 Following the elimination of ten patients  
13 who dropped out of the study due to poor health and  
14 four patients who did not reach the initial evaluation  
15 period at three months, 76 patients remained  
16 available for efficacy studies. Of these, two  
17 patients mentioned earlier were explanted, leaving 74  
18 patients in the pool.

19 The sponsor reports efficacy data on 60  
20 patients who did have auditory precepts.

21 Patients who did have auditory precepts  
22 were tested with close set speech and phoning

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1 recognition tests and one open set sentence  
2 recognition test. Lip reading enhancement with the  
3 activation of the ABI was also investigated. Patients  
4 were also tested on environmental sound recognition.

5 Overall patients who did have auditory  
6 precepts enjoyed some degree of environmental sound  
7 and auditory speech recognition. Many patients  
8 demonstrated an improvement of lip reading abilities  
9 with the activation of the ABI.

10 Responses to questionnaires further  
11 substantiate overall moderate auditory benefit  
12 obtained by these patients with the ABI.

13 Based on the data submitted and the  
14 similarities and differences between the nucleus 24  
15 21-electrode ABI system and the nucleus 22 eight-  
16 electrode ABI system, it would be my recommendation  
17 that the sponsor's request for approval of nucleus 24  
18 ABI should be granted.

19 The 21-electrode system capable of  
20 monopolar and bipolar stimulation, coupled with the  
21 SPrint processor, will likely represent an advantage  
22 relative to the nucleus 22 ABI system.

1           It is also important to know that there  
2 were no significant threats associated with the ABI  
3 beyond those typically associated with post neurophos.  
4 (phonetic) and craniotomy, acoustic neuroma resection,  
5 and the placement of the Cochlear implant type  
6 receiver-stimulator. It is, therefore, considered  
7 that the hearing benefit of this device for  
8 neurofibromatosis Type 2 patients exceeds the risk of  
9 implantation.

10           It is, however, of some concern that 16  
11 patients failed to stimulate. It is important to  
12 include the proportion of patients who did not  
13 stimulate to those that did stimulate accurately and  
14 to represent results from the patients who did not  
15 stimulate appropriately.

16           And these are my recommendations. The  
17 sponsor should modify the reporting of the efficacy  
18 data in all appropriate place to include results from  
19 patients without auditory precepts post implantation.  
20 the sponsor should modify the presentation of the  
21 efficacy results in a manner appropriate with a single  
22 subject binomial statistical design. This should

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1 include performance ranges representing appropriately  
2 the non-stimulable patients and the percent of  
3 patients relative to the available 74, not 60, whose  
4 performance was significantly different from chance.

5 The sponsor should provide preoperative  
6 audiological information on the patients participating  
7 in the clinical trials. This should include  
8 preoperative pure tone thresholds, speech recognition  
9 results, and length of severe to profound hearing  
10 loss, where appropriate. If the patient had  
11 measurable hearing in the contralateral ear with  
12 respect to the implanted side, this should also be  
13 reported.

14 This information may help in counseling  
15 patients and also in timing the surgery and in the  
16 decision making process as at what point should the  
17 acoustic neuroma be resected and an ABI be implanted,  
18 and if, in fact, preoperative hearing does have a  
19 positive effect, maybe the timing could be earlier and  
20 patients would avoid having no hearing for a  
21 substantial amount of time.

22 In other words, it may not be beneficial

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1 to wait until the patient is completely deaf.

2 The sponsor should substantially improve  
3 the section on intraoperative neurophysiology in the  
4 surgeon's manual.

5 And finally, given the overall small  
6 number of currently implanted patients and the  
7 relatively large number of patients without auditory  
8 precepts, I would recommend some period that I'm sure  
9 will be discussed of post approval studies.

10 Thank you.

11 CHAIRMAN PATOW: Thank you, Dr. Kileny.

12 I'd now like to ask the panel to consider  
13 the two main questions that have been posed. One is:  
14 do the efficacy data from the nucleus 22 ABI system,  
15 eight electrodes, support approval of the nucleus 24  
16 ABI system, 21 electrodes?

17 And secondly, does the hearing benefit  
18 from this device for the neurofibromatosis Type 2  
19 patient exceed the risks of implantation?

20 I think let's take them in order one at a  
21 time and start with the first question. We've heard  
22 from Dr. Woodson and Dr. Kileny some information, but

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1 I'd like to have a sense from the rest of the  
2 committee if they're comfortable with the use of data  
3 from one system to support this request on a different  
4 system.

5 Comments? Dr. Shelton.

6 DR. SHELTON: I feel comfortable with  
7 that. I think that the nucleus 24 receiver-stimulator  
8 now approved, we all have experience with that in this  
9 country, and it's been reliable.

10 The only thing that's not proven is the 21  
11 electrode, and I think that our experience with  
12 electrode design and construction has come along. I  
13 would feel comfortable approving it this way.

14 CHAIRMAN PATOW: Dr. Gulya, can we get --

15 DR. GULYA: I pretty much feel the same.

16 CHAIRMAN PATOW: The same.

17 DR. HOOD: Linda Hood.

18 I would agree with that. I think that  
19 there is sufficient experience with the 24. It offers  
20 more opportunity for adjustment and has been proven in  
21 other ways.

22 CHAIRMAN PATOW: Dr. Canady, anything in

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1 the neurosurgical literature that would lead us to  
2 perhaps a different conclusion?

3 DR. CANADY: No, I would agree.

4 DR. KAHN: I agree. I think there's  
5 sufficient data.

6 CHAIRMAN PATOW: Dr. Roeser?

7 DR. ROESER: I agree.

8 CHAIRMAN PATOW: How about Dr. Francis?

9 No?

10 DR. FRANCIS: The same.

11 CHAIRMAN PATOW: The same. Okay.

12 Thank you. I think we have a consensus  
13 then that use of this data to support this PMI is  
14 appropriate, and we feel that it's appropriate.

15 Let's go then to the second question.  
16 Does the hearing benefit from this device for the  
17 neurofibromatosis Type 2 patient exceed the risk of  
18 implantation?

19 There are a number of smaller sub-  
20 questions, I think, underneath here, and I think they  
21 have to do with how data was collected and what  
22 patients would be included when you look at the

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1 concept of benefit. I think what I'd like to do is  
2 start the discussion with discussion of the total  
3 number of subjects that we think should be included in  
4 any of the claims related to benefit.

5 Is it appropriate just to include those  
6 that have had precept afterwards or should the entire  
7 population of patients be included or what subset?

8 DR. WOODSON: I think the issue has to do  
9 with whether you're looking at the percent of patients  
10 that had benefit versus the quality of that benefit,  
11 and those are two different questions.

12 And I think in my mind trying to resolve  
13 what the difference was because, like I said, I  
14 thought, gee, why are they carving out the best ones  
15 to get their numbers on, and it bothered me.

16 But there's two questions. One is how  
17 likely am I to be able to get some hearing, and then  
18 if I get it, what's the likelihood of that.

19 Now, the idea of having it displayed in a  
20 range, as you suggested, really makes a lot of sense.  
21 You know, it could be zero; it could be 20. But I  
22 think the idea of saying you've got a one in so many

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1 chances of getting hearing, and if you get hearing,  
2 this gives you an idea of how it sounds is reasonable,  
3 as long as it's presented really clearly.

4 CHAIRMAN PATOW: So for you it sounds like  
5 the presentation in the materials and claims is an  
6 important feature.

7 DR. WOODSON: Yeah.

8 CHAIRMAN PATOW: Dr. Roeser?

9 DR. ROESER: I agree with Dr. Woodson.  
10 It's really two questions. I was looking in the  
11 labeling material, and I did not see where it  
12 indicated that some patients did not stimulate. I  
13 might have missed it. It might be in there somewhere.

14 CHAIRMAN PATOW: It actually --

15 DR. ROESER: And if it's in there, then I  
16 think it's recognized that there are patients who  
17 don't stimulate.

18 And once we resolve that issue, then we  
19 could look at the wording of the claims and talk about  
20 those who did.

21 CHAIRMAN PATOW: Let me just if I could  
22 tell you where those are found so that we're all on

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1 the same page. In the proposed package insert on page  
2 104, under the section "Medical Surgical  
3 Complications," this is Attachment 17(a), Volume 20,  
4 Attachment 17(a). On page 104, "Adverse Events," it  
5 lists "Medical Surgical Complications."

6 And the first sentence there is, "Sixteen  
7 of the 90, or 17.8 percent, ABI recipients were not  
8 able to perceive sound with the ABI."

9 Then there's a second reference to the  
10 same percentage, which is on page 108 under "Clinical  
11 Considerations." The last sentence in the first  
12 paragraph essentially restates that same information.

13 I would just like to point out that that  
14 information, however, is not included in between there  
15 under clinical study results on page 106, and that for  
16 me is perhaps where this information also needs to be  
17 inserted.

18 Dr. Canady.

19 DR. CANADY: One possibility which might  
20 resolve it for everybody is to calculate the  
21 effectiveness data with and without and present both.  
22 So if you look at the group of all patients who were

1 implanted, calculate the effectiveness data; make  
2 comments regarding the fact that there were 17 percent  
3 that had no response from the beginning, and then  
4 calculate the data again, the same effectiveness for  
5 those who did have a response.

6 Because I think as an individual, some  
7 people would want to look and just say, "What is my  
8 benefit in general?" and look to the first table, and  
9 others would have made the decision they're going to  
10 go ahead and presume they're in the effective group.  
11 What is the outcome?

12 And I think if we just calculate them both  
13 ways and present it, it might provide the consumer  
14 with the maximum benefit.

15 CHAIRMAN PATOW: Dr. Kileny?

16 DR. KILENY: I mean, I don't think anybody  
17 here wants to turn off patients from choosing this  
18 treatment when it's the only one available for hearing  
19 restoration of these patients, but at the same time,  
20 I think it's important for patients and for future  
21 professionals who will be involved with this type of  
22 treatment to have data and numbers that they can look

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1 at and make some decisions themselves.

2 And I think Dr. Canady's suggestion is a  
3 good one.

4 The other issue is when you report the  
5 percent of non-stimulable patients relative to what  
6 pool you report it to, do you really report it  
7 relative to the 90 patients, surviving patients who  
8 were implanted or you report it relative to the 74  
9 patients who, in fact, were available for the study on  
10 which there are reports?

11 Because data is really only available in  
12 74 patients. So if we report the percent of non-  
13 stimulable patients, it is my belief that it should be  
14 reported relative to the 74 because those are the only  
15 ones that we have knowledge on. We don't have data on  
16 the remaining 16.

17 CHAIRMAN PATOW: Dr. Hood.

18 DR. HOOD: I'm wondering if we could ask  
19 the sponsor about that. My impression was that some  
20 or most of the other patients did stimulate, but  
21 weren't available for three and six month testing and  
22 follow-up.

1 CHAIRMAN PATOW: Would you be able to  
2 provide us with that information?

3 MS. ARNDT: Sure, absolutely. I'll get  
4 the right folder.

5 Correct me if I'm wrong, Dr. Kileny, but  
6 I think the way that you're coming up with the 74  
7 number is the 60 subjects that we've included as the  
8 effectiveness sample, the ten patients that we said  
9 missed their three or six month evaluations, and then  
10 additional patients who had not -- had not reached  
11 their three month evaluation at the time of database  
12 closure.

13 Okay. With respect to the ten subjects  
14 who missed their three and six month evaluations, we  
15 do know that seven of those ten subjects are  
16 successful patients. They're users of the device.  
17 They did come back and picked up an evaluation  
18 interval at a later amount of time. So they are not  
19 lost to follow-up. Seven of the ten are, in fact,  
20 good users, successful users.

21 Three of the ten are non-users, with two  
22 of those three really being lost to us with respect to

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1 follow-up.

2 Is that the information that you needed?

3 DR. KILENY: Well, then --

4 MS. ARNDT: Okay, but they all did  
5 stimulate.

6 PARTICIPANTS: Oh, they all stimulated?

7 MS. ARNDT: They all stimulated, but three  
8 of them are non-users, with two of them being lost to  
9 us for purposes of follow-up.

10 DR. SHELTON: But when you say they  
11 stimulate, is that a six week period? You do the  
12 initial stim. at six weeks?

13 MS. ARNDT: Yes.

14 DR. SHELTON: Okay.

15 MS. ARNDT: So they do have functional  
16 devices as far as we know.

17 DR. KILENY: And you do have data on the  
18 seven that did stimulate, but not necessarily at the  
19 six months interval.

20 MS. ARNDT: That's right, right.

21 DR. KILENY: Why isn't --

22 MS. ARNDT: So our data in a way is

1 conservative.

2 DR. KILENY: Right, but then this, again,  
3 changes the numbers that we're talking about. Now  
4 we're talking about -- first of all, I think the data  
5 from those seven should be included, especially if  
6 they stimulate. So those scores should be included  
7 with maybe an asterisk indicating that this was not  
8 obtained at the six month point, and the number of  
9 non-stimulable patients relative to the total pool  
10 should be then restated because now you have 19 out of  
11 the, I guess, 90, and I'm not sure what happened to  
12 the four that didn't reach the evaluation stage.

13 But what I'm trying to get at I think that  
14 these numbers need to be reconciled and reported  
15 because if you have seven that did stimulate, there  
16 are obviously scores on them. Three of those  
17 apparently don't stimulate. So those should be added  
18 to the 16 who did not.

19 MS. ARNDT: No, no. That's not quite  
20 right.

21 DR. KILENY: And the percentages should be  
22 recalculated.

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1 MS. ARNDT: All of these ten patients  
2 stimulated. So their devices were operational at the  
3 time of activation. Seven of the ten went on to miss  
4 their three and six month intervals, test intervals,  
5 but we picked them up and were able to evaluate them  
6 on the speech perception test at a later interval.

7 Three of the seven, they did stimulate so  
8 the device was functional at activation, but they did  
9 not elect to basically come back, although we are in  
10 contact with one of the three, and the other two have  
11 been lost to us, but they all stimulated.

12 Let me make sure that I understand. In  
13 order to aggregate this data in a meaningful way you  
14 have to make some kind of a decision about what data  
15 you're going to aggregate. Our decision was that we  
16 would pick out a six month data point as a fairly good  
17 indicator of a medium range outcome. We would be very  
18 conservative, and for every patient who, because of  
19 their condition, health concerns, et cetera, who did  
20 not have six month data but had three month data, we  
21 would report that, and we've got those numbers for  
22 you.

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1 To continue on that trail, and now we're  
2 going to be adding data that maybe is picked up at 24  
3 months or 36 months and pooling that all together is  
4 not quite as clean, and that's what you'd like to see  
5 us do; is that correct?

6 CHAIRMAN PATOW: I think that's one of  
7 the --

8 DR. KILENY: Well, I think that --

9 CHAIRMAN PATOW: It needs to be discussed.

10 DR. KILENY: Somehow that data needs to be  
11 accounted for because right now the way the data has  
12 been presented in the submission and in your  
13 presentations, it didn't address these issues. So  
14 maybe in a narrative fashion at least, it needs to be  
15 addressed.

16 MS. ARNDT: That's certainly one way to do  
17 it.

18 DR. KILENY: Appropriately and accurately.

19 MS. ARNDT: We could retain the  
20 effectiveness data as reported for the 60 subjects,  
21 but then describe the outcomes for this particular  
22 set.

1 CHAIRMAN PATOW: Thank you very much.

2 DR. GULYA: Could I jump in here?

3 Julie Gulya.

4 I think probably a separate description of  
5 these outlier patients would be appropriate. When you  
6 set up a clinical trial, you want to say when your  
7 follow-ups are going to be, and sometimes it doesn't  
8 make any difference whether you get somebody's blood  
9 value at three months or four months or whatever, but  
10 I have a real concern in including somebody who's two  
11 years down the road where we know that there is a  
12 substantial learning effect with these devices.

13 So I would have real problems including  
14 the individuals that you didn't have the three and six  
15 month data for, and they may be 24 months, 36 months,  
16 whatever. When we don't then tell the consumer that,  
17 well, this is going to then probably skew the data a  
18 little towards the better because they're going to  
19 have more experience and, therefore, more learning and  
20 probably better performance.

21 I think the only way I would really feel  
22 comfortable including those patients would be in a

1 separate descriptor rather than lumping them in with  
2 the rest of the data.

3 CHAIRMAN PATOW: Dr. Shelton.

4 DR. SHELTON: I'm concerned that if we get  
5 too much data in these claims they won't be effective  
6 communication tools for the patients. It sounds like  
7 we're going to be handing them a research paper and  
8 just say, "Read the results," rather than trying to  
9 give them some general guidelines on what to expect  
10 after surgery.

11 So I would actually favor trying to keep  
12 them more simple if possible.

13 CHAIRMAN PATOW: Thank you. Thank you.

14 MS. ARNDT: I do have -- can fill you in  
15 on one more piece that Dr. Kileny requested, if this  
16 is a good time. I've got the proportion of patients  
17 tested at three months and at six months. Is that  
18 helpful?

19 CHAIRMAN PATOW: Is that a piece of  
20 information that you need?

21 DR. KILENY: Three versus six months?

22 MS. ARNDT: Yes, un-huh. Seventy-seven

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1 percent of the 60 patients were evaluated at six  
2 months. So the submission includes six month data  
3 points for those individuals, and the remaining 23  
4 percent, or 14 patients, were tested at three months.  
5 So it's 14 patients, 23 percent at three months; 46  
6 patients, 77 percent, at six months.

7 CHAIRMAN PATOW: All right. Thank you.

8 I'd like to then go back to the question  
9 again. Does the hearing benefit from this device for  
10 the neurofibromatosis Type 2 patient exceed the risk  
11 of implantation?

12 And look at the second part of that, that  
13 is, the surgical risks. Are there any concerns of the  
14 panel related to the implantation procedure itself,  
15 explanation, or the risk, the medical risks of this  
16 device?

17 DR. CANADY: I just had two comments. One  
18 is I have concerns not in the way in which it is being  
19 performed now. I think it probably does not add  
20 substantially to the risk, but I think I could  
21 envision a situation of a patient who's had bilateral  
22 surgery and then went back at some point for an

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1 implant, and I would think it would be important to  
2 state that the risk in that situation would be  
3 different.

4 And the second thing is I think we need to  
5 just note, and I think it's important to the consumer  
6 data note, that the average implant age here is 33 and  
7 the life expectancy is 40.

8 CHAIRMAN PATOW: Is that something that  
9 you feel should be in the labeling or how does that --

10 DR. CANADY: Well, I think it impacts the  
11 usefulness over time of the device. I mean, in  
12 general -- we haven't talked about it -- but in  
13 general, NF2 is a fatal disease, and with a life  
14 expectancy of -- so we're talking at least in this  
15 study, and I think it's a reasonable representation of  
16 when the second acoustic is removed, a seven year life  
17 span for the entire device in some patients.

18 So I think you have to include the risk in  
19 terms of the amount of time you're going to be using  
20 the device, although I'm not sure a deaf person would  
21 view it that way.

22 CHAIRMAN PATOW: We had some concerns

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1 earlier about whether two deaths were related to the  
2 device or not.

3 DR. CANADY: I think they're related to  
4 the operative procedure.

5 CHAIRMAN PATOW: To the procedure.

6 DR. CANADY: And I think that they would  
7 be related to an operative procedure that was done in  
8 that location even without tumor being the purpose of  
9 it.

10 CHAIRMAN PATOW: And there was also a  
11 concern about CSF leaks. Has that been addressed or  
12 is that still a concern?

13 DR. FRANCIS: Yes. I'm comfortable with  
14 the response that the CSF leak rate did not increase  
15 in this series of patients, and although the data was  
16 not necessarily represented, it appears that that was  
17 the finding from Dr. Brackmann.

18 CHAIRMAN PATOW: Were there other concerns  
19 about the medical complications of this device, the  
20 risk of implantation?

21 Dr. Kileny.

22 DR. KILENY: Perhaps somebody from the

1 sponsor group could clarify this. Is there any reason  
2 why the proportion of non-stimulable patients is  
3 larger in the U.S. sample than in the European sample?

4 I guess there was one out of 27 versus 16  
5 out of I guess it's debatable now what's the pool, but  
6 let's say in the high -- in the mid-80s or so.

7 CHAIRMAN PATOW: Would the sponsor?

8 DR. HITSELBERGER: Well, obviously there  
9 are better surgeons in Europe.

10 (Laughter.)

11 DR. HITSELBERGER: No. What this is, I  
12 think if you take a small group of our patients, I  
13 think you could find the same thing. I think our  
14 sample is a lot larger, for one thing, and I think if  
15 you broke it down our results would be comparable to  
16 the European group.

17 In addition, as we've mentioned this  
18 morning, there's a disparity in the sampling itself,  
19 in the techniques used, you know, to ascertain the  
20 result.

21 CHAIRMAN PATOW: Thank you.

22 Dr. Shelton?

1 DR. SHELTON: A follow-up question on  
2 that, Bill. Did anyone look at the effect of surgeon  
3 experience in non-stimulable patients? In other  
4 words, did most of the non-stimulable patients come  
5 from the center with the highest volume or from the  
6 centers with the lowest volume, or was there any  
7 correlation at all?

8 is this a surgeon learning curve that  
9 we're seeing or is just the anatomy of the cochlear  
10 nucleus that can't be overcome?

11 MS. ARNDT: As you well know, most of the  
12 study subjects came from House Ear Institute, and  
13 their results on that particular measure of non-  
14 stimulation are better than the other sites. So  
15 clearly, they're a center of excellence. They attract  
16 patients worldwide for these kinds of procedures, and  
17 we'd like very much to address these kinds of  
18 discrepancies by recommending very intensive training  
19 of new teams.

20 CHAIRMAN PATOW: There were some issues  
21 related to the labeling of MRI. I just wanted to have  
22 the panel discuss the risks of MRI and the

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1       implantation of this device and whether they see that  
2       as an issue.

3                   DR. SHELTON: I think it's an important  
4       issue for this patient population, and as was brought  
5       up earlier in the panel, I think it would be good if  
6       the device came without the magnet in place, and that  
7       way the surgeon had to put the magnet in place if he  
8       wanted it there because it seems like that's the way  
9       it's been used for most of the patients so far, and  
10      I'd anticipate that's how it would be used in the  
11      future.

12                   CHAIRMAN PATOW: How do other members of  
13      the panel feel about that suggestion? There's general  
14      agreement.

15                   A question came up also about  
16      neurophysiologic monitoring and the extent to which  
17      monitoring is used intraoperatively. Dr. Kileny,  
18      would you talk to the panel a little about your  
19      concerns there and whether you think changes need to  
20      be made to improve the or decrease the risk of  
21      implantation?

22                   DR. KILENY: Well, I think it's clearly

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1 based on statements by the sponsor and by the  
2 submission. Really electrophysiology is quite  
3 important in contributing to the success of this  
4 procedure in terms of having a stimuable device.

5 And the surgeon's manual is very detailed  
6 and well put together in terms of the surgical  
7 procedure. Clearly a lot of thought has gone into  
8 that.

9 The portion of electrophysiology is  
10 lacking. There are descriptions there that are not  
11 necessarily accurate in terms of describing the  
12 specific response. I think that the manual should  
13 contain more detail on the electrophysiological  
14 measures, standardized recording electrode placement,  
15 discussion of electrophysiologic events in terms of  
16 recording sites, as well as their temporal and  
17 amplitude characteristics as they relate to different  
18 cranial nerves or other brain structures other than  
19 the cochlear nucleus.

20 I think it's very important. In the  
21 European study, as I read the submission, the one  
22 patient who did not stimulate did have a response, and

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1 that response was very characteristic, as it was  
2 described, for trigeminal nerve stimulation, for  
3 instance, but it wasn't recognized, and apparently the  
4 electrode was probably much closer to the trigeminal  
5 nucleus than the cochlear nucleus.

6 So I think this is a very important  
7 component, and I think that the training should also  
8 be quite rigorous and standardized in training the  
9 neurophysiologists who will be doing this monitoring  
10 not only in recognizing or describing an event  
11 associated with cochlear nucleus stimulation, but also  
12 recognizing events associated with other specific  
13 structures because that would be very helpful in  
14 distinguishing between an appropriate and an  
15 inappropriate placement.

16 So that's an area that I certainly have  
17 found lacking, and I don't think it's a very big deal  
18 to improve that, but I think it needs to be improved  
19 quite a bit.

20 CHAIRMAN PATOW: Other comments? Dr.  
21 Francis.

22 DR. FRANCIS: I just wondered if there was

1 any systematic difference in the performance of  
2 patients who still had hearing in the contralateral  
3 ear, if in, you know, the spread of the data that you  
4 have here they tended to skew more to one side or the  
5 other of the data.

6 Do you have any information on that?  
7 Would that be all right for us to get that kind of  
8 information? Again, the outcomes of the one-third  
9 that still had the other ear to be operated on  
10 presumably having residual hearing in that ear versus  
11 the bilaterally deaf.

12 CHAIRMAN PATOW: Would the sponsor like to  
13 respond?

14 MS. ARNDT: We've not specifically  
15 separated out the two segments of the population and  
16 looked at it in a statistical way, but we certainly do  
17 know that patients who have a significant amount of  
18 hearing in their unimplanted ear are very unlikely to  
19 use the device until they have to. They hang onto  
20 their good ear for all they can for as long as they  
21 can.

22 Steve Otto has seen a lot of these

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1 patients, and I'm wondering if you can comment on  
2 that, Steve.

3 CHAIRMAN PATOW: Can you identify  
4 yourself, please?

5 DR. OTTO: Sure. I'm Steve Otto from  
6 House Ear Institute, and I work with a lot of these  
7 patients.

8 And if they have hearing in their other  
9 ear, they don't use their implant very much. They use  
10 it in the clinic when they come by for evaluations,  
11 and in general as the hearing loss progresses in their  
12 other ear, then they start to use their implant more  
13 and more, and performance is directly correlated with  
14 experience with their implant.

15 Everybody usually starts low, and  
16 eventually you start to see some patients performing  
17 very well, and you start to see a large distribution  
18 after that.

19 CHAIRMAN PATOW: Thank you.

20 Dr. Kileny.

21 DR. KILENY: \*\* Just a question to Steve  
22 Otto.

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1 Can you at least informally comment on the  
2 performance of patients who had residual hearing in  
3 the contralateral ear? When time came that they were  
4 actually using their implant, did you find any  
5 difference between how those patients did as opposed  
6 to those that had no hearing for a while and then they  
7 were implanted or the patients who have complete  
8 auditory deprivation, either ear or both ears, as  
9 opposed to the ones who did have some hearing in the  
10 contralateral ear?

11 DR. OTTO: I'm not sure exactly what  
12 you're asking, Paul. Ask me again another way.

13 DR. KILENY: Well, do you find the  
14 patients who had residual hearing in the contralateral  
15 ear they did not use their implant immediately because  
16 they did not feel the need to? Did those patients  
17 perhaps do better eventually when they were using  
18 their implant than patients who did not have hearing?

19 DR. OTTO: In general, my opinion is that,  
20 yes, they did do better because they had an  
21 opportunity to use their implants as their hearing in  
22 their other ear went out. So there's that.

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1 But the other issue is how did they feel,  
2 and as you can imagine becoming suddenly deaf with  
3 nothing to fall back on would be a much more difficult  
4 psychological situation than having some sort of  
5 hearing to fall back on and some hearing with a  
6 different sound. Even though it was a different sound  
7 and a new sound, it still was sound.

8 CHAIRMAN PATOW: Thank you.

9 Dr. Roeser.

10 DR. ROESER: From the presentation this  
11 morning, I was under the impression that the decision  
12 to implant the first ear was based on the residual  
13 hearing of the second ear. In other words, if there  
14 was no residual hearing in both ears, then implanting  
15 the first ear would be the choice.

16 If that's not the case, and I'm hearing  
17 that, then what is the criteria or what are the  
18 circumstances for implanting first or second ear?

19 DR. BRACKMANN: Derald Brackmann.

20 We offer that to patients at the time of  
21 first site implantation. Several reasons to do that.

22 Number one, it makes them -- gives them an

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1 opportunity to use the device while they still have  
2 hearing, to learn to use it so that when their second  
3 tumor is removed they're not suddenly totally deaf,  
4 and this has been a big psychological boost.

5 They're sort of made the transition from  
6 hearing and all of a sudden their hearing aid becomes  
7 less and less useful, and they begin to use the ABI  
8 more and more and more.

9 You also have an opportunity -- we have  
10 had an occasion where the first device did not work,  
11 and it gives us then the second opportunity to provide  
12 the patient with a useful device without doing  
13 additional surgery.

14 So we explain that to them and offer them  
15 that. Some patients choose to have it done with the  
16 first side. Others choose to wait.

17 CHAIRMAN PATOW: Thank you, Dr. Brackmann.

18 Is there any feeling that that kind of  
19 information should be included in the surgeon's  
20 information packet?

21 Dr. Shelton? \*\*

22 DR. SHELTON: I've got something

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1 different.

2 CHAIRMAN PATOW: Something different. Any  
3 comments on -- I'm just curious. You've asked the  
4 question about the strategy.

5 DR. ROESER: Well, this morning I just  
6 assumed that it was based on hearing, and what I'm  
7 hearing is that it's not, and perhaps that should be  
8 part of the surgeon's manual or somewhere in the  
9 information to be able to distinguish what the  
10 criteria are.

11 CHAIRMAN PATOW: What the indications are.

12 Dr. Woodson, did you have a comment?

13 DR. WOODSON: I have a different issue I  
14 wanted to bring up.

15 CHAIRMAN PATOW: Then let's go on to a  
16 different issue. I think Dr. Shelton was first, and  
17 then we'll -

18 DR. SHELTON: Yeah, I just wanted to get  
19 back to monitoring. I was going to make another  
20 comment about the surgeon's instruction manual and  
21 monitoring. I think there should be a better  
22 description of monitoring nine. I think according to

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1 Bill Hitzelberger's comments, monitoring nine was very  
2 important, and the manual just says, "Put the  
3 electrodes in the patient's throat." I think it needs  
4 to be more specific about that.

5 (Laughter.)

6 DR. SHELTON: Monitoring nine in my hands  
7 reliably has been very difficult, and so having a good  
8 description of how to get reliable monitoring would be  
9 very helpful.

10 CHAIRMAN PATOW: Thank you.

11 Dr. Woodson.

12 DR. WOODSON: I'm not sure, you know, what  
13 point there is in bringing this up, but in reading the  
14 indications, it occurred to me, you know, it says not  
15 indicated if you use a gamma knife, and if I was a  
16 patient and someone said, "Gee, you know, if I have  
17 this done with a gamma knife I won't have the option  
18 of an implant," that would certainly push me towards  
19 having surgery rather than gamma knife.

20 And I'm just wondering clearly it hasn't  
21 been done in patients with gamma knife and so the data  
22 is not there so that if someone wanted to do it,

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1 they'd have to do that study, but I'm just wondering  
2 based on what you have, would it be too risky to  
3 operate on somebody who's had gamma knife, or is it  
4 the thought that it might not work as well because of  
5 damage?

6 I'd like some insight on that.

7 CHAIRMAN PATOW: Dr. Brackmann.

8 DR. BRACKMANN: That recommendation was  
9 made based upon two very early patients in the study.  
10 Both of them -- one had gamma knife; one had proton  
11 beam. In both cases, it was probably not done as it  
12 would now be done. It was very large doses. One  
13 patient had all of the cranial nerves from six through  
14 12 out on that side.

15 Looking back we should have predicted that  
16 she probably would not have been a candidate.

17 The other patient was a gamma knife  
18 patient who was appropriately done, who had a late  
19 ictal (phonetic) infarct and infarcted the cochlear  
20 nucleus.

21 We have since done several patients. The  
22 number I can't tell you, but we have since done

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1 several patients post gamma knife successfully. So  
2 this is, if anything, a precaution that's overstated  
3 and perhaps it should be altered to say that in  
4 certain cases or something to that effect.

5 But it is possible with appropriately done  
6 gamma knife that they're not contraindicated to do an  
7 ABI.

8 DR. WOODSON: So instead of  
9 contraindicated in the labeling, extreme caution in  
10 the --

11 DR. BRACKMANN: Something to that effect  
12 or in cases of gamma knife, the cochlear nucleus  
13 should be carefully studied on MRI to make sure of its  
14 integrity.

15 CHAIRMAN PATOW: Dr. Francis.

16 DR. FRANCIS: I hate to beat a dead horse,  
17 but the question, again, of the different groups of  
18 patients, there's the one third again that still had  
19 residual hearing and the two thirds that did not, and  
20 I really was referring to the objective data results,  
21 not so much on use data, but really just to be  
22 absolutely certain that what we're presenting to the

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1 patient is, indeed, going to be representative of the  
2 majority of the patients that are going to get this  
3 implant.

4 MS. ARNDT: My impression is that the  
5 objective data may be poor for the first side patients  
6 because they're not using their ABI on a day-to-day  
7 basis. They're not well practiced, but we have not  
8 formally done that analysis. So we would need to do  
9 that to state that conclusively.

10 CHAIRMAN PATOW: Thank you.

11 One of the issues that was brought up  
12 briefly was the issue of recommended versus required  
13 training, and is there an opinion of the panel  
14 regarding whether the risk of implantation would be  
15 reduced if there was required training versus  
16 recommended training?

17 What is the panel's thoughts on -- Dr.  
18 Kileny.

19 DR. KILENY: I can only comment on the  
20 intraoperative electrophysiology, and I believe that  
21 if that were standardized and there was specific  
22 training involved with that, that might actually

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1 improve the odds for effective stimulation. So I  
2 would recommend that that would be, i guess, required  
3 for that purpose.

4 CHAIRMAN PATOW: How about for insertion  
5 of the implant itself?

6 Dr. Shelton.

7 DR. SHELTON: I think it should be  
8 required. I think Bill Hitselberger will testify that  
9 finding the lateral recess in a severely distorted  
10 brain stem by a big tumor is a very difficult  
11 procedure. It is not something that a neurosurgeon  
12 would normally have that expertise. I think having  
13 the training is going to be very important to make  
14 that successful.

15 CHAIRMAN PATOW: Dr. Duffell.

16 DR. DUFFELL: This issue of training and  
17 credentialing for procedures is really important to  
18 industry because if the FDA forces the manufacturer to  
19 put required training or certification to do a  
20 procedure in there, it puts us in a tremendous  
21 liability situation.

22 We are not teaching institutions. We are

1 not credentialed ourselves, and oftentimes to, you  
2 know, train individuals to do this.

3 Really the better thing from an industry  
4 standpoint is always to be in the position to say that  
5 it is strongly encouraged or strongly recommended. I  
6 think it's incumbent on the industry certainly from a  
7 product liability sense as well to make sure that we  
8 provide proper training tools to those institutions  
9 that can appropriately credential and train and teach  
10 people how to do these procedures.

11 So, you know, I would ask the panel in its  
12 deliberations that follow this to at least keep that  
13 in mind; that the term "required" means then, in turn,  
14 we will have a requirement to assess that in some way  
15 and certify that it has been done, and it's a much  
16 better route for us to have that we are required to  
17 provide the tools for teaching and the wherewithal for  
18 that, but not actually certify and train.

19 CHAIRMAN PATOW: Thank you.

20 Other comments from panel members on  
21 training?

22 I would also agree that in my opinion that

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1 idea of having strong recommendations is certainly  
2 what should be done.

3 DR. DUFFELL: And it's not without  
4 precedence in other areas.

5 DR. CANADY: I think, you know, the Midas  
6 Rex model to me is an example, where you train for six  
7 years using the Midas Rex, and then you have to pay  
8 \$2,000 to take a course to teach you what you already  
9 know.

10 I mean I think that required training is  
11 a very big issue with the first generation in terms of  
12 someone has to learn, but once you learn, and if you  
13 are a resident at the House Institute and you operate  
14 with Dr. Hitselberger for six years, probably at the  
15 end of it you're going to know how to do it, and you  
16 don't need to go take a course.

17 CHAIRMAN PATOW: Thank you.

18 One other issue related to the second  
19 question is that of post approval studies. Is there  
20 a need for a post approval study to assess whether the  
21 hearing benefit exceeds the <sup>\*\*</sup> risk of implantation?

22 I think one of our reviewers may have

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1 suggested that. Can I have comments by the panel  
2 about any needs for later evaluation of data?

3 Dr. Roeser.

4 DR. ROESER: The data that I saw today  
5 were convincing to me because we're talking about  
6 going from nothing to something, and we're in a  
7 situation where we're able to provide benefit to  
8 individuals who normally would receive nothing. So  
9 I'm personally comfortable with what I saw relative to  
10 effectiveness.

11 CHAIRMAN PATOW: Thank you.

12 One of the reviewers mentioned that  
13 because of the percentage of 17.8 percent patients  
14 without auditory precept, that this was, in their  
15 opinion, a large enough number that perhaps there  
16 needed to be follow-up. Does the panel have a similar  
17 opinion or are we comfortable that in this situation  
18 it's okay?

19 Dr. Hood.

20 DR. HOOD: I would agree with Dr. Roeser  
21 that I think that the data do demonstrate  
22 effectiveness, and that it's really sufficient to show

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1 that.

2 CHAIRMAN PATOW: Dr. Duffell?

3 DR. DUFFELL: Just one other comment for  
4 the panel's consideration, too. I mean, industry is  
5 required, especially with an implant of this sort,  
6 that there's implant registration cards, and  
7 correspondingly complaint monitoring and medical  
8 device reporting, which certainly gives FDA a means of  
9 monitoring the safety end of things.

10 Now, it doesn't do as much for you on the  
11 perceived benefits end of the equation because it  
12 doesn't look at outcome, but it does certainly give  
13 you a feedback as to whether or not you are seeing new  
14 complications or new hazards that you weren't  
15 previously aware of. So that does give you a type of  
16 post market surveillance, although it's not certainly  
17 a clinical trial.

18 CHAIRMAN PATOW: Dr. Kileny.

19 DR. KILENY: I was the reviewer who  
20 recommended that, and it's really not so much related  
21 to this question whether the risk-benefits ratio --  
22 that was not my concern. My concern was to prove that

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1 over time the stability of this device in terms of  
2 stimulation and the type of surveillance that I would  
3 recommend could be simply done by mail, not  
4 necessarily by testing, to ascertain that a patient  
5 who now has had the implant for X number of years  
6 continues to stimulate.

7 And obviously if there are some adverse  
8 effects that have cropped up over time, that should be  
9 noted, too, but I don't believe that it's necessary  
10 for this type of surveillance to include some lengthy  
11 and complex test paradigms, but just simply to  
12 ascertain that there's longevity and stability of the  
13 device in terms of stimulation.

14 CHAIRMAN PATOW: Thank you.

15 Ms. Brogdon.

16 MS. BROGDON: I'd like to ask a question  
17 of the panel.

18 CHAIRMAN PATOW: Yes.

19 MS. BROGDON: Manufacturers of approved  
20 devices are required to report under what's called MDR  
21 reporting medical device failures. My question to the  
22 panel would be: would you interpret a non-stimulating

1 device to be a device failure?

2 Because I have a feeling that that  
3 question will have to be answered at some point.  
4 Would we expect manufacturers and users to report  
5 those or not?

6 CHAIRMAN PATOW: Comments from the panel?

7 DR. WOODSON: Dr. Woodson.

8 CHAIRMAN PATOW: Yes.

9 DR. WOODSON: Clearly the device has not  
10 failed because they can verify that it's working when  
11 it's inside you, right? And that's how they know it's  
12 non-stimulable and not a device failure because if it  
13 wasn't working, they might want to even take it out  
14 and put another one in.

15 MS. BROGDON: Right. Thank you.

16 CHAIRMAN PATOW: Dr. Kileny?

17 DR. KILENY: This is a question addressed  
18 to the sponsor, and it does relate to these issues.  
19 A SPrint processor with the 24 ABI does have neural  
20 response telemetry capabilities. This neural response  
21 telemetry at least as far as I know has not been done  
22 with the ABI.

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1 Is that somewhere in the planning? That  
2 would certainly facilitate resolving these questions  
3 if neural response telemetry is established with the  
4 ABI.

5 CHAIRMAN PATOW: Would you care to  
6 comment?

7 MS. ARNDT: We're very interested in  
8 looking at NRT using the ABI. We've not done that yet  
9 in a systematic way on a large scale. We hope that it  
10 will be a very useful tool, but it kind of remains to  
11 be seen. It really needs to be evaluated.

12 CHAIRMAN PATOW: Thank you.

13 Are there any other concerns then related  
14 to -- Nancy, does that provide you with the  
15 information you were looking for?

16 MS. BROGDON: Yes. Thank you.

17 CHAIRMAN PATOW: Any other concerns then  
18 related to the hearing benefit versus the risk of  
19 implantation?

20 (No response.)

21 CHAIRMAN PATOW: I'd like to then go  
22 around the table and just do a brief poll of the

1 panelists regarding this question: whether they do  
2 feel that the hearing benefit from this device exceeds  
3 the risk of implantation

4 Dr. Canada.

5 DR. CANADY: Yes.

6 CHAIRMAN PATOW: Dr. Hood.

7 DR. HOOD: Yes.

8 CHAIRMAN PATOW: Dr. Gulya.

9 DR. GULYA: Yes.

10 CHAIRMAN PATOW: Dr. Shelton.

11 DR. SHELTON: Yes.

12 CHAIRMAN PATOW: And Dr. Kahn.

13 DR. KAHN: Yes.

14 CHAIRMAN PATOW: Dr. Kileny.

15 DR. KILENY: Yes.

16 CHAIRMAN PATOW: Dr. Woodson.

17 DR. WOODSON: Yes.

18 CHAIRMAN PATOW: Dr. Roeser.

19 DR. ROESER: Yes.

20 CHAIRMAN PATOW: Dr. Francis.

21 DR. FRANCIS: Yes.

22 CHAIRMAN PATOW: Yes. All in agreement.

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1 Thank you.

2 At this point I'd like to turn to the  
3 claims which can be found at the back of the  
4 information provide this morning, to have the panel  
5 look at each of the claims to see if they feel that  
6 they are clear.

7 When I looked through the material  
8 previously provided by the sponsor, the indicate that  
9 ABI implant recipients receive a user manual and  
10 information booklet about static electricity and  
11 warranty information, but I don't see that the claims  
12 themselves are specifically provided in any of those  
13 three documents.

14 And in fact, they probably will be  
15 included in I would think some marketing materials and  
16 other places that we don't see in those particular  
17 three documents.

18 So I'd like to turn then if everyone is on  
19 package insert, therapeutic claims, and the first one,  
20 identification of environmental sounds. This morning  
21 there was discussion of the fact that -- and also this  
22 afternoon -- that the percentage of subjects, 82

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1 percent of subjects, 49 of 60, did not include the  
2 entire set of patients that were entered into the  
3 trial.

4 My concern is that those patients who did  
5 not have auditory precept are not included anywhere in  
6 these claims, although they are included in the  
7 patient -- the user manual. However, someone who has  
8 seen marketing materials and is not yet an implant  
9 recipient may not necessarily receive the user manual  
10 and, therefore, might not have that information.

11 I would just query the panel at this  
12 point. Do they feel that other subjects who did not  
13 have auditory precept should be some way represented  
14 in these claims?

15 Comments? Dr. Roeser.

16 DR. ROESER: One way that that could be  
17 dealt with is to indicate if it was only the subjects  
18 who stimulated. So if you said 82 percent of the  
19 subjects who received stimulation or who stimulated,  
20 49 out of 60 scored, et cetera, and that would clarify  
21 that it was only that group of subjects who were being  
22 used for that claim.

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1 It doesn't represent those who didn't  
2 stimulate, but it does represent those who did  
3 stimulate.

4 CHAIRMAN PATOW: Dr. Kileny.

5 DR. KILENY: Well, I think this claim  
6 should perhaps be preceded by another claim, and  
7 again, the numbers have changed, and the appropriate  
8 percentage should be reported, but what percent of  
9 patients are reasonably expected to receive effective  
10 stimulation?

11 So there could be a claim that would  
12 indicate that, and that would be followed by the  
13 present claim then stating what percent of those that  
14 stimulated effectively exceeded chance scores and so  
15 forth and so on.

16 But if there would be a claim preceding  
17 that stating the percent that is expected reasonably  
18 to stimulate, I think that would work for me.

19 I don't know if you could have a  
20 reasonable expectation, although we could discuss  
21 that. For me --

22 DR. WOODSON: Could you say what the

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1 experience has been?

2 CHAIRMAN PATOW: -- I think you would have  
3 to say what the experience has been.

4 Dr. Gulya?

5 DR. GULYA: That's basically what I was  
6 going to say. I was going to also suggest basically  
7 the same idea that the first claim be that of  
8 blankety-blank patients implanted, the appropriate  
9 percentage received stimulation, and then you go on to  
10 clarify of those who were stimuable, what benefits  
11 were derived from that stimulation. I think that  
12 would be fair.

13 CHAIRMAN PATOW: Dr. Shelton?

14 DR. SHELTON: I favor that also. I think  
15 that would be a much clearer way.

16 CHAIRMAN PATOW: Other comments?

17 Are there other concerns about the wording  
18 of the claims? There is the acknowledged  
19 typographical error in the claim regarding removal of  
20 the second side tumor. That's where we had 61 percent  
21 of subjects, 19 out of 31, and that, of course, will  
22 need to be corrected.

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