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CENTER FOR MEDICARE AND MEDICAID SERVICES

Medicare Coverage Advisory Committee

Meeting of the Medical and Surgical Procedures Panel

June 12, 2002

Baltimore Convention Center

One West Pratt Street

Baltimore, Maryland

1 Panelists

2

3 Chairperson

4 Alan M. Garber, MD, PhD

5

6 Voting Members

7 Angus M. McBryde, MD, FACS

8 Les J. Zendle, MD

9 James P. Rathmell, MD

10 Bruce Sigsbee, MD

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12 Consumer Representative

13 Phyllis E. Greenberger, MSW

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15 Temporary Voting Members

16 Kim J. Burchiel, MD

17 Thomas V. Holohan, MA, MD, FACP

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19 Guests

20 Kenneth Follett, MD, PhD

21 William J. Weiner, MD

22 Irene Litvan, MD

23 S. Satya-Murti, MD

24 Joan I. Samuelson

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CMS Liaison

Steve Phurrough, MD, MPA

Executive Secretary

Michelle Atkinson

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1 PANEL PROCEEDINGS

2 (The meeting was called to order at 8:08
3 a.m., Wednesday, June 12, 2002.)

4 MS. ATKINSON: Good morning, and welcome,
5 committee chairperson, panelists and guests. I am
6 Michelle Atkinson and I am the executive secretary
7 of the Medical and Surgical Procedures Panel of the
8 Medicare Coverage Advisory Committee. The panel is
9 here today to hear and discuss evidence regarding
10 deep brain stimulation for Parkinson's disease. In
11 evaluating the recommendations presented to you
12 today, CMS encourages the committee to consider all
13 relevant forms of information, including but not
14 limited to professional society statements, clinical
15 guidelines and other testimony you may hear during
16 the course of this committee meeting.

17 The following announcement addresses
18 conflict of interest issues associated with this
19 meeting and is made part of the record to preclude
20 even the appearance of impropriety. The conflict of
21 interest statutes prohibit special government
22 employees from participating in matters that could
23 affect their or their employer's financial
24 interests. To determine if any conflict existed the
25 Agency reviewed all financial interests reported by

1 the committee participants. The Agency has
2 determined that all members may participate in the
3 matters before the committee today

4 With respect to other participants, we ask
5 in the interest of fairness that all persons making
6 statements or presentations to this committee
7 disclose any current or previous financial
8 involvement with any firm whose products or services
9 they may wish to comment on. This includes direct
10 financial investments, consulting fees, and
11 significant institutional support.

12 I call your attention to the invited
13 speakers, who are not part of the panel, but will be
14 part of our discussion. Also, due to circumstances
15 beyond her control, our temporary industry rep,
16 Christine Grant, will not be available until the
17 afternoon session.

18 And I would now like to turn the meeting
19 over to Dr. Steve Phurrough, who will give his
20 opening remarks, then Chairman Dr. Alan Garber, who
21 will ask the panel members to introduce themselves
22 and to disclose, for the record, any involvement
23 with the topics to be presented.

24 DR. PHURROUGH: Thank you, Michelle.

25 I'm Steve Phurrough. I am presently the

1 division director of Medical and Surgical Services
2 in the Coverage and Analysis Group. We are the
3 division that is looking at this particular issue.
4 And, for a few weeks, I'm the acting director of
5 Coverage and Analysis. Sean Tunis is serving as the
6 acting chief medical officer for CMS.

7 On behalf of CMS, we would like to welcome
8 you here and thank you for your willingness to serve
9 on this panel and to assist us in giving us advice
10 on the level of evidences that we have here for this
11 particular issue.

12 I also thank the speakers for their
13 attendance and their willingness to assist us in
14 providing us information.

15 With that, Alan?

16 DR. GARBER: Thank you, Steve.

17 I want to second what Steve just said and
18 thank the speakers and panelists for taking the time
19 to attend the meeting today.

20 The panel had a conference call recently
21 to help go over the questions and to clarify the
22 questions that the panel will be asked to address,
23 and I think that that effort was very successful.
24 In trying to formulate the questions, it was very
25 tempting -- at least for me, and I think for others,

1 as well -- to try and think about the -- and get
2 into discussions of the substance, but we largely
3 avoided -- we did avoid discussing the substance of
4 the questions. And by that, I mean we didn't begin
5 the deliberations early. Yet I think it gave us a
6 clear idea of where we think the questions need to
7 go and what kinds of -- what kinds of topics are
8 likely to come up today in the discussion.

9 I do hope that -- I know that people have
10 planes to catch and so on, and I'm going to try to
11 keep us very tightly to this schedule and, if at all
12 possible, actually to move quickly, where we have
13 opportunities to move quickly. And I just want to
14 urge all the speakers not to exceed their allotted
15 time. So we'll be very strict about enforcing that.

16 And, with that, I'd like to just turn it
17 over to our first speaker, who is Perry Bridger,
18 from CMS.

19 MR. BRIDGER: Thank you. Good morning,
20 and thank you.

21 Chairman Garber, distinguished panelists,
22 invited guests, and members of the public, it is an
23 honor to present to you today on behalf of the Deep-
24 brain stimulation Analysis Team at the Centers for
25 Medicare and Medicaid Services.

1 For the next ten minutes or so, I'm going
2 to briefly describe Parkinson's disease, discuss
3 with you the history of Medicare coverage for deep-
4 brain stimulation, give a quick overview of the
5 current coverage request, present the voting and
6 discussion questions that will be your focus today.

7 Finally, I'll introduce Dr. Perry Cohen,
8 who will be reading Dr. Barry Green's statement.
9 Dr. Green is the requestor of this national coverage
10 termination request and could not be here today to
11 address you.

12 The CMS Review Team that has been working
13 on this issue, are myself, lead analyst; Dr. Larry
14 Schott, a neuro-radiologist and our lead medical
15 officer; Dr. Steve Phurrough; Michelle Atkinson, our
16 executive secretary, who you know well; Tanisha
17 Carino, and William Larson.

18 Very briefly, Parkinson's disease is age-
19 related, chronic, neurodegenerative disease whose
20 underlying abnormality is the progressive loss of
21 dopamine-producing cells in the brain, generally
22 characterized by the symptoms of tremor, rigidity,
23 bradykinesia, and postural instability.

24 The onset of idiopathic Parkinson's
25 disease most often occurs between the ages of 45 and

1 65. And currently, there is no known cure, although
2 research for neuro protective and restorative
3 therapies are underway. Currently, only symptomatic
4 therapies are available.

5 Levodopa remains the gold standard for
6 treatment used on concert with other agents such as
7 dopamine agonists and anticholinergics. Surgical
8 lesioning therapy and deep-brain stimulation are --
9 generally considered after medical treatment cannot
10 adequately balance control of the disease with the
11 side effects of the medication.

12 Medtronic will be presenting to you
13 shortly, but I just briefly want to explain that
14 deep-brain stimulation is the stereotactic placement
15 of an electrode and delivery of electrical
16 stimulation to certain areas of the brain. In
17 general, it's thought that the high-frequency
18 stimulation of the neuron induces functional
19 inhibition, and deep-brain stimulation simulates the
20 effect of a surgical lesion, but does not
21 deliberately destroy the tissue.

22 The Medtronic Activa Tremor Control System
23 PMA was approved in July of 1997 for a unilateral
24 thalamic stimulation for tremor suppression, and a
25 recent supplement was approved for bilateral globus

1 pallidus internus or subthalamic nucleus stimulation
2 for other Parkinson's symptoms. Celia Witten is
3 here from the FDA and will be explaining a little
4 bit to you about the FDA process, and go more in
5 depth about the approvals for the device.

6 In 1997, Medicare amended our national
7 coverage policy for the treatment of motor function
8 disorders with electrical stimulation, which are
9 currently not covered, to allow our contractors the
10 discretion to cover deep-brain stimulation. And
11 currently, all Medicare contractors cover unilateral
12 thalamic stimulation, and many Medicare contractors
13 cover bilateral stimulation of the STN or GPi.

14 Our current request was initiated by Barry
15 Green, a Parkinson's patient in Texas, a state where
16 Medicare does not currently cover the bilateral
17 indication. The request was formally accepted for a
18 national-coverage determination on October 19th,
19 2001.

20 The current request has prompted us to
21 consider both the unilateral and bilateral
22 indications for use of this modality. In addition,
23 we obtained a BlueCross and BlueShield Technology
24 Evaluation Center technology assessment of deep-
25 brain stimulation. And Joan Vatz, the primary

1 assessor, will be presenting that assessment to you
2 later in the morning.

3 The panel has received the following
4 materials, all of which are publicly available, many
5 of them on our Web site. A complete set of the
6 material is also available on the desk outside of
7 this room.

8 You have had the opportunity to read the
9 technology assessment, the unilateral study
10 description, and other materials related to deep-
11 brain stimulation. After hearing public comments
12 and scheduled commentaries presented here today,
13 you'll be asked a series of voting and discussion
14 questions, and I'd like to briefly outline those for
15 you now.

16 The first question the panel will discuss
17 is the following. Is the evidence adequate to
18 determine the clinical effectiveness of bilateral
19 subthalamic nucleus deep-brain stimulation for a
20 well-defined set of Medicare patients with
21 Parkinson's disease? If the evidence is adequate,
22 what is the size, if any, of the overall health
23 effect of this intervention?

24 We have asked you to use the MPAC's own
25 categories of effectiveness, which I will review for

1 you after I present the remaining two voting
2 questions.

3 And I'd just like to read these into the
4 record. Panel Voting Question Number 2. Is the
5 evidence adequate to determine the clinical
6 effectiveness of bilateral GPi DBS for a well-
7 defined set of Medicare patients with Parkinson's
8 disease? And if that evidence is adequate, what is
9 the size, if any, of the overall health effect?

10 Panel Voting Question Number 3 relates to
11 the unilateral indication and asks, is the evidence
12 adequate to determine the clinical effectiveness of
13 unilateral thalamic DBS for essential tremor and/or
14 Parkinsonian tremor for a well-defined set of
15 Medicare patients with Parkinson's disease? And if
16 the evidence is adequate, what is the size, if any,
17 of the overall health effect?

18 The following are the categories of
19 effectiveness, as previously determined by the MPAC,
20 and there are seven categories: breakthrough
21 technology, technology is more effective, as
22 effective but with advantages, as effective and with
23 no advantages, less effective but with advantages,
24 less effective but with no advantages, and not
25 effective.

1 In addition to the voting questions that
2 I've just described, we have posed to you three
3 discussion questions not directly addressed by the
4 scientific evidence that we would like the panel to
5 discuss, and they are the following. Available
6 clinical evidence evaluates bilateral STN or GPi
7 deep-brain stimulation in early-onset Parkinson's
8 disease patients. Can these results be generalized
9 to late-onset advanced Parkinson's disease patients?

10 Discussion Question 2. For coverage
11 purposes, should Medicare patients be considered
12 candidates for unilateral thalamic or bilateral STN
13 or GPi DBS only if their characteristics closely
14 match those of the patients included in the
15 available study?

16 And, finally, Discussion Question 3. DBS,
17 in the clinical literature, is performed by highly
18 trained providers at experienced facilities. Should
19 facility and provider criteria to perform DBS in
20 Medicare patients be part of any positive coverage
21 decision?

22 I would like to thank all of the panel and
23 all of the participants in today's meeting for
24 devoting their time and effort to this very
25 important topic.

1 At this point, I'd like to introduce Dr.
2 Perry Cohen, who will be reading Dr. Barry Green's
3 statement into the record for you. Dr. Cohen?

4 DR. COHEN: Thank you.

5 My name is Perry Cohen and -- another
6 Perry. I've been asked by Barry Green to read his
7 statement. He is in Texas in the -- I think he's
8 recently undergone surgery and is not available to
9 make the statement himself.

10 I have my own opinions on the subject, but
11 these are all Barry Green's -- this is entirely
12 Barry Green's statement. I had previously served on
13 -- as patient representative on the FDA panel that
14 reviewed deep-brain stimulation about two years ago.

15 Members of the panel, invited guests and
16 audience, I want to thank you for the opportunity to
17 address you in this public forum. I am the national
18 requestor for the adoption of coverage by CMS for
19 the bilateral subthalamic nucleus deep-brain
20 stimulation.

21 As revised on January 7th, the bilateral
22 deep-brain stimulation of the globus pallidus
23 interna was included. After further consideration,
24 they are also evaluating the unilateral thalamic
25 stimulation for essential tremor and Parkinson's

1 Tremor. They have renamed the title of the study
2 the "Deep-Brain Stimulation, DBS, for Parkinson's
3 disease."

4 As the advocate for many fellow patients,
5 I want to offer constructive suggestions for dealing
6 with the process undertaken. The exact time frames
7 can be readily seen in the Table of Actions and
8 tracking data at the end of this presentation. One,
9 quality of operations, the equipment to be utilized,
10 and the patient. I think the operations or
11 procedures used by each surgeon, the operating
12 facility, and the company chosen to supply the
13 special equipment should undergo a general test of
14 applicability for each individual. Any state agent
15 or other agency spending national Medicare dollars
16 should provide the results of the test of
17 applicability.

18 Meaning: This would apply to all
19 decisions made by the Medical and Surgical
20 Procedures Panel of the Medicare coverage
21 committees.

22 Two, cost of unilateral versus bilateral
23 operations. The cost appears not to be considered a
24 factor in the CMS decision between unilateral and
25 bilateral DBS. I suggest that those laser

1 bilaterals are not the same bilaterals that are
2 being considered in the procedures and should not
3 have been used in comparative studies. Because the
4 operation is slated as costing from \$60,000 to
5 \$80,000 -- my own operation cost \$80,000 at
6 Presbyterian Hospital, and the doctors have not been
7 paid as yet -- it would seem to me that Medicare
8 would be concerned about this and, therefore, push
9 for bilaterals, which is two unilaterals, but done
10 during the same operation. Therefore, the cost
11 would be far less than two independent unilaterals.
12 You and I know that cost is always a factor when it
13 comes to Medicare.

14 The research was completed by 17 groups
15 sponsored by Medtronic, NIH, et cetera, which
16 indicated that the study for the bilateral STN/DBS
17 is clearly not and does not have the same problems
18 that the laser bilateral pallidotomy had. Thus, the
19 comparison was ill conceived. Furthermore, the cost
20 for a unilateral ranged from \$60,000 to \$80,000. A
21 bilateral is \$85,000 to \$90,000. It clearly seems
22 that we should take the less expensive way to go.

23 In terms of time, the same is true. A
24 single bilateral takes one hospital stay, whereas
25 two bilaterals take two hospital stays. The

1 bilateral operation requires one framing of the head
2 by the halo unit. The two unilaterals require the
3 head frame to be put on twice on the same patient,
4 and the hospital charges would be double.

5 Meaning: If carefully considered by this
6 committee, the cost and effectiveness can be clearly
7 monitored, and the cost to the patient and hospital
8 may be kept at a minimum.

9 Three, the time it's taken from the
10 request to the almost final resolution today. I
11 would suggest that the committee should oversee that
12 the potential two-year interval could have been
13 completed in at least a year ahead of what had
14 occurred, and probably earlier. Medicare should
15 have maintained close ties with the FDA. These ties
16 would have allowed the FDA's decision to be made
17 more quickly. I feel strongly that CMS could have
18 avoided the issue and some of its time by focusing
19 on the January 14th date.

20 Meaning: The national panels of CMS
21 should have stronger positive relationships, rather
22 than an apparent adversarial relationship. The
23 patient should be the one considered over any other
24 indicator.

25 Four, complete, informative, and better

1 graphics for patient booklets. Overseeing patient
2 booklets should have been one of the committee's
3 major targets. The FDA was in the best position to
4 force its study groups to prepare a better patient
5 booklet. Each team of neurologists,
6 neurosurgeons --

7 DR. GARBER: Excuse me, Dr. Cohen. You've
8 exceeded the time. And I think this letter is very
9 helpful, but I just want to point out that copies of
10 the -- of this memo are in each panelist's
11 portfolio, and I think they're out front for the --
12 oh, they're not? Okay, we will make copies
13 available for members of the meeting.

14 DR. COHEN: Very well.

15 DR. GARBER: Pardon me?

16 DR. COHEN: Okay. I didn't write the
17 letter.

18 DR. GARBER: No, I understand. I
19 understand. I appreciate your willingness to come
20 up here and present it --

21 DR. COHEN: Okay.

22 DR. GARBER: -- but we only have five
23 minutes --

24 DR. COHEN: Well, would you like for me to
25 stop here?

1 DR. GARBER: Yeah, if there are just a few
2 brief comments you want to make, that would be fine
3 now, but I think, since we all have copies of this,
4 we can take a look at the memo ourselves.

5 DR. COHEN: I could make my own comments,
6 but I don't know if that's in order here.

7 DR. GARBER: No, I -- you may later on
8 today, when we --

9 DR. COHEN: Okay. Well, there's just one
10 more item here.

11 So the key here is to look at the
12 patient's needs as well as the doctor's needs and to
13 keep that paramount, which -- I assume that is the
14 purpose. And there's a million patients that are
15 waiting for this procedure -- not a million patients
16 need the procedure, but it's -- the data that I've
17 have seen have shown it to be very effective, where
18 other treatments fail.

19 DR. GARBER: Thank you very much.

20 All right, we're about to move into --
21 Perry, was there anything else? Perry, are you done
22 with your -- oh, well -- yeah, okay, he's done.

23 And then we'll -- the next will be a
24 presentation from Medtronic given by Dr. Bakay -- is
25 that the correct pronunciation? -- and Dr.

1 Montgomery.

2 And I need to ask every speaker, and
3 especially in the public session, to declare your
4 name, your affiliation, and any conflict of interest
5 or any potential financial or other interests you
6 would have in the topic today.

7 MR. OWENS: Good morning. I'm Cliff
8 Owens. I'm vice president and general manager of
9 the Global Movement Disorder Business for Medtronic,
10 and I'd like to introduce our two speakers.

11 This morning, these two physicians are
12 going to outline the clinical evidence of Activa
13 brain-stimulation therapy for the treatment of
14 advanced levodopa response of Parkinson's disease
15 and essential tremor to provide you with the
16 evidence to support approval of a national Medicare
17 coverage policy.

18 Activa is not a cure for either one of
19 these diseases. It is a therapy that significantly
20 extends the time when patients are able to function
21 more normally. Activa is reversible so that when --
22 if and when a cure is found, the devices can be
23 removed and the cure implemented. Additionally,
24 unlike the ablative therapies it replaces, the
25 Activa system is adjustable, allowing dosing that

1 best fits the level of disease in each patient.

2 The two physicians that we have here today
3 are experts in the area of neurological movement
4 disorders. Dr. Erwin Montgomery is the head of the
5 Movement Disorders Section, the director of the
6 American Parkinson's disease Advanced Center for
7 Research, medical director, American Parkinson's
8 disease Association Information Referral Center, the
9 co-director of the Center for Functional and
10 Restorative Neurosurgery, and a member of the
11 Department of Neurology and Neurosciences at the
12 Lerner Research Institute of the Cleveland Clinic
13 Foundation in Cleveland, Ohio. He has numerous
14 medical achievements, and, for the second time, I
15 will not list those today.

16 Dr. Roy Bakay is professor and vice
17 chairman of the Department of Neurological Surgery
18 at Rush Presbyterian St. Luke's Medical Center at
19 the Chicago at the Chicago Institute of Neurosurgery
20 and Neuroresearch. Dr. Bakay is a member of the
21 AANS and CNS Joint Washington Committee, on the
22 Editorial Board of Neurosurgery, and also has a very
23 long list of medical achievements.

24 Both Dr. Montgomery and Dr. Bakay are
25 active members of the brain-stimulation implant

1 teams in their respective institutions. They are
2 experts in the procedure and will answer all of the
3 medical questions.

4 The Activa Parkinson's disease clinical
5 trials will be reviewed, including 18 centers from
6 around the world. The database contains over 32,000
7 data points. And, therefore, in the audience, we
8 have several Medtronic people that may, from time to
9 time, help answer specific questions.

10 Thank you, and now I'd like to introduce
11 Dr. Montgomery.

12 DR. MONTGOMERY: Good morning. It's a
13 pleasure to be here to talk to the panel.

14 And as Cliff mentioned, I am a neurologist
15 at the Cleveland Clinic Foundation. And in terms of
16 any conflict of interest, we do receive research
17 grant support from Medtronic for some of our
18 research activities there at the Cleveland Clinic
19 Foundation.

20 And what I'm going to do is talk to you a
21 little bit about some of the clinical data regarding
22 Activa Therapy, both for Parkinson's disease, as
23 well as for a essential tremor. I'm going to be
24 sharing with you some data from thalamic stimulation
25 as well as stimulation the globus pallidus internal

1 segment, as well as the substantia nigra or subthalamic
2 nucleus.

3 And so this -- drawings here demonstrates
4 the various devices. You can see, for example, the
5 actual implanted leads here that are implanted into
6 the various targets. And you can see from this
7 volunteer, a gentleman who has the leads placed in
8 the subthalamic nucleus bilaterally. You can see
9 the leads are then in place. They exit through a
10 small burr hole and attach to an extension wire that
11 then is tunneled subcutaneously to the impulse
12 generator that's implanted underneath the skin over
13 the chest, just beneath the clavicle. So this kind
14 of demonstrates the usual procedures, then, for a
15 subthalamic nucleus as well as globus pallidus.
16 Thalamic surgery would typically be unilateral.

17 Here you can see a drawing of the impulse
18 generator, the Selectra. This is the programming
19 module that the physician can use to program the
20 device. And here, you can see an external magnet
21 that the patient or the physician can use to turn
22 the stimulator on or off.

23 And so I'm going to describe some of the
24 results of some of the trials. And I'll think
25 that as you -- as you see some of these results, I

1 think you will agree that this truly is a
2 breakthrough technology in the very definition of
3 the word "breakthrough." I think you will see that,
4 really, the comparison, in terms of the
5 effectiveness of this therapy, is not against the
6 medication, and it does represent, really, a totally
7 different approach, a totally new approach, for the
8 treatment of patients with Parkinson's disease and
9 essential tremor.

10 And as I go through some of the subsequent
11 clinical data, I want to emphasize to you that the
12 -- the types of patients that were enrolled in these
13 studies. These were end-stage patients, in terms of
14 the Parkinson's disease study for subthalamic
15 nucleus and globus pallidus. These were patients in
16 whom nothing worked, in terms of medication. These
17 were patients who were treated by some of the
18 world's leaders in movement disorders, and they gave
19 up, virtually, on these patients.

20 So, for these patients, the issue was not
21 medication versus surgery. For these patients, it
22 was surgery or nothing, in terms of their efficacy.
23 And so I can -- I am sure you can appreciate that
24 these were difficult end-stage patients, and I think
25 it's very important to keep, then, the results of

1 the clinical trial in that context.

2 And, as you'll see, then, that the average
3 on time was increased by -- can we go back? -- the
4 average on time was increased by nearly six hours
5 for patients with subthalamic nucleus and the globus
6 pallidus stimulation. This represents nearly a
7 doubling of the "on" times that these patients have.
8 This means that, now, that the patient is
9 functional, can get up, care for themselves, feed
10 themselves, participate in activities of daily
11 living.

12 You can also see that the dyskinetic "on"
13 time -- that is, these patients are now mobile.
14 They can get up. They can move around. Their
15 tremor is improved -- their rate of kinesia,
16 slowness of movements -- improve. But before, they
17 were plagued by severe involuntary movement, severe
18 dyskinesia. And, for many of these patients, it is
19 often a difficult choice of being immobile, or being
20 mobile, but too mobile, so mobile that they actually
21 couldn't function. And, many times, the dyskinesia
22 is more disabling than the Parkinsonian symptoms, as
23 well.

24 And you can see, then, that the amount of
25 dyskinesia was substantially decreased by these

1 therapies and that this is not just a few patients
2 getting dramatically better, but a large percentage
3 -- over 87 percent have had significant improvements
4 in their motor examination, the neurological
5 examinations, at that 12 months when the medications
6 were -- when they were fasted from the medication.

7 And actually now most of the Medicare
8 local carriers do cover this therapy, but I submit
9 to you that a national policy is, indeed, needed.

10 And this shows a very important measure.
11 This is the "on" time, without dyskinesia. Again,
12 this is when patients are mobile. They can get up,
13 care for themselves, do things that they need to do,
14 and, at the same time, not plagued by the severe
15 involuntary movements. And you can see here that 74
16 percent of the younger Parkinson's patients have
17 gotten significant improvement, in terms of their
18 "on" time. And 53 percent of even older Parkinson's
19 patients got significantly better. So better than
20 half of these patients, now, were much more
21 functional following deep-brain stimulation.

22 This shows the "on" time with dyskinesia.
23 And this shows that over 71 percent of these
24 patients -- these younger Parkinson's patients --
25 had a significant reduction in the dyskinesia. So

1 they're still mobile, but not plagued by these
2 severe involuntary movements. And when you look at
3 the older population, again, 46 -- nearly half of
4 these patients -- had significant reduction in their
5 dyskinesia -- again, quite a remarkable benefit.

6 This shows the UPDRS score, which is the
7 motor examination, and it -- a more objective
8 assessment of the patient's responsiveness to
9 therapy. And again, I think you can see the data is
10 quite overwhelming. The degree of improvement and
11 the number of patients that improved with this
12 therapy, whether they're younger than 65 or older
13 than 65 -- again, very dramatic improvement. So I
14 think that, again, for these patients in whom
15 medication is not -- no longer an option, this truly
16 does represent breakthrough therapy.

17 I'm going to show you some additional
18 data. This relates to unilateral thalamic
19 stimulation for the treatment of tremor both in
20 patients with Parkinson's disease and essential
21 tremor. And again, you'll see that the results have
22 been quite dramatic. The average tremor-rating
23 score went from a 3.3 to 0.78.

24 Let me put that in context for you. This
25 is based on the tremor rating scale where zero is no

1 tremor, and four is such severe tremor that the
2 person can't even perform the task. So, for
3 example, we will ask them to bring their finger to
4 their nose. Actually, we don't have them bring it
5 to their nose, because we're afraid they're going to
6 poke their eye, so we have them bring it to their
7 chin. And these patients are so severe that they
8 can't even bring their finger to the tip of their
9 nose or to the tip of their chin. And that would
10 give them a ratings score of four. So you can see,
11 then, many of these patients have clearly
12 approximated that severe tremor.

13 And then look at the dramatic reduction in
14 their tremor. One is just intermittent tremor, so
15 quite dramatic improvement. And we see the same
16 degree of improvement, then, with patients with
17 essential tremor.

18 And then this goes -- this shows your
19 form, the improvement in tremor for Parkinson's
20 patients versus essential-tremor patients -- and
21 again, divided into the two age groups -- less than
22 65 years of age and equal to 65 or older -- again,
23 quite dramatic improvement. And again, these
24 assessments were made a year after the implantation
25 of the device.

1 So those are just some of my brief
2 introduction to some of the clinical data. And at
3 this point, I'll turn the podium over to Dr. Bakay.

4 DR. BAKAY: Thank you. I'm privileged to
5 be here and present some of this to you.

6 The appropriate candidates for bilateral
7 STN or GPi deep-brain stimulation are patients who
8 have advanced symptoms but yet have retained some
9 ability to respond to levodopa therapy. I think
10 that's the central element of this.

11 Evaluation of these patients require an
12 expert, like Dr. Montgomery, to make sure that
13 they've had adequate trials of medication and that
14 they are then refractory and no longer responsive,
15 in most cases, to the adequate control of
16 medication. And then they have to be surgical
17 candidates, in the sense that they have to be able
18 to tolerate the stresses of surgery. And obviously,
19 those are candidates that one would evaluate
20 separately. And then the final aspect is approved
21 with the appropriate labeling.

22 The appropriate candidates for the
23 unilateral thalamic stimulation are patients who
24 have disabling tremor from essential tremor or from
25 Parkinson's disease. The tremor must be found to be

1 functionally disabling. The tremor is then also
2 refractory to pharmacological therapies. And,
3 again, the patients have to be able to undergo
4 surgical intervention -- and, again, consistent with
5 approved labeling.

6 In order to perform surgery, you have to
7 have the appropriate equipment, appropriate staff.
8 The appropriate equipment, of course, is -- requires
9 the stereotactic frame, the ability to image the
10 patient, the ability to understand and know the
11 electrophysiology to be able to ensure that the lead
12 is placed properly.

13 The neurosurgeons have undergone a great
14 number of years of training within the neurosurgery
15 residency period. All of the trainees are exposed
16 to stereotactic and functional training to a variety
17 of degrees. There are, in fact, fellowships for
18 additional training thereafter.

19 I think, as I mentioned before, the real
20 essential element to any team approach to this is
21 that one has to have a neurologist involved -- a
22 neurologist involved who can be able to evaluate
23 these patients and make sure that they have had
24 appropriate medical therapy before they undergo the
25 surgical therapy.

1 The neuro physiologist is an elective
2 member. Some of the neurologists and neurosurgeons
3 have more than sufficient neurophysiological
4 understanding to be able to conduct these. Neuro
5 psychiatrists are obviously very helpful, in terms
6 of evaluating patients, preoperatively. We don't
7 want to be performing patients who are demented
8 patients who have underlying depression and other
9 things that need to be treated before they undergo
10 any type of surgical intervention.

11 In terms of training, there's a variety of
12 training available, both through Medtronic and
13 through professional organizations. You can see the
14 number of things there that Medtronic offers, and
15 they can expand upon that, if necessary.

16 In terms of professional organizations, we
17 have courses, and we just finished a series of
18 courses at each of the meetings, nationally, as well
19 as individual courses such as the one sponsored by
20 the Cleveland Clinic just recently in South
21 Carolina.

22 So, in summary, then, we feel that there
23 is compelling evidence of the clinical effectiveness
24 for bilateral STN or bilateral GPi stimulation that
25 there is, in fact, also more than adequate evidence

1 for a unilateral thalamic stimulation for tremor.

2 There is evidence that the Medicare
3 patient population will be one that will be very
4 positively affected by this treatment. And the
5 thing to insist upon is that there is adequate
6 ability to perform this surgery satisfactorily.

7 Thank you.

8 MS. ATKINSON: Now I would like to
9 introduce Joan Vatz, from BlueCross and BlueShield.

10 DR. VATZ: The report I'm presenting this
11 morning was reviewed by the Blue Cross and --

12 DR. GARBER: All right. Joan?

13 DR. ZENDLE: Alan, if there is a question
14 of the speakers, do you want to do that first?

15 DR. GARBER: Yes, brief questions just for
16 clarification, because I think if it's relating to
17 the discussion, we'd like to defer it. I hope that
18 both of you will be staying through at least the
19 morning's part of the proceeding, because your
20 presentation touches upon, very directly, a number
21 of areas of questions that I think the panel will
22 want to explore further.

23 But are there any questions of
24 clarification, at this point? Okay, thank you.
25 Sorry, Joan.

1 DR. VATZ: The report I'm presenting this
2 morning was reviewed by the BlueCross and BlueShield
3 Association Medical Advisory Panel in December of
4 2001 and was published as a technology assessment in
5 January 2002. It represents the work of the
6 Technology Evaluation Center, one of several AHRQ
7 designated evidence practice centers in the United
8 States.

9 My own background is in the practice of
10 internal medicine, including the care of some
11 Parkinson's disease patients. And I have a
12 fellowship training in technology assessment.

13 Parkinson's disease is a chronic,
14 progressive, neurodegenerative disease that usually
15 appears after the age of 40. Its incidence
16 increases with advancing age until it reaches a peak
17 at about the age of 75. And it currently affects
18 about a million and a half people in the United
19 States.

20 The disease impairs a person's ability to
21 control movement. The first symptoms are usually a
22 tremor, trembling, or shaking on one side of the
23 body. Patients also can experience constantly
24 contracted-muscle rigidity, substantially slower
25 movements, bradykinesia, and inability to initiate

1 movement, akinesia, abnormal involuntary movement,
2 dyskinesia, and impaired balance and coordination.
3 These symptoms are related to dopamine deficiency
4 and usually respond to levodopa.

5 Although pharmacologic treatment with
6 levodopa and adjunctive drugs can restore smooth
7 motor movements up to five to ten years in most
8 patients, medication effectiveness diminishes with
9 time. Furthermore, and this is important, this --
10 the degenerative nature of the disease is not
11 confined solely to the dopaminergic system. The
12 brain may be affected more globally as the disease
13 progresses. Thus, symptoms that are not responsive
14 to levodopa may develop. These symptoms include
15 dementia, motor symptoms that affect speech and
16 swallowing, sleep disturbances, depression.

17 The diagnosis of early Parkinson's disease
18 may be difficult. Traditionally, the presence of
19 two of the three classic symptoms of Parkinson's
20 disease provided the basis of diagnosis: resting
21 tremor, rigidity, or bradykinesia. However,
22 clinical diagnosis based upon these criteria alone
23 were found to be incorrect in 25 percent of cases in
24 the London-Britain Bank study in 1992. MRI studies
25 support this misdiagnosis rate. (Inaudible)

1 reported in 1998 that 25 percent of patients with
2 Parkinsonian symptoms have an atypical disorder,
3 such as multiple-system apathy or progressive
4 supranuclear palsy, rather than idiopathic
5 Parkinson's disease. Thus, the diagnosis of
6 Parkinson's disease has shifted somewhat, and these
7 are predictors that are more often used now.

8 Specialists in nucleus disorders
9 distinguish at least two major subtypes of
10 Parkinson's disease -- a tremor-dominant subtype and
11 a rigid, akinetic subtype. It is generally accepted
12 that patients with unilateral tremor-dominant
13 disease seem to progress less rapidly, have less
14 cognizant dysfunction, and respond differently to
15 anti-Parkinsonian medication than patients with the
16 rigid, akinetic subtype of disease. Patients with
17 the rigid, akinetic subtype have symptoms that are
18 more symmetrical and experience more dystonia, more
19 axonal involvement, and early dyskinesia.

20 Everyone learns in medical school this
21 definition of Parkinson's disease. The corpus
22 striatum is part of the basal ganglia. It's made up
23 of two cellular masses, these nucleuses. These
24 masses arise as a single body in early development
25 and then separate as the brain develops. They

1 remain continuous centrally -- how can you make the
2 slide go back; okay, thank you -- and are connected
3 directly by a number of slender gray bridges across
4 the internal capsule, which you can see in this
5 diagram.

6 Parkinson's disease, then, is the
7 degeneration of the monoaminergic neurons in the
8 substantia nigra. These neurons project neuritic
9 processes through the striatum shown here that -- to
10 modulate activities of the extrapyramidal system to
11 two critical functions: the production of dopamine
12 and the regulation of its release from these
13 terminals. Certain motor symptoms of Parkinson's
14 disease appear when this modulation is lost, as
15 these cells gradually die.

16 In fact, however, Parkinson's disease is
17 also a complex global disease involving the
18 progressive death of many selected groups of neurons
19 throughout the brain. Here are some of them, as
20 listed in Lang & Lozano's 1998 review. This is
21 sections of the brain showing where this area's
22 nuclei lie. Here are some more of them that are
23 affected in Parkinson's disease.

24 It's important to have a solid sense of
25 the neuroanatomic complexity of Parkinson's disease.

1 I'd also like to spend a few minutes to call your
2 attention to the definitions in Table A of the
3 BlueCross and BlueShield assessment. This has terms
4 of -- definitions and terms used in studies of
5 Parkinson's disease. For practitioners unfamiliar
6 with the study of Parkinson's disease, these terms
7 may seem rather arcane.

8 The first one, "off" period, refers to a
9 variety of conditions ranging from brief periods of
10 relative immobility and loss of dexterity, due to a
11 temporary loss of medication effect, to the
12 condition that occurs after prolonged withdrawal of
13 anti-Parkinsonian medication. Advancing Parkinson's
14 disease is characterized, then, by a lengthening of
15 these "off" periods, or periods of relative
16 immobility and loss of dexterity that occur
17 gradually as the dose of levodopa wears off.

18 The "off" condition is an operational
19 definition in which the term "off" ignores what true
20 "off" may be in the patient's life or that there may
21 be several different types of "off" for any given
22 patient. This term was developed as a working
23 definition in 1992 to promote standardization and
24 comparability in Parkinson's disease studies.

25 Now it usually refers to a standard

1 practically defined "off" condition created for
2 purposes of a study by withdrawal of medication for
3 12 hours. In practice, this is often simply the
4 state the patient is in in the morning before taking
5 the first dose of levodopa or anti-Parkinsonian
6 medication. There are a few other terms where "off"
7 is a condition that both the patient and the
8 physician agree is as severe as the symptoms ever
9 become.

10 "On" periods are periods of maximum
11 mobility and dexterity when medication is working.
12 There is a "best on" condition.

13 And there are motor fluctuations, which
14 are abrupt, unpredictable "off" periods -- that is,
15 periods of relative immobility and lost dexterity
16 that may last from a minute to an hour and are
17 followed by an equally abrupt return of medication
18 effectiveness, or an "on" period. Such on/off
19 fluctuations may occur frequently throughout the day
20 or even during an hour and are not temporally
21 related to levodopa intake. Motor fluctuations
22 occur in approximately 50 percent of patients after
23 five years of levodopa therapy, and, at this stage,
24 usually affect patients for less than 25 percent of
25 their waking hours.

1 Dyskinesia is -- consists of abnormal
2 involuntary movements. These are highly variable
3 movements. With time, they become a major cause of
4 disability in Parkinson's disease. One type of
5 dyskinesia seen early in the course of treatment
6 consists of abnormal movements, usually at the head,
7 neck, torso, or respiratory muscles. And these
8 occur when the effective medication is at its peak.
9 Many patients, particularly early in the course of
10 the illness, are unaware of the presence of these
11 movements, and they are reversible and rapidly
12 disappear if levodopa is withdrawn or if the dosage
13 reduced. There are other kinds of dyskinesias that
14 develop in later Parkinson's disease.

15 Dystonia -- some patients develop painful
16 "off-period" dystonia, which is an increase of
17 muscle tone resulting in fixed, abnormal postures
18 and sometimes abnormal movements.

19 There are a number of tools used for the
20 evaluation of Parkinson's disease -- these two
21 slides show them -- and it's important to have a
22 good sense of these terms before going on, because
23 they appear over and over in the studies people will
24 be talking about today.

25 The UPDRS is perhaps the most widely used

1 measure. It was published in 1987 and consists of a
2 comprehensive inventory of symptoms and signs of
3 Parkinson's disease, which I divided into sections
4 pertaining to mood and mentation, activities of
5 daily living, motor function, muscle rigidity,
6 speech, and gait. Scores range from zero, which is
7 normal, to 176, which is the worst possible.

8 Patients are questioned and examined in both the
9 off-medication state, usually before the first
10 morning dose, and then the on-medication state,
11 which is usually defined as the best test scores
12 measured during the day when the patient is taking
13 the levodopa.

14 This slide shows a sample of one of the
15 items for postural stability. A patient is
16 subjected to a strong, sudden posterior displacement
17 produced by a pull on the shoulders. While standing
18 erect with the eyes open and feet slightly apart,
19 the patient is prepared, and then the examiner
20 observes which of these responses the patient has.

21 The Schwab and England scale is a measure
22 designed exclusively to evaluate performance of
23 activities of daily living, and the scoring is the
24 reverse of the UPDRS, with 100 indicating normal,
25 and zero, the worst possible.

1 The Hoehn and Yahr staging system is one
2 of the oldest measures used in Parkinson's disease.
3 It consists of six major stages and emphasizes
4 mobility.

5 There are some other subjective patient-
6 generated ways of looking at Parkinson's disease.
7 All in all, I think you can tell, evaluation of
8 treatment for Parkinson's disease is extremely labor
9 intensive. Symptom severity changes from week to
10 week, from day to day, from minute to minute. So
11 the purpose of these is to obtain some more data
12 points.

13 First, there are diaries. These are from
14 the Deep Brain Study Group Multicenter Trial, the
15 diary evaluations that we used in that. Another
16 method used is home video recordings at frequent
17 intervals, which is more labor intensive, but has a
18 few advantages over the diaries, in that the videos
19 can be examined blindly and rated by an objective
20 examiner permitting blinding of the examiner and
21 some standardization of the rating, and then they
22 allow a more -- a larger number of data points to be
23 examined, which may screen for some of the noise
24 generated by fluctuations in the disease. These
25 have been used in some of the cellular

1 transplantation studies of Parkinson's disease.

2 Treatment options for advanced disease
3 consist of medication or surgical options shown in
4 this slide. But, as noted, medication becomes less
5 effective with time. And the unilateral procedures
6 offer limited benefits for patients with bilateral
7 disease; thus, the interest in bilateral deep-brain
8 stimulation.

9 The two targets under study are relatively
10 small structures -- the subthalamic nucleus, which
11 you can barely see here, but this shows how it all
12 relates to the extrapyramidal system. It's a small
13 ovoid nucleus with a volume 150 to 200 cubic
14 millimeters in humans. It lies a little bit lateral
15 to the substantia nigra and is bounded externally by
16 the internal capsule. The globus pallidus interna
17 is a larger structure -- banana shaped with a volume
18 of about 500 cubic millimeters in humans and is
19 bounded by the internal capsule, caudally, and by
20 the optic tract, ventrally. Both of these
21 structures are anatomically complex in that both
22 contain sensory motor regions, and both contain
23 complete thalamatotopic organization.

24 How does deep-brain stimulation work? No
25 one knows for sure, but here are some of the

1 theories that have been proposed in the literature.

2 And now we'll get to the body of the
3 assessment. We used three search methods to
4 generate our reference list. And these study-
5 selection criteria -- here are a few more of them.

6 Since we were interested in bilateral
7 stimulation, mainly because Parkinson's disease is a
8 bilateral disease, studies in which outcomes for
9 unilateral procedures were analyzed together, where
10 those of bilateral were excluded from the
11 assessment.

12 Also, some other studies examine single
13 outcomes, such as the affect of deep-brain
14 stimulation on voice production. These studies,
15 which focused on a single outcome, are required to
16 use such highly specialized measures, were also
17 excluded as beyond the scope of the assessment.

18 Finally, there is concern over the
19 potential adverse affects of bilateral procedures
20 upon neuropsychiatric function. Since it is the
21 bilaterality of the procedure, rather than the
22 choice of targets, that is the primary concern in
23 these studies, outcomes of studies of either nucleus
24 were considered together in the case of
25 neuropsychological evaluations.

1 This assessment was formulated with these
2 -- were structured with these -- with this
3 formulation, these four segments.

4 Patient indications. These were the
5 patient indications that were provided in most of
6 the -- in all, I would say, of the studies that we
7 used. If you look in the assessment, on pages 24
8 through 29, in the fourth column -- it's a very busy
9 table, but it shows some of the patient
10 characteristics, as well as inclusion and exclusion
11 criteria used.

12 Despite the use of these indications, it's
13 still a little hard to determine, in this entire
14 body of literature, exactly who these patients are.
15 Some studies exclude patients with abnormal MRIs,
16 while others have patient cohorts with nearly a 50-
17 percent rate of MRI abnormality. Some present
18 extensive baseline staging information, while others
19 do not.

20 With advanced age and exclusion factor --
21 it's never stated, really, as such -- patients as
22 old as 74 have been studied. However, most patients
23 are younger than 65 at the time of implantation in
24 the studies that we included in this.

25 The technologies to be compared. To

1 examine this procedure, the ideal comparison would
2 be best medical management from a specialized
3 movement disorder. Another possible comparison
4 would be with the accepted unilateral surgical
5 treatment, a unilateral pallidotomy. Most trials,
6 however, compared deep-brain stimulation in the
7 "off" and "on" condition with the patient's
8 preoperative baseline control. Whether this
9 baseline condition always consisted of careful best-
10 medical management as a protocol cannot be
11 determined from most of these trials.

12 These are the health outcomes, the
13 benefits to be expected from deep-brain stimulation.
14 They lie in the realm of motor improvement and
15 medication reduction. These four key benefits were
16 reported in most of the trials.

17 Adverse effects consists of these
18 conditions related to the procedures, to the device,
19 and to stimulation.

20 Because of the experience with bilateral
21 ablative procedures, which carry a high risk of
22 postoperative cognitive dysfunction, the question
23 arises, does bilateral deep-brain stimulation pose a
24 similar risk? So we looked at studies that examine
25 neuropsychiatric function, as well.

1 The specific -- the assessment poses this
2 specific question.

3 And then the analysis of the evidence. We
4 found that there was no large prospective randomized
5 study with long-term follow-up of bilateral deep-
6 brain stimulation. In no published studies are
7 patients randomized prospectively to treatment on --
8 that compared deep-brain stimulation with best
9 medical management. There is one small pilot study
10 that is prospectively randomized, and that compares
11 subthalamic nucleus and globus pallidus interna
12 targets. And that study is by Dr. Burchiel in 1998.

13 The reported patient numbers -- the
14 reporting of patient numbers is complicated by the
15 possibilities that outcomes from some patients may
16 have been published in more than one of the reports
17 included in this assessment, so we tried to get
18 around it by the following logic.

19 If you look at Table 1, in the fourth
20 column, you can see the number of patients listed in
21 each study. If none of the -- if no patients
22 described in any of the single-center trials were
23 included also in the deep-brain study-group trial,
24 then we have outcomes in the published literature
25 for 287 patients. However, many of the

1 investigators in the deep-brain study-group trial
2 have also published single-center trials. And if you
3 assume that the deep-brain study-group published
4 outcomes from all or some of the same patients in
5 the single-center trials, then the outcome -- we'd
6 have outcomes for as few as 186 patients.

7 Since we couldn't tell from the literature
8 which was which, we chose to go with this
9 conservative number of 186 patients. And in the
10 discussion of the outcomes, we assumed that all the
11 deep-brain study-group investigators have published
12 outcomes on the same patients in both single-center
13 trials and the multicenter trial. That leaves 186
14 patients for the subthalamic nucleus studies, and
15 53, as a conservative figure, for the globus
16 pallidus interna. It may be more than that, but we
17 don't know for sure.

18 Randomization is a design issue. Only
19 one -- only the one pilot study provides a true
20 randomization. The multicenter trial randomization
21 consists of including all patients who underwent
22 implantation. And then in the postoperative
23 examination sequence, patients were randomized in
24 terms of the crossover examination of whether they
25 were examined with stimulation "on" first or

1 stimulation "off" first.

2 Outcomes. Things like home diaries
3 provide some questions about validation and
4 standardization. Still, despite this, the published
5 evidence is quite compelling, both because of the
6 numbers of effectively treated patients and because
7 of the consistency of the patients -- the
8 consistency of the findings across the study and the
9 magnitude of the clinical improvement.

10 There are, in the assessment, 14 published
11 trials describing motor outcomes among 186 patients,
12 with follow-up at six months for 151 one of these,
13 and, for at least 12 months for 116 patients.

14 There are nine published trials examining
15 the globus pallidus interna as a target with motor
16 outcomes among 53 patients and follow-up from three
17 months to as long as 30 months. Ten trials examine
18 neuropsychiatric function after treatment in at
19 least 139 patients.

20 The key outcomes in these trials are these
21 four, which we have looked at before. For the sake
22 of time, however, we can focus, as we look at these
23 outcomes, upon the outcomes reported in the deep-
24 brain study-group report, which was published in the
25 New England Journal in September of 2001.

1 Motor improvement in the "off" condition
2 -- that's the condition when the patient is
3 relatively immobile, in terms of the study design,
4 but it would be the condition the patient has during
5 the day when their doses of levodopa wear off. Mean
6 UPDRS scores improved by 51 percent with the
7 subthalamic nucleus stimulation, and by 35 percent
8 among the globus pallidus interna patients.

9 Similar motor improvement was reported in
10 all 14 studies of the -- using the subthalamic
11 nucleus as a target, and in eight of the nine
12 studies of the globus pallidus interna.

13 Activities of daily living improved also
14 in the "off" condition by 44 percent and 38 percent.
15 Percentage of time with good mobility increased
16 dramatically. The daily levodopa equivalent dosage
17 was reduced among patients with subthalamic nucleus
18 stimulation, but this was not possible among
19 patients with -- when the globus pallidus interna
20 was the target.

21 Complications are similar to those known
22 for thalamic stimulation. Persistent neurologic
23 deficit was reported in the deep-brain study-group
24 among seven of the 143 patients, or 2.8 percent.
25 Infections occurred in four of the 143 patients,

1 seizures in four of the 143 patients, lead migration
2 in five, and stimulation-induced dyskinesia
3 requiring parameter adjustment in five. These were
4 the major complications.

5 These can be compared -- if you look in
6 the assessment at Table 4, on page 45 -- with
7 complications reported after a ablative pallidal
8 surgery. Intracranial hemorrhage was reported in
9 four studies of pallidotomy with incidents of 1.5 to
10 12 percent. Postoperative confusion occurred in
11 four to ten percent of patients. And cognitive
12 difficulty occurred in up to 12.5 percent of
13 patients.

14 Observations from patients with
15 hemiparkinsonism suggest that the right and left
16 basal ganglia have distinctly different roles in the
17 mediation of verbal and visual spatial abilities.
18 For example, patients with right hemiparkinsonism --
19 that is, disease that involves the left basal
20 ganglia -- these patients show greater deficits in
21 verbal abilities than patients with right
22 hemiparkinsonism.

23 Conversely, patients with left
24 hemiparkinsonism -- with right hemiparkinsonism --
25 no, I get the left and right mixed up. I'm sorry.

1 Patients with left hemiparkinsonism -- that is,
2 disease that involves the right basal ganglia --
3 tend to have more profound visual spatial defects.

4 Laterality of a surgically-created lesion
5 has been found to be a significant determinant of
6 neuropsychological sequelae after unilateral
7 pallidotomy. Thus, some patients who were generally
8 pleased with the motor outcomes of their pallidotomy
9 were often restricted, then, in their ability to
10 function properly at work or in social settings by
11 behavioral changes and losses in verbal fluency.

12 Thus, the question of whether bilateral
13 deep-brain stimulation poses a similar risk is an
14 important one, and there are ten studies reviewed in
15 this assessment. They're presented on pages 65
16 through 69. They evaluate 139 patients. Nearly all
17 of these studies find some degree of loss in verbal
18 learning and/or language function.

19 In one of the most-recently publication --
20 most recent publications by Allegret and Colleagues
21 -- it's the first article in your literature volume
22 -- memory, visuospatial, and frontal function were
23 evaluated in 15 patients three months after
24 bilateral implantation. It was found that, in this
25 group, bilateral subthalamic nucleus deep-brain

1 stimulation produced a mixture of beneficial
2 changes, including moderate improvement in
3 prefrontal task and obsessive-compulsive traits, and
4 detrimental changes, which consisted of moderate
5 deterioration of verbal memory. The authors
6 conclude that since, in general, all surgical
7 procedures for Parkinson's disease involving the
8 left or both hemispheres appear to negatively affect
9 verbal memory, and since all involved nuclei are
10 related to memory processes, some change in learning
11 ability after these procedures as -- is to be
12 expected. So there is consensus, in general, among
13 these studies that the risk, while present, is
14 minimal.

15 And these are the criteria -- the
16 BlueCross and BlueShield Association Technology
17 Evaluation Criteria. We created a discussion base
18 that follows, sort of, the order I've given you of
19 this data. And -- based upon these criteria -- and
20 based upon the evidence, bilateral deep-brain
21 stimulation of the subthalamic nucleus or the globus
22 pallidus interna for patients with advanced disease
23 was voted to meet these TEC criteria in December.

24 DR. GARBER: Thank you, Joan. Any
25 questions of clarification? Okay.

1 MS. ATKINSON: I would like to introduce
2 Celia -- Dr. Celia Witten from FDA.

3 DR. WITTEN: I'd like to thank you for
4 inviting me to come and present the FDA's review
5 process for these devices and what we based our
6 review decision on. I'm Dr. Witten, and I'm the
7 division director of the division in the Center for
8 Devices that's in charge of pre-market review of,
9 among other things, neurological devices.

10 There's a number of different pathways by
11 which a product can be approved, and I've listed
12 them here on this slide. The one that's, by far,
13 the most common is the first one, the pre-market
14 notification, or so-called 510(k) pathway. And FDA
15 approves probably upwards of 4,000 products a year
16 for that pathway. But that isn't a pathway for
17 fairly novel products, like this one, which went
18 through the pre-market approval pathway.

19 So other than just saying that our
20 criteria for approving products in these different
21 categories are different, I'm going to move on and
22 focus on the criteria for approval and the process
23 for approval of pre-market approval applications.

24 So I guess I actually went through the --
25 slipped by the first slide, which was an outline of

1 my talk. So I'll just mention that I'm going to
2 give you a little bit of regulatory background, and
3 then I'm going to talk about the history of these
4 submissions, and then go on and give a little bit of
5 detail primarily from the summary of safety and
6 effectiveness that you have in your package that was
7 provided you in advance.

8 So, to continue with the regulatory
9 background, a product like this would be studied
10 under investigational device exemption, which is the
11 mechanism by which FDA regulates clinical studies
12 that are performed on unapproved devices to support
13 a marketing application. And they can support a
14 marketing application of any one of those types of
15 devices.

16 We only are -- have authority over studies
17 performed in the United States. So studies
18 performed outside of the United States, or sites
19 that perform studies outside the United States,
20 aren't under the IDE regulations.

21 And the IDE is -- under an IDE, a sponsor
22 will perform a study to get a systematic collection
23 of safety and effectiveness data. And, in this
24 case, this was considered a significant-risk study,
25 so it's approved by the FDA and approved by the

1 Institutional Review Board of the centers that
2 conduct those studies.

3 For a PMA, a sponsor needs to show that
4 there's reasonable assurance of safety and
5 effectiveness. And I'm going to give you the
6 regulatory definition of safety and effectiveness in
7 a subsequent slide. And those are defined on the
8 basis of risk and benefit to the patient and
9 clinically significant results to the patient
10 population for which -- for the target patient
11 population.

12 In a PMA application, we generally would
13 see clinical data from an IDE study, although not a
14 hundred percent of the time, and a summary of safety
15 and effectiveness with proposed labeling for the
16 product. And the product is then reviewed by the
17 ODE division, which, in this case, is the division
18 that I'm the director of. And we get other reviews
19 from other Center for Device offices, as needed.

20 In this case, this product, for both the
21 original application and the subsequent application,
22 were reviewed by an FDA advisory panel, as well.

23 We have a regulatory definition of "valid
24 scientific evidence," and there's a hierarchy of
25 valid scientific evidence of which the highest rank

1 is well-controlled investigations. And this
2 hierarchy of evidence includes partially controlled
3 studies, trials without matched controls, well-
4 documented case histories, and reports of
5 significant human experience.

6 And, as Dr. Vatz has already pointed out,
7 there aren't well-controlled investigations or -- in
8 the sense of randomized studies against another
9 treatment, but the evidence that we looked at for
10 this -- these marketing applications certainly fit
11 within the spectrum of valid scientific evidence, as
12 our definition gives us.

13 The definition of "safety" is, "Reasonable
14 assurance that a device is safe when it can be
15 determined, based upon valid scientific evidence,
16 that the probable benefits to health under
17 conditions of use outweigh any probable risks."

18 And what I want to just point out here and
19 also under the definition for "effectiveness" is the
20 "under conditions of use" part, and that is, we
21 don't approve just the device. It's the device plus
22 the particular use that it's -- that -- for which
23 that device is intended.

24 And so in this -- that's why there were
25 two separate approvals, the original approval for

1 the tremor indication, followed by the indication
2 for the Parkinson's indication, because of our
3 regulatory scheme that the product is the product
4 plus what it's supposed to be used for.

5 Our definition of "effectiveness,"
6 "Reasonable assurance that a device is effective
7 when, in a significant portion of the target
8 population, the use of the device for its intended
9 uses and conditions of use will provide clinically
10 significant results."

11 So, again, it's -- it's specific use.
12 It's the device plus its use, and we are directed to
13 look at clinically significant results in that
14 target population.

15 Moving on to the history of this, as has
16 already been mentioned, the original approval was
17 for unilateral thalamic stimulation for tremor
18 suppression. And there was a supplement approved
19 early this calendar year for bilateral globus
20 pallidus or subthalamic nucleus stimulation for
21 Parkinson's symptoms. In each case, the application
22 was reviewed by an FDA Advisory Panel, who recommend
23 approval for the product.

24 The indications for use -- I'm not going
25 to read them. They're in your package. But it's

1 for suppression of tremor in the upper extremity.

2 And, as has been mentioned, it's for unilateral
3 tremor suppression -- unilateral use.

4 The tremor study was for patients with
5 Parkinson's disease or central tremor that was
6 disabling and not adequately controlled by
7 medications.

8 I'm just going to mention here that the
9 mean age in this study in the U.S. was 67 years, and
10 in Europe was 63 years.

11 Effectiveness. There were -- the
12 effectiveness was based on a rating scale from zero
13 to four for tremor in Parkinson's based on one of
14 the questions in the UPDRS, and for the central
15 tremor based on one of the questions in the tremor
16 rating scale. The questions are slightly different,
17 but the rating scale in both cases are on a zero-to-
18 four basis. And the analysis was based on comparing
19 equivalent and individual patients with stimulation
20 "on" compared to stimulation "off," and with
21 stimulation "on" compared to the patient's pre-
22 implant state.

23 The Parkinson's disease indication for use
24 is for bilateral stimulation as adjunctive therapy
25 in reducing some of the symptoms of advance

1 levodopa-responsive Parkinson's disease not
2 adequately controlled with medication.

3 I'm -- I put this slide in -- this is the
4 precautions from the label and from our summary of
5 safety and effectiveness for this product. And the
6 point I want to make here is just that I know the
7 question is going to come up about what a precaution
8 means compared to a contraindication, and we have in
9 here uses -- specific populations that -- we don't
10 have specific safety and effectiveness information
11 for these populations. But this is not a
12 contraindication. And so this is just information
13 that -- for example, in the case of over the age of
14 75 years, that we don't have specific information in
15 the population, but it is not a contraindication in
16 the FDA labeling for that product.

17 The study supporting this indication was
18 in 160 patients. There's a slight error on this
19 slide. There were 18 centers, four in the U.S., and
20 14 outside of the U.S. But some of these were in
21 Canada and Australia. So there were 18 centers,
22 four in the U.S., and 14 outside the U.S.

23 The inclusion criteria is ages 30 to 75.
24 They were patients with idiopathic Parkinson's with
25 a good levodopa response, as has already been

1 mentioned previously. That's one of the factors
2 that is felt to predict an ability to respond with
3 this device. And patients had to have a certain
4 criteria in terms of severity of their Parkinson's
5 disease, as characterized in the last three bullets
6 on this slide.

7 Sixty-six-point-nine percent of the
8 patients were males. The mean age of disease onset
9 was 43.9 years, and the mean age at the time of
10 implantation was 58 years, with a range of 32 to 75
11 years.

12 The parameters -- there were a number of
13 parameters assessed in the study. The ones that we
14 focused on in our assessment for safety and
15 effectiveness were the UPDRS -- motor portion of the
16 UPDRS, the patient diaries regarding the "on" and
17 "off" states in dyskinesias, and also, of course,
18 safety.

19 And some of the safety events that are
20 most concerning -- and these are on the basis of the
21 number of patients with each event. So 12 out of
22 160 patients had intracranial hemorrhage, 17 had
23 device-related infection, 16 had paresis/asthenia,
24 and 13 had hemiplegia or hemiparesis. And some of ,
25 a patient with intracranial hemorrhage and

1 hemiplegia would have been counted in both
2 categories.

3 What we looked at for total motor exam
4 scores. The symptoms of Parkinson's disease
5 improved for 56 out of 117 patients while on
6 medication, and improved for 102 out of 117 patients
7 while off medication.

8 And I'll just mention again that this
9 "off" medication, as Dr. Vatz has already said, is
10 not the "off" state -- it's not the "off" state
11 mentioned in motor fluctuation. It's practically
12 defined "off," where the patient is off medication
13 for a certain period of time prior to their
14 assessment.

15 Now, what we looked at more closely is --
16 we wanted to look at what patients improved -- what
17 was the definition of improvement for an individual
18 patient. So what this histogram shows you is the
19 number of patients who had no change. And no
20 change, in this case, was defined as no change of --
21 or a change of less than five points. So for a
22 patient to get into the right-hand side or the white
23 bars of this histogram, which shows improvement,
24 they had to have improved by at least five points on
25 the total motor exam score of the UPDRS.

1 And in this case, we're looking at the
2 patients who improved in the total motor exam "off"
3 mediation by target. And, again, this is "off" as
4 defined as having been off their medications
5 overnight.

6 And the comparisons made here and in the
7 prior slide are between the preimplantation state
8 and the 12-month state.

9 Looking at the diary results, the duration
10 of the "on" time was increased by an average of 6.7
11 hours and 6.1 hours in the GPi and STN patients,
12 respectfully. And the duration of "on" time with
13 dyskinesia is decreased in both groups, as well.

14 Here, again, we've got a histogram that
15 shows the magnitude of the improvement in the
16 patients in these two groups. And, on the right,
17 you see the definition of "improvement" is "improved
18 by at least an hour." And the histogram shows --
19 breaks down a little bit further. Patients who
20 improved between one and four hours is a plus-one
21 category, and for the -- plus-two category means the
22 patient improved between four and seven hours, in
23 terms of their amount of "on" time; and then the
24 plus-three category, between seven and ten hours.
25 So that -- there's an ability to see a little bit

1 more the amount of benefit that the individual
2 patients received from this treatment.

3 And this slide shows you the absolute
4 change in "on" time with dyskinesias, by target.
5 I'm not going to read it. But, again, there's a
6 breakdown to show how much individual patients
7 improved on this parameter.

8 So I'll stop here and ask if there's any
9 questions. Thank you.

10 DR. GARBER: Okay, thank you.

11 And now we have the scheduled public
12 comments.

13 MS. ATKINSON: Our first speaker is Dr.
14 David Charles.

15 DR. CHARLES: I'd like to thank the Chair
16 and members of the Advisory Committee.

17 My name is David Charles, and I'm on the
18 faculty of Vanderbilt University in Nashville,
19 Tennessee.

20 My research in the area of deep-brain
21 stimulation is supported by private not-for-profit
22 foundations, Medtronic, Incorporated, and the
23 governments of both France and the United States.
24 At Vanderbilt University, I'm director of the
25 Neurology Residency Program and also director the

1 Movement Disorders Clinic. My practice is primarily
2 focused in movement disorders and in the area of the
3 application of deep-brain stimulation for the
4 treatment of tremor and Parkinson's disease.

5 I've worked with patients with Parkinson's
6 disease and the application of this therapy since
7 1994, and served as a Fulbright Scholar in France,
8 studying this therapy.

9 Today, I rise on behalf of the American
10 Academy of Neurology, speaking on behalf of this
11 organization, which is the largest organization
12 representing neurologists in the United States, over
13 15,000 members, representing both the members and
14 our patients.

15 I will not review here the data regarding
16 DBS, but will give you the position statement of the
17 American Academy of Neurology. And that is that we
18 encourage this advisory panel, in the strongest
19 possible terms, to recommend a national policy
20 coverage decision for the application of deep-brain
21 stimulation for the treatment of tremor and
22 Parkinson's disease.

23 Deep-brain stimulation for the treatment
24 of Parkinson's disease, particularly stimulation of
25 the subthalamic nucleus, represent the most

1 significant advance in the treatment of Parkinson's
2 disease in almost 30 years. The American Academy of
3 Neurology is fortunate to have had many of its
4 members participate in this research, both in the
5 United States and in Europe.

6 While it's not in the purview of this
7 committee to consider, the American Academy of
8 Neurology would also like to state for the record
9 that, for Medicare patients to actually have access
10 to this therapy there must be an appropriate
11 reimbursement policy that covers every aspect of
12 this therapy, including the preoperative evaluation,
13 the implantation of the device, and the follow up
14 for the patients through the remainder of their
15 care.

16 I thank the committee for the opportunity
17 to speak.

18 DR. GARBER: Thank you.

19 MS. ATKINSON: Our next speaker is the
20 Jante's, Ellen and Dale.

21 MS. JANTE: Thank you for your time today.
22 I don't have the credentials of all the other
23 speakers that you've heard so far, but Dale has --
24 you could you stand up for a second? -- Dale has
25 Parkinson's, and we're very personally involved, and

1 we wanted you to hear from someone who was.

2 For most of us today, this is a pretty
3 normal day. Maybe you don't do what you're doing
4 today every day, but you're living a normal life.
5 This day, for Dale and I, is monumental, and for
6 thousands of other patients like Dale.

7 We aren't going to preach to you today
8 about Parkinson's disease. You already know it.
9 You've seen patients, I hope, who have it. And we
10 would like to tell you, though, what an average day
11 is like. First of all, there are no average days,
12 but just a glimpse.

13 The possibility that subthalamic deep-
14 brain stimulation surgery could offer Dale and
15 others -- excuse me -- a semi-normal life would be a
16 miracle. Dale is 56 years old now -- not unlike the
17 age of several of you, I'm sure, in the room -- and
18 was diagnosed with Parkinson's when he was 43. His
19 symptoms started with a tremor. No problem. We can
20 deal with that. Unless you're an accountant, and
21 you need to use the computer to do your work.

22 The month he was diagnosed, he lost his
23 job and all healthcare insurance. Fortunately, he
24 qualified for high-risk insurance, which costs --
25 which had \$1,000 deductibles and \$300-a-month

1 payments. Since he had no job, we used our savings
2 to pay for that insurance so that he would have
3 coverage.

4 Fortunately, since then, he's been covered
5 by Medicare, and he's on total disability, he has
6 been for a few years. We had to appeal for five
7 years to qualify for Medicare, even though he could
8 not work. And he's also covered by the Veterans
9 Administration, because he's a Vietnam veteran.

10 The tremors led to stiffness and
11 difficulty walking. His ability to think and speak
12 is diminished because of this disease and the 43
13 pills he takes every single day. No one knows what
14 the results or the interaction of all these
15 medications is to other parts of his body. The 14
16 prescriptions that are refilled every months cause
17 major side effects. In fact, three years ago, Dale
18 suffered congestive heart failure as a result of the
19 medication, Mirapex.

20 Fortunately, his heart has recovered. And
21 that's the good news. And his cardiologist feels
22 that his heart would be fine if he underwent brain
23 surgery.

24 Since entering this room this morning at
25 7:30 a.m., Dale came in "on" -- you may not have

1 realized that he had Parkinson's. Since then, he's
2 been "on" -- just took his medication, so he'll
3 remain "on" for quite some time now before those
4 medications kick in.

5 His day revolves around his medications.
6 It takes him one and a half hours in the morning to
7 be able walk after taking the medication. Until
8 then, he can only sit in his chair. He takes pills
9 every three to four hours. Approximately one hour
10 before a dose, he freezes up -- cannot move at all
11 and cannot function for at least another hour.

12 Even when his medications work, he
13 stumbles, falls, has slurred speech, he drools, and
14 has involuntary movements. There are no good ways
15 -- no good days anymore, just good minutes. He
16 can't plan for anything, because he may not be able
17 to move or communicate. Last Saturday night, he
18 crawled to bed on his hands and knees just to get to
19 bed, because he could no longer walk. There's no
20 wheelchair in our house. Dale knows that once that
21 wheelchair comes in the house, he'll never get out.

22 We're asking you today to put that
23 wheelchair time on for him and others like him.
24 But, in spite of this, he considers himself lucky,
25 because his friends with Parkinson's who are the

1 same age as him are in wheelchairs.

2 I'm going to skip part of this, because I
3 know I'm running out of time, right?

4 He researched the effectiveness of
5 pallidotomy and thalamotomy and decided that was not
6 for us. Two -- the lesions would cause too much
7 permanent damage. But he began studying the
8 Emory study on DBS.

9 We debated whether he could have the
10 surgery to correct his tremors so that he could eat
11 without dropping his food, work on a computer,
12 address himself unaided, and feel more relaxed in
13 public. And then the stiffness set in.

14 Just helping the tremor isn't enough.
15 Just imagine how badly you would have to feel to ask
16 to have two holes drilled in your brain. How bad
17 would you have to be?

18 So I want to know what the price we can
19 pay for the value of living a normal life. Surely
20 you know someone with Parkinson's. Everyone does.
21 I would hope that you would act for a better quality
22 of life for those people.

23 We live in Wisconsin. Medicare does not
24 cover this surgery in Wisconsin. We're covered by
25 WPS. So we believe that we could cut his -- and

1 obviously other people could, too -- cut their
2 medication by 40 to 80 percent, and he could improve
3 that much.

4 We wondered what we could do to impress
5 you today. First of all, we came at our own
6 expense. We are thrilled to be here today with
7 professionals who have -- who can make the decision
8 to help us. Then we asked for signatures. And, on
9 May 17th, we began gathering signatures. There's
10 almost 3,000 signatures of people that have
11 Parkinson's, and caregivers, and other people we
12 know that are concerned about this.

13 So we are asking you to make difference
14 for thousands and thousands of patients, like Dale,
15 who are awaiting this much-needed treatment. We ask
16 you to help those who can't help themselves.

17 Dale is thinking positively, believing
18 that, if you had a relative with Parkinson's, you
19 would not hesitate to give them a better chance for
20 life. So we encourage you to give Medicare your
21 blessing, to nationally cover DBS surgery.

22 We thank you very much for your attention
23 to this issue today.

24 DR. GARBER: Thank you.

25 MS. ATKINSON: And our last speaker, Dr.

1 Frederick Lenz.

2 DR. GARBER: Okay, I'm going to ask the
3 sense of the panel. Several of you, I know, are
4 interested in carrying out the deliberations fairly
5 rapidly, if it's possible to do so. Would you like
6 to take a short break now? Or no break, and just
7 people go out when they want and move into
8 deliberations? What is the sense of the panel?

9 PANELISTS: No break.

10 DR. GARBER: No break, okay.

11 So we will now move into open panel
12 deliberations. And, at this point, I'd like to just
13 go around the room, since everyone is present, and
14 have each panelist briefly introduce themselves.

15 Joan Samuelson?

16 MS. SAMUELSON: Thank you. I am the
17 president of the Parkinson's Action Network, which
18 is a nationwide advocacy group on behalf of the
19 Parkinson's community.

20 I've had Parkinson's for 16 years. I am
21 one of the lucky ones who was able to walk into the
22 room when I -- when the medication is working, but I
23 just wanted to mention that. And, for those of you
24 who don't live closely with Parkinson's, you got a
25 good summary of it from Mrs. Jante -- and I thank

1 you for that -- but I wanted to reiterate that.

2 When I wake up in the morning, it takes me
3 an hour to be able to move. And I apologize for
4 being late, but it took a little longer this
5 morning.

6 That's the foundation from which I
7 approach the approval of this device, and I'm
8 privileged to be a part of the panel.

9 Thank you.

10 DR. GARBER: Thank you.

11 Dr. Satya-Murti?

12 DR. SATYA-MURTI: I am Satya-Murti. I am
13 a neurologist with an academic background. I still
14 practice neurology at a defined location. And I'm
15 also a carrier medical director for Medicare for
16 three Midwest states, and I've been doing that for
17 several years.

18 And my questions, eventually, would, of
19 course, be more technical, and they would cover
20 neurologic aspects and some coverage-issue
21 questions.

22 And we are one of the -- probably not one
23 -- I was the first one to write a Medicare coverage
24 policy for this condition, if that calls for any
25 dubious distinction.

1 Thank you.

2 DR. LITVAN: I'm Irene Litvan. I'm a
3 neurologist. I'm the chief of the Cognitive
4 Neuropharmacology Unit. I'm affiliated with John
5 Hopkins, and I have participated with Dr. Hallad in
6 the review of the surgery indications in Parkinson's
7 disease as a task force for the American Academy of
8 Neurology, and I've been following all these issues
9 for several years.

10 Thank you for inviting me.

11 DR. WEINER: I'm Dr. William Weiner. I'm
12 a professor of neurology and chair of the Department
13 of Neurology at the University of Maryland School of
14 Medicine, and the director of the Maryland
15 Parkinson's disease and Related Movement Disorder
16 Center. I've been involved in taking care of
17 Parkinson's patients and performing clinical
18 research in Parkinson's disease since 1968-69, and
19 have a longstanding interest in these issues.

20 DR. FOLLETT: I'm Ken FOLLETT, professor
21 of neurosurgery at the University of Iowa Hospitals
22 and at the Iowa City Veterans Administration Medical
23 Center.

24 I am the principal investigator of the
25 VA/NIH collaborative trial, which will compare best-

1 medical therapy to deep-brain stimulation and will
2 compare deep-brain stimulation of the subthalamic
3 nucleus to globus pallidus.

4 This trial has just begun enrollment
5 within the last four weeks or so. We plan on
6 enrolling a total of 326 patients into this trial.
7 It is a prospective randomized control trial.
8 Patient enrollment is going to take about two years,
9 and it will involve a minimum two-year follow-up for
10 each patient. So we're looking about four years
11 down the road, five years down the road, before we
12 have results from the trial, but we anticipate that
13 this study will answer many of the questions that
14 have been raised in discussions related to the
15 effectiveness of deep-brain stimulation and whether
16 one site for deep-brain stimulation might be
17 superior to the other.

18 DR. HOLOHAN: My name is Tom Holohan. I'm
19 chief of patient care services for the Veterans
20 Health Administration. With respect to Medicare,
21 I'm the chair of the Drugs, Biologics, and
22 Therapeutics Panel, and, like Dr. Garber, am a
23 member of the Medicare Coverage Advisory Committee
24 Executive Committee.

25 MS. GREENBERGER: I'm Phyllis Greenberger,

1 president and CEO of the Society for Women's Health
2 Research. I'm the consumer representative, and my
3 mother has Parkinson's.

4 DR. BURCHIEL: I'm Kim Burchiel. I am
5 chairman of neurological surgery at Oregon Health
6 and Science University. I've been doing movement-
7 disorder research for most of my career. I sit on
8 the Diagnostic Imaging Panel of MCAC, and have been
9 seconded to this panel for this particular issue,
10 and it's a pleasure to be here.

11 DR. SIGSBEE: My name is Bruce Sigsbee.
12 I'm a panel member. I'm a neurologist practicing in
13 Massachusetts in private practice, but also a member
14 of -- at the Department of Neurology of Brigham and
15 Women Medical Center. Perhaps 40 percent of my
16 practice has to do with movement disorders.

17 DR. RATHMELL: I'm Jim Rathmell. I'm an
18 associate professor of anesthesiology, and I
19 specialize in pain medicine at the University of
20 Vermont. I'm chair of the American Society of
21 Anesthesiologists Committee on Pain Medicine, and
22 I'm a standing member of the committee.

23 DR. ZENDLE: My name is Les Zendle. I'm
24 the associate medical director of the Southern
25 California Permanente Medical Group. I am an

1 internist and a geriatrician. I was on the
2 BlueCross/BlueShield Association Medical Advisory
3 Panel from '93 until '99, and I've been associated
4 Medicare coverage determination panels since '99.

5 DR. MC BRYDE: Angus McBryde. I'm a
6 professor of orthopedics at South Carolina. And I
7 come at this kind of as prevention of hip fracture,
8 interested in gait examination in kiddies, as well
9 as things of this sort, and I'm glad to be here.

10 DR. PHURROUGH: And I'm Steve Phurrough.
11 I'm the CMS liaison for the committee.

12 DR. GARBER: Alan Garber. I -- of course,
13 I am the chair of this panel. I'm a -- an internist
14 -- general internist with the Department of Veterans
15 Affairs, and a professor of medicine at Stanford,
16 where I also direct the Center for Health Policy and
17 Sanford Primary Care and Outcomes Research.

18 Now, our last public speaker has arrived,
19 so I hope you won't mind if we go a little bit out
20 of sequence here and give him a chance to speak.

21 MS. ATKINSON: Dr. Frederick Lenz?

22 DR. LENZ: I would like to start off by
23 just saying a few words about the history behind
24 this. I guess the three facts that have led to the
25 situation where surgery is again being considered an

1 important part of the treatment of movement
2 disorders is: The neurologist's recognition that
3 they had come to the end of what they could do in
4 patients with advanced Parkinson's disease or tremor
5 or dystonia.

6 The second thing was the three sites that
7 you keep hearing about are all understood
8 physiologically much better than they ever were in
9 the past, and it's now clear that there's increased
10 activity in each of these conditions for which
11 surgery is now being performed.

12 And so, of course, this -- the
13 demonstration that there was increased activity in
14 these areas led to surgery which involved lesioning
15 or destroying these areas in order to decrease the
16 amount of activity. And the -- and then, of course,
17 that was unpalatable to the neurologists and the
18 surgeons and everyone else, and so it was a great
19 step forward when the French group demonstrated that
20 high-frequency stimulation had the same effect as
21 lesioning.

22 So the targets that we're talking about
23 are all part of one circuit and the increased
24 activity in all of them. And, for reasons that are
25 not entirely clear -- or there is a different

1 spectrum of effectiveness in the treatment of each
2 of these different conditions. And, although the
3 exact indications for one or another site in a
4 particular condition is not fully worked out, there
5 are a number of double-blind trials of different
6 sites in the treatment of, particularly, Parkinson's
7 disease.

8 So the indications for choosing these
9 sites are, in the case of the thalamic target, the
10 -- the best recognized indications are Parkinsonian
11 and central tremor. The other kinds of tremor, such
12 as intention tremor or rubril tremors are still an
13 area where the indications are not entirely clear.

14 The -- in the case of GPi stimulation,
15 which again is one of these basal nuclei which are
16 all interconnected, the indications are advanced
17 Parkinson's disease or dystonia.

18 And then the third target, the subthalamic
19 nucleus, the only target at -- the only accepted
20 indication, at present -- although there are a
21 number of others being proposed, the only accepted
22 is advanced Parkinson's disease.

23 In carrying out these procedures, it's --
24 some very basic things. It's essential to have a
25 movement-disorder neurologist who can evaluate the

1 patients to decide what the diagnosis is, in fact,
2 and the -- and also whether maximal medical therapy
3 has been employed in the case of a particulate
4 individual. And the third thing is to adjust the
5 stimulators, because, particularly in the case of
6 Parkinson's disease, the medications and stimulators
7 are adjusted simultaneously.

8 So the -- those are the -- what I would
9 view as the indications for these procedures. And
10 the other thing to say is that it's -- different
11 centers vary as far as carrying out these
12 procedures. Probably in the best of all possible
13 worlds, you would have a physiologist or a -- or
14 someone who is expert in electrophysiology to locate
15 the electrodes appropriately.

16 You have to understand, the size of these
17 targets is measured in terms of a small number of
18 millimeters between the -- the mentalis intermedius,
19 which is the thalamic target, is about a tenth of an
20 inch in depth at about the level that we implant.
21 And the -- and subthalamic nucleus is sort of a
22 small, bean-sized structure. So it's essential to
23 get -- to confirm your target physiologically
24 somehow.

25 And the -- I think those are probably the

1 main technical requirements.

2 There are a number of programs that have
3 been devised to optimize the radiologic targeting
4 that's carried out so that you get the best possible
5 radiologic fix on the nucleus that we're after and
6 then confirm that physiologically.

7 Contraindications for these procedures --

8 DR. GARBER: Dr. Lenz? Dr. Lenz, pardon
9 me, but you've used up your time. I'm sure that we
10 will have questions for you shortly, though.

11 MS. ATKINSON: And also, one more thing.
12 Could you please disclose, for the record, whether
13 you have any financial involvement.

14 DR. LENZ: No.

15 MS. ATKINSON: Thank you.

16 DR. GARBER: Okay, thank you.

17 So, now we will return to the open panel
18 deliberations. And before we -- I thought that what
19 we would do is go through the questions. But this
20 would also be a good time to direct any questions
21 that panel members have toward this morning's
22 speakers. And please keep in mind that our main
23 concern, of course, is to get information that will
24 help us address the questions that CMS has put
25 before us.

1 Dr. Litvan and then Dr. Weiner?

2 DR. LITVAN: The question I have is
3 something that we discussed in our conference call
4 and is, How much of training is necessary for a
5 neurosurgeon to be able to become good at practicing
6 deep-brain stimulation in these areas? And is there
7 any curve of learning? And is there any requirement
8 as -- as many number of procedures made before
9 someone is trained? And what is the rate of
10 complications that would be allowed as to still
11 continue to have the risk-benefit ratio?

12 I was looking at the -- some of the
13 presentations -- some of the publications, and it
14 seems like some centers do have much more
15 complications and do seem not to have good,
16 beneficial effects on the patients; whereas, there
17 are others that are excellent, you know, in terms --
18 so would you give us some sense?

19 DR. BAKAY: Well, that's a very complex
20 issue. Certainly, neurosurgeons in their training
21 are exposed to stereotactics. That's part of a sub-
22 specialization within the subspecialty of
23 neurosurgery. Many people have taken on that as an
24 -- a particular area of expertise.

25 As to -- as to the number of complications

1 and that sort of thing, that is -- that is part of
2 the learning curve. In fact, all the data you saw
3 is part of the learning curve. You know, most of
4 these centers are starting up to do these
5 procedures. So I would anticipate that most of the
6 complication rates, early on, are going to be much
7 more -- higher than those that will occur later on,
8 as one refines the procedure.

9 Certain things as lead fractures, we were
10 initially instructed to place the lead down in the
11 cervical region. Well, that turns out to be a very
12 bad place to put it, because lead fractures are
13 extremely common. Lead connections now are placed
14 in -- on the cranial surface. Lead erosions from
15 the rather large connector now are less common, as
16 there is a smaller connector available. So there
17 are improvements, both in the technology and in the
18 -- in the surgical techniques.

19 Obviously, the rate of complication should
20 be relatively low, in terms of severe complications,
21 those of hemiparesis, blindness, et cetera. And how
22 low? Probably in the -- somewhere in the three to
23 four percent range, I would anticipate. In terms of
24 expertise, that may even be -- they may be able to
25 generate that even lower.

1 Certain complications such as infections
2 are very difficult to control despite the use of
3 perioperative antibiotics. It is said there's more
4 bacteria in your mouth than there are people in the
5 world, so it's a constant struggle to keep
6 infections down and out, but that is something that
7 we can improve technically as we do the operation
8 more frequently.

9 In terms of who should be doing the
10 procedure, I don't think this should be done by
11 somebody does not have experience with it in some
12 form or another, whether they got it through their
13 training program or whether they acquire it through
14 some of the continuing education. But that's my
15 personal opinion.

16 Does that answer that satisfactorily? It
17 was series of question you answered, and I hope I
18 covered most of it.

19 DR. LITVAN: Yeah. Is there a minimum
20 amount of time that you think it is necessary? Of
21 course, this is your opinion, but as -- in
22 practicing --

23 DR. BAKAY: I think there's two things.
24 One is training. The other is the center. I think
25 a multi-disciplinary approach is really quite

1 essential to these.

2 These are very complicated patients. The
3 neurosurgeon is basically a technician in this
4 aspect. The patient is under the control of a
5 neurologist, in general, and very much should be,
6 because of the complexity of the medical treatment.
7 And it's obviously the -- that when the medical
8 treatment fails, when there are marked fluctuations
9 in the patients' responsiveness to medication, that
10 you then become a surgical candidate. It's not
11 something that you do up front.

12 So medicine is the first aspect. And most
13 of these patients should be treated by an expert in
14 movement disorders, or at least screened by an
15 expert in movement disorders, and not simply sent to
16 a neurosurgeon or somebody decides that they want to
17 have their surgery based on the fact that they were
18 told they had this disease and now want to have the
19 surgery. So some sort of screening element, I
20 think, is necessary, in terms of expertise.

21 And in terms of the surgery, obviously,
22 the more experience, the better. That's the case in
23 all things. But you have to start someplace, and I
24 think there are a number of ways in which someone
25 who is not currently involved with this can get up

1 to speed relatively quickly, and that involves
2 courses, but also visitation to centers that do the
3 procedure and then -- and then some potential
4 assistance while they are starting to do their first
5 initial procedures. It can be achieved by a variety
6 of ways.

7 DR. BURCHIEL: I'd like to respond to
8 that.

9 DR. GARBER: Dr. Weiner?

10 DR. BURCHIEL: Could I respond to that?

11 DR. GARBER: Go ahead.

12 DR. BURCHIEL: I mean, I think you've put
13 your finger on the Achilles heel of a lot of
14 surgical training, that this is a new procedure,
15 which, I think, officially neurosurgery says is part
16 of the training. But I think Roy knows, and every
17 other neurosurgeon knows, here, that there are
18 people that are -- that are dedicated to this in
19 certain programs. And other programs don't have
20 anybody like this. And so there's a wide variety of
21 training in -- within a neurosurgical residency
22 program.

23 And without becoming too prescriptive, I
24 think that the decision down the road is going to
25 have to incorporate some sort of criteria of who can

1 and can't do this. I mean, is it a weekend course?
2 Is it a -- one visit, watching somebody from the
3 corner? Or is it a year? Nobody knows. I do think
4 those things tend to sort themselves out.

5 But we -- neurosurgery does not have
6 official fellowships in any area, this included.
7 There are unofficial fellowships out there, where
8 someone can go to Dr. Bakay or a number -- Dr. Lenz
9 or other folks -- and learn this procedure very
10 well. But then you might have to ask those folks,
11 What does it require?

12 There's -- there clearly is a learning
13 curve, and I would submit it's probably not a
14 weekend. It's something longer than that.

15 But I -- it would almost seem more
16 reasonable for this to be a local carrier decision
17 that the -- that CMS shouldn't be too prescriptive
18 about this, and that -- should leave that to the
19 carriers to make those decisions.

20 DR. GARBER: Dr. Satya-Murti?

21 DR. SATYA-MURTI: Yeah, thank you. These
22 are pertinent questions. I had them on my eye -- in
23 my own mind, as well. When I first wrote the
24 policy, I did, with some trepidation and hesitation,
25 say that there ought to be some experience built

1 into it. It's often difficult to separate coverage
2 from science. Try as we may, the two go hand in
3 hand, and we find it more and more so in Medicare.

4 So one other criterion, besides the number
5 of surgeries or years in experience, would be how
6 much time does the prospective movement-disorder
7 specialist and neurosurgeon spend on performing this
8 procedure? Drawing strength from cardiac surgery
9 and previous data collected on centers of excellence
10 and volume versus outcomes, I -- as a carrier, I do
11 have some proposals that, if CMS finds it
12 applicable, we can apply to this, but I also endorse
13 that there ought to be some numbers put to this,
14 even though it's only a lattice on which we can
15 build later.

16 And I'd like to propose that at least 50
17 percent of the surgeon or movement-disorder
18 neurologists, their time ought to be expended in
19 running such a clinic and performing surgery. So
20 that's just a number I would like to start with, if,
21 at all, we address that.

22 DR. GARBBER: Yeah, let's follow up on that
23 when we get -- go through the questions. I think
24 that will be very pertinent.

25 Dr. Weiner?

1 DR. WEINER: I'd like to just sort of
2 follow up on this question about the training. I
3 mean, it does get to be very difficult to know who
4 should do it or who should do it, but as a
5 neurologist, I mean, if a neurosurgeon is trained in
6 stereotactic procedures and is doing biopsies, for
7 example, is this sort of just considered -- you're
8 moving to a slightly different "gadget", so to
9 speak, in the OR? You know, in other words, if
10 you're a stereotactic surgeon -- you know, for
11 example, would a weekend course be sufficient, as
12 opposed to if you've never done a stereotactic
13 procedure?

14 DR. BURCHIEL: Well, I would say
15 absolutely not. This is -- this is not just a
16 flavor or stereotactics. This is a whole different
17 thing. And others may have other opinions, but I do
18 think this is not simply something you can pick up
19 in a few hours.

20 DR. BAKAY: No, I think -- I think this is
21 a very complicated and difficult issue. The -- if
22 you have some familiarity with stereotactics, you're
23 much better off than somebody who's never done one,
24 but you still have to understand the anatomy and the
25 electrophysiology of this area. You have to

1 understand what the stimulator will do and will not
2 do. You have to understand, What do you do when you
3 get into problems? And these things take time to
4 experience.

5 And, you know, there are centers that have
6 been doing this for quite a long time, and I don't
7 think these centers could lay down absolute criteria
8 for what you should do. It is an area of
9 difficulty. There is -- as Kim said, there is no
10 certification as a stereotactic or functional
11 neurosurgeon.

12 DR. GARBER: Dr. Montgomery? Or Dr. Lenz,
13 did you want to comment?

14 DR. MONTGOMERY: Yeah, I think the
15 questions that you're asking about the experience
16 and training of the neurosurgeon has to be broadened
17 to include the experience and training of the team.
18 And as Dr. Bakay mentioned, it's not just the
19 neurosurgeon and that the
20 neurologist/neurophysiologist is very much involved
21 in the deliberations in the operating room and
22 making the judgments as to where to place the lead
23 and assessing the effects of stimulation the
24 operating room. So you have to look at the combined
25 team, and I think that, you know, there can be

1 balances and tradeoffs, depending on the various
2 members of the team. So --

3 My only other concern, though, is that, in
4 establishing any policy, I would urge flexibility.
5 I -- this field is evolving rapidly, and we're very
6 much involved in developing techniques and
7 methodologies that will greatly reduce the required
8 sophistication of the users. We're developing
9 expert systems for doing the electrophysiology. And
10 so my hope is that very soon we'll see that the
11 technical requirements, in terms of the level of
12 sophistication, will get considerably less.

13 And my concern is any policy that's not
14 flexible, that's carved into stone, really could
15 wind up hurting this field rather than helping.

16 DR. LENZ: I think that depending on the
17 means used to localize the target, you're going to
18 need training in one of a -- one of a number of
19 fields, particularly radiology, because the
20 techniques that are used to light up the -- and
21 recognize on an MR scan -- the targets, are not
22 necessarily straightforward. Electrophysiology is a
23 complete field on its own, and if you're using a
24 microelectrode, that's something that can only be
25 learned over probably a year or so.

1 And the other thing is it's a totally
2 different mindset from the way most neurosurgeons do
3 intracranial procedures, which is -- in this kind of
4 surgery, you're trying to identify the physiologic
5 target. What most intracranial neurosurgeons do is
6 just try to stay away from areas where they know
7 they can get into trouble. And so it's a totally
8 different mindset, and I think it takes a
9 significant amount of training.

10 And I would echo again what Dr. Montgomery
11 said, which is that the neurologist -- it's
12 absolutely key that they be a very experienced
13 movement-disorder neurologist making these decisions
14 about indications for surgery.

15 DR. GARBER: Okay, thank you.

16 Les Zendle, I think you were next.

17 DR. ZENDLE: Actually, he was before me.

18 DR. GARBER: Oh. Jim?

19 DR. RATHMELL: To extend on that, now you
20 have someone who has gone out and gotten experience,
21 come into your center, and the team has come to your
22 center and spent some time with you. You feel that
23 they're on the verge of launching this. Now they go
24 out, and they're trying to decide this unilateral
25 versus the different -- you know, unilateral,

1 bilateral versus the various target sites. It
2 appears as though the data is yet to come. How are
3 they going to make those decisions? How do you
4 recommend them, aside from recommendations from the
5 manufacturer themselves that have been advised by
6 experts, like yourself? Is that the way you would
7 expect new folks approaching this field to apply it?

8 DR. BAKAY: Well, in terms of approaching
9 the target, there is -- you know, obviously if the
10 tremor is the predominant symptom, many -- in
11 essential tremor, there is only one target, so you
12 don't have concern. In terms of -- in terms of
13 Parkinson's disease others would say that the
14 subthalamic nucleus does tremor just as well as VIM,
15 Why don't you just put in there, and it will take
16 care of the other problems that'll occur later? So
17 there are difference of opinion and difference of
18 philosophy.

19 I think it's like having multiple
20 medications. You don't have to say that that
21 medication is good only for this particular type of
22 Parkinson patient or that particular type of
23 Parkinson's patient. There is overlap, and these
24 are really treating symptoms of the disease.

25 And so the fact that we don't know what is

1 the better site really isn't, to me, a major
2 question. You have two good sites that are -- that
3 are equally efficacious.

4 I think we need to leave it to the
5 surgical team to decide how they're going to do the
6 surgery, whether they're going to do it in one
7 stroke or two. I think there are a number of cases
8 where a unilateral stimulator is all that you really
9 need, especially in patients with asymmetrical
10 disease. And I think there are times when we will
11 go out to do a bilateral procedure and see how the
12 patient does after the first one. If there is some
13 confusion, if you've lost your examination during
14 that time, you stop and come back another day, or
15 you may plan ahead of time that this is a patient
16 who is not going to tolerate sitting, and do it in
17 two stages. I think that ought to be left to the
18 discretion of the surgeon. That'll be worked out
19 over time.

20 And there's not the data available to hit
21 that as a -- as a -- you know, like a pill that you
22 could take a Q4 hours or whether you should take it
23 Q8. This will -- this is something that'll work out
24 in time.

25 You have two good targets. You have the

1 ability to use either one. And I think some of
2 these studies that are undergoing will help us, but
3 may not -- you know, the final answer may not come
4 for many years as to which is the better site and
5 why. I mean, we may find that you can decrease the
6 medication off the STN, but there may be more
7 cognitive side effects with that procedure. So
8 which is the better one? You know, that'll have to
9 be sorted out, and it'll take time to do that, but
10 these will sort out with time.

11 The fact is that you've got two effective
12 treatments, and that they ought to go forward.

13 DR. GARBER: Okay, Dr. Montgomery.

14 DR. MONTGOMERY: I don't want you to have
15 the impression that we're -- that the decision is a
16 roll of the dice. That's absolutely not true. I
17 think most movement disorders -- neurologists,
18 there's a very strong and emerging consensus in
19 terms of the approach to answering these questions.
20 So this is not willie-nillie a roll of the dice, and
21 it's not high -- you know, idiosyncratic to each
22 movement-disorder neurologist. There is an emerging
23 and strong consensus. First.

24 The second point is -- is that both
25 therapies, in terms of STN and GPi, are effective.

1 They are both remarkably effective, and they are
2 both associated with a paucity of significant
3 complications. The perioperative morbidity rate is
4 very reasonable for both procedures.

5 I do not think at this point in time that
6 we do a patient any disservice by selecting GPi
7 versus STN, or selecting STN versus GPi. I think
8 there's a growing consensus that thalamic
9 stimulation is really not -- not a good target, and
10 that's because we all recognize that, while it is
11 very effective for tremor, it is not effective for
12 bradykinesia, it's not effective for postural
13 stability.

14 And even though a patient may initially
15 present with tremor, over the course of the next few
16 years, he's going to develop all of the other
17 symptoms, so I -- you know, and if you just look at
18 the number of centers, there are very few of the
19 major centers that are implanting thalamic
20 stimulators anymore.

21 And our own decision, our choice of doing
22 STN versus GPi is really a technical issue. We tend
23 to favor the subthalamic nucleus, because we can get
24 to it much easier. It requires fewer penetrations
25 from the microelectrode to find the optimal target

1 than does GPi.

2 And then I think in terms of the
3 prospective study -- what I'd look to the
4 prospective study to help answer is not relative to
5 the efficacy of STN versus GPi, but to help sort out
6 some of the cognitive issues and complication
7 issues. But even still that, those are fairly
8 minimal considerations when you contrast with the
9 degree of improvement that these -- either of these
10 therapies make.

11 So I hope you don't take away the
12 impression that this is something that's arbitrary,
13 that, you know, we make the decision by plucking
14 something out of thin air, and that we need long-
15 term studies to answer that question. There is
16 already a very strong consensus in the community.

17 DR. GARBER: Dr. Holohan?

18 DR. HOLOHAN: Yeah, I think we're getting
19 away from the original question, which was a
20 question about criteria for experience and training.

21 In terms of the location of the placement
22 of the electrodes, if there were evidence favoring
23 one location versus the other, it would be unethical
24 for the VA to carry out the trial that, in fact,
25 we're carrying out, where patients are randomized.

1 I don't know that -- how far, Alan, you
2 want to get into the issue of training and
3 experience. There obviously are probably a majority
4 opinion, I would presume, in this group. But the
5 question we really asked is whether we think
6 Medicare should impose criteria for centers that do
7 this. I don't think we have to develop them. I
8 would submit that it's probably difficult, and
9 perhaps inappropriate.

10 In that light, I'd like to ask Dr.
11 Follett, who is probably the one most responsible
12 for the institution of the VA trial, to talk about
13 the criteria that the VA used to select the six
14 centers, not with respect to their research
15 abilities, but with respect to their abilities to
16 accomplish the surgical procedure that's part of the
17 collaborative study. Would you be willing to
18 elaborate on that a little bit?

19 DR. FOLLETT: I'll give it a try. I'd
20 like to point out -- I want to make one comment to
21 emphasize what Dr. Montgomery mentioned. The fact
22 that we have multiple targets isn't bad. It doesn't
23 mean we don't understand the therapies -- we don't
24 know whether one works, the other doesn't work. The
25 fact that we have multiple targets, I think, is

1 good. It gives us an element of flexibility with
2 these therapies and lets this multi-disciplinary
3 team try to tailor the treatment to the needs of
4 each individual patient.

5 The purpose, I think, of the collaborative
6 trial, in particular, isn't necessarily to find out
7 whether one site is really better than the other,
8 but I think it's to find out which site is best for
9 a certain set of symptoms, which site is best for a
10 certain subset of patients. So we want to try to
11 address this issue of tailoring the therapy to the
12 patient, that Dr. Rathmell raised. For the time
13 being, we have to rely upon the expertise of a
14 multi-disciplinary team to evaluate the patient and
15 decide which of these surgical options is best
16 suited to the needs of that patient.

17 DR. RATHMELL: And I just -- I want to
18 emphasize -- what I'm hearing from you is, if this
19 goes out -- my question was, to the general
20 practitioner, how does he decide? How does he or
21 she decide, okay? And it sounds like what I'm
22 hearing from you, it doesn't matter. It's okay to
23 choose on an individual basis. It's okay, in your
24 view, for each center to decide on their own amongst
25 these therapies individually. They're all equally

1 acceptable at this point in time.

2 DR. FOLLETT: At this point, each of these
3 therapies -- and we're talking about STN versus GPi
4 implants -- they seem to be comparable. But -- and
5 I wouldn't say that it's up to the general
6 practitioner to select which to use. I think it's
7 up to the multi-disciplinary team at each center to
8 decide which therapy would be best in their hands,
9 in their center for that patient.

10 DR. GARBER: Well, maybe -- you know,
11 we're getting a little off track here. This is --

12 DR. BAKAY: (Inaudible.)

13 DR. GARBER: -- something that we need to
14 discuss. No, no. I'll let you finish. I just
15 wanted to say, in terms of the structure of the
16 discussion, this is getting very deeply into
17 something that we have in order as we go through the
18 questions. We're getting a little off track here.
19 This is something we need to ask you, but I just
20 want to say, in terms of the structure of the
21 discussion, this is getting very deeply into
22 something that we have to, in order as we go through
23 the question, what should be the target, we will
24 need, since this isn't a role of the dice, we will
25 need some information on how to decide, and you will

1 be allowed to do that. I would like to continue
2 discussion in the context of hearing Dr. FOLLETT's
3 point and then if there are questions directly
4 related to the discussion here that should not occur
5 in the discussion context of going through the
6 questions later, then you can ask them now, and to
7 clarify things like what should be the target, or
8 what we need to do implants in globus pallidus and
9 subthalamic nucleus.

10 DR. FOLLETT: Let me come back and say
11 that in neurosurgery, we have as an organization, we
12 have never prescribed a number in order to show
13 competencies, and I think the same holds for the
14 technique of deep brain stimulation. There probably
15 isn't a minimum number of procedures to become
16 competent, it depends on his training and so on.
17 For the VA study, in order to maintain at least, to
18 try to maintain a standard uniform quality, we did
19 decide that an eligible surgeon in order to meet our
20 selective criteria, should have performed a minimum
21 of 15 to 20 implants, and I don't recall the exact
22 number. There should have been a minimum number of
23 pallidotomies and a minimum number of implants.

24 But, in addition to the basic mechanics
25 of handling the wires during surgery, there are the

1 added skills that Dr. Bakay mentioned, and Dr.
2 Montgomery, in terms of identifying the proper
3 targets, and that begins to draw up on the need for
4 intraoperative electrophysiology testing, whether
5 it's microelectric recording, micro stimulation or
6 macro stimulation.

7 So overall, we felt that at least a
8 minimum of something on the order of 15 or 20
9 implants should have been performed by the surgeon
10 in order to meet the minimum criteria to participate
11 in the study.

12 DR. GARBER: Okay --

13 DR. HOLOHAN: There were other criteria,
14 beyond the neurosurgeon, though, in terms of your
15 reference to the multi-disciplinary group.

16 DR. FOLLETT: That's correct. In addition
17 to having a neurosurgeon who was technically
18 qualified to perform the surgery, we did require
19 that the centers have a multi-disciplinary team,
20 which include a neurologist, who has training and
21 expertise in the management of movement disorders,
22 and also a center that has a neuropsychologist with
23 some expertise in the evaluation and management of
24 patients have movement disorders.

25 DR. GARBER: Okay, thank you. Les Zandle

1 and then Bruce Sigsbee, and then we'll move on.

2 DR. ZENDLE: Yeah, I don't want to address
3 the neurosurgical technical implantation issues, but
4 I was very impressed with Dr. Bharchua's letter that
5 we got prior to the meeting, and I think it's in the
6 packet, that talked about the correct diagnosis and
7 the fact that there -- some patients without
8 Parkinson's disease -- or a correct diagnosis, or
9 patients with early Parkinson's disease that are
10 being encouraged by neurosurgeons to have this
11 procedures, and a lot of advertising on television,
12 et cetera. I wonder if you could address that
13 issue, because I think that -- I would hope we would
14 be concerned that the right patients are getting
15 this procedure.

16 DR. MONTGOMERY: The issue comes, in terms
17 of the differential diagnosis of Parkinsonism. And
18 when we talk about Parkinsonism, we're talking about
19 a spectrum of disorders ranging from idiopathic
20 Parkinson's disease, which accounts for about 24
21 percent of all patients with Parkinsonism, and then
22 there are the atypicals, supra nuclear palsy, multi-
23 systems atrophy, cerebellar atrophy.

24 Quite -- occasionally the differential
25 diagnosis can be very, very difficult, but there are

1 now fairly well-established criteria that we use to
2 minimize the risk of inclusion of somebody who
3 doesn't have idiopathic Parkinson's disease. The
4 United Kingdom Brain Bank study, which did a
5 postmortem controlled study. And looking back at
6 the types of symptoms that could distinguish an
7 atypical Parkinsonism from someone with Parkinson's
8 disease idiopathic is pretty well worked out.

9 And I think most movement-disorders
10 neurologists are well aware of those criteria. We
11 specifically look for things like limitation of
12 volition eye gaze. We specifically look for
13 symptoms of profound dysautonomia. We look for
14 ataxia. We look for upgoing toes, hyperreflexia.

15 So I think that the criteria are fairly
16 robust, in terms of making that sort of distinction.
17 And most neurologists, and certainly most movement-
18 disorders neurologists, are familiar with those
19 sorts of criteria.

20 Is that going to exclude the occasional
21 patient with atypical Parkinsonism getting the
22 surgery? No. I think that's an inherent risk in
23 this procedure, but I think it is going to be very,
24 very minimal.

25 DR. WEINER: Well, I think, if it's okay

1 to follow up on the question about patient
2 selection, I had wanted to ask both you and Dr.
3 Bakay, in terms of your presentations about how you
4 phrase the degree of levodopa responsiveness or what
5 was the role of that. And the reason -- the reason
6 was is that it was my understanding that patients
7 who have the correct diagnosis and who have
8 levodopa-responsive Parkinson's disease still have
9 to have some period of time in which they respond to
10 their medication. And I think you both referred to
11 the fact that levodopa didn't work anymore, so that
12 -- you might get people confused -- a general
13 neurologist, for example, confused with an atypical
14 Parkinson patient who never responds to the
15 medication, and never did, or who responded
16 minimally and then lost that. So I wonder if you
17 could clarify the levodopa responsiveness.

18 DR. MONTGOMERY: Certainly. Well, going
19 back to the autopsy control study by Lees and Hughes
20 in the United Kingdom, and they did a retrospective
21 analysis and found that those patients who had
22 autopsy-proven idiopathic Parkinson's disease by the
23 presence of Lewy bodies, and when they went back and
24 looked at the records, 97 percent of those
25 individuals had some history of response to

1 levodopa. When they went back and looked at the
2 patients with atypical Parkinsonism, only about a
3 quarter ever had any kind of reference in the past
4 medical record of any response to levodopa. So I
5 think the notion of having had some levodopa
6 responsiveness is a good criteria for helping assess
7 a surgical candidacy.

8 Now, but, as Dr. Weiner points out, what
9 does it mean to have a levodopa response? And, at
10 the same time, it sounds almost paradoxical that
11 we're requiring them to be refractory to levodopa
12 and yet at the same time insisting that they have a
13 levodopa response. What we -- what we look for in
14 selecting patients is some history that the patient
15 had some improvement of their symptoms, even if it
16 was brief, even if it was complicated by side
17 effects, but some history of ring responsiveness.

18 Perhaps the biggest issue that we have is
19 making sure they've had an adequate trial. You
20 know, 600 milligrams of levodopa per day is not an
21 adequate trial of levodopa.

22 So I think that we're very confident that
23 if a person has had some improvement in their
24 Parkinson's symptoms, even if it's only brief, even
25 if it's associated with significant side effects,

1 like dyskinesia, that that still constitutes fairly
2 strong criteria for a reasonable conclusion that the
3 patient has idiopathic Parkinson's disease.

4 DR. WEINER: But even beyond the
5 diagnostic question that you're elucidating, what
6 about the -- in selecting the patient, do they still
7 have to have some time period of levodopa
8 responsiveness in order to be a surgical candidate?

9 DR. MONTGOMERY: Yeah, I agree. And I
10 don't think that we've taken any patient to the
11 operating room who has not had some improvement.
12 But, again, the question is what degree of
13 improvement.

14 I can tell you, when we looked at the
15 pallidotomy study, in working with Dr. Lang and Dr.
16 Lozano, we went back, and that had -- that was a
17 very positive outcome -- we went back and actually
18 looked at the degree of improvement on the UPDRS
19 scores following an administration of levodopa, and
20 there was no correlation with the postoperative
21 outcome. So you cannot use the magnitude of
22 levodopa response as a criteria for admitting
23 patients to surgery. And if you did, you would
24 really just exclude a large number of patients who
25 need the surgery. So that -- you know, that's a bit

1 problematic.

2 DR. BAKAY: I think one of the problems is
3 that -- is that you get into some of the side
4 effects of the medication. And so if you're just
5 strictly using the UPDRS score, you can get into
6 problems.

7 But what you want to see is the
8 fluctuation, and I think that's really critical --
9 is how good are they on their best "on," and then
10 compare that to how bad they are on the "off" score.
11 And there should be a clear, significant difference
12 and -- in the eyes of the neurologist who's doing
13 that evaluation.

14 And, again, I'd emphasize that that's a
15 role for a neurologist and not a neurosurgeon, that
16 these things are sometimes rather subtle, and
17 sometimes they're very dramatic. And the people
18 that I see that are going to improve the most are
19 the ones that have the marked fluctuations, and
20 those are marked fluctuations in terms of responses
21 going from frozen, to being able, to do something,
22 to being extremely dyskinetic. And somewhere in
23 there -- and exactly what percentage improvement,
24 it's very difficult to say. I mean, we tried to
25 include that in several of our NIH studies, and it's

1 extremely difficult to make a set criteria of how
2 much improvement you want to see. It's more of a
3 gestalten. As you get more experience, it becomes
4 clearer and clearer, but it is a gestalten.

5 DR. MONTGOMERY: Just one more -- maybe a
6 point of humility? I mean, we've heard of point of
7 orders, but this is a point of humility.

8 Actually, we really don't know, because
9 almost every study has required levodopa
10 responsiveness to get into the study. Nobody's done
11 surgery on patients who have demonstrated no
12 levodopa responsiveness, and so we don't know that,
13 you know, that we're not excluding patients who
14 could otherwise benefit.

15 DR. BAKAY: That's not true. There have
16 been patients that have -- and you just don't find
17 them in the literature. Those patients are
18 frequently not reported. Dr. Lozano's got a few.
19 The Emory group's got a few.

20 Atypical patients have been done, in terms
21 of trying to evaluate these patients, but they have
22 not been part of a formal study. But the -- almost
23 all of us that have experience with atypicals
24 realize that they do not very well.

25 DR. GARBBER: Okay, Dr. Sigsbee?

1 DR. SIGSBEE: Just one comment. The whole
2 area of neurodegenerative disease in the nervous
3 system is a moving target. As we look at the
4 underlying molecular biology, we're recognizing that
5 certain disorders can have a wide spectrum of
6 possible clinical manifestations. But I think it's
7 still -- you can fairly reliably, through the
8 criteria discussed, identify people who have
9 idiopathic Parkinson's, whether a combination of
10 levodopa responsiveness and other clinical criteria.

11 I do have, I think, another question here,
12 as I would like to ask about the Medtronic marketing
13 for this device. And I would like to preface that
14 by saying that I'm aware of one device that's used
15 to help control seizures that is very heavily
16 marketed. I know a neurologist who is not an
17 epileptologist who went away to a weekend course,
18 was certified and is -- now does it in conjunction
19 with a surgeon -- tends to look at a failure of a
20 few anticonvulsants and then go to this particular
21 procedure, as opposed to epilepsy centers where they
22 look at a whole spectrum of surgical interventions.

23 There's another device that I know of
24 that's recently been available to physicians for
25 treatment of abdominal aortic aneurysms. That

1 device manufacturer works closely with the local
2 credentials committee, sets criteria for training of
3 the individuals, has somebody who is expert in it
4 come and observe a number of surgeries, and, only
5 after that individual is signed off, can those
6 individuals do it independently, both in terms of
7 case selection and the technical expertise.

8 And with those comments in mind, I wonder
9 if Medtronic would comment on their marketing plan.

10 MR. OWENS: I'd be happy to. I think you
11 will find that we are very consistent with what the
12 movement-disorder neurologist and neurosurgeons have
13 said. Our approach is to have centers that are well
14 trained that are supported by a team that has a
15 clear understanding of this. We do not want to have
16 any patient implanted without the best possibility
17 of good outcomes.

18 We are marketing this from the standpoint
19 of making sure that patients are informed about the
20 opportunity, but we are telling them to see, first,
21 their neurologist, then move on to the movement-
22 disorder neurologist, and then move to the
23 neurosurgeon. We are -- have already planned and
24 continue to have a number of courses where we make
25 sure that people that are interested in doing this

1 procedure are very well trained and then have the
2 opportunity to follow up with key people, and a
3 number of people who are on the panel here, to make
4 sure that they understand this clearly and to know
5 exactly what to do.

6 I do think that the comments about having
7 a -- the team approach are critical, that you need
8 to have a movement-disorder neurologist there that
9 is clearly aware of what to do. We also very much
10 focus on the procedure itself. We have devices for
11 microelectrode recording that are available. We
12 have surgical-planning techniques and software that
13 are available that we encourage, if they will
14 improve the determination of the proper anatomical
15 and functional targets that those are specifically
16 used by those surgeons. And in almost every case,
17 they are.

18 We are taking a very focused approach to
19 functional stereotactic neurosurgeons. There will
20 be stereotactic neurosurgeons, obviously, that will
21 do this. And I think that either Dr. Bakay or
22 Montgomery or Dr. Follett made a comment about the
23 rapid evolution of this technology as we move
24 forward. And that is one of the things that we are
25 working very closely with and trying to ensure that

1 -- that, as that moves forward, safety of the
2 patients is the number-one criteria that we're --
3 or criterion that we're looking at.

4 DR. GARBER: Okay. Yes, Dr. Satya-Murti?

5 DR. SATYA-MURTI: These are important
6 comments. I want to ask, particularly Drs. Witten
7 and also to you, have you been able to identify --
8 or Medtronic, for that matter -- retrospectively,
9 some commonalities where patients have not done
10 well?

11 I have some who have not done well. And
12 it is my suspicion, in my own scanning of the
13 literature, that those with preexisting dementia in
14 whom testing has not been adequately done,
15 particularly formal neuropsychological, tend to fare
16 less well.

17 In any case, with the greater numbers that
18 you have in your dossier, what, really, are some of
19 the identifying features of those who have not done
20 well, let's say, 3 to 12 months away from this?

21 And as far as publication bias, I agree
22 with you Dr. Bakay, that I also have patients, and
23 there are some in the literature, where tremors,
24 especially MS tremors, where the surgery has been
25 done, they have not done well. So we ought to give

1 cognizance to the fact those who have not done well
2 have never entered the publication spectrum.

3 DR. MONTGOMERY: We have certainly had our
4 fair share of patients who have not done as well as
5 we would have hoped, and we have gone back and
6 looked at the formal neuropsychological testing that
7 we do always preoperative to try to identify some
8 predictor of who is not going to do well. And our
9 experience is -- like most other people's experience
10 -- is that, while there are trends that one can
11 identify as predictors, nothing with sufficient ROC
12 -- area under the ROC curve reliability for that.

13 And, just anecdotally, the ones that we
14 find -- in thinking back at the ones who did not do
15 well -- one of the big issues is impulsivity, lack
16 of self restraint, lack of self awareness, in terms
17 of their limitations. And I think it's quite
18 interesting. What we find is that often those sorts
19 of things are very difficult to identify on specific
20 neuro psych measures, and often families are unaware
21 of it. And what we typically find is that their
22 motor symptoms improve, but now they're in a
23 position to be mobile enough to get into trouble,
24 and then the families and the patients -- and the
25 families get very concerned about that.

1 But, again, we take a very strict -- and
2 perhaps one reason why we're not able to identify
3 very specific predictors of outcome in that regard
4 is that we have a very strict entry criteria. And
5 so there's just not a lot of variance in our outcome
6 that we can then parse back over the predictors to
7 identify statistically what would be a predictor.

8 So, at this point, it's still very much a
9 judgment on the part of the movement-disorders
10 expert. I mean, I can't think of a single patient
11 who's not -- who's had a completely normal neuro
12 psych battery, and so it becomes a matter of
13 exercising judgment as to what degree there is
14 cognitive impairment and how it might relate on
15 their ability to take full advantage of the
16 improvement of their motor symptoms.

17 DR. SATYA-MURTI: That's why I'm asking
18 about pool data. Has anybody looked at it in a case
19 controlled study fashion backwards to see what could
20 have been the features, those who didn't do well --
21 not just neuro psychologically, those whose
22 improvement in UPDRS scores were just not as good?

23 DR. MONTGOMERY: Well, I can't -- I know
24 that those are -- those are -- those kinds of
25 studies and those kinds of analyses are underway,

1 and I can't speak to them specifically for deep-
2 brain stimulation.

3 I can tell you of our experience with
4 pallidotomy. And this is primarily in Dr. Lang and
5 Dr. Lozano's group. And, again, we find things that
6 are -- trend towards prediction, but nothing that --
7 nothing that I would feel comfortable as using as a
8 litmus test to offer surgery to a patient or not. I
9 think it requires considered judgment on the part of
10 experienced physicians and surgeons.

11 DR. SATYA-MURTI: Wouldn't that be reason
12 enough to be cautious in preselection? That's what
13 we're talking about here.

14 DR. MONTGOMERY: But my experience working
15 with physicians is that they do exercise that degree
16 of caution, that they do exercise that degree of
17 concern.

18 We have -- I can tell you in my own
19 experiences that we have lots and lots of
20 neurosurgeons that come and visit our institution,
21 lots and lots neurologists who come and visit our
22 institution with the idea of doing this surgery, and
23 I can tell you that at least half of them that I've
24 followed up have elected not do to the surgery, have
25 elected not to do this, because they realize that

1 the investment that would be required to do it right
2 is beyond what they're willing to invest. So at
3 least my experience has been fairly positive in that
4 regard.

5 DR. BAKAY: Yeah, I would -- I would also
6 emphasize that, because, in teaching a number of
7 these courses, one of the things that we're quite
8 happy with is if they come and realize that they
9 cannot do this -- you know, not just that they can
10 do it, but that they can't do it. And there are
11 certain situations when that may be the case.

12 I think there's a number of reasons for
13 failure. One is selecting the wrong patient.
14 Obviously, someone who doesn't respond, that
15 certainly can be the case. We're not going to make
16 dementia better, so patients that are demented, we
17 try to avoid. There is the potential for cognitive
18 impairment from the surgery, so obviously you run
19 the risk of making those patients worse, so you --
20 but where exactly you draw the line is a difficult
21 thing. You look at their MRI scans. If their MRI
22 scans have all kinds of other disease, you try to
23 avoid those patients also.

24 So there are criteria, but each of those
25 criteria are relatively soft. And when the

1 pallidotomy experience, which is much broader --
2 I've done over 350 pallidotomies, but only about 200
3 deep-brain stimulators, so my experience there is
4 much broader. But, even there, there is a
5 difference of opinion as to what should be included
6 and what shouldn't be included, in terms of the
7 patient evaluation.

8 Then there are complications. And those
9 patients you have to eliminate also from your
10 evaluation, as the complication may have affected
11 the bad result. And then, finally, you may not have
12 been on target. And if you're not on target, then
13 you obviously have the opportunity to correct that
14 in this type of therapy, whereas you wouldn't with
15 lesion therapy.

16 So there are a lot of reasons why you have
17 failure, and there aren't good, hard criteria to say
18 that there's one thing, or even a combination of
19 things, that you should use for exclusion criteria.
20 And, again, this is -- this is -- this isn't -- this
21 is the area of the art of the surgery, in that one
22 has to have experience. And one -- with experience,
23 one gains the idea of what you can and cannot do. I
24 think there's no way around that, that obviously the
25 best surgery is -- are done by those that really

1 understand what it is that they want to do, have a
2 great deal of experience, have good training. But
3 that's, you know -- that's not something that you
4 can somehow quantify, put a P-value to or --

5 DR. GARBER: Excuse me. Dr. Vatz and Dr.
6 Witten, did you want to address the question?
7 You've looked a great deal of evidence about -- are
8 there anything that clearly -- any data that clearly
9 indicate who -- people who do not seem to benefit,
10 either because of high side-effect rates or because
11 they simply don't get any efficacy from the
12 procedure?

13 DR. WITTEN: Unfortunately, I can't really
14 add anything to this. We don't have that kind of
15 information based on the study. And that's why, as
16 I say, the -- we had listed a number of populations
17 as precautions, but we don't have any information
18 that any specific population does not do well.

19 DR. VATZ: Just off the top of my head,
20 from what I remember of the -- all of the small
21 single-center studies -- I can't remember the
22 details, but one of the studies in which half of the
23 patients had a lot of MRI abnormalities -- it was an
24 Italian study -- the patients with the MRI
25 abnormalities tended not to do as well. Now, how

1 closely those MRIs were read -- you know, if they
2 were huge MRI abnormalities or little bits of
3 atrophy, you know, I can't tell, but that -- that's
4 one thing that comes to mind.

5 DR. BAKAY: Yeah, that's the problem.
6 Most of these patients will have some type of
7 abnormality on an MRI, something of -- small or
8 something that's major. And you have to sort it out
9 as to whether this is something major and a patient
10 to avoid, or whether this a minor problem that you
11 can go ahead and proceed with the surgery.

12 DR. SATYA-MURTI: Dr. Garber, I'm not,
13 again, saying the fact that there is no improvement.
14 Obviously, I'm covering it, and I've been covering
15 this for a long time. All I'm saying, in as much as
16 there as there is publication bias, there is
17 presentation bias, too. We are only hearing from
18 those who have done well. Not to take away the
19 credit for that, but we are not hearing from those
20 who have not done well or what the reason is why
21 they didn't well either. So --

22 DR. GARBER: Okay, thank you. You know,
23 I'd really like to get to the questions. And we
24 spent much more time on -- now, this discussion is
25 very pertinent, but I would like us to frame it in

1 the context of the questions.

2 I'll recognize two other people who have
3 had their hands up, and then that's it. We'll go to
4 the questions.

5 Okay, Jim Rathmell, then Bruce Sigsbee.

6 Or was it -- Kim, were you next?

7 DR. RATHMELL: I want to go --

8 DR. GARBER: Sorry.

9 DR. RATHMELL: I want to go to the
10 question, so --

11 DR. SIGSBEE: Well, actually, this is
12 directly relevant to one of the questions that we
13 have. There is an age-related difference in the
14 response. And the older age strata don't do quite
15 as well. And I wonder if you could comment on that.
16 Is that -- the biology of Parkinson's a little bit
17 different in older individuals? Are the targets
18 harder to find? Is it concurrent brain diseases?
19 Or is it all of the above?

20 DR. BAKAY: All of the above. They
21 do -- do not do as well as younger patients who have
22 less disease or younger patients with more disease.
23 That's just a part of the biology. You can't turn
24 the clock back on those patients. You can't say,
25 well, you know, you reach 66 and we're not going to

1 do these -- the surgery on you anymore.

2 It still is effective in those patients.

3 If you look at those graphs, you'll still see that
4 there are a number of those patients that do have
5 dramatic improvements. There are just not as many
6 of them in the most dramatic aspect as there are of
7 the younger patients. They still do respond, and
8 respond well, and I think that's the critical
9 aspect.

10 This population that's going to be covered
11 by Medicare will be a group that, for the most part,
12 will respond and will respond reasonably well. It's
13 not going to be as good as younger patients, but we
14 can't bring them back to that younger age to do them
15 earlier.

16 DR. MONTGOMERY: Yeah, I would agree. I
17 mean, I think it's almost a matter of common sense.
18 We don't expect our older patients are going to do
19 as well as our younger patients.

20 I mean, we had a 47 year old who's running
21 triathlons, and we certainly don't tell our older
22 patients that they're going to experience anything
23 nearly that dramatic. And older patients are more
24 prone to complications and side effects.

25 But I can tell you we've operated on very

1 old 80 year olds who have done as well or better
2 than some of our 50 year olds. Certainly one can
3 draw a trend, but it is only a trend, and when it
4 comes, then, to trying to predict what an individual
5 older patient -- how an individual older patient is
6 going to response, I think that's -- it's highly,
7 highly problematic.

8 Again, going back to our detailed analysis
9 of our pallidotomy data, we did see a trend, but the
10 adjusted R-square for that -- it was very, very
11 poor. Again, I think it requires judgment on the
12 part of the physician. Is this a younger 75 year
13 old, or is this an older 50 year old? These are the
14 judgments that we're called upon to make in terms of
15 individualizing any therapy.

16 DR. GARBER: Yes, Kim?

17 DR. BURCHIEL: One -- just one comment
18 that might sort of tie this together. I mean, I
19 think this has been a field that's evolved over the
20 last five to ten years, and what's happened is
21 things have settled out. I mean, consensus keeps
22 coming up. And, unfortunately, that's the level of
23 evidence right now for things like relationship to,
24 you know, complications and certain demographic
25 criteria of the patients, or experience, or any of

1 the other things we could enumerate today. We don't
2 know, and we're just at the point now where we can
3 begin to ask those relevant questions. That's why
4 the VA study is going to be so important, the VA-NIH
5 study.

6 So we're at that level of sort of class-
7 three, maybe class-two evidence, right now on all
8 those issues. You know, when you -- and when you
9 look at the field -- what's happened over the last
10 five years, what's progressed in the direction that
11 we've avoided those things -- Parkinson's, plus;
12 dementia -- you know, the age issue is sort of a
13 plus-minus question at this point, is what relevance
14 does that have to patient selection.

15 And I think there's some other criteria.
16 Posture instability, we know, is not so well
17 treated, but that's a kind of a subtlety. I think
18 those are things now that we begin to ask
19 intelligent questions, but we don't have the data to
20 go to to answer specifics about level of training,
21 relationship to complications and most of the other
22 things that have come up today. We have a feeling
23 of the answer, but we don't know the answers.

24 DR. GARBER: Okay, we're now going to turn
25 to the voting questions. And I'd just like to point

1 out, the discussion questions are sort of questions
2 that will help in the interpretation of how we
3 answer the primary questions. And a number of these
4 issues have already come up in the discussion, such
5 as who is qualified to actually perform the
6 procedure. So that's something that we will now
7 revisit.

8 The first voting question -- Perry has put
9 up the panel voting questions here -- is, "Is the
10 evidence adequate to determine the clinical
11 effectiveness for a well-defined set of Medicare
12 patients with Parkinson's disease?"

13 And then if we conclude that, indeed, the
14 evidence is adequate, we need to address the size of
15 the overall health effect -- and, for the panelists,
16 that is on the second page of the handout that --
17 the category's effectiveness are on the second page
18 of the handout that has the voting questions.

19 So, first, I would like the panelists to
20 consider this first voting question, which is really
21 quite fundamental, "Is the evidence adequate to
22 determine the clinical effectiveness?" We don't now
23 have to say who that well-defined set of Medicare
24 patients is, if we think that there is some well-
25 defined set for which the answer to this question is

1 affirmative.

2 Irene?

3 DR. LITVAN: Yeah, I do believe that there
4 is enough evidence that this is a breakthrough
5 technology that has definitely changed the
6 management of patients with Parkinson's disease and
7 that the size of the response on those which the
8 surgery is indicated is significant -- is
9 approximately 50 percent, and I think that there is
10 a lot of data coming from different centers --
11 multicenter studies, that would support that.

12 DR. GARBER: Yes, Dr. Weiner?

13 DR. WEINER: Yeah, I would -- I would
14 reiterate what Dr. Litvan said. I think the
15 evidence is adequate to support coverage of this.
16 And, in particular, I'd point out that the -- I
17 think, the last two drugs that were approved for
18 Parkinson's disease by the FDA were the Ketochol and
19 methyl transinhibitors, Entacapone and Tolcapone.
20 And, in those studies, the pivotal studies increase
21 the "on" time by about two hours. And the data here
22 are suggesting that the "on" time can be increased
23 by six hours.

24 So I can tell you, from using the drugs,
25 that an increase of two hours of "on" time for

1 patients makes a tremendous difference to people.

2 And sometimes even that little can be the difference
3 between someone who has to live in an assisted-
4 living facility or a nursing home, so that the
5 possibility of increasing "on" time by six hours
6 really, I think, does qualify as a breakthrough
7 therapy.

8 DR. GARBER: Yes --

9 DR. SATYA-MURTI: I would say it's more
10 effective, obviously, but I'm not sure it's
11 breakthrough technology. I would say it's more --

12 DR. GARBER: Wait, wait. Let's defer the
13 question until after we vote on this one. But,
14 yeah, we will get to that if we answer affirmative
15 to this one.

16 Yeah, Ken?

17 DR. FOLLETT: I have two comments, one of
18 which actually relates to this last point. First of
19 all, there has not yet been a study comparing deep-
20 brain stimulation to best medical -- what we call
21 best-medical therapy. But, as Dr. Montgomery
22 pointed out earlier, we reserve this treatment for
23 those patients who've really reached their limit
24 with what can be done with medications.

25 The VA-NIH study was put together with

1 this consensus of opinion that deep-brain
2 stimulation really is effective, and we wanted to
3 look at some of the intricacies of its application.
4 And I think the data support the fact that this --
5 the therapy is effective for those patients who have
6 failed so-called best-medical therapy.

7 And I would also like to point out that,
8 in the course of planning for the VA study, we did a
9 survey of the centers of excellence that were
10 recruited into the study to find out what their
11 strategies have been over the last several years for
12 the use of surgery for the treatment of Parkinson's
13 disease. Notably, four to five years ago, most
14 centers were still performing pallidotomies. And
15 about two years ago, there was a very dramatic shift
16 to where virtually every center, if not every
17 center, virtually abandoned lesioning techniques and
18 moved toward deep-brain stimulation. And in that
19 sense, this really does border on what would be
20 classified on breakthrough technology to where it
21 has now become the surgical standard of care for the
22 treatment of Parkinson's disease.

23 DR. GARBER: Any other comments? Tom?

24 DR. HOLOHAN: I don't know if any of the
25 CMS representatives can answer this question, but

1 we've kind of floated a little bit around the idea
2 of age. Mrs. Jante testified that her husband,
3 who's in his 50s is a Medicare beneficiary. Does
4 Medicare have any data on the average age of
5 Parkinson's disease patients for which Medicare is
6 responsible for coverage?

7 MR. BRIDGER: We have a number of
8 beneficiaries under 65 who fall into the disability
9 category, but I don't think we have the age number.
10 I think it's 12,000 --

11 MALE VOICE: Fifteen thousand.

12 MALE VOICE: -- 15,000.

13 MR. BRIDGER: Yeah, we -- I don't have any
14 -- I don't have any specific numbers about the
15 average age of the Medicare patient who has been
16 diagnosed with Parkinson's, but there is
17 approximately between 15,000 and 20,000 Medicare
18 patients who are under the age of 65 who are
19 disabled who have a principal diagnosis of
20 Parkinson's.

21 DR. HOLOHAN: Okay, so -- so if we're,
22 then, looking at a well-defined set, it sounds as
23 though age is not an issue then, or may not be an
24 issue.

25 DR. GARBER: Yeah, I -- this was something

1 that did come up on the conference call. I don't
2 think you were able to participate -- were you -- I
3 don't recall that you were on then. But that's
4 right, the well-defined set does not have too many
5 people over age 65. And I think most of us would
6 agree with -- whatever that number is -- say, around
7 15,000 people -- that is a substantial number of
8 Medicare beneficiaries who are at least potential
9 candidates for this therapy and, I think the
10 implication is, who fit within the range of patients
11 studied in the literature.

12 DR. ZENDLE: Well, I just want to clarify,
13 though. That does not limit it to only those
14 Parkinson patients under age 65.

15 DR. GARBER: No, no, not at all. The
16 question is, can you identify some set. It's just
17 saying that that's a necessary condition, that's
18 all, that there is some set.

19 Okay, so I would entertain a motion, if
20 there's no further discussion, for -- regarding
21 Question 1 about adequacy of evidence.

22 And let me just underscore, we haven't
23 really, in the discussion, thus far, distinguished
24 between subthalamic nucleus and globus pallidus, but
25 the voting question should be about subthalamic

1 nucleus, unless the panelists would like to change
2 the questions.

3 DR. SIGSBEE: Alan?

4 DR. GARBER: Yeah? I'm sorry.

5 DR. SIGSBEE: Could I suggest, based on
6 earlier testimony, that there does not seem to be
7 any clear evidence discrimination between the two
8 targets, that we combine them in a single question?

9 DR. ZENDLE: I would second that.

10 DR. GARBER: Okay. Any discussion?

11 Could I just ask you for clarification?

12 How, specifically, would you change the language?

13 Is that "clinical effectiveness of STN or GPi" -- or

14 it "and" -- what language are you --

15 MALE VOICE: Is there any benefit to --

16 (inaudible) --

17 MALE VOICE: Or.

18 DR. GARBER: Okay. Yeah, Steve, why don't
19 you go ahead and --

20 DR. PHURROUGH: Even though we could
21 combine them, I guess my question would be, is there
22 a benefit to combining them, since we're going to
23 answer the same question?

24 DR. SATYA-MURTI: Yes, there is, I would
25 say, because there are other putative targets. If

1 we don't specify them by actual anatomic site, there
2 is a tendency to -- for this to dilute into
3 cerebellum and other areas. So I think it would be
4 a good, from both science and coverage point of
5 view.

6 DR. ZENDLE: And I think the idea of
7 separating them was because there was some thought
8 that there might be a difference in our conclusions.
9 And I think that we all feel that there won't be,
10 and, therefore, let's just do it together.

11 DR. GARBER: Okay. Bruce, did you have
12 specific language that you want to use?

13 DR. SIGSBEE: That I was going to take the
14 language here and just do "STN or GPi."

15 MALE VOICE: No, "and." There is evidence
16 to determine the clinical effectiveness of both.

17 MALE VOICE: Yeah, yeah. Well, okay --

18 DR. SATYA-MURTI: If you say "and," it
19 could call for targeting both sides, or one after
20 the other serially, so I think "or" is better.

21 MALE VOICE: Well --

22 DR. SATYA-MURTI: And that leaves that
23 option open. If you try STN --

24 DR. GARBER: I think there would have to
25 be -- I think, logically, what Les says is correct,

1 it needs to be "and," because we're saying, I think,
2 that both sites are effective.

3 MR. BRIDGER: Dr. Garber?

4 DR. GARBER: Yeah?

5 MR. BRIDGER: May I make a comment? I
6 think one of the reasons why -- the reason why we
7 separated the question so that Question Number 1
8 relates to the subthalamic nucleus, and Question
9 Number 2, the same wording, asks the same question
10 about the GPi, is because of the way that the
11 assessment was performed and how we were looking at
12 the evidence, breaking down the studies looking at
13 the separate targets, so that you've got, broken
14 down, by studies and numbers, results for the two
15 targets.

16 So the benefit of combining the two
17 questions potentially could confuse the issue rather
18 than trying to keep them separate. And if your --
19 if your end result is the same for both questions,
20 then that's the way it will go. But I think, for
21 reasons of making it simpler to understand the flow
22 of the review of the literature, they were broken
23 down this way.

24 DR. SIGSBEE: Mr. Chairman, in the
25 interest of time, can I withdraw my suggestion so we

1 don't have to --

2 DR. GARBER: And will the --

3 DR. SIGSBEE: -- discuss this any further
4 and just --

5 DR. GARBER: -- seconder withdraw their
6 seconding?

7 DR. ZENDLE: Yeah, but, you know, the
8 reason we're having this difficulty is that some
9 people are referring to, "Is there enough clinical
10 evidence to make a determination," versus, "What
11 should the coverage language say?"

12 DR. GARBER: Yeah, but --

13 DR. ZENDLE: And I agree that with the
14 coverage language, you're going to have different
15 language than when you talk about the evidence,
16 so --

17 DR. GARBER: Well, I think what the --

18 DR. ZENDLE: -- I guess I was trying to be
19 a purist about the medical evidence.

20 DR. GARBER: Yeah. I think in terms of
21 what's going to work best in terms of advising CMS,
22 CMS can be our guide there, so -- now, let me just
23 say -- so that motion is withdrawn, so we're back to
24 the original language.

25 But before we vote on this, we did have a

1 -- Michelle has pointed out that we had a session
2 for open public comments in the afternoon, which we
3 -- we should probably give public speakers who
4 hadn't been previously scheduled a chance to speak
5 now if they wish to address the issues. So let me
6 just ask, is there anyone who would like to speak?

7 VOICE: (Inaudible.)

8 DR. GARBER: No, actually, in general, are
9 you -- yeah, now would be the time to speak, even if
10 it's not on this issue.

11 So we have one speaker. Is there anybody
12 else who wishes to speak? Go ahead, Dr. Cohen.

13 DR. COHEN: Well -- hello? -- yes. I was
14 a patient representative on the FDA panel that
15 addressed this issue. That's now more than two
16 years ago. So, as a patient and representing other
17 patients, and particularly the patient who came here
18 from Wisconsin to speak to you, I think that the
19 time has come for Medicare to make a decision.

20 I'm -- I think the process has been
21 dragging out a little bit too long. You've already
22 heard from the panel that this is a -- deep-brain
23 stimulation is the accepted medical practice in most
24 medical centers, and pallidotomies are not -- no
25 longer done. That's an important change that has

1 already occurred.

2 And, on the issue of quality, which,
3 apparently, the FDA is -- outside of the quality of
4 treatment and quality of care, which is outside the
5 purview of the FDA, Medicare has a -- has a --
6 through the payment mechanism, has something to say
7 about that.

8 One of the major issues of concern that
9 came to me out of the FDA review of the -- of deep-
10 brain stimulation was what has been discussed here
11 earlier quite a lot this morning, the issue of the
12 quality of the team, the quality of the surgeon, the
13 quality of the neurologist. And in -- so that while
14 you're doing the studies to refine the technique, I
15 think there's a lot of patients that are waiting to
16 be, sort of, liberated from their condition.

17 So the last point I wanted to make was
18 that, with regard to quality, that Medicare can set
19 the standards that the private sector will tend to
20 follow, and that would be of benefit to the patient
21 undergoing the surgery.

22 And that's about all. Thank you.

23 MS. ATKINSON: Dr. Cohen, before you
24 leave, for the record, could you please state
25 whether you have any financial interests or anything

1 to disclose.

2 DR. COHEN: No, I have no financial
3 interest in -- and I came here under -- on my own
4 nickel.

5 MS. ATKINSON: Okay, thank you.

6 DR. GARBER: Okay. Yeah, Steve has just
7 pointed out that, procedurally, only the voting
8 members of the panel can make a motion and second it
9 or vote on it. And I would entertain a motion, with
10 respect to Voting Question 1. Okay, yeah, you've
11 got -- you want to read that?

12 MS. ATKINSON: For today's panel meeting,
13 voting members present are Dr. Angus McBryde, Dr.
14 Les Zendle, Dr. James Rathmell, Dr. Bruce Sigsbee,
15 Dr. Kim Burchiel, and Dr. Thomas Holohan. And the
16 chairperson, Dr. Alan Garber, will vote in the event
17 of a tie. A quorum is present. No one has been
18 recused because of conflicts of interest.

19 DR. GARBER: Yeah, okay, so --

20 MALE VOICE: (Inaudible) -- the first
21 question?

22 DR. GARBER: Now, I'd like to call for a
23 motion. The first question is the one that is on
24 the screen there. We -- the motion to amend that
25 question has been withdrawn, so -- but we don't have

1 a motion on the floor.

2 DR. ZENDLE: So moved.

3 DR. SIGSBEE: Second.

4 DR. GARBER: Okay, which is approval of --
5 and answer --

6 DR. ZENDLE: Question 1.

7 DR. GARBER: --affirmative? Is that what
8 the motion is? And there was a second.

9 Any further discussion? We're right now
10 only considering, "Is the evidence adequate?" Okay,
11 voting members only.

12 MS. GREENBERGER: Excuse me.

13 DR. GARBER: Sorry.

14 MS. GREENBERGER: May I just make a
15 comment? I'm not a voting member, but I didn't make
16 a comment during the discussion. My comments really
17 will pertain to the effectiveness criteria, because
18 I sense that there's a consensus that the evidence
19 is adequate, but I wouldn't want to go without
20 saying that I believe it certainly is.

21 DR. GARBER: Okay, thank you.

22 Okay, so all in favor of the motion, which
23 is to answer the first question in the affirmative?

24 (A unanimous show of hands by the voting
25 members.)

1 DR. GARBER: Opposed?

2 (No response.)

3 DR. GARBER: Okay. Now, just for
4 reporting purposes, because I will need to present
5 our deliberations to the executive committee, if any
6 individual member could just give me a statement
7 about why they believe the evidence is adequate.
8 This is -- I'm not questioning your vote, but I will
9 need to report what the critical items of evidence
10 were. So does anyone voting in the affirmative care
11 to answer that? Kim?

12 DR. BURCHIEL: I would submit that the
13 evidence, although not class-one evidence, is so
14 consistent in the variety of studies and the
15 outcomes that the evidence is -- I think, somebody
16 whose word "compelling." I think Joan used that. I
17 think we have detailed reports now from FDA, from
18 BlueCross TEC assessment, and representatives from
19 industry and from academic, neurology, neurosurgery
20 -- they all attest to the compelling evidence. And
21 I was swayed by that.

22 DR. GARBER: Okay. Bruce?

23 DR. SIGSBEE: I'd like to perhaps amplify
24 on that. One of the concerns has been it's been
25 compared in a randomized way to best medical

1 treatment. In a certain sense, it is, in that the
2 patients serve as their own controls. Presumably,
3 they've already exhausted medical/pharmacological
4 intervention. And then there's a 12-month
5 comparison to their pre- and postoperative state.
6 And perhaps that's one of the cleanest controls you
7 can have in this circumstance. So I think that
8 there is very solid science behind this procedure.

9 DR. GARBER: Anyone else? Okay. Oh, yes,
10 sorry. Go ahead, Angus.

11 DR. MC BRYDE: I believe they ought to be
12 included, since this is a substitute. This is
13 actually a next generation that's more effective
14 than the procedure, ablation and so forth, that we
15 had earlier. So that should be looked at as a
16 continuity to -- (inaudible).

17 DR. GARBER: Okay.

18 DR. HOLOHAN: I also think that the
19 evidence indicates that the risk-benefit ratio is
20 reasonable in these patients.

21 DR. GARBER: Now, a -- I'd like to just
22 ask the panel's sense. Rather than answering size
23 of effect now, would you care to vote on the second
24 question about GPI before we address size of effect,
25 since the panel seems to think that they were --

1 there's little reason to distinguish the two sites?

2 Would that be the way people would like to proceed?

3 Okay, so then I'll entertain a question
4 about that first bullet under Panel Voting Question
5 2, which is identical, except it says "for bilateral
6 internal globus pallidus" instead of "subthalamic
7 nucleus."

8 DR. RATHMELL: So moved.

9 DR. ZENDLE: Second.

10 DR. GARBER: A yes vote will be an answer
11 in the affirmative on this one. Any discussion?
12 All in favor?

13 (A unanimous show of hands by the voting
14 members.)

15 DR. GARBER: Opposed?

16 (No response.)

17 DR. GARBER: And may I infer that your
18 reasons for voting in this way on this question are
19 the same as on the last one?

20 (Panel indicating in the affirmative.)

21 DR. GARBER: Okay. Thanks. For the
22 record? Okay.

23 MS. ATKINSON: For the record, the first
24 question, "Is the evidence adequate to determine the
25 clinical effectiveness of bilateral subthalamic

1 nucleus deep-brain stimulation for a well-defined
2 set of Medicare patients with Parkinson's disease,"
3 the vote was unanimous.

4 The second question, "Is the evidence
5 adequate to determine the clinical effectiveness of
6 bilateral internal globus pallidus deep-brain
7 stimulation for a well-defined set of Medicare
8 patients with Parkinson's disease," the vote was
9 unanimous.

10 DR. GARBER: Okay, thank you.

11 Now, we will address that second bullet,
12 which is -- oh, yeah, I think that would be helpful,
13 Perry, if you put on the category's effectiveness.
14 That is how effective is, "We have determined that
15 there is adequate evidence to conclude that it's
16 effective." And now we need to assign it to a
17 category.

18 DR. ZENDLE: Point of information?

19 DR. GARBER: And again, we can choose to
20 have the discussion in terms of both GPi and STN
21 combined or separately.

22 DR. ZENDLE: Point of information?

23 DR. GARBER: Yes, Les?

24 DR. ZENDLE: I want to try to understand a
25 little bit -- and maybe, Alan, you're the person to

1 answer this question -- the difference between
2 "breakthrough technology" and "more effective." I
3 was struck that "more effective" uses the words
4 "small benefit," and the "breakthrough" implies a
5 "large benefit," but then also uses the words
6 "standard of care."

7 And I think we've talked about that this
8 probably is the surgical standard of care, but does
9 not replace medical therapy. It's only after
10 medical therapy has failed. I'm a little worried
11 that if we just say it's -- "breakthrough
12 technology" is now the standard of care, that it
13 might imply different than what I just said.

14 And I wonder, is there a way to clarify
15 that, or are we really stuck with these -- just
16 those two choices?

17 DR. LITVAN: Well --

18 DR. GARBER: Well, just -- sorry?

19 DR. LITVAN: No, I was going to say that
20 it becomes the standard care once the medical
21 treatment has failed, and I think that -- that is
22 what is missing.

23 DR. GARBER: Yeah, and, as a procedural
24 point, if we want to use the language that Dr.
25 Litvan just suggested, that's something the panel is

1 free to do to clarify it.

2 Tom Holohan was also a part of those
3 discussions. And this is the language that the
4 executive committee chose to adopt. We have not had
5 a lot of experience. We've had some experience
6 assigning interventions to these categories of
7 effectiveness, and I think we should view these as
8 guidelines. But if there's a problem with the
9 language, the panel should feel -- I think we should
10 try to fit within these categories, but if we have a
11 good reason to say we want to modify them in some
12 way, then that -- the panel should feel free to do
13 so.

14 Tom, did you want to comment on the
15 categories at all?

16 DR. HOLOHAN: And maybe frame a motion
17 that says it the way we would probably vote
18 affirmative on it.

19 DR. GARBER: Thank you very much.

20 (Laughter.)

21 DR. HOLOHAN: I think that the sticking
22 point with "more effective" is the issue of a "small
23 effect" or the perception of a "small effect." I
24 think that all of the data on both of these
25 procedures provides at least evidence of a "moderate

1 effect," not a "small effect."

2 I'm concerned about the use of the word
3 "breakthrough technology" for the reasons that I
4 think you've eloquently expressed.

5 Would the panel agree to use the phrase
6 "more effective" with a modifier, which is "more
7 effective showing -- with evidence showing a
8 moderate improvement in patients who have failed
9 medical therapy" -- in lieu of "breakthrough
10 technology"?

11 DR. LITVAN: Can I --

12 DR. ZENDLE: That doesn't address the
13 pallidotomy-versus-stimulation issue, which I think
14 -- I am impressed that it basically has become the
15 surgical standard of care in people that have failed
16 -- although once improved, but now failed medical
17 therapy.

18 DR. LITVAN: So it is standard of care,
19 and so it should be "breakthrough."

20 DR. ZENDLE: For people who qualify for
21 surgical therapy, it is --

22 DR. LITVAN: It is the --

23 DR. ZENDLE: -- the standard of care.

24 DR. LITVAN: -- standard of care, and so
25 it is a breakthrough.

1 DR. GARBER: Yeah, I think that if you
2 look back to the page with the discussion questions
3 -- the discussion questions, two of them are getting
4 at the idea, really, of who is the right candidate
5 population. And it is perfectly appropriate for
6 this panel, in assigning this to a category of
7 effectiveness to specify in which patient population
8 that that classification -- so, for example, you
9 could conclude that it's marginally effective, or
10 even harmful, in some subset of patients, yet a
11 breakthrough in another.

12 And I believe that what we should do
13 insofar as this information is address this for the
14 -- for all the relevant patient populations that
15 have been studied.

16 Now, Dr. Litvan, Dr. Satya-Murti, and then
17 Dr. Sigsbee.

18 DR. SATYA-MURTI: On -- I would be more
19 comfortable if it said "moderate" instead of
20 "small," because, as we have seen, it seems to be
21 more than small. The reason we've been avoiding
22 standard of care is that, were it to be standard of
23 care, then the question will come -- on this
24 instances where this was not performed, then the
25 question would come, Did you not know that this is

1 the standard of care? Why was this not given the
2 treatment of choice? And these may be frail
3 patients and so on, so it may have a legal tentacle
4 that extends by calling it "standard of care,"
5 meaning that that's what they should have.

6 So the improvement is moderate. Until we
7 get further data as to which candidates are ideal, I
8 would prefer that it not be called "standard of
9 care" yet, because that seems to be the only way to
10 qualify it to "breakthrough technology."

11 DR. HOLOHAN: What you're saying is if you
12 don't get it, you're getting substandard care.

13 DR. SATYA-MURTI: If you're not given the
14 surgical option, that's right. The implication is
15 putting as "standard of care" -- because it's
16 language -- the phrase "standard of care" finds
17 application in CFR and Medicare regulations in
18 multiple places. So, you're right, the negative
19 implication of that is, why did this patient not get
20 the standard of care? So at least avoid that. The
21 "moderate" would avoid putting in -- boxing it into
22 either --

23 DR. HOLOHAN: I would support striking the
24 "standard of care" terminology for every reason that
25 he said, plus many others. Setting a national

1 standard of care would have implications even beyond
2 Medicare, and I think it would be -- it's awkward
3 and unnecessary.

4 I think all you're trying to do is
5 differentiate, I think, for all panelists, is the
6 difference between the "small effect," which is more
7 effective than a -- you can call it "moderate" or
8 "large" or whatever. But I would support striking
9 language that refers to "standard of care."

10 DR. PHURROUGH: Let me make just a
11 procedural comment here. These categories of
12 effectiveness were defined by the executive
13 committee and given to the panelists to use. So I
14 believe what we need to do is, if you have some
15 disagreement with the categories, is not change the
16 categories, but to modify it. So what's asked for
17 in the guidelines --

18 DR. HOLOHAN: What's the difference
19 between "change" and "modify"?

20 DR. PHURROUGH: You -- what the
21 recommendation should be is that it falls into the
22 category or "more effective," but -- or falls into
23 the category of "breakthrough technology," but not
24 say we're going to change the definition of
25 "breakthrough technology," since those definitions

1 have been given to us to use.

2 DR. ZENDLE: Could a member of the
3 executive committee give us an example of what they
4 consider -- or what has been classified as a
5 "breakthrough technology"?

6 DR. GARBER: There hasn't been one yet
7 that the executive committee has reviewed. But,
8 also, I appreciate what Steve said, except, as one
9 of the authors of these, I thought that these were
10 going to be subject to revision, and I think that
11 the panel can actually help the executive committee
12 by identifying areas where these definitions of the
13 categories don't seem to work.

14 And what -- if I captured the sense of the
15 panel correctly, I think the panelists who have
16 spoken are uncomfortable with saying it's standard
17 of care, but it's also not simply a small
18 improvement. It's something that's a substantial
19 improvement. And what I hear you saying is that
20 it's substantially more effective, which is
21 somewhere between what the executive committee
22 called "breakthrough" and what it called "more
23 effective."

24 And I believe, Steve, if I'm correct, that
25 it would help the executive committee to have the

1 panel make a determination, like "it's substantially
2 more effective" without necessarily buying into the
3 exact language in these two categories.

4 DR. PHURROUGH: You can make whatever
5 recommendations and -- to the change of these to the
6 executive committee, but I don't think we need to
7 change the definitions, as they are. We can
8 recommend that the executive committee change them,
9 but we can -- I think you can -- you can "qualify,"
10 if that's the better term, qualify what those
11 definitions are.

12 DR. ZENDLE: I'll make a motion, if you'd
13 like.

14 DR. GARBER: Okay. Well, Dr. Litvan had
15 her hand up, so let --

16 DR. LITVAN: What I wanted to say is that
17 one way to go around this is to say "for those
18 patients in which this is indicated." So you're
19 going to select a set of patients. And, obviously,
20 this is not retrospective, but prospective, because
21 this is new technology. It's not something that
22 existed ten years ago.

23 So I think we should -- can be less
24 concerned if you really think that these patients --
25 there is an indication for a patient. But I think

1 that if you don't say that it is a standard of care,
2 someone may say that they -- the patient may not
3 qualify with not real reasons for not qualifying it,
4 and they will definitely get a substandard of care,
5 because, at the present time, if the patient has
6 certain features that is not responding to the
7 medication and has the appropriate good health and
8 the diagnosis is appropriate, it should undergo this
9 kind of surgery.

10 DR. GARBER: Okay, well, then you can vote
11 to say that it's "breakthrough," if I understand
12 correctly.

13 DR. LITVAN: Well, I think that if you do
14 make some qualifications to this --

15 DR. GARBER: About which -- the patient
16 population applies to it.

17 Okay, Les was next and then Bruce.

18 DR. ZENDLE: Just to get something on the
19 table. I would make a motion that we -- the panel
20 approve a statement that says that "this technology"
21 -- and it would be the first one, I guess -- "is
22 substantially more effective than the ablative
23 surgical option in patients -- in these selected
24 patients," or however you want to word it.

25 If you just say "it's more effective than

1 other surgical options," then you get into the STN-
2 versus-GPi thing, and I don't want to do that. So I
3 think if we just say that it's "substantially more
4 effective than the ablative surgical option," I
5 think that would --

6 DR. WEINER: No, I don't think that's
7 going to work, because I don't know that we have
8 evidence about that, that DBS is substantially
9 better than an ablative option. I don't think
10 that's the question.

11 DR. GARBER: Well, the issue -- well,
12 okay, we -- we will have to say what it's compared
13 to. But, right now, we are -- the voting question
14 was about the evidence, and I suppose we can -- we
15 probably should have said what it was compared to
16 when we were voting on whether the evidence was
17 adequate, but it's -- it's compared to some
18 alternatives that we thought that the literature
19 addressed.

20 DR. LITVAN: (Inaudible) -- is medical
21 care.

22 DR. GARBER: Yeah, so maybe it's against
23 medication. But, Bruce, you had your hand up?

24 DR. SIGSBEE: I think we should strike
25 discussion of "standard of care." Standard of care

1 often has nothing to do with efficacy, and I know
2 there's a lot of things in medicine that are
3 considered standard of care, but there's no evidence
4 that they're effective and -- for example, Heparin
5 with strokes.

6 The -- it's a semantic discussion here.
7 And "more effective" implies that you have something
8 to compare it to. And is ablative surgery truly
9 comparative? In this circumstance, you have a
10 bilateral technique that improves overall motor
11 function, compared to a unilateral that, at best,
12 improves just one side of the body. And if you
13 don't have a good comparative intervention, then it
14 -- presumably "breakthrough" is the word to use.

15 I am a little uncomfortable with
16 "breakthrough," because it's somewhat of a dramatic
17 term and it -- you know -- (inaudible) -- standard
18 -- (inaudible) -- going out, we have breakthrough,
19 this, that, or other thing. And perhaps a somewhat
20 different term needs to be crafted to indicate that,
21 at least at this point, there is no equivalent
22 technology to provide this particular treatment for
23 patients.

24 DR. BURCHEIL: Could I make a friendly
25 amendment to the motion on the -- there is a motion

1 on the floor, isn't there?

2 DR. GARBER: No.

3 DR. ZENDLE: It has not been --

4 (inaudible) --

5 DR. GARBER: Well, it didn't get a second.

6 DR. ZENDLE: It sort of -- go ahead and --
7 what's your suggestion?

8 DR. GARBER: Unless there's a second, it
9 will fail for the lack of a second. There's no
10 second, so there's no motion on the floor.

11 DR. BURCHEIL: (Inaudible) -- amendment.

12 DR. ZENDLE: So make a motion.

13 DR. BURCHEIL: To bypass this and squeeze
14 in another category here called "substantially more
15 effective," with the language being, "The new
16 intervention improves health outcomes by a
17 substantial margin, as compared with established
18 services or medical items."

19 DR. ZENDLE: Great.

20 DR. GARBER: I'm sorry, I couldn't hear
21 the last part. As compared with what?

22 DR. BURCHEIL: Same language. I'm just
23 putting in "substantially more effective."

24 DR. GARBER: Oh, okay. It says "compared
25 with established services."

1 DR. BURCHEIL: "The new intervention
2 improves health outcomes by a substantial margin, as
3 compared with established services or medical
4 items."

5 DR. SATYA-MURTI: Either that or more than
6 -- (inaudible), because the binding and obligatory
7 effect of standard of care is somewhat fearsome, I
8 think.

9 DR. ZENDLE: I'll second his motion.

10 DR. GARBER: Okay, so we have a motion
11 that's seconded. Tom?

12 DR. HOLOHAN: Let me make an observation.
13 We've talked about effective compared to what, and
14 people have proposed unilateral or destructive
15 lesions. In fact, all of the data that appeared in
16 the BlueCross TEC assessment was basically relevant
17 to medical therapy, drug therapy. None of those
18 studies were comparative. There never has been a
19 comparative study done of destructive lesions --
20 GPi, STN. All of the data we have compares it to
21 medical therapy, and I think we should restrict
22 ourselves to that.

23 DR. GARBER: So there's a question -- Kim,
24 your proposal was to apply the category of
25 "substantially more effective," as you defined it --

1 DR. BURCHIEL: Yes.

2 DR. GARBER: -- to -- at this point, we're
3 talking about STN. Then there's an option that we
4 have, I believe -- and, Steve, maybe you can address
5 this -- which is to explain what we mean it's
6 compared to. And I don't think that has to go into
7 the -- answer the question, but can be in the
8 explanatory text. In which case, what Tom just said
9 would appropriately appear as an explanatory point
10 under this main motion. That's just a procedural
11 question. And, Steve, does that --

12 DR. PHURROUGH: Yeah. I think, as Kim's
13 motion, I think, takes into account my concerns of
14 changing categories, versus adding or qualifying --

15 DR. GARBER: Uh-huh.

16 DR. PHURROUGH: -- and then leaving it, as
17 Kim moved, and then explaining that would
18 procedurally be appropriate.

19 DR. GARBER: Okay, so -- now -- so the
20 other aspect to this is, we can vote on this
21 question and then we can get the sense of the panel
22 about whether they want to make the qualification
23 that Tom suggested or any other qualifications, for
24 that matter. Is that okay, procedurally?

25 So we just first vote on Kim's motion,

1 which is actually the motion that's on the floor.

2 DR. ZENDLE: Second.

3 DR. GARBER: Okay. Any further
4 discussion? And maybe we could read that again.
5 Kim, would you mind?

6 DR. BURCHIEL: Substantially more
7 effective. "The new intervention improves health
8 outcomes by a substantial margin, as compared with
9 established services or medical items."

10 DR. GARBER: Okay. All in -- any further
11 -- Joan?

12 MS. SAMUELSON: I do have a comment, yeah,
13 which goes to the definition of "breakthrough," I
14 think, and -- and the relevance of pallidotomy. I'm
15 a lawyer by training, so the distinctions make a
16 difference to me, although I apologize for not
17 having the scientific background. But my lay
18 understanding is this really has shelved some of the
19 ablative surgery as the standard of care, because
20 they were available because some alternative to the
21 medication was so desperately needed because there
22 was no alternative, and people were willing to take
23 the risks associated with pallidotomy. And they're
24 not being conducted now, because there is this
25 alternative, so there is a relevance, I think.

1 DR. BURCHEIL: Can I answer that, as an
2 active practitioner in this field? Is that the
3 ablative options haven't disappeared.

4 MS. SAMUELSON: I understand they haven't
5 disappeared. It's certainly -- from a lay patient
6 perspective in the community --

7 DR. BURCHEIL: It -- they simply represent
8 another alternative, and there has been a shift in
9 the field -- a massive shift, albeit, but towards
10 deep-brain stimulation, but pallidotomies are still
11 being done --

12 MS. SAMUELSON: Right.

13 DR. BURCHEIL: -- thalamotomies are still
14 being done. I mean, these are still being done.
15 It's just another arrow in the quiver. So we have
16 now an important technology which, in most aspects
17 has supplanted ablative procedures, but it hasn't
18 completely eliminated them.

19 MS. SAMUELSON: I -- and I understand
20 that. I think the fact that it is a massive shift
21 goes to the issue of how breakthrough it is, and I
22 appreciate that that sounds a bit dramatic, but it
23 -- I think it's a profound new option, and
24 "breakthrough" is a word that makes sense to me.

25 DR. SIGSBEE: Our role is to comment on

1 the quality of the data. And, at present, we do not
2 have good comparative data to ablative procedures.
3 And so that, based on the science and the evidence
4 here, I'm not sure that we can make that statement.

5 DR. GARBER: Yeah, I think that that's the
6 crux of the matter here, which is that we had a very
7 carefully done review that was addressing a somewhat
8 different question than the one that you just
9 raised. So, you know, we haven't had the same kind
10 of systematic review of the evidence that it's
11 superior to, say, thalamotomy. And consequently, it
12 leaves us in an awkward position, because we're
13 really talking about what we've looked at the
14 evidence for, and the panelists could still conclude
15 it's a breakthrough, in which case they need to vote
16 against this motion. Or you could say that, based
17 on literature, according to Tom's qualification
18 there, that it is substantially more effective.

19 MS. SAMUELSON: My concern was that maybe
20 the tail was beginning to wag the dog, that the
21 concern about the comparison within -- between
22 surgeries was encouraging a downgrading, a bit, of
23 the overall significance of this, and that that's
24 what the motion would be doing, when there's several
25 other indicators that this is a profound new option

1 -- the possibility of reduction of medication, the
2 increased "on" time -- the enormous increase of "on"
3 time in some cases, when that is such a massively
4 important factor in the life of a person who's
5 living with Parkinson's, and the consequences of it
6 for them.

7 DR. GARBER: Yeah, well, you know, I think
8 that one thing that's important to keep in mind is
9 we knew it would be hard to assign interventions to
10 categories. We had a lot of discussions about
11 wording in categories, and so on.

12 It's important to keep in mind that all of
13 our discussion today is going to be part of the
14 public record. And I can't speak for CMS, but I
15 imagine this is not going to make a big difference,
16 which category we assign it to, in terms of their
17 coverage decision, because we've concluded already
18 that there's adequate evidence. And if we also
19 conclude that it's substantially more effective -- I
20 think we've given very clear guidance to CMS that we
21 think this is something that should be covered.

22 DR. ZENDLE: I have a question --

23 DR. LITVAN: Well, I agree with what
24 you're saying, but I think her point is well taken.
25 This has dramatically changed our practice in

1 neurology, and I think that needs to be reflected in
2 some way.

3 DR. GARBER: Yeah, but the people should
4 vote -- if you believe this does not belong in the
5 category "substantially more effective," you should
6 vote against the motion that's on the table and,
7 instead, offer another motion for assigning it to a
8 different category. But right now, we'll just vote
9 on whether it's substantially more effective.

10 DR. SATYA-MURTI: The language we choose
11 here, I don't think will change its availability.
12 If we overstate the efficacy, there is a chance it
13 will be inappropriately performed. So that I don't
14 think whatever language we choose here will change
15 the availability of this procedure to individuals
16 who need it.

17 DR. GARBER: Ken?

18 DR. FOLLETT: Just one additional point.
19 We don't know for a fact that deep-brain stimulation
20 is more effective than pallidotomy, because the
21 issue has never been studied. We believe that it's
22 safer. For example, there are few, if any,
23 neurosurgeons who would perform bilateral
24 pallidotomies anymore, but it may be that bilateral
25 pallidotomy is every bit as effective, clinically,

1 as DBS. We simply don't know. It's just that DBS
2 appears to be safer.

3 Okay, thank you.

4 DR. LITVAN: Well, we do know that it has
5 more side effects, though -- bilateral --

6 DR. FOLLETT: It is safer. That's what I
7 meant to say.

8 DR. GARBER: Yeah. Yeah. Okay, all in
9 favor of the motion, say aye.

10 (A chorus of ayes.)

11 DR. GARBER: Opposed?

12 (No response.)

13 DR. GARBER: Okay.

14 MS. ATKINSON: The motion that was on the
15 table is that, "substantially more effective, the
16 new intervention improves health outcomes by a
17 substantial margin, as compared to established
18 services or medical items," was unanimous.

19 DR. GARBER: Okay, and --

20 DR. ZENDLE: I would move the same
21 language for the second question.

22 DR. GARBER: Okay, so for GPi, same
23 question.

24 DR. HOLOHAN: Second.

25 DR. GARBER: Second. Okay, any

1 discussion? All in favor?

2 (A unanimous show of hands by the voting
3 members.)

4 DR. GARBER: All opposed?

5 (No response.)

6 DR. GARBER: Okay, now, the next thing is
7 just an issue of guidance, and I don't know that we
8 need a formal vote, but I want to get the sense of
9 the panel about whether they concur with the point
10 that Tom Holohan made about the fact that the
11 literature that we have reviewed really applies to
12 the comparison with medical therapy.

13 DR. BURCHEIL: Can I -- can I address that
14 for --

15 DR. GARBER: Uh-huh.

16 DR. BURCHEIL: It does, indirectly.
17 Because by entrance criteria, the studies we have
18 basically say these are patients that are previously
19 levodopa-responsive that are now medically
20 intractable. But, as Ken's pointed out and a number
21 of other people, we don't have a study which
22 compares to medical therapy, period. So it's a
23 little weaker than a comparative analysis.

24 DR. FOLLETT: I -- yeah, I thought I said
25 that.

1 DR. BURCHEIL: Okay, maybe you did.

2 DR. LITVAN: Well, you have -- yeah, it's
3 true that there isn't, because there hasn't been
4 any --

5 DR. BURCHEIL: It hasn't been done.

6 DR. LITVAN: -- yeah, a randomized study
7 that would do it. But, on the other hand, there is
8 no other possibility than -- (inaudible) -- history.

9 DR. GARBER: Tom, do you want to just
10 restate what the point is?

11 DR. HOLOHAN: Yeah. If you look at the
12 published studies that made up the bulk of the
13 BlueCross/BlueShield Technology Assessment, the
14 improvements were, for the most part, recorded in
15 the UPDRS score. And those were improvements
16 comparing patients' post-treatment with stimulation
17 to pretreatment. And there were some that -- some
18 comparisons of "on" and "off" with stimulation.

19 So the direct comparison was really in
20 improvements in the UPDRS, for the most part, using
21 deep-brain stimulation of either the STN or GPi, or
22 not using it. So the direct comparison, although
23 not prospectively randomized controlled trial, was
24 with medical therapy available to the patients at
25 the time.

1 There was no comparison between STN and
2 GPI -- the VA will do that. There was no comparison
3 bilateral versus unilateral. And there was no
4 comparison of deep-brain stimulation versus ablative
5 therapy.

6 So, although an imperfect comparison, it's
7 the only thing we have, in terms of a measure of
8 effectiveness of DBS of either the STN or GPI
9 compared to anything. The comparison was toward the
10 responses to medical treatment, drug therapy.

11 DR. GARBER: So -- well, this is going to
12 anticipate the discussion about who this generalizes
13 to. I know this is an oversimplification, but could
14 we put it that it was comparing these therapies --
15 that is, DBS in the different sites, with little
16 ability to distinguish between the effects of the
17 sites -- to continued standard therapy among
18 patients who had failed medications?

19 DR. HOLOHAN: Yes.

20 DR. GARBER: Would that be just a fair --
21 I realize that that's not a hundred percent true,
22 but it might be -- is that a fair simple statement
23 of what -- (inaudible) -- so I can --

24 DR. ZENDLE: Could you just add "who have
25 previously responded, but now are" --

1 DR. GARBER: Yeah, "who had some evidence
2 of response to -- "

3 DR. ZENDLE: -- "but who now are not
4 responding."

5 DR. GARBER: -- "are not responding
6 adequately." Would that be fair?

7 (Affirmative responses.)

8 Okay. So that will give, I think, CMS
9 some guidance about who we think this applies to.
10 And would it also be fair to say that we don't see
11 strong evidence of differences by age sufficient to
12 say that the results do not hold, say, for the
13 elderly, as opposed to the younger people with
14 Parkinson's"?

15 (Affirmative responses.)

16 DR. GARBER: Okay.

17 DR. HOLOHAN: Can I comment on that?

18 DR. GARBER: Sure.

19 DR. HOLOHAN: The data that Medtronic
20 provided us -- and this one of the reasons I was
21 trying to beat on CMS about age distribution to
22 their patients -- there were a couple of categories
23 where there were statistically significant different
24 differences in adverse effects in age, broken down
25 into over 65 and under 65 -- cardiovascular

1 disorders, confusion, and, probably more
2 importantly, paresis, hemiplegia, and intracranial
3 hemorrhage.

4 Now, it's true that most of the -- most,
5 but not all, of the intracranial hemorrhage in the
6 studies in the reported in the BlueCross/BlueShield
7 TEC assessment were not major. A few were. But
8 hemiplegia is a very significant adverse effect, and
9 it occurred almost five times as frequently in
10 people over the age of 65 as in people under the age
11 of 65.

12 So I don't think we can be too cavalier
13 about saying there is no relationship between
14 adverse effects and age. I'm not sure how you can
15 craft that.

16 DR. ZENDLE: Yeah, well, I -- while there
17 is no -- while you can't say there is no
18 relationship between adverse effects and age, I
19 think the point is -- is that age alone is not the
20 determining factor. And I can't remember who said
21 -- but there are older patients who do very well and
22 don't have complications, and there are younger
23 patients that can have complications. It's a factor
24 to consider by the clinician, but I don't think
25 that, in terms of stating that there's evidence to

1 determine clinical effectiveness, should be affected
2 by age.

3 DR. LITVAN: Probably it's related to
4 associated disorders that occur in aging as you see
5 that also vascular events, in general, are
6 increasing in age population.

7 DR. HOLOHAN: All that's true, but that's
8 not -- that's not the point I made. The point I
9 made was that the proportion of adverse, some very
10 serious, at least based on the Medtronic data,
11 clearly relates to age. And I don't think we can
12 make a differentiation in terms of which patients
13 are suitable, but I think it would be perhaps a -- I
14 don't want to use the term "irresponsible," but I
15 think that it's appropriate that we make some
16 comment about the apparent increase in age-related
17 adverse effects.

18 DR. GARBER: Ken, did you want --

19 DR. SATYA-MURTI: One problem I had with
20 that age was, that's the age at which surgery was
21 done, but it doesn't reflect on how long they've had
22 PD and how badly they've done with meds. So it may
23 be not only age itself, but also the poor
24 responsiveness over the years. This person operated
25 at 66 may have had it from 25; whereas, the next 66

1 may have had the onset only at the age 61 --
2 clinical onset. So --

3 DR. GARBER: Well, just -- in the interest
4 of moving this to a relative statement, maybe I can
5 try paraphrasing Tom a little bit and see if I have
6 the agreement of the panel, which is that there is
7 evidence of continued benefit with advancing age,
8 and also evidence that risks of the procedure
9 increase with age.

10 Ken?

11 DR. FOLLETT: Yeah, I span these two
12 points that we heard from Dr. Bakay and Dr. Holohan.
13 With -- there are increasing risks of surgery for
14 almost any surgical procedure with advancing age.
15 It was Dr. Bakay's point. The older the patient,
16 the more likely there will be some type of
17 complication. But, on the other hand, I agree that
18 perhaps we need some comment about the impact of
19 age.

20 I'm very concerned about making a strong
21 statement based upon the Medtronic data, because
22 those came from an entirely unselected patient
23 population. We don't know why patients were offered
24 STN implants versus GPi implants. Perhaps the more
25 infirm patients were the ones who tended to have the

1 GPI implants. And the site of implant in the
2 Medtronic data was determined solely at the
3 discretion of the implanting physician. So I think
4 the --

5 DR. GARBER: Yeah, well, I have to say, by
6 the way, that we almost always are in a situation
7 where we don't have a lot of data on subgroups
8 defined anyway, whether it's age or other clinical
9 characteristics and so on. And so we would have to
10 qualify anything we said by noting that we had
11 either small numbers, which is the case here, or not
12 such great -- not such well-designed studies.

13 DR. LITVAN: Has anyone analyzed the
14 hypertension or history of coronary disease?

15 DR. HOLOHAN: No.

16 DR. LITVAN: No?

17 DR. HOLOHAN: No.

18 DR. GARBER: Bruce?

19 DR. SIGSBEE: I would be very hesitant,
20 based on this Medtronic data, to make that
21 statement. If you look at several of the
22 categories, in fact, they're more frequent in the
23 younger age group. And you have to remember,
24 statistics is looking at what's the chance that this
25 occurs on a random basis. You're looking at so many

1 criteria that some of them, just on a random basis,
2 may be more in one group than another. And the
3 numbers are very small here. So I think we have to
4 be very careful about making assumptions based on
5 the statistics presented here.

6 Now, I think we would all agree that
7 probably this is more risk as one gets older, but I
8 -- but the -- given the numbers, I'm hesitant to
9 really support that statement.

10 DR. GARBER: So the -- but we're left with
11 the question, if we are asked, "Is there any
12 difference with age?" That is, are people who all
13 -- they're as well off, not as well off, better off,
14 compared to people who are younger -- getting this
15 procedure. What should our answer be?

16 DR. ZENDLE: I think your statement was
17 accurate, that they -- they benefit, but there tends
18 to be higher complication rates in older people.

19 DR. GARBER: And that the evidence base -
20 - I'd further qualify that by saying that the
21 evidence base is very thin.

22 DR. BURCHEIL: Why don't you just say that
23 the evidence is inadequate to answer that question
24 -- I mean, that the absence of proof is not the same
25 as proof of absence.

1 DR. GARBER: Well, this is an example
2 where we will be asked about: Is there any
3 indication of trends? And you can say either there
4 are or there are not trends, and then you can -- you
5 certainly have to -- have to say that the evidence
6 is insufficient to draw any firm conclusions.

7 DR. LITVAN: I think there is evidence
8 that -- enough evidence that there is some benefit,
9 but there is not -- and perhaps more complications.
10 And so you can say those, that -- but the numbers
11 are not --

12 DR. GARBER: And the -- and the study
13 designs are not such that you can draw --

14 DR. LITVAN: Right. I mean, the question
15 has not been addressed in a specific study, so
16 conclusions cannot be hard.

17 DR. SIGSBEE: Perhaps we can just simplify
18 it by saying that, for the age group over 65, there
19 is evidence that it is an effective intervention
20 with a reasonable risk-benefit ratio.

21 DR. LITVAN: With a what?

22 DR. GARBER: But that's -- that's not what
23 I think I've heard, which is -- you can't reconcile
24 that with there not being a lot of evidence
25 separately for the over 65.

1 DR. SIGSBEE: But, I think, rather than --
2 than looking at it compared to the under 65, you're
3 looking at just the total complication rate for that
4 age group for inter-operative and other
5 complications, that it still seems to be a
6 reasonable risk-benefit ratio in that age group.

7 Do we -- do we have evidence that it is
8 any -- clearly different than operating under --
9 under 65 on that?

10 DR. GARBBER: That's a question of burden
11 of proof. But I guess that, Bruce, one of the
12 things I would have to say is where -- what we've
13 seen good evidence for is in a heterogeneous
14 population of patients, which includes both young
15 and old, in fairly well-designed, though not
16 perfect, studies, but fairly well-designed -- there
17 is clear evidence that benefits exceed risks. But
18 we're on much shakier ground with much more limited
19 data when we try to stratify by age. I mean,
20 it's --

21 DR. HOLOHAN: And the average age of the
22 studies cited in the BlueCross/BlueShield TEC report
23 was 58.

24 DR. ZENDLE: Alan, isn't the point that
25 the conclusions we've reached, there's no evidence

1 for us to differentiate the effect between the under
2 65 and over 65? And I really think that's -- we
3 should just leave it there.

4 DR. GARBER: Yeah, well, I would just say
5 there is very little evidence to enable us to draw
6 conclusions. And then -- about over 65 versus the
7 under 65 -- and then we can say what the direction
8 of the evidence is and point out that it's not
9 really adequate. Are people comfortable with that?

10 (Affirmative responses.)

11 DR. GARBER: Okay. All right.

12 Now, we have a -- our big-three question,
13 which is now the same technology -- or not the same
14 technology -- it's unilateral thalamic DBS for a
15 central tremor and/or Parkinsonian tremor for a
16 well-defined set of Medicare patients with
17 Parkinson's disease. Does anybody want to make a
18 motion with regard to this question?

19 DR. ZENDLE: Can you clarify? That
20 obviously wasn't part of the BlueCross/BlueShield
21 TEC assessment, correct? That wasn't addressed in
22 the BlueCross TEC assessment. So where is it
23 addressed?

24 DR. RATHMELL: Have we had any -- and
25 we've had no testimony. Although there was an in-

1 house analysis distributed to us --

2 (Inaudible colloquy.)

3 DR. GARBER: Yeah. Perry?

4 MR. BRIDGER: I'll comment on that
5 question. The representatives from Medtronic
6 presented data to you, as well as Dr. Witten,
7 related to the initial study about the unilateral
8 indications.

9 In addition, because the TEC assessment
10 did not address the unilateral, we did a separate
11 analysis of the unilateral evidence by using
12 standard search methodology and generated a study
13 descriptions table, which you all received in your
14 packet, that outlined the findings of all of those
15 studies as well as with some commentary after that.

16 So, in terms of the kind of evidence that
17 you've received for the unilateral indications,
18 although you don't have a formal technology
19 assessment, you received those descriptions table as
20 well as all of the articles and then the Medtronic
21 and FDA presentation of that original data.

22 DR. LITVAN: And the evidence seemed to be
23 that there is a clear benefit, and there was a
24 reduced -- a reduction from almost -- from four to
25 almost one in tremors.

1 DR. BURCHEIL: Can I say that the area of
2 confusion here is we don't have a nice, clear-cut
3 TEC assessment to go to and say, "This is what" --

4 DR. LITVAN: Oh, all right, but --

5 DR. BURCHEIL: But I -- we've heard --
6 we've heard references to the FDA, to BlueCross's
7 prior assessment and also to current practice. I
8 think Roy touched on that a little bit.

9 It's -- this is a dramatic effect. It --
10 in every way, it's at least as good as what we see
11 with this other. And a very separate group of
12 patients. I mean, we're treating tremor with VIM
13 stimulation. We're not treating the cardinal
14 symptoms of Parkinson's disease --

15 DR. LITVAN: Right.

16 DR. BURCHEIL: -- other than tremor. And
17 we're also treating this other population of
18 patients, which are essential tremor patients, which
19 is, by some estimates, five to ten times more common
20 than Parkinson's, so a huge impact on the Medicare
21 population. And these patients are in that --
22 clearly in that age range. And so it's a little --

23 Hope we don't miss the point here. This
24 is a huge effect. It -- the benefit is absolutely
25 clear cut. And I'm sorry we don't have that

1 assessment to go to, but I can attest, as a
2 practitioner, again, this is not a subtlety. This
3 is a --

4 And this has been well digested by the
5 movement-disorder field now, so much so that it's --
6 I think we're almost going back to this now because
7 it never was touched on before, and it's been sort
8 of lumped in to this discussion.

9 DR. GARBER: Jim and then Les.

10 DR. RATHMELL: So this is what I -- during
11 our teleconference, was one of my principal
12 discomforts here is that we had no summary of it,
13 although we could have gone through individual --
14 you know, each of the studies were elucidated in the
15 table. You had to really go and look at each one of
16 those and then come up with your own reasonable
17 summary. And your testimony is the strongest thing
18 that I've heard. I came away with, "I don't know,
19 but maybe the evidence isn't there."

20 DR. LITVAN: No, the --

21 DR. RATHMELL: It certainly hasn't been
22 summarized for us in any understandable way.

23 DR. BURCHEIL: I think it's a process
24 issue more than anything else. I think we backed
25 into this, because it never -- this panel didn't

1 exist when this technology was approved -- or it was
2 just in its very earliest days when it was approved
3 by FDA. And that's the way things used to be done.
4 And because it's DBS, because it's deep-brain
5 stimulation, because it's movement disorders, it's
6 being annealed to his discussion, but it really is,
7 to some extent, a separate issue and -- but one,
8 again, that's been very clearly documented in the
9 literature.

10 And I think, again, as a -- just as a
11 testimonial, you might look at the data. It's
12 better than the data that we have for STN and GPi.
13 And there's a nice study, for example, in the New
14 England Journal comparing it to ablative procedures,
15 like thalamotomy. We have more data for DBS for
16 tremor than we do for GPi/STN.

17 DR. ZENDLE: So you're familiar with the
18 process. How would you go about, as a non-
19 specialist who's coming -- you know, the data is put
20 before you a few weeks before this, and we don't
21 have the data, yet we have to vote on whether we
22 have enough data to make this assessment. How would
23 you go about -- you know, we're here where we are.
24 How would you move from --

25 DR. RATHMELL: Trust me.

1 (Laughter.)

2 DR. ZENDLE: Can you clarify? Because it
3 appears to me that this is being promoted as being
4 effective for suppression of tremor associated with
5 either essential tremor or Parkinson's disease. Is
6 that --

7 DR. RATHMELL: Correct.

8 DR. ZENDLE: -- true?

9 DR. GARBER: And that corresponds to
10 what's been studied in the literature.

11 I actually -- I've got to say, I think
12 Jim's criticisms are really good points. And when I
13 received this, I was part of the
14 BlueCross/BlueShield Medical Advisory Panel -- I
15 think you were, too, Les, at the time --

16 DR. ZENDLE: Oh, two years ago.

17 DR. GARBER: -- yeah, when -- when we went
18 over unilateral -- and the evidence was pretty
19 compelling that it was effective, and it was similar
20 to the evidence that you see for bilateral. And,
21 you know, I -- so I didn't bother looking over all
22 the articles again, and I know we all had the
23 opportunity to do it, if we really wanted to, but --
24 but, I mean, basically, I think it's --
25 procedurally, this was not ideal.

1 But in terms of the substance, the
2 evidence base was very similar. I mean, you can
3 poke at the studies -- and this one thing where
4 having a report -- an evidence report like we had
5 for the other indications would be helpful, because
6 you don't really know, without going through the
7 studies, what their selection criteria were -- in
8 great detail, although that was in the table. But
9 study design flaws and so on, it's hard to get a
10 sense for that.

11 But I can tell you that my recollection,
12 having gone through this earlier, is that the
13 evidence is very similar. It was pretty much
14 equally compelling. And the effects, I thought,
15 were, in broad terms, similar. So I didn't see this
16 as very different. But I have to admit, it was
17 based on evidence that we weren't presented with. I
18 did have an evidence report available. And perhaps
19 it would be better if everyone had had that evidence
20 report, or a newly prepared one.

21 DR. SATYA-MURTI: I also agree this is an
22 older surgery, but I'd like to add this applies only
23 to ventralis intermedius. So I think thalamus is
24 too broad, and it received multiple inputs --
25 somatosensory and so forth. So this needs to be --

1 data is there -- data are there, but it's only for
2 VIM.

3 I'd like to ask the other panel members if
4 they agree, instead of just saying broadly thalamus,
5 which is huge compared to subthalamic region we are
6 talking about, and as multiple representations.

7 DR. BURCHEIL: As Roy said, that's the
8 target. I don't think anybody would disagree with
9 that.

10 DR. LITVAN: Yeah.

11 DR. SATYA-MURTI: So we should make this
12 -- (inaudible) --

13 MALE VOICE: Should we change the
14 language, then?

15 DR. SATYA-MURTI: Well, you should be more
16 specific. I think VIM is the most specific language
17 -- ventralis intermedius, or VIM, and that's the one
18 we had data on. And it even precedes STN and GPi.

19 DR. GARBER: Well, this would be a good
20 time for a motion to -- we don't have any motion on
21 the floor right now, do we? No, we don't. So if
22 you have a motion with specific language, that would
23 -- this would be an appropriate time.

24 DR. BURCHEIL: There's another -- one
25 other issue, before amendments --

1 DR. GARBER: Uh-huh.

2 DR. BURCHEIL: Just one other thing I'd
3 like to bring up, which was -- and I don't want to
4 open up a can of worms here, but the -- I noticed in
5 an ANS/CNS statement, they caught something that I
6 caught in the BlueCross assessment, which was,
7 effectively, that bilateral stimulation of the
8 thalamus for tremor is not done because of untoward
9 effects on oral pharyngeal musculature, dysphasia,
10 dysarthria.

11 I can tell you, that couldn't be more
12 wrong. It's done all the time, and quite
13 effectively, and there is literature on this.

14 So, again, this -- we're going to pin
15 ourselves down to unilateral thalamic DBS, which is
16 what the FDA approval is for. We're really not
17 hitting what is the actual practice today, which is
18 bilateral stem. And, frankly, most patients that
19 get this technology -- and I'd ask Roy or anybody
20 else here that does this to comment on that -- or
21 Ken.

22 DR. FOLLETT: Yeah, I would second that
23 very strongly. I think it does some of our patients
24 a real disservice to restrict this by language to
25 unilateral applications. There are many patients

1 who undergo bilateral implantation of thalamic
2 stimulation leads for treatment of bilateral tremor,
3 and they do very well.

4 DR. GARBER: But do we have evidence? Do
5 we have a complete assembly of evidence on
6 bilateral?

7 DR. LITVAN: The problem, I think, is
8 because of the history of bilateral thalamic lesion
9 that caused a lot of side effects that this is not
10 placed there and there are no studies to support it.

11 DR. BURCHEIL: Well, no, that's true.
12 Actually, there are studies that are -- do
13 incorporate substantial numbers of bilateral
14 stimulation, though, but we don't -- (inaudible) --
15 hasn't seen that, and there has not been a specific
16 technology assessment on that question, because it's
17 not -- it's not been officially approved by FDA.

18 DR. GARBER: You see, one of the things to
19 keep in mind is that if we haven't seen the
20 evidence, it would be hard to vote affirmatively for
21 this with broader language. And if we voted for it
22 -- that this statement is true for unilateral, it
23 doesn't say that bilateral is not effective or that
24 there's not evidence. It just says we didn't
25 address that question.

1 Tom, you had your hand up?

2 DR. HOLOHAN: Yeah, I don't want to sound
3 too legalistic, but if we include bilateral, what
4 we're basically doing is informing Medicare of our
5 endorsement of an unlabeled use of an approved
6 device. Now, Medicare has held, for a long time,
7 that device approval for labeled indications is a
8 necessary, but not a sufficient, condition for
9 coverage. And we'd be doing that in this
10 circumstance where we do not have the body of
11 evidence presented to all of the members of this
12 panel, as we have for DBS, for STN, and GPi. And I
13 think that could put CMS in a very, very, very
14 awkward position.

15 In the past, they have covered an
16 unlabeled use of an approved device only in the
17 presence of substantial -- one might argue,
18 overwhelming -- evidence that that was appropriate
19 treatment. And we're kind of pushing the envelope
20 there, where most of the people -- I don't
21 disbelieve our experts, but most of the panel
22 members have not seen that evidence for even
23 unilateral.

24 DR. GARBER: Okay. Well, thank you. We
25 still don't have a motion on the floor.

1 DR. SIGSBEE: I'd like to make a motion.

2 DR. GARBER: Okay, Bruce?

3 DR. SIGSBEE: I'd like to make a motion
4 that the -- that it is substantially more effective,
5 with the same language that we've used before, than
6 alternatives.

7 DR. GARBER: Well, we first have to -- we
8 haven't -- we first have to address evidence
9 adequacy on this one. We haven't voted on that yet.
10 And we don't even have a motion on it.

11 DR. SIGSBEE: Well, I would like to make a
12 motion that the evidence is adequate to determine
13 that it is an effective therapy for central tremor
14 and/or Parkinsonian tremor.

15 And I'd like to point out the Medtronic
16 data. If I remember, the number was roughly -- it
17 was for Parkinsonian tremor, it was -- the score of
18 approximately 3.8 out of four to one, which, if you
19 know -- if tremors -- this is a dramatic difference
20 for somebody who is dysfunctional, versus very
21 functional. And while not quite the same shift for
22 essential tremor, a very similar one for central
23 tremor. And, again, that's probably where the major
24 use is here. And, again, it's somebody who's failed
25 medical therapy and is responding to this. And our

1 medical therapies for a central tremor are somewhat
2 limited.

3 DR. GARBER: All right. There was an
4 earlier discussion about whether we wanted language
5 as broad as "unilateral thalamic."

6 DR. BURCHEIL: Yeah, a friendly amendment
7 to change that language as to "unilateral" -

8 MALE VOICE: Subthalamic?

9 DR. BURCHEIL: -- no -- "thalamic,
10 parenthesis, ventralis intermedius, or VIM, end
11 parenthesis, DBS. So qualify thalamic as ventralis
12 intermedius.

13 DR. GARBER: Would you accept that as a --

14 DR. SIGSBEE: I agree, absolutely, yes.

15 DR. GARBER: Okay. So I'll take that as a
16 motion and a second.

17 MALE VOICE: Does the word "unilateral" or
18 "bilateral" or neither appear in the motion?

19 DR. GARBER: This was unilateral.

20 MALE VOICE: The motion was --

21 DR. SIGSBEE: Unilateral.

22 DR. GARBER: Unilateral.

23 DR. SIGSBEE: That's all we have the
24 evidence for.

25 MALE VOICE: Okay.

1 DR. GARBER: Okay. Discussion?

2 DR. ZENDLE: Point of information?

3 DR. GARBER: Yes?

4 DR. ZENDLE: What are the consequences of
5 us saying that we haven't really been presented this
6 evidence and basically making no -- seeing no
7 opinion on this? In other words, is there enough
8 information from the -- answering the two previous
9 questions that allows CMS to make their coverage
10 determination on unilateral DBS?

11 MR. BRIDGER: Dr. Garber, may I make a
12 comment?

13 DR. GARBER: Yes.

14 MR. BRIDGER: I just wanted to point out
15 some issues with the thalamic, or VIM, data. The
16 Medtronic approval data was based entirely on
17 unilateral procedures. The data that's presented in
18 the study descriptions that we prepared for you was
19 not -- we did not search for unilateral or
20 bilateral. So you'll see that the majority of those
21 studies have patients that underwent bilateral VIM.
22 It's hard -- I didn't break -- we didn't break down
23 specifically the numbers, unilateral versus
24 bilateral, but I think it's probably 60-40,
25 unilateral versus bilateral, maybe 70-30.

1 Maybe one suggestion that I could make
2 would be that you could consider the question, as
3 written, but then, either with a motion or
4 discussion, potentially discuss the fact that the
5 bilateral VIM data doesn't seem adequate to make a
6 determination or is not adequate for us to comment
7 on at this point.

8 DR. SATYA-MURTI: If I may, I'd like to
9 point out what happens, in practice. Usually, the
10 contralateral side to the dominant side is done as
11 unilateral, and the patient responds so well he or
12 she seeks the other side. So it's often done -- I
13 don't know if it's often, but it's -- I know, for a
14 fact, instances where it's done bilateral, but in a
15 staged setting. So would that be unilateral or
16 bilateral? Because it's unilateral at one time, and
17 -- (inaudible) -- with the requirements, but then it
18 is bilateral eventually.

19 DR. HOLOHAN: Sequential unilateral?

20 MR. BRIDGER: Yes, that's right.

21 DR. HOLOHAN: And that's very difficult to
22 pick up in the literature, because
23 in -- typically, it was not reported in the studies
24 whether the procedures were done at the same time or
25 whether they were sequential.

1 DR. SATYA-MURTI: Yeah, simultaneous or
2 staged. So to avoid that, I put down that
3 simultaneous is not as warranted or as desirable as
4 staged bilateral.

5 DR. GARBER: Well, in terms of how we
6 should proceed, right now we have a motion and a
7 second on a modified version of this specific
8 question on the unilateral. And the minutes will
9 reflect this discussion that we didn't have evidence
10 on sequential bilateral versus simultaneous
11 bilateral, or bilateral in any form, specifically
12 broken up on this question. People have already
13 made those questions. So, Perry, does that meet the
14 needs of CMS?

15 MR. BRIDGER: CMS has not limited in its
16 coverage to only things that this panel discusses,
17 or -- (inaudible). So the fact that we did not
18 present you evidence on bilateral doesn't prevent
19 you from giving us some suggestion that there might
20 be evidence for bilateral. It's not something that
21 you would vote on, since it's not a vote in
22 question, but we certainly will take that
23 information and could make a coverage decision that
24 included bilateral thalamic if we did our own
25 evidence search and found it.

1 DR. GARBER: Well, I guess -- at least I
2 don't feel comfortable using our process to discuss
3 a question where we haven't been presented with data
4 in any formal sense. And I guess, you know, we can
5 have our discussion of that, but it's a little
6 different from addressing the questions where we've
7 been given a lot of information.

8 We have a motion and a second. Is there
9 any further discussion on the motion on the floor?

10 Okay, all in favor, say aye.

11 (A chorus of ayes.)

12 DR. GARBER: Opposed?

13 (No response.)

14 DR. RATHMELL: Abstain.

15 DR. ZENDLE: Abstain.

16 DR. GARBER: One abstention.

17 DR. ZENLDE: Two.

18 DR. GARBER: Two abstentions.

19 MS. ATKINSON: For the third question, "Is
20 the evidence adequate to determine the clinical
21 effectiveness of unilateral thalamic DBS for
22 essential and/or Parkinsonian tremor for a well-
23 defined set of Medicare patients with Parkinson's
24 disease," two abstentions, and four fors.

25 DR. GARBER: And could I ask, for the

1 record, the people who abstained?

2 DR. ZENDLE: I abstained because I don't
3 feel, as a non-neurologist, that I have enough
4 information to say that there is adequate evidence,
5 because it wasn't all presented and analyzed for us
6 this time.

7 DR. RATHMELL: Yeah, mine exactly. I
8 mean, I respect the testimony that's been given here
9 on the floor, but, in terms of advanced preparation,
10 we were just given the studies individually to
11 synthesize on our own, and that's contrary to what
12 we're usually given.

13 DR. GARBER: Right. Okay, thank you.

14 Now, we --

15 DR. HOLOHAN: Do you want explanations for
16 the yes votes, or --

17 DR. GARBER: Okay, yeah. Go ahead, Tom.

18 DR. HOLOHAN: I supported it mainly
19 because I read through, painfully, the extra studies
20 submitted by Medicare on unilateral -- or labeled as
21 unilateral stimulation, which, in fact, were, as
22 described, a mixture of unilateral and bilateral.
23 And I thought the evidence was reasonable, that it
24 was effective and supported by the FDA's approval of
25 the device for that indication.

1 DR. GARBER: Yeah, if I might just make a
2 little comment here, I think it will be very helpful
3 to us, whenever CMS wants us to look at any
4 subgroup, either defined by the treatment or the
5 population, that it's helpful to have the data
6 broken out according to those subgroups, and, if
7 they can't do it, to have a statement that it wasn't
8 possible to do so we have this done in very clear
9 terms. It's very confusing otherwise. You have to
10 dig through and realize, as Tom did, that there's
11 actually a mixture. So, in general, I think we can
12 give better guidance to CMS if we get the data
13 packaged in a way that enables us to make those
14 distinctions.

15 Okay, so we, next, are asked to consider
16 the size of the overall health effect. And I think
17 we already heard one statement about it. But any
18 discussion or a motion with regard to the size of
19 the overall health effect?

20 DR. BURCHEIL: I would move --

21 DR. GARBER: Is this a suggestion?

22 DR. BURCHEIL: -- I would move that this
23 be placed in the same category, that it's
24 substantially more effective.

25 DR. HOLOHAN: Second.

1 DR. GARBER: Okay. Any discussion? All
2 in favor?

3 (A show of hands by Dr. McBryde, Dr.
4 Sigsbee, Dr. Burchell and Dr. Holohan.)

5 DR. GARBER: Opposed?

6 (No response.)

7 DR. GARBER: I guess -- we may need to
8 know. I'm not sure we know.

9 DR. ZENDLE: Two abstained.

10 DR. GARBER: Two abstentions, again?
11 Okay, well, that makes sense.

12 MS. SAMUELSON: I would like to, for the
13 record, just echo what you said about -- about
14 recommendations on providing the data in a clear
15 form, because my impression is this will have an
16 important and negative effect on the patient
17 population and the much larger patient population
18 with essential tremor because of the extra cost and
19 risk and simply the physical burden of two
20 surgeries.

21 DR. GARBER: Thank you.

22 We have three discussion questions. I
23 think we've implicitly discussed a good bit of one
24 and two, and we've had a lot of discussion, but no
25 conclusion, about the third. And would it be

1 appropriate, Perry and Steve, if we went to the
2 third about who should -- this is basically about
3 who should be considered qualified to carry out the
4 procedure. Is that where -- (inaudible) -- at this
5 point?

6 DR. ZENDLE: Does CMS really need that
7 guidance?

8 DR. PHURROUGH: We'd like guidance in all
9 three. The --

10 DR. GARBER: Okay. We can take them in
11 order.

12 DR. ZENDLE: Have we received enough, is
13 the question, in the discussion already?

14 DR. PHURROUGH: Um --

15 DR. ZENDLE: Because we're not going to
16 vote on these.

17 DR. PHURROUGH: Actually, we've had
18 significant discussion on one and three.

19 DR. GARBER: Well, the issue in number two
20 -- and this did come up a little bit on the phone
21 conversation as -- it's kind of difficult to answer.
22 If you take the whole body of evidence, it's hard to
23 know what you mean by "closely matching the
24 patient," because the -- and I think this is part of
25 the sense of the discussion. We had fairly diverse

1 patient populations included in the study, so the
2 question would be, Who might be a candidate who was
3 not represented in the studies?

4 DR. LITVAN: I think that there -- in most
5 of the studies, they use the same criteria. That is
6 basically what it was -- has been said here -- that
7 is, patients that do have Parkinson's disease,
8 according to current criteria, that have failed
9 medical treatment but still have some benefit from
10 levodopa therapy, and they don't have other
11 contraindications, they don't have dementia. And I
12 think -- et cetera -- all these are in the
13 literature -- I mean, in every study that you see.
14 And I think that that would be the patient
15 population that this should be indicated.

16 DR. GARBER: I guess maybe -- then that --
17 a contrary would be someone who has not failed
18 medical therapy. They are not represented. And
19 does the panel want to address that group of
20 patients? That's the sort of thing you have in --

21 DR. BURCHEIL: Can you generalize this
22 outside the conclusion criteria, which, as Dr.
23 Litvan said, is fairly consistent --

24 DR. GARBER: Right.

25 DR. BURCHEIL: -- among all the studies.

1 DR. GARBER: And we did hear a little bit
2 already from the panel on that question. But does
3 anybody want to make statement about that?

4 DR. LITVAN: Well, I think that you
5 cannot, because that -- for that, we don't have any
6 evidence. And what we have is that there are --
7 there are no good responses. I mean, if you include
8 patients that are demented, or if you include
9 patients that have other diseases, or if -- you
10 know, if you start opening this up to a different
11 patient population than the one that really has been
12 giving us the evidence.

13 DR. BURCHEIL: Not only don't we have
14 evidence, but it's not likely we're going to get
15 that kind of evidence. I mean, even the new study
16 coming up is going to take patients in at a
17 medically intractable level. So --

18 DR. GARBER: I think you have a fairly
19 consistent set of comments here from the panel on
20 that question.

21 DR. BURCHEIL: So on the flip side of
22 that, if -- what happens to that group of patients
23 that may benefit? That if we say, yeah, we favor
24 you, sticking close to the characteristics, and if
25 they then limit it to exactly those criteria,

1 they're going to --

2 DR. GARBER: I think the question was
3 whether there would be --

4 DR. LITVAN: Well, one thing is
5 indications, another thing is characteristics. For
6 example, characteristics is that the age group was a
7 little bit -- you know, there was a problem with the
8 age group at surgery. And that's not exactly what
9 we're saying. There is -- what we're saying is that
10 the age group is larger than just those that have
11 been indicated. But, on the other hand, the
12 diagnosis has to be restricted, and there has to be
13 no other complications and things like that. So
14 it's not exactly close to in every respect.

15 DR. RATHMELL: Yeah, I hear what you're
16 saying, but the problem is they're going to have to
17 take this and make a list of criteria, and they'll
18 say, well, age, no, the panel didn't think -- but,
19 in terms of response to levodopa, that was very
20 important. So how do they make the distinction
21 between one and the other?

22 DR. BURCHEIL: I think this is one of
23 those things that has hit a pretty good consensus
24 now, that most of the local carriers have a --
25 (inaudible) -- about three or four -- I mean, you

1 know, Parkinson's disease, previously levodopa-
2 responsive, now medically intractable by the
3 definition, which may vary, but probably, ideally,
4 should be an accomplished center, and not demented
5 to the point of nonfunctionality. And I don't know
6 if -- there's no hard number been assigned to that.

7 So, I mean, those are the entry criteria,
8 and I thought the question was whether patients
9 could be taken earlier than that. And that -- we
10 sort of touched on that issue. A patient who says,
11 "You know what? I don't want to take those drugs.
12 I just want to go right to the stimulator," you
13 know, as soon as they developed their first tremor.
14 And I don't -- I think that we have -- we are -- we
15 don't have evidence on that, and we're not likely
16 going to get evidence on that in the near future.

17 DR. RATHMELL: And we're comfortable
18 interpreting the inclusion criteria of the articles
19 and your recommendation that we don't generalize it
20 outside those inclusion criteria.

21 DR. SATYA-MURTI: Most carriers have a set
22 of inclusion criteria based on one publication or
23 another, many referring on the New England Journal.
24 You could, again, gather them together or task it to
25 some of the carriers to put together.

1 And one other criterion we require is that
2 there not be a focal lesion identified by imaging
3 studies. In other words, if there was a lacunar
4 infarct in the region where the stimulation was
5 going to take place, then we don't know what the
6 effect would be. So there are common criterion, and
7 they're very comparable among all carriers now
8 permitting -- (inaudible).

9 DR. PHURROUGH: There's a part of Question
10 1 that I don't believe we've touched on today that
11 I'd like to discuss just briefly. Most of the
12 studies talked about patients who had early-onset
13 Parkinson's disease. And is there a difference in
14 patients who have early-onset Parkinson's, versus
15 those who have late-onset Parkinson's? And would
16 DBS be used differently in those two different
17 population groups?

18 DR. BURCHEIL: I've always found onset
19 identification to be very difficult. That's just
20 the age question turned around.

21 DR. SATYA-MURTI: No, it's not really how
22 old you are. It's how old you are when you get the
23 disease. It's not when you -- (inaudible).

24 DR. BURCHEIL: Right. It's the length of
25 disease. And advance -- treatment -- you know, the

1 stage of the disease.

2 DR. PHURROUGH: And obviously, there isn't
3 evidence, but it -- using you as a group of expert
4 panelists, is there any way to differentiate that
5 group or treat them identically?

6 DR. LITVAN: No, the treatment would be
7 the same. I think it's a question of age, the
8 amount of time to get to surgery, and that's -- and
9 still be below age 75.

10 DR. GARBER: I guess, Steve, is your
11 question -- it's really -- granted that there's no
12 direct evidence on the question, or inadequate
13 direct evidence -- what should our presumption be,
14 that there is or is not a difference? And I might
15 add that's after controlling for other clinical
16 characteristics, like the severity of the disease
17 and whether they had responded to medications. Is
18 that what this statement's getting at?

19 DR. PHURROUGH: Yes.

20 DR. GARBER: So is there -- should there
21 be a presumption that it will be equally effective,
22 knowing that there isn't direct -- or is there a
23 presumption that it's also effective knowing that
24 there's not direct data on the point?

25 Tom?

1 DR. HOLOHAN: Is there any evidence that
2 drug-therapy effectiveness differs according to
3 early- or late-onset Parkinson's disease? I'm -- we
4 have a whole bunch of neurologists here, I'm --

5 DR. PHURROUGH: That's the main purpose
6 for the questions, because we had a whole bunch of
7 neurologists.

8 DR. LITVAN: There is no evidence. And
9 there is no evidence --

10 DR. PHURROUGH: So if --

11 DR. LITVAN: -- it is -- we're talking
12 about --

13 (Inaudible colloquy.)

14 DR. HOLOHAN: I don't think we can answer
15 the question. You could turn it around and say
16 there is no compelling evidence against generalizing
17 the benefit to late onset versus early onset.

18 DR. GARBER: Yeah, I think that -- Steve,
19 one of the issues here is -- at least with the
20 surgery -- with the DBS for the elderly versus the
21 young -- we had inadequate evidence, yet it raised
22 some red flags, okay, and I think one question is,
23 are there any red flags, or is there just no reason
24 at all to think there's a difference between early
25 and late onset, in terms of response?

1 Dr. Montgomery?

2 DR. MONTGOMERY: I'm sorry. Actually, a
3 few years ago, Joe Jankovic did the study where he
4 looked at early onset versus late onset and did find
5 some mild differences in terms of the percentage
6 that have tremor and the percentage that have
7 postural gait instability and dementia. And the
8 results were -- they were statistically significant,
9 but huge overlap.

10 We subsequently did a longitudinal
11 prospective study at the University of Arizona
12 looking at age of onset in terms of symptomatology,
13 responsiveness to medication, and really found no
14 significant difference in early onset versus late
15 onset. The big issue was the duration of the
16 disease, per se. And I think -- so I think that
17 there really is no significant difference in terms
18 of the responsiveness to therapies.

19 DR. GARBER: You know, the thing to always
20 keep in mind is, Does this add independent
21 information, as compared with all the other clinical
22 characteristics that you have? And that may be
23 what's critical here, perhaps, how severe it is at
24 the time that you're considering the treatment.

25 So is that enough of a --

1 DR. PHURROUGH: I think so.

2 DR. GARBER: Okay. So I would like to
3 return, though, to the provider criteria. And I had
4 the sense that we actually had -- there were several
5 themes that came up repeatedly in our earlier
6 questioning, and this is something that people are
7 very interested in, obviously, because we jumped
8 right into it, and that included having a
9 multidisciplinary team, some amount of experience on
10 the part of the neurosurgeon, but also it sounded
11 like having experienced neurophysiologists,
12 electrophysiologists, and so on.

13 So I guess the issue is, How detailed
14 should we be in providing guidance about this? And
15 what more can we say on the issue?

16 DR. WEINER: To go back to what was said
17 earlier, I think that this part of it should be as
18 nonspecific as possible because of the rapid
19 evolution that's going on in the field. And if one
20 wanted to say some words about the neurosurgeon and
21 the neurologist, that would be fine, but -- I mean,
22 it's conceivable in a few years electrophysiology
23 might be replaced by another technique that is
24 better than that. So I think we have to be careful
25 about being very specific about beyond the team

1 members, the neurologists, and the neurosurgeon.

2 DR. GARBER: Well, you know --

3 DR. LITVAN: It has to be --

4 DR. GARBER: -- I have to point out one
5 thing here, which is that when we look at
6 procedures, the -- one of the issues in whether you
7 have to have a highly specialized facility is how
8 dangerous it is. And I must say, although people
9 have said that this actually a fairly safe
10 procedure, the numbers suggest it's not a very safe
11 procedure in the sense that there's a high rate of
12 fairly serious side effects in at least some of the
13 studies. It may be fair to say, however -- and I
14 believe this is really true -- that the risks are
15 very acceptable in relation to the benefits.

16 But when you have something that's got
17 substantial risk with something like hemiplegia and
18 hemiparesis, that's when you start to say, well, we
19 really should look into making sure it's done in
20 places that have low complication rates. So I think
21 that's part of the motivation for not being truly
22 laissez faire about who should do the procedure.
23 I'm sure that's part of CMS's concern.

24 I think -- maybe we should just go around
25 the table, since there's so many hands up.

1 Bruce?

2 DR. SIGSBEE: Again, I think we have to be
3 careful, because the other side of this is access.
4 And that, for institutions who may legitimately want
5 to get started, they're not going to have a track
6 record. And if you require a track record before
7 you will pay for it, you may preclude medical
8 beneficiaries from having adequate access.

9 So there's the flip side to this, and I
10 think you have to be very careful about who does
11 this, but there also is a role for physicians making
12 reasonable judgments, and I think Dr. Montgomery is
13 right, is that the large majority of physicians make
14 good judgments about what they can and can't do or
15 should and shouldn't do. There's a few --
16 (inaudible), but not very many. And how can you put
17 quality into a regulation? I think it's a little
18 bit hard.

19 DR. GARBER: Kim?

20 DR. BURCHIEL: It's kind of hard not to be
21 -- not to at least acknowledge what's been said,
22 that this is a difficult procedure. It goes beyond
23 the usual training of a neurosurgeon and I -- and,
24 frankly, most neurologists. It's -- it requires a
25 specialized team.

1 I think somehow, either at the level of
2 CMS or the local carriers, there are going to have
3 to be criteria for what defines a center, because
4 I'm, personally, very nervous about the idea of this
5 proliferating into centers that do a few of these a
6 year, in which case the surgical techniques won't be
7 as well worked out, and the experience won't be
8 there, and there's a -- and we're basically living
9 in a perpetual learning curve.

10 And the other thing that we find with this
11 procedure is, if the technique is difficult, the
12 follow-up is more difficult. It requires a huge
13 amount of effort by medical practitioners,
14 physicians, nurse practitioners, and others, because
15 the outcome ultimately on this may make -- may have
16 more to do with how closely these patients are
17 followed and adjusted than they do exactly where the
18 electrode is in the subthalamic nucleus.

19 So I do think we can't be mute on this. I
20 think CMS needs to think about some criteria for
21 training and experience.

22 DR. GARBER: Phyllis?

23 DR. GREENBERGER: I was wondering if any
24 of the local carriers had certain requirements, and
25 whether there's been any comparison within the

1 states and outcomes to know whether, in fact, those
2 were realistic and necessary?

3 DR. SATYA-MURTI: I can address some of
4 that. The local carriers -- we do ask for criteria
5 along these lines, that there ought to be previous
6 experience. And other medical directors call me and
7 ask -- either they duplicate the same language or,
8 as I said, the majority of the person -- the
9 neurologists and neurosurgeons, their time should be
10 devoted to performing this type of surgery or this
11 type of evaluation. I haven't put down any
12 percentage. So that seems to be one de facto way of
13 making sure that this does happen in the right
14 hands.

15 And the second would be that, for those
16 new centers Dr. Sigsbee mentioned, I have often
17 advised that it need not be, from day one, that the
18 new center person has to have experience, but if you
19 retro-activate that and say that they ought to have
20 performed 12 of 15 or 20 within the past two years,
21 this would enable those who have taken the training
22 and taken a year to establish the program.

23 So, in practice, if you leave it at the
24 carrier level, there are ways of getting around it,
25 and if you so authorize the carriers to do so. So

1 we have ways of survival.

2 DR. GARBER: Tom?

3 DR. HOLOHAN: You know, actually, this
4 really isn't new for CMS, formerly, when they were
5 wearing their HCFA uniforms. The same process was
6 used for approval of centers to do liver
7 transplantation. Medicare put together an outside
8 board of experts whose only job was to develop
9 appropriate criteria for them. And a similar
10 approach was followed -- I don't know if this was in
11 the coverage manual or not, but, when they covered
12 carotid endartorectomy, it was approved for use in
13 centers that had less than 3.1 percent mortality
14 rate for that procedure, which is -- appears, from
15 the literature, to be the cutoff for risk and
16 benefit. So --

17 DR. SATYA-MURTI: There is precedence,
18 yeah.

19 DR. HOLOHAN: Right, I -- I think,
20 certainly -- the only question we're asked is,
21 Should there be criteria to perform DBS? And I --
22 I'm getting the impression it's the general view of
23 the panel that, yes, there should be criteria. I
24 realize everybody has to do something the first
25 time, but low volumes of technically demanding

1 procedures are generally not a good thing.

2 And there was a comment -- a question, I
3 think, to Medtronic about marketing. I think Dr.
4 Zendle raised that question. Oh, I'm sorry -- Dr.
5 Sigsbee.

6 Back when Medicare was debating covering
7 laparoscopic surgery, there were organizations that
8 gave certificates of proficiency in laparoscopic
9 surgery to surgeons who attended a video course.
10 These people could then take this back to their
11 hospital credentialing committee -- privileging
12 committee, and get privileges to do laparoscopic
13 surgery. And I'm not implying that this would
14 happen here, but it has happened in the past.

15 DR. GARBER: Ken?

16 DR. BURCHIEL: Well, actually, Kim made
17 most of my comments, so I'll keep this brief, but I
18 think we do need some general guidelines. We talked
19 a lot about qualifications as a surgeon -- number of
20 implants, for example -- but, as Kim pointed out,
21 the surgical technique is only one side of this
22 triangle that I view this process as. There's
23 patient selection as one side, surgical technique as
24 a second, and then patient management after the
25 surgery as a third side. And just like you can't

1 have a triangle without three sides, you can't have
2 a good outcome with this technique without having
3 each of those three components.

4 Accordingly, I think it's important that
5 we look at qualifications of the implanting center,
6 which includes: Do they have the proper equipment,
7 the proper facilities? Do they have a qualified
8 neurologist? Do they have a qualified neurosurgeon?

9 I think what we need to strive toward
10 accomplishing is to reduce, or perhaps eliminate,
11 those centers or physicians who would dabble in this
12 therapy, kind of the casual implanter, the one who
13 does just a few or a handful each year. And we
14 should promote the idea of centers of excellence to
15 -- which we believe would promote good outcomes.
16 And realizing that access is important, we need to
17 give some leeway to get the new centers up and
18 running.

19 DR. LITVAN: Well, I fully agree with what
20 you said. I mean, all the points I was going to
21 make were made. The only thing I would add is that
22 I think that for new centers -- or even for those
23 established, too -- perhaps there could be some kind
24 of evaluation on a -- I don't know how you can do
25 that, but on the degree of -- on the outcome, in

1 fact. And if they have mortalities or paresis or
2 intracranial hemorrhage, whatever they do more than
3 the average amount on a year basis or every two
4 years or whatever.

5 DR. GARBER: Yes. Angus?

6 DR. MC BRYDE: Well, I was just going to
7 say, like so many things in the cardia area and
8 orthopedics, renal transplants, you've got to look
9 at the infrastructure. You look at the people that
10 are doing it. They need to be in depth. You've got
11 to have a neurologist trained, neurosurgeon trained,
12 you've got to have a hospital that's got a full-
13 service subspecialty availability, you've got to
14 have a radiology department that's got the in-depth
15 MRI 3-D capacity, not just for this, but available
16 in other areas. So it's in the infrastructure and
17 it's the team that you could look. You can do
18 pretty well with this, like you can with the early
19 days of cardiac bypass, whatever.

20 DR. SIGSBEE: Can I make a motion that the
21 answer to the question is yes?

22 (Laughter.)

23 DR. GARBER: Les?

24 DR. ZENDLE: Yeah, I agree with that. I
25 would just add one thing, though, and that's that

1 this is very consistent with the recommendations
2 from the Leapfrog Group, which is looking at the
3 volume of certain surgical procedures. It is
4 somewhat controversial in that there isn't always
5 good data as to what the number should be and what
6 the outcomes are, but I really think that as we
7 address the patient safety and quality issues in
8 this country, we need to move in that direction, and
9 I think CMS ought to be joining Leapfrog and the
10 other groups that are moving that direction.

11 DR. GARBER: Jim, did you have -- okay, I
12 don't think we need a formal vote on this.

13 DR. ZENDLE: Move we adjourn.

14 DR. GARBER: Yeah, we will entertain a
15 motion for adjournment.

16 Is there any other announcement? Steve,
17 did you want to make an announcement?

18 DR. PHURROUGH: Yeah, I just want to thank
19 the panel for their time, both the voting members
20 and the guests. This -- your recommendations will
21 be forwarded to the executive committee, and, at
22 present, that's scheduled to be --

23 DR. GARBER: July 17th.

24 DR. PHURROUGH: -- September 25th.

25 MS. GREENBERGER: Once it goes to the

1 executive committee, then, I'm assuming they vote
2 positively, how long does it take for it actually to
3 be, you know, an official coverage decision and --

4 DR. PHURROUGH: We will then write our
5 coverage decision after that meeting. We have a
6 maximum of 60 days, though I suspect it will not
7 take us that long. And then once we write our
8 coverage decision, then Medicare has to write
9 instructions. Those instructions are only released
10 once a quarter. So we're probably talking about
11 instructions to the contractors, carriers first of
12 the year.

13 MS. GREENBERGER: And then what happens in
14 terms of the termination of the level of
15 reimbursement?

16 DR. PHURROUGH: We don't get involved.
17 Since it's already performed now, I don't suspect
18 there's -- will be reimbursement issues. They'll be
19 reimbursed as they're being reimbursed now.

20 MS. GREENBERGER: I think it varies.

21 DR. PHURROUGH: If people think they're
22 being reimbursed well enough now, that's an entirely
23 separate issue that coverage doesn't get involved
24 in.

25 DR. GARBER: Before people vote with their

1 feet, I would entertain a motion so we could have a
2 formal vote on adjournment.

3 DR. ZENDLE: So moved.

4 DR. SIGSBEE: Second.

5 DR. GARBER: All in favor?

6 (Chorus of ayes.)

7 DR. GARBER: Thank you, everyone. Thank
8 you to the speakers and -- the public speakers and
9 our invited speakers. Thank you to the panel.

10 [Whereupon, at 12:25 p.m., the meeting was
11 adjourned.]