Transcript of October 18, 2000 Meeting

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SACRAL NERVE STIMULATION

FOR THE TREATMENT OF URINARY INCONTINENCE

HEALTH CARE FINANCING ADMINISTRATION
Medicare Coverage Advisory Committee
Medical and Surgical Procedures Panel

October 18, 2000

Baltimore Convention Center
Baltimore, Maryland

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P R O C E E D I N G S.

MS. CONRAD: Good morning. And welcome, panel chairperson, members, guests and temporary nonvoting members. I am Connie Conrad, executive secretary of the Medical and Surgical Procedures Panel of the Medicare Coverage Advisory Committee.

The panel is here today to provide advice an recommendations to the Agency regarding sacral nerve stimulation for the treatment of refractor urinary urge incontinence and refractory frequency syndrome.

At the conclusion of today's session, panel members will be asked to vote on a series of questions. The answers to those questions will constitute this panel's recommendation, which will be submitted to the Executive Committee. When the Executive Committee ratifies the recommendation, it will officially transmit that recommendation to HCFA.

HCFA will then develop a national coverage policy within 60 days of receipt of that recommendation.

For the purposes of today's panel, Dr. Adrian Oleck, medical director of the durable medical equipment regional carrier for Region B received an appointment, temporary nonvoting member status. Dr. Oleck's expertise will enhance this

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panel's deliberative process.

In addition, we welcome Dr. Eileen Helzner, industry representative to the medical devices and prosthetics panel, who also received an appointment to temporary nonvoting status.

The following announcement addresses conflict of address issues associated with this meeting and is made a part of the record to preclude even the appearance of impropriety. To determine if any conflict exists, the Agency reviewed the submitted agenda and all financial interests reported by panel participants. The conflict of interest statute prohibits special government employees from participating that could affect their or their employers' financial interests.

Les, would you make a brief statement for me please?

DR. ZENDLE: Yes. I wanted to let the panel know that I actually just discovered last night that Dr. Sharif Aboseif, who is the director of the neurology program at Kaiser Permanente Los Angeles, is participating in an IRB approved registry sponsored by Medtronic and is currently preparing a publication on the outcomes of patients who have undergone sacral nerve implantation.

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I have no knowledge of the results, and I and Kaiser Permanent have no financial interest in the outcome of the study.

MS. CONRAD: Thank you, Les.

The Agency has determined that all members and consultants may participate in the matters before the panel today. With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations

disclose any current or previous financial involvement with any firm whose product or services they may wish to comment on. Thank you.

Dr. Garber.

DR. GARBER: Welcome, everyone. Today I believe all the panel members have a copy of the questions that were in your blue portfolio. We are going to be looking at sacral nerve stimulation for two indications, refractory urge incontinence and refractory urgency frequency syndrome. I think that we will just proceed to ask Jennifer Doherty to present the questions.

MS. CONRAD: Jennifer?

MS. DOHERTY: Thank you and good morning, panel members. In the last panel meeting, you discussed pelvic floor stimulation and biofeedback.

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Today you will discuss the effectiveness of sacral nerve stimulation. Following the public comment period, Dr. Mitch Burken will more fully address the issues that I am about to talk about right now, and answer any questions that you should have.

As many of you know, urinary incontinence, otherwise known as UI, is a major problem in the United States. It affects approximately 13 million adults each year, and at least half of all nursing home residents. These individuals may experience a loss of self esteem and depression. These types of problems have an overall negative impact on quality of life. Unfortunately, there is a great deal of social stigma attached with incontinence, which is one reason why many sufferers do not seek medical attention for this problem. As a result, UI is both under reported an under diagnosed.

There are several treatment options for individuals affected by UI. Patients usually start with behavioral modifications such as bladder training. If that is ineffective, patients commonly move to pharmacologic treatments. Other options include surgical interventions, such as sacral nerve stimulation, otherwise known as SNS.

The sacral nerves are located near the

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sacrum, which is the large bone at the bottom of the spine. These nerves are important because they help to control bladder contractions. The sacral nerve stimulator is a pulse generator about the size of a pacemaker. It is implanted in the abdominal wall. A wire lead is then attached to the sacral nerves. Electric impulses are sent from the generator to the sacral nerves through the implanted wire. These impulses cause the nerve to contract, which gives the patient ability to void. Patients are given a preliminary test to determine if an implantable stimulator will be effective.

You have had the opportunity to review literature on sacral nerve stimulation. HCFA provided the following: Two Blue Cross/Blue Shield technology assessments, one on sacral nerve stimulation in urge incontinence, and the second on sacral nerve stimulation and urgency frequency syndrome. In addition, articles reflecting both clinical and nonclinical trials were provided.

The panel will review the scientific evidence, hear public comment and make recommendations to HCFA about the effectiveness of sacral nerve stimulation. More specifically, you will be asked to vote on two questions.

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Question number one: Is the scientific evidence adequate to draw conclusions about the effectiveness of sacral nerve stimulation in the Medicare population for the following two indications: Refractory urinary urge incontinence, and refractory urgency frequency syndrome.

Dr. Burken will later provide definitions of refractory urge incontinence and urgency frequency syndrome. In answering the question, please consider the following points: The adequacy of the study design; the consistency of results across studies; their applicability to the Medicare population; and their generalizability beyond the research setting. We ask you consider the whole spectrum of information presented, which includes expert testimony and public comments.

If the evidence is adequate to draw

conclusions about sacral nerve stimulation and the panel votes affirmatively on question one, the panel will move to question two, which addresses the size and direction of effectiveness. If the panel votes negatively on question one, please do not proceed to the second question.

Question two asks: If the evidence is adequate to draw conclusions, what is the size, if

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any, of the overall health effect of sacral nerve stimulation compared with alternative treatments for refractory cases? Please note that alternatives are typically other surgical options.

When answering the question, the panel will be asked to place the size and direction of effectiveness into one of the following seven categories: Breakthrough technology, more effective, as effective but with advantages, as effective and with no advantages, less effective but with advantages, less effective and with no advantages, or not effective.

Thank you for your time this morning, and we look forward to a productive meeting.

MS. CONRAD: Thank you, Jennifer.

Let's proceed with the public presentations. The first speaker on the list is John Brizzolara, followed by Jeffrey Welgoss.

DR. BRIZZOLARA: Good morning, panel members. I want to thank the committee for giving me the opportunity to speak with you about my experience with sacral nerve stimulation. I think you may have some data there, I'm going to speak to that data, and my presentation at the end, I think, will answer most of the four questions that we will be addressing

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today, if not directly, indirectly.

As I said, my name is John Brizzolara. I'm a private practice urologist in Little Rock, Arkansas. My practice is a general urology practice with a heavy emphasis on urinary incontinence and pelvic floor dysfunction or urgency frequency and pelvic pain. To give you a little bit of background data on the practice, the population, or the medical

draw area of Little Rock is approximately 550,000 people. I am in a 12 member urology group. We see a large Medicare population; Arkansas is a large Medicare state. Looking at billing records over the last several years, it will range anywhere from 55 to 65 percent Medicare billing, so we do take care of a large Medicare population.

I would like to address my experience with sacral nerve stimulation. I began implanting in March of 1999 after an excellent training course. Since that time I have implanted 52 pulse generators and of that 52, 19 have been in the Medicare population. In order to get to the 19 permanent implants, I started with 30 patients who I felt were candidates for temporary test stimulation. In order for a patient to qualify for the temporary test stimulation, they have to have failed conservative

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management, and conservative management generally encompasses pharmacologic treatment or behavioral modification, or sometimes intravesical treatment.

I had 30 patients that fulfilled that criteria. They all filled out the required voiding diaries and after reviewing the diaries, these 30 patients then went on to temporary stimulation, or test stimulation. Out of that 30, I felt that 70 percent, that 19 of those 30, had better than a 70 percent improvement in one of the treatments that we were looking for. So these patients then went on to permanent implantation and I will give you the data on the permanent implantation of those 19, and this has been over an 18-month period of time.

19 patients total. 11 patients or 57 percent had total resolution of their symptoms. 31 percent or six patients had better than a 50 percent resolution. One patient had better than 30 percent improvement, and in that one patient, that 30 percent was significant; it made a large impact on their quality of life. And then there was one patient that for some reason did not achieve the efficacy with the permanent implant that they did in the test stimulation; I'm not sure why. But of those 19, most of them had significantly good results.

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Prior to treatment, overall, these patients were using on an average of four pads per day and these weren't small pads, these were large pads. So some people were using eight, some two, but on average, approximately four. After treatment, they decreased up to 40 percent, which was significant. Urge symptoms, pelvic pain, decreased 80 percent overall.

30 percent of the patients prior to treatment were undergoing some type of intravesical treatment which would require the patient to come into the office at least one day a week for six weeks to receive an installation, and sometimes the patients would do this four and five times a year, which results in multiple visits to the office and quite a large expense. After treatment, no patients were receiving any type of intravesical treatment requiring them to come to the office.

Prior to treatment, all patients were on some type of pharmacologic treatment. That would be a combination of anticholinergics, tricyclic antidepressants, alpha blockers, Valium, pain medication, and most of it was polypharmacy, a large expense right there. After treatment, oral pharmacologic agents were decreased to only 10

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percent, a significant decrease.

Prior to treatment, and this is very very important in the Medicare population, prior to treatment, only 20 percent of these patients could sleep through the entire night without getting up. Most these people were getting up an average of four times a night. If you take the Medicare population and you do not allow this population to get adequate sleep and they are getting up four times a nigh at intervals of every hour, they begin to suffer from sleep deprivation, which then results in depression, the immune system is not up to par, and they subsequently suffer other medical problems. So this impacts the Medicare population tremendously if they're not sleeping well at night. After treatment, greater than 40 percent of the patients slept all

night long and of the ones that did not sleep all night long, on average they were just getting up two times at night. So they are all getting at least four hours of consecutive sleep, which is extremely important.

Quality of life issues, which is probably the reason that we do most of our treatment, impacts this population tremendously. This is a population of patients that, the majority are retired, most of

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them have the financial means to go and do what they'd like to do. If you're suffering from pelvic floor dysfunction and urinary incontinence, it significantly impacts your ability to get out and do what you want to do.

Prior to treatment, the majority of these people could not take a 30-minute car ride. Now in Little Rock, Arkansas, 30 minutes will probably get you to the mall, to a church, to a relative's, to a grocery store. But once you're there, that's going to give you about five minutes to visit, to worship, to buy your food and then you have to go find a bathroom. That's a real problem.

After the treatment, and this is amazing, after the treatment, 81 percent of these people could take a one-hour car ride, most of them over that. So this allowed them to get out and do what they want to do. Otherwise, they're sitting at home depressed, can't mingle, and it impacts them greatly.

In my practice, if we're treating a group of patients, we will do patient satisfaction surveys. And I don't know if you all have this data. But in a private practice, patient satisfaction surveys are very very important. And so I looked at three different things, were they satisfied with the

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treatment, would they recommend it to a friend or family, and would they repeat the procedure. And I did a simple scale, zero to ten, zero being no, ten being yes, 100 percent I would do it.

On whether or not they were satisfied, all patients were more than 70 percent satisfied, two patients were 70, seven were 80, three were 90, and

six were 100 percent. Whether or not they would recommend it to a friend or family, all more than 90 percent felt they would, 16 said 100 percent they would and two said 90 percent they would. Whether or not they would repeat the procedure I think tells the story. All of them said, probably 80 percent, yes, I would repeat it; two said 80, one said 90, and 16 said 10.

So in the private practice, in a community based urology practice, in which there's a large Medicare population, I think and feel that sacral nerve stimulation provides a very viable treatment option for this refractory group of patients that we really had nothing to do before. It improves their quality of life, their self image, and their overall well being.

The way I have looked at this is that prior to sacral nerve stimulation, there was a

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puzzle, a jigsaw puzzle on urinary incontinence, and we had most of the pieces, and there was a defect right in the center for this huge group of patients that had refractory urge incontinence or urgency frequency. Other than disfiguring surgery, which doesn't work in probably 20 percent of the people, we had nothing to offer them. And thanks to the work of Siegel, Schmidt, Vinson, and Hadsuna and Chancellor, and the people in Europe that have done just an excellent excellent study, a lot of patients, large number of data, we finally have something, we have that other piece of the puzzle to fit in here.

And I don't know whether Dr. Holtgrewe or not will agree with me, but if you look at urology in the last 15 years, we have probably had three big events. We have had lithotripsy, we have -- that have impacted patients' lives. We've had lithotripsy, we have had the introduction of intravesical BCG for the treatment of bladder cancer, which has saved a lot of people's bladders. And then we have sacral nerve stimulation, and it really fits up there. It was a good study, it was done well, and it's going to make a big impact. Thank you.

MS. CONRAD: Thank you, Dr. Brizzolara.

DR. ZENDLE: A question. You may have said it and I just don't see it written here, is how long of a follow-up was this? It says research period December '99 to January 2000.

DR. BRIZZOLARA: Actually, it started March 1999 is when I first started doing the first implant. Now the data that you have there, the --

DR. ZENDLE: Before and after?

DR. BRIZZOLARA: Yeah, before and after, is three months. The last patient you have there that was implanted, was three months ago. There have been a few since then that were not included.

DR. ZENDLE: So it's a measurement of three months?

DR. BRIZZOLARA: Right. Yes, sir?

DR. SIGSBEE: A couple of questions. I appreciate you coming here today and presenting this material. First of all, why would there be a reconduction in pelvic pain? And the second is your series obviously is a relatively small series; did you apply any statistics to your results?

DR. BRIZZOLARA: I agree, it's a small series, it's growing from a -- I'll address the first question first.

The pelvic pain problem that we run into, I rarely see that in a patient that also doesn't have urgency frequency. Now, why does the technology work, we're not too sure. There's multiple theories about the activation or more or less infantile pathways that are reactivated because of trauma or whatever. But if you see a patient that has urgency frequency and it continues, then I see these people that develop pelvic pain that seem to then go on to IC. If you can break it at first, if you can stop the urgency frequency syndrome early, if you can pick a patient up one and two and three years after they have started, then you can usually stop the pelvic pain. But you rarely see pelvic pain without urgency frequency, so you're going to get both of those at the same time. Why you have pelvic pain, I don't think anybody knows at this stage.

My data obviously is a small series because it just began 18 months ago, and I have been very selective. My criteria has been at 70 percent improvement on test stimulation, as opposed to FDA requirements of 50, so it would be larger if those were included.

My statistical data, there have been no -- there has not been a good statistical analysis done on this data. Whether or not it's statistically significant would have to be something for the

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statisticians, but from a community base, it statistically impacts my patients to the good, and that's where I need to look at it, because I need to be able to offer a patient when they come into my office with fairly good assuredness that yes, this is going to work. That's the advantage. There's nothing else in medicine that I can think of, no other treatment, that we can actually test first at a relatively inexpensive cost, that allows us to with 70 to 80 percent assuredness, that a permanent surgical procedure is going to take care of that. Where before, the patient came in and they had refractory urgency, urge incontinence, the only thing I had to offer them was an augmentation, cystoplasty or a cystectomy, which is a large surgical procedure, with probably only 20 to 30 percent improvement.

Maybe I carried on too long.

MS. CONRAD: Thank you. I may have missed it; did you state for the record financial involvement?

DR. BRIZZOLARA: I do not have financial involvement.

MS. CONRAD: Thank you, sir. Jeffrey Welgoss, followed by Roger Dmochowski.

DR. WELGOSS: Thanks. You got it right

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the first time before so that's okay, I have no problems with that.

Thank you. It's great to be here to present some statements on behalf of the American Urogynecologic Society. I'm Jeff Welgoss, I'm a practicing urogynecologist in Northern Virginia, and

a member of the American Urogynecologic Society. I'm going to refer to that as AUGS, just so I don't have to repeat it several times. AUGS is a 21 year old nonprofit organization with nearly 1,000 members who have a special interest and/or expertise in the field of urogynecology and reconstructive pelvic surgery. Our membership includes gynecologists, urologists and allied health professionals in academic and clinical practices. The mission of our society is to promote research and education in the specialty and to improve the quality and delivery of health care to women with pelvic floor disorders. I have no financial disclosures to report, and on behalf of AUGS, I'm pleased to provide expert testimony on the clinical value of sacral nerve stimulation, or perhaps more accurate, sacral neuromodulation in the treatment of refractory urinary urge incontinence and urgency frequency.

Personally, I have been using this therapy

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for the last two and a half years in private practice. Urinary incontinence has been estimated to effect up to or perhaps over 20 million patients, most of whom are women, with an annual cost approximation in the neighborhood of $30 billion. Urge continence is a condition where an individual is unable to hold urine in response to the sensation of urgency. This sensation may be triggered by bladder volume and environmental stimuli.

As far as other definitions, urgency is characterized as the powerful sensation to void, and AUGS would agree with the definition of urinary frequency as greater than seven voids daily. Members of our society of AUGS were involved in the drafting of the 1992 and '96 versions of the Agency for Health Care Policy and Research guidelines, which recommended that a trial of behavioral interventions be applied to all appropriate patients with urge incontinence prior to the use of more invasive treatment such as drugs and surgery, and we continue to support these recommendations.

Behavioral treatments for urge incontinence include bladder training and pelvic

muscle exercises. Biofeedback and pelvic floor electrical stimulation can be used as an adjunct to pelvic floor muscle exercises to improve the patient's ability to learn and perform these techniques.

Pharmacologic treatment has also been successful in treating urge incontinence and overactive bladder. However, pharmacologic treatment is not without significant side effects, and has to be discontinued in some patients due to the side effects.

All these noninvasive modalities, however, are not effective for all patients suffering from lower urinary track dysfunction such as urge incontinence and urgency frequency. In a situation where first-line behavioral and pharmacologic therapies fail in obtaining remission, AUGS supports the use of surgical treatment methods that allow patients to regain a quality of life.

Sacral nerve stimulation is reversible therapy for treatment of refractory urgency frequency and urge incontinence, and we support the use of sacral nerve stimulation for the treatment of refractory urge incontinence and urgency frequency, as well as urinary retention in those patients who have failed behavioral treatment including biofeedback, pelvic floor electrical stimulation, or found pharmacologic treatments ineffective or not tolerable.

The therapeutic effects of sacral nerve stimulation rely on electrical stimulation of the sacral nerve located in the low region of the spine. The treatment or urinary incontinence with sacral nerve stimulation involves stimulation by the implantable system that you have already heard about, including a lead, a neurostimulator and a connection between the two. Prior to implanting the nerve stimulator, the patient must first demonstrate a positive response during the test stimulation period. This consists of a three-to-seven day home evaluation, with an internal lead and external

stimulator, where the patients complete a voiding diary to assess their symptoms. Results at baseline are compared with results during the test stimulation and we would like our patients to demonstrate at least a 50 percent reduction in the primary symptom to be interested for long-term therapy.

Following the successful test stimulation period and after consultation between the patient and physician, the therapy may proceed with the implanting of the sacral nerve stimulator system. The surgical procedure takes between one and three

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hours and is usually performed under general anesthesia.

Now just a little bit about data, some of which you already have. The focus of the TEC assessment is on a single study, Medtronics Multi-Center Clinical Study, using the Inter-Stim system. The study is designed as a prospective randomized trial, and we would like to add, in the comparison group, patients actually served as their own controls.

Of a total enrollment of 581, 260 patients were eligible for implantation. Some of the highlights, I would just like to highlight again. In patients with urge incontinence, 79 percent of implanted patients experienced a decrease of 50 percent or more in incontinence symptoms. 45 percent of the implanted patients reported they were completely dry. Out of the patients with heavy urinary leakage at baseline, 70 percent had eliminated heavy leaks.

Moving on to urgency frequency, approximately a third of implanted patients reduced their number of voids per day by at least 50 percent. An additional third of patients with a baseline frequency of seven or more voids daily reached normal

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voiding frequency. 61 percent increased their volume per void by at least 50 percent, and 82 percent improved their degree of urgency prior to voiding, demonstrated by increased volumes over baseline with the same or reduced degree of frequency.

Now these numbers are all very well and good. I would like to stress, however, these were patients who were failed by numerous other therapies prior to sacral nerve stimulation, so we're talking about a population of patients who have been selected out to be people who have kind of failed just about everything else we had to offer them prior to that point.

Following up on that, to further document the effects of sacral nerve stimulation on voiding function at six months post-implantation, the stimulation was temporarily turned off and voiding diaries again collected. Statistical analysis of the voiding diaries demonstrated a close return to baseline symptoms for those patients with urge incontinence, urgency frequency and retention. So discontinuation of the stimulation resulted in a return of this dysfunctional voiding pattern.

It indicates that the reduction of symptoms for urinary voiding dysfunction observed

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with sacral nerve stimulation was attributable to the therapy. In addition, these studies demonstrated that the effects of sacral nerve stimulation therapy are reversible and not dissociated with any kind of deterioration of bladder function.

Now that's the largest study. When we look at the remainder of the data, essentially these results are consistent with just about every study that has been expressed, and I include a bibliography of some of the pertinent literature.

Just to kind of flesh this out, put a little skin on this for you, I'm not going to talk about necessarily large clinical studies, but I just want to talk about one patient, and I can give you a whole bunch of anecdotal stories, but once the yellow light comes on I'll stop. But I want to just talk about one patient now who is a patient and now a friend of mine.

Carol is 37 years old, two young kids, had urgency frequency over the last four to five years. She had been treated with numerous anticholinergics, she had been treated with Elmiron, she had been

treated with bladder retraining, pelvic floor muscle exercises, pelvic floor electrical stimulation, essentially everything that the medical community had

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to offer, yet she still had to void every hour. Some of you I assume have driven in D.C. And know that driving in D.C. Can sometimes be a challenge.

Because of this problem, because she had to void every hour, Carol stopped going out any time remotely close to rush hour. She stopped going to her child's soccer games. She was afraid to drive down to Richmond, so she became almost a social outcast from her friends, from her friends at church, from her children's social activities, and it really impacted her life as far as how she could perform as a mother, and this was a 37 year old very vital, very healthy, very bright woman.

After having failed all the medical therapies, finally was implanted after a test stimulation period, and now voids approximately every three hours. She's able to go to her kids soccer game, she's able to see her church again, she's back. I've got a letter from her mother, a thank you letter from her mother in Miami, saying you know, thank you for removing this dark cloud of bladder problems from my daughter.

So just to flush it out, this is a real therapy that affects patients' lives. So, concluding, I want to say that sacral nerve

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stimulation provides patients and their physicians with another effective treatment option to manage urge incontinence, urgency frequency and nonobstructive urinary retention. Sacral nerve stimulation is notably effective in cases refractory to or inappropriate for conventional therapy. To further describe the importance of sacral nerve stimulation, AUGS would stress that this is a breakthrough technology and has been proven to be of significant benefit to many patients with refractory urgency and urge incontinence who have failed standard therapies.

Patients with these voiding functions

found to be refractive to standard therapy should be evaluated by a physician trained in the diagnosis and treatment of voiding dysfunction. If it is determined that these patients are candidates for sacral nerve stimulation, they should be offered testing and implantation of sacral nerve stimulation devices as indicated.

The American Urogynecologic Society is hopeful that a positive coverage policy for this therapy will help to further research and development of the therapy by the manufacturing community and continue providing quality health care options for Medicare beneficiaries. Thank you for your attention.

DR. ZENDLE: Question. Could you just clarify that you're speaking on behalf of the American Urogynecologic Society, who feels that this is breakthrough technology of proven benefit?

DR. WELGOSS: Yes.

DR. ZENDLE: So you're speaking on behalf of them?

DR. WELGOSS: I am speaking on behalf of the American Urogynecologic Society.

DR. ZENDLE: And the last thing is, in the last paragraph you say that AUGS is hopeful for a positive coverage policy so that it will help to further research and development of this therapy. Can you just explain, if it's proven, why you think there should be more research, or is it something different?

DR. WELGOSS: Well, I think we've got a fairly valuable body of research already. I think that ongoing research, not only in urinary urgency, urinary frequency, is going to be helpful in defining perhaps better those patients that are going to be most effectively treated by the therapy.

There are also a number of other things. John alluded to earlier about pelvic pain syndrome and exactly why this works and some of the stuff, there are theories but nobody knows for sure. But we've noticed that patients with pelvic pain

disorders, interstitial cystitis, often improve with their pain in addition to the two issues we're talking about today. In addition, we found that patients with colorectal dysfunction have also improved, patients with constipation and irritable bowel, patients with fecal incontinence.

So, I think the area for further research may be in different indications and also hopefully fine tuning those patients who are going to be best able to benefit from the therapy.

DR. ZENDLE: Thank you.

DR. TUNIS: I just want to ask one quick question. I know we have spoken in the context of other incontinence therapies, and I'm just curious. In your experience, sir, what's the estimated size of the subpopulation of patients with urgency, urgency frequency who have failed all the other levels of interventions you've discussed, the pharmacologic, the behavioral, the pelvic floor and the biofeedback? What pool of patients does that leave, in your experience?

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DR. WELGOSS: I think when you take the 20 million or so Americans that leak urine, this is obviously comparably a smaller pool. Fortunately, most patients will respond to pharmacological and behavioral therapies. I don't know that there's any real estimate as to exactly how large that pool is. Now, there are some studies that would suggest that somewhere 50 and 60 percent of patients are unhappy with the current incontinence therapy that they are undergoing. Whether or not those are patients that are willing to undergo a slightly more involved surgery, a more invasive procedure rather than continue to take medication and just being unhappy, nobody has really defined. But I think there is a body of patients that are unhappy with the therapies that they're undergoing, and it's probably not as large as 50 percent of everybody with urge incontinence, but it's not as small, I think, as we think.

MS. CONRAD: Thank you. Roger Dmochowski, followed by George Mamo.

DR. DMOCHOWSKI: Good morning, panel. My name is Roger Dmochowski, and I am presenting the position statement of the American Urologic Association on neuromodulation for the management of voiding dysfunction. My only relationship with Medtronic is that of an implanting physician.

You have been bombarded with a substantial amount of information. We have given you a similar bibliography, I think, to what you may have seen from several other sources. I would reference our bibliography in your packet and also have you correlate that with whatever else you have in your packet from other sources.

There has been much discussion today about demographics of incontinence and I think part of the problem that you have to deal with is what we have to deal with as treating physicians. And I as a urologist will tell you that the demographics of this disease are changing. Some of that is due to improved patient awareness and patient acknowledgment of better therapies out there. We saw a slide earlier that said 13 million people have incontinence, recent studies have estimated 17 to 20 million have incontinence, 80 to 85 percent of those are actually women. So that's probably a more realistic number, but please keep in mind that you may in six months see a slide that tells you it's 25 million, because again, as the respondents to varying survey analysis increase, the number does go up.

Most importantly and of importance to you as a Medicare advisory group, are in the female population over 60, 30 to 35 percent of those patients actually will experience voiding dysfunction including incontinence. So that's a very important point to keep in mind in terms of the overall effect of, disease effect, disease magnitude of effect in that population.

It's hard -- it was a very interesting question that Dr. Tunis asked regarding what are the estimates regarding how many patients actually have the specific disease that we've been asked to

evaluate today, which is refractory urgency incontinence, patients who either have not tolerated standard therapies or have failed standard therapies. I can tell you that there is interesting data out of the pharmaceutical world that says there are actually 1.5 to 3 million patients actually actively on pharmaceutical medication for OB, quote-unquote, overactive bladder, which is urgency frequency and urge incontinence, as previously defined.

There are other data that Medtronic I believe has on file, regarding estimates that they have regarding the estimated incident of patients who may be applicable for implant therapy. So again,

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keep in mind from the standpoint of what you need to in terms of evaluating the overall magnitude of treatment effect is that again, the numbers are changing, and they are going up rather than down.

I think many of you are familiar with the actual device and the overall point of therapy, which is direct stimulation or neuromodulation of the pelvic arc. We don't really know why this therapy work. There are some very good animal studies to suggest some neuroplasticity and downgrading of reflex activity within the sacral reflex, or arc, both from the afferent and efferent circumstance. But if you wanted one unifying pathophysiologic explanation for why this modality works, we don't have it yet, but it does work.

As has been mentioned, the therapy is delivered via a low sacral approach, and the best results are obtained with simultaneous fluoroscopic implantation. Some investigators also use electromyography to help implantation effect.

As has been alluded, there are two phases, both a test and a permanent phase. The test phase is a much shorter phase of three to seven days, where the patient actually via diary communicates with the physician of the overall response they had to

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therapy.

The device is composed of two main components. One is the lead, which is actually the

contact point between the nerve and the system, and then obviously a generator which is implanted through a separate incision in a site somewhat distant from the actual lead implant site. There are other alternative methods being currently evaluated which we don't have much data for, with regard to implantation of devices at alternate areas of the nerve system for neuromodulation, specifically the posterior tibial nerve. Much has been done with the old acupuncture treatments.

We will limit our literature analysis to four basic articles, mainly because of the panel's requirement that they really consider randomized control data as the most important decision-making process. There is a substantial body of secondary information, what would be considered quote-unquote, secondary information, which you're well aware of, but from the standpoint of randomized control trials, I would like to reference the trials by Bosch and Schmidt, as well as Hassouna, in 1999 and 2000, respectively, which really formed the basis of the FDA application by Medtronic for device approval.

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The numbers are fairly dramatic; again, these are patients who have failed other therapies and intensive other therapies, and you see numbers in the order of 60 percent cured, substantially improved in Bosch's study, and 70 percent in Schmidt's study. Again, very impressive rates when you consider this refractory population to other interventions.

I think a point the panel must keep in mind to make a balanced decision regarding this is that currently there is a device revision rate that's approximating 30 to 35 percent which you should be aware of, and that has something to do with the fact that the technology is still somewhat in evolution in terms of the best way to implant it and ways to maintain permanent lead contact with the sacral reflex arc.

As I alluded to, Hassouna's publication in 2000 specifically dealt with urgency and frequency. The prior two were urge incontinence studies. And again, when you look at the effect of this treatment

on urgency and frequency, again, you see substantial reduction in both frequency and volume voided, as well as degree of sensation of urgency.

And again, urgency is a very subjective phenomenon which is really best analyzed by analog

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scales or subjective assessments; it's very difficult to get a quantitation of that in any objective format.

In a very interesting publication which is not specifically a randomized controlled publication, but one that you should be aware of is one that was recently published by Siegel et al., which demonstrates the effect of this therapy is maintained in the majority of patients at 24 months, which again implies the chronicity of therapy does not impact upon overall response.

I think in making your decision you must consider that we don't have a substantial body of randomized control data to make a decision with, but what is out there is well done data and would certainly be classified as primary in terms of the instructions that you have been given. And as I alluded to, there are other secondary type data, objective well done scientific publications that are not randomized control, but which again, vouch for the efficacy of the therapy as delineated by the randomized control trials.

As I alluded to, the revision rates are something that are the function of the technologic development. I think there will be an expected

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decrease with time as device innovations occur and as implanting physicians really get over their learning curve and become much more familiar with the therapy. But most importantly, there are no serious morbidities associated with the implantation of this therapy.

And again, I think it's important to realize that there is a necessary expertise that physicians have for this implantation; it's not something that can be done without a training course and rigorous proctoring for the person to reach, or

the implanting physician to become capable of performing the implant without supervision.

Based upon the analysis of the literature, the American Urologic Association would like to go on record to you as saying that we believe this is a level 1 or breakthrough technology. It really does represent a tremendous step forward for patients who otherwise had only an option of surgical intervention.

The surgical intervention that was most commonly used in these patients is bladder augmentation, which has, if you look at the pooled data from the literature, again, there's no randomized control data really to look at bladder

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augmentation, but only about 30 to 35 percent of those patients actually do well on that therapy. So again, you have a substantial improvement over a straightforward surgical intervention with this type of intervention.

We believe it does have a high magnitude of treatment effect for patients who have failed primary therapies, and those therapies were alluded to previously by the AUGS presentation. I think it does have, and we do think from the American Urologic standpoint, that it has a probable substantive effect on the Medicare beneficiary population. Thank you.

MS. CONRAD: Thank you very much. George Mamo, and the next speaker will be Kristine Whitmore.

DR. MAMO: Good morning. I would like to thank the panel for allowing me to present today. My name is George Mamo, and I am a private practice urologist here in the Baltimore area. I have a specialized interest in urinary incontinence and voiding dysfunction, and I have been doing this for about eight years since I finished my residency here in Maryland, University of Maryland.

I direct the Maryland Bladder Center, which is located at St. Agnes Hospital just a few miles from here, and I have been doing this therapy

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for about two, two and a half years now. I have become a very active implanter, I have done about 58

or maybe 60 implanted generators since I started doing this, and I have become a firm believer in this therapy.

My relationship with Medtronic is that I am a proctor. As you may know, most physicians that want to do this therapy have to go through an FDA required process where they go through a two-day certification course and they have been to be proctored in all the surgeries when they do them. So I travel around, and I proctor these physicians. I am here on my own behalf and on behalf of my patients who have this terrible problem.

I feel strongly about Inter-stim and I think that has provided us with a very good tool that we never had before. Most patients have been treated before with behavioral modification or medication and other ways of dealing with this problem, but all this has failed. I know of no more treatment options, and none that are as effective.

I have a brief presentation today on my experience with geriatric patients. In my practice, we have a very large geriatric population. This is the data I just presented just two days ago at the

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Mid-Atlantic section of the American Urological Association, which I would like to also present here.

We looked at 34 consecutive patients, all from a range of 60 to 81, so the mean age was 70, and all these patients have refractory urge urinary incontinence. Most of them were female, 82 percent, and most of them have had this problem for many years, and the mean number of years for this condition was about 2.3. They all have gone through all the traditional treating modalities, including medication, with anticholinergenic drugs in particular, 97 percent. 91 percent underwent behavior modification with pelvic floor exercises, biofeedback, EMG, change in their voiding habits, change in dietary habits. 40 percent underwent some form of nonsurgical intervention such as urethral violation, bladder hyperdistention, and so on. And approximately 63 percent have had some kind of surgery, mainly some form of bladder suspension.

They all underwent the usual evaluation with a history and physical examination, and the urodynamics testing. They all were evaluated with a 48-hour voiding diary which looked at urge incontinence episodes, pad usage, and frequency, and the same was done in follow-up.

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Of the 34 patients that underwent percutaneous nerve stimulation, 14 of those or 41 percent were successful and went on to permanent implantation. Six were dry and eight were greater than 50 percent improved.

I would like to add here that about ten of those patients that failed had a problem with lead migration and the lead moved before we could get an adequate response, so we don't know if those patients would have responded, so I would guess that there is probably a certain percent of those that may have gone on to permanent implantation, so this 41 percent may actually be a higher number.

Of the 14 patients that went on to permanent implantation, at about six months follow-up, three were dry, six had a greater than 50 percent improvement in their symptoms, three failed and two -- three had less than 50 percent improvement, and two failed. So our overall success rate was about 65 percent.

We compared voiding diaries before surgery and after, and if you look at the number of leakage episodes per day, this went down from 7.93 preop to 3.96. The number of pads used went down from 5.11 to 2.32 pads, and both of these were statistically

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significant. The voiding episodes per 24 hours went from 11.75 to 9.5, and this was not statistically significant.

We asked patients about how they felt about the therapy. 11 of the 14 were satisfied and would have the operation again, and 12 would recommend it to family and friends.

We did not experience any major complications or problems with this. Most patients did well. None of the patients were explanted, none

of the patients developed any infections or chronic pain. We had two patients that had lower extremity ipsolateral pain for a few weeks after surgery, that resolved spontaneously.

So, I could like to conclude that sacral neuromodulation in the geriatric population is effective, and I feel that it definitely has a role in these patients. I would also like to add that, in the geriatric patients in particular, those I think, if you look at the nursing home admission rate, I think that urinary incontinence is probably one of the main causes of nursing home admissions, and I think if we can make an impact on the management of these patients, then we could make an impact on the nursing home population. There is a lot of -- a lot

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of these patients don't want to leave home, don't want to go to nursing home, but because of the problem with incontinence, they even end up having to, that creates a major problem for their family members, whoever supports them at home, and they end up in a nursing home prematurely. So I think if we can make an impact on their management of their incontinence, we can make an impact on the nursing home admissions and there is a lot of ramifications to that. I think that's all I have to say. Thank you.

MS. CONRAD: Thank you, Dr. Mamo.

DR. MAVES: Let me just ask you, can you take us through sort of, I guess what I need is a treatment algorithm, for how patients end up to this, and sort of what the success are. I think you sort of mentioned using meds, behavioral modification, nonsurgical treatments, and surgery, and you gave some percentages of patients in your experience that had those. But sort of some rough numbers regarding success, I guess kind of getting down to what can we expect as a progression sort of, of patients through this, and what's their chance of success with each one of those, in your experience?

DR. MAMO: A typical patient that comes to

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me with urinary incontinence, after they go through

their initial evaluation and testing, I usually try to do some kind of behavioral modification. I start with some simple things like getting them on a time voiding schedule, so they void every hour, every two hours, as opposed to waiting three hours to go urinate. I try to change some of the things in their diet like stopping caffeine or spicy food in a diet, which can irritate the bladder. I start them on some keen of pelvic floor strengthening regimen, biofeedback or EMG or electrical stimulation, or Kegel exercises.

Once they go through that process for a few weeks, if they have not -- or a few months in terms of the pelvic floor strengthening, I go on to medication. I try some form of anticholinergenic drug, Ditropan or Datril or so on. And it's once they fail those then, if I feel that the patient is still having significant symptoms and they are not happy or content with their problem, or if they've had side effects with the medication even though they have responded, I will look at considering this option.

Dr. MAVES: And what's your sense, if you start out with a hundred patients, how many get

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better after sort of conservative management?

DR. MAMO: I would say with conservative management, 28 to 30 percent. With medication, you add another probably another 30, 40 percent. I would say there is maybe about 40 percent of patients, 40, maybe 35, who will not respond to any of those and have to go on to potentially become Inter-stim candidates.

MS. CONRAD: Thank you, Dr. Mamo.

DR. SIGSBEE: Just one more quick question. About 35 percent do not have a good response at least as you categorized it here. Do you have any particular characteristics of that population? You obviously go through a selection process. Why do those particular people not have a good response?

THE WITNESS: I don't know if I have a good answer to that. Part of this, I think there may

be a psychological component to this, but I really don't know why these patients do not respond. I think there is something physiological or anatomical that we're aware of that explains that, but I don't think I have an answer to that.

DR. GARBER: Okay. Let me just make a suggestion to the panel. We have a large number of

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speakers this morning and it might be best to hold your general questions to the end, and I hope that the speakers will stay here so we will have a change to ask all of you questions, because I suspect some of these questions will be addressed in some of the other presentations. So I would like to ask you to limit your questions as much as possible after each speaker speaks, to points of clarification and so on. And the general questions, hopefully we can pose at the end of the public speaking section. Thank you.

DR. MAMO: Thank you.

MS. CONRAD: Kristine Whitmore, followed by Nancy Muller.

DR. WHITMORE: Good morning, distinguished panel members. Thank you for giving me the opportunity to testify here today about this most important topic. I am a proctor for Medtronic and have no other disclosures to review, and I am here as a patient advocate.

My name is Kristine Whitmore. I am a clinical associate professor of urology at MCP Hanneman University, and director of the pelvic floor institute at Graduate Hospital in Philadelphia. I have seen more than 10,000 patients with frequency, urgency, pelvic pain and/or urge incontinence over

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the past 15 years, and have been involved in greater than 20 clinical and basic science research protocols. I am also a board member of the Interstitial Cystitis Association, and I will be testifying this morning on their behalf.

The ICA is a national nonprofit organization dedicated to improving the lives of patients who suffer from interstitial cystitis or IC, all of whom have frequency and urgency. IC is a

chronic inflammatory condition of the bladder that frequently goes undiagnosed with patients seeing more than five physicians and waiting up to five and more years for diagnosis.

The cause of IC is unknown. Therefore, there is no cure. Treatment options are minimal and no one treatment is uniformly effective for everyone. IC symptoms include bladder pain, urinary urgency, persistent, and day and nighttime frequencies of up to 60 times a day, suprapubic or perineal pain and supra-pressure pressure on bladder filling. Although the average age of onset is 40, 25 percent of IC patients are under the age of 30 and 20 percent are well over the age of 65. Although 90 percent are women, preliminary studies of men with nonbacterial prostatitis indicate they may have IC as well.

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One million U.S. Citizens have this condition and an exhaustive plethora of treatments are usually utilized, conservative in nature, but they fail to provide symptom relief in more than 35 percent of patients. 17 million Americans have overactive bladder, and IC is perhaps the most drastic form of the overactive bladder.

I would like to share with you some preliminary data that I have collected that shows that sacral nerve stimulation is an efficacious form of treatment for patients with pelvic floor dysfunction, inability to contract the muscles, inability to relax high tone muscle spasm. These patients all have urge incontinence and/or interstitial cystitis. May I have the slide?

So, our purpose was to evaluate the use of neuromodulation utilizing the Inter-stim device, in patients with bladder related symptoms and other pelvic floor disorders. We implanted 17 patients. 15 were females, the mean age was 60, the mean follow-up period was 13.4 months, 22 months the greatest. The primary end point was the patient's perceptions of symptoms. Old fashioned, zero percent no improvement, 25 percent mild, 50 percent moderate, 75 percent marked, and 100 percent cured. 15 of the

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17 had urge incontinence. All 17 had bladder overdistension cystoscopic evidence of interstitial cystitis. 10 had pelvic pain as a significant symptom on a persistent basis. Two had fecal incontinence which was due to anal sphincter incompetence. Five had constipation, and three had diarrhea.

So as we can see, there is quite an overlap of pelvic floor disorders. Most people don't have just frequency and urgency; most people have frequency urgency, pelvic floor dysfunction, and/or concomitant bowel problems. 16 of the 17 considered the procedure a success; up to 82 percent of patients reported at least marked, or 75 percent improvement, for all of their symptoms, except for those who had sphincteric incompetency fecal incontinence. There was an average of 9.3 reprogramming events. After the implant is implanted, we follow them up regularly, usually at monthly intervals. The mean amplitude of a max of 10 was 3.1 volts.

In the urge incontinence group, 1 cured, 12 had marked marked improvement, so that we can see 70 percent had a success of 75 percent or more improvement in symptoms. In the interstitial cystitis population there is no cure available at

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this time, but 82 two percent had marked improvement, which is significant seeing that 35 percent of IC patients in general report no persistent relief in their symptoms with our other modalities of treatment.

Pelvic pain on a persistent basis was found in 10 patients and again, this is usually due to pelvic floor muscle dysfunction or a high tone pelvic floor. 20 percent cured, 50 percent had greater than 75 percent improvement, so that 70 percent were significantly better in terms of their pain, which also impacts sexual function. 80 percent of patients with interstitial cystitis have sexual dysfunction based on a pain basis. These patients now are able to have sexual activity again, which greatly impacts their quality of life.

And interestingly, GI results of the five

who had constipation, four were markedly improved. Of the diarrhea patients, two of the three were markedly improved. And as we mentioned, there were failures in the sphincteric anal incontinence. The therapy obviously was not chosen for these people, this was a concomitant disorder.

So you can see a significant reduction in bowel problems as well as bladder problems. There

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thus was a significant symptom relief reported by patients with urge incontinence, interstitial cystitis, pelvic pain, diarrhea and constipation. Sacral nerve stimulation continues to be an efficacious form of treatment for patients with pelvic floor dysfunction.

En route is a multicenter studies on symptoms improvement with a test stimulation portion of the procedure in patients with diagnosed IC, and also follow-up data which will show scientific evidence that is of statistical quality, will be delivered on voiding diary, O'Leary symptom, and problem index for IC, Likert scales for urgency and pain, a Rosen's sex questionnaire and a bowel diary.

IC is a severe form of the overactive bladder affecting one million Americans. Inter-stim therapy is a valuable form of therapy for patients refractory to standard conservative therapy, and may prevent cystectomy, radical surgery, as the only therapy left for a group of patients who has failed all conventional therapies for IC. I would encourage you to vote yes on this breakthrough technology.

I will give you one brief story. Wally is 48 years old. He has been a television talk show host for 22 years. I met him four years ago, on the

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verge of being fired because he was on narcotics, couldn't focus, he had gained weight, because he had frequency urgency and severe pelvic floor dysfunction with pain. He had tried dietary modification, bladder retraining, physical therapy for his pelvic floor muscle dysfunction, Elmiron therapy, which is a drug that is used commonly for Elmiron, and pretty high level antidepressants and narcotics. He is 2.2

years out now. Wally has a television show, he has a large following, he has no narcotic utilization, he is off his antidepressants, and he is sexually active again for the first time in almost 16 years. Thank you very much.

MS. CONRAD: Thank you, Dr. Whitmore. Nancy Muller, please, followed by Janet Smith. We do have a cancellation, if you're following. Dave Gordon is not here today.

DR. MULLER: As the executive director of the National Association for Continence, I am both honored and pleased to be with such leading authorities speaking on the value of sacral nerve stimulation in the treatment of refractory urge and urge frequency incontinence. My association, by the way, with Medtronic is that the company is one of about 18 industry council members contributing to our

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organization. I am here today as a patient advocate.

First of all, who and what is represented by the National Association for Continence or NAFC? We're the single largest, most prolific consumer advocacy organization devoted exclusively to incontinence in the world, and I can personally attest to this because I have represented NAFC at gatherings such the International Incontinence Society meeting, as far as away as Athens, and World Health Organizations on the subject in Bonn.

While the mailing list of our quarterly newsletters reaches initially 130,000 individuals, we know that the readership is at least a quarter of a million people, because our literature is so freely shared by our readers. We are broadly funded by industry, foundations, health care professionals, and our consumer members. We have a proactive agenda, not a work plan driven by the funding of special interest groups. Since our inception about 20 years ago, our mission of consumer advocacy, education and information dissemination through networking, has not faltered.

Well, you know the numbers on incontinence, you heard them earlier. As many as 25 million Americans suffer from urinary incontinence,

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and at least 18 million of those are experiencing chronic rather than transient incontinence. But how do these consumers, how do these individuals really feel? Well according to the research that we have conducted on our newsletter readership, 20 percent of survey respondents indicate that their incontinence is a major problem, and there is no statistical difference in these responses by gender. Those in the lowest income bracket are disproportionately more seriously affected they say, as are those under age 45, because of the quality of life they feel they're sacrificing. And satisfaction with treatment or dissatisfaction as the case may be, is not a function of how much they are spending on managing or trying to treat their incontinence.

We have done now six of these surveys over the last 20 years, our most recent was completed last year, and the one before that in 1996. And as you heard from an earlier speaker, the level of dissatisfaction with treatment for a variety of reasons is quite high. It hovers around 62 to 63 percent of the people responding to the survey. This may partially bespeak the sheer complexity of properly diagnosing and treating incontinence, but it also suggests that there are gaps in what people have

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access to.

Where can consumers turn? Well, sacral nerve stimulation should be explored as a midline option, we feel as an organization. Patients seeking answers may have unsuccessfully enrolled in everything ranging from pharmacotherapy, hydrodistension, external stimulation in the form of transcutaneous biofeedback, urethral dilation, pain management of different degrees and sorts, cones, timed voiding, psychological counseling, and even surgery sometimes. Just imagine, over the years and years of undergoing this, how frustrated they must feel.

And I hasten to point out that consumers tell us in the research that we conduct that they actually prefer conservative therapy. In fact, a

majority of respondents to our more most recent consumer survey indicated that they were most pleased with the behavioral therapies that they had pursued for their incontinence. But, I will add that the ones that are most pleased tend to also be the ones who either suffer from slight leakage or have been diagnosed with stress or stress urge incontinence. The reason I point this out is that sacral nerve stimulation is designed to treat the symptoms of urge

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or urge frequency incontinence, not stress incontinence.

And I will add just two more statistics that I think are revealing. Only 3.3 percent of our survey respondents considered themselves cured following what they deemed to be their most helpful treatment, and only 8.6 percent expressed that they were very pleased with their outcomes. Clearly, there's a gap.

Why does urge and urge frequency incontinence affect peoples lives so significantly, why is it so much more debilitating and isolating than stress incontinence? Well, there are a couple of reasons. First of all, it's just downright unpredictable. You have already heard the stories about trying to get through traffic and to children's soccer games, or to attend church. The accidents tend to be larger, in other words, when urine is lost, a larger amount of urine is lost that it typically is with stress incontinence, and absorbent products aren't always enough protection, so there's room for lots of social embarrassment. The frequency of urination tethers the individual to the toilet or to a urinal; it thereby restricts their freedom and their activities.

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Those without access to sacral nerve stimulation, who are otherwise valid candidates, face a more drastic and more morbid option, such as urinary diversion, or they simply face remaining incontinent and miserable. Finally, we have a less radical, or less extreme choice.

But who are these people? Just think of

them as individuals. They are individuals with multiple sclerosis or spinal cord lesions, or neurologic disorders, just to name a few examples. How much do our country's continence care specialists believe in sacral nerve stimulation? Well already, even though this is a relatively new procedure, 120 of NAFC's 750 continence referral affiliates are fully trained in sacral nerve stimulation. Now, this database of sources, names that we give to consumers when they call us asking for help, go through an elaborate grid of questions by us to qualify them, and I think it's significant that on that list of those trained in sacral nerve stimulation include the likes of Rod Appel at the Cleveland Clinic, Janelle Foote at Shepard Spinal Cord Injury Center in Atlanta; both of them are on our board of directors. Neil Galloway, who's head of the continence center at Emory, and Alan Wing, the co-chair of the Bladder

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Health Council, just to name a few.

What we're really talking about here is quality of living, not life or death scenarios, and in this day and age, we are living the reality of chronic illnesses and conditions, not catastrophic traumas that threaten our existence. And when people don't have access to answers and they suffer from retractable urge or urge frequency incontinence, they have a tendency to do a few things. They restrict their water or fluids, leading to constipation, which exacerbates their symptoms. This can lead to also dehydration or chronic urinary tract infection, all which need medical intervention. Or they may suffer from slips and falls when rushing to the toilet and this can result in broken hips, and fractures, arthritic conditions, immobility, and again, they are still saddled with their incontinence.

I would like to echo Dr. Brizzolara's remarks about sleep deprivation and disorientation and depression, already a major problem in the elderly. And I echo too Dr. Mamo's remarks regarding incontinence in nursing home admissions. Research does show that it's the top two or three reasons that families and care givers take an individual to a

nursing home.

I call this panel to action to recognize sacral nerve stimulation among the repertoire of options for individuals, as a medical necessity when other more conservative treatments fail, and to return dignity to life, and life to living. Thank you very much.

DR. OLECK: I just have a question. A number of the physicians have talked about satisfaction surveys that they have done on their patients and we know that sometimes patients may feel pressured in their response to questions from the physician who did that. I am just wondering whether your organization does any satisfaction surveys with respect to various treatments for urinary incontinence, and if you in particular, whether you have done any kind of survey with respect to this procedure?

DR. MULLER: Our surveys have just begun to ask questions about satisfaction with treatment because in the past our questions focused more on just how motivated people had been to seek proper diagnosis and treatment. And we're now, as more and more are seeking treatment, we are turning our questions to that. We have not segregated questions regarding satisfaction in such a way that we could correlate sacral nerve stimulation treatment with their responses to their level of satisfaction, mainly just because the numbers are still too small to be statistically valid. But we are starting to compare responses by diagnosis, and that's what I spoke about a few minutes ago regarding those satisfied who had been diagnosed with stress, versus those who had pursued nonbehavioral treatment.

DR. OLECK: Thank you.

DR. ZENDLE: Do you have focus groups and groups for patients with incontinence so that if patients who underwent this were unhappy with it, you would have heard, or if here they are happy with it, do you hear, or isn't that really the function or purpose or role of your organization?

DR. MULLER: Generally, we hear when people are frustrated, those are the people who are calling us saying they've tried this, they tried that. We are, because we are a national organization, it's a little hard to organize focus groups around the country, because it's a little hard to get, to solicit people to sit in a room and talk about their incontinence. We have in the past year just formed a new consumer advisory panel, so those are questions that we can begin to ask, but what we

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try to do is match up people with resources for further treatment.

We don't know all the reasons for why they are dissatisfied, we don't know if it's because they had unrealistic expectations in the first place, we don't know if it's because they went to a health care provider who wasn't fully trained in incontinence diagnosis and treatment, or if they just got misdiagnosed and therefore, mistreated. So we don't really don't know all the reasons for why they are unhappy.

MS. CONRAD: Thank you. Janet Smith please, followed by Kimberly Oleson.

DR. SMITH: I'm Dr. Janet Smith. I'm in solo private practice in Sioux Falls, South Dakota, and I'm here on behalf of my patients. I have no interest in Medtronic except that I implant and use the nerve stimulator myself. I started in February and so far I've implanted 12 patients, so they are small in number but the results have been significant.

And if you would have told me seven years ago when I started doing more pelvic floor dysfunction that I would be doing these instead of radical prostatectomies and nephrectomies, as a

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surgeon, you know, to treat the patients conservatively goes against our training basically, from way back when. And these patients had been the most satisfying patients I have ever dealt with, and now with the new Inter-Stim device, I have something else I have to offer for those patients that do not

respond to the conservative treatments.

What I'd like to do is just mention a couple things that haven't been mentioned. As far as the test stimulation, it's probably at least six months before my patients are even considered to be an Inter-stim candidate. I my mention it earlier if they've been to multiple physicians, if they're voiding like 30 times a day, or I doubt whether medical management, conservative management is going to work, at least I mention it to them to give them hope, that something can be done if we don't get resolution of their symptoms.

The test stimulation, they need to do a diary ahead of time. The test stimulation, a lot of time I'll be there an hour to an hour and a half, trying to get the temporary lead placements into maximum position. So it is time consuming and you have to be patient. If they pass the test stimulation, which two-thirds of my patients do pass

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it, which shows a 50 percent of improvement in their symptoms, and these patients are so happy when they come back to get their wires removed that you don't even have to look at their diary, you know how happy they are, and it's that dramatic.

For the permanent implant it does take about an hour up to two hours to do the permanent implant, and then the patients do go home and usually in seven to ten days, we activate it. So these patients, because they've been through so much, are usually patient with the process of getting it in, plus they've had their test stimulation so they know how the permanent implant is going to work.

And I know some of the speakers talked about the geriatric population, but a lot of these patients because of back injuries, some because of their bladder, are on disability or Medicare as fairly young patients, so some of my patients are even in their 20s and 30s on Medicare.

You have copies of the letters and I would just like to go through a couple of them. The first one is Phyllis, and Phyllis is a diabetic and has urgency frequency but also was not emptying

completely, so her urine was like a sewer for four years that I knew her. I couldn't get the infections

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cleared. I finally put her on intermittent cathing, she went on insulin to help control her diabetes, we diagnosed reflux so she had a bilateral reimplantation; at the same time I tried to wrap her bladder to make it empty better. It didn't work. She couldn't do self cath herself, so her husband did it twice a day to try to get her bladder empty. Even though all this was done, she was on antibiotics, I tried her on Volmax, Hytrin, Urecholine, everything that I had to offer, her urine was still constantly infected.

She had two test stimulations. The first one didn't work, and so she was willing to try a second one, and the second one we did under fluoroscopy, and it was a matter of two millimeters, of moving the wire to get a response or not get a response, so she actually did see an improvement with the second test stimulation. She has now been implanted for five months, she is not cathing herself anymore, her urine has been sterile now for four months.

The next one is Donna. Donna always says she's my problem child. I did a sling on her that failed, I did a second sling, this time using bovine graft, which she eroded, but everything was scarred

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in very nicely, but she still had incontinence. So I did chonigen injections three times, and again, she had significant urgency, frequency urge incontinence. With the Inter-stim she is now dry. She can go camping again without having to find a bathroom every place or go behind a tree, and she has significant improvement in her quality of life.

Sherry is a 40 year old who has chronic fatigue syndrome, fibromyalgia, and kidney stones. We couldn't have her drink much because she was living in the bathroom, or she wouldn't drink anything. Nothing we tried worked for here, and again, she is a successful Inter-stim patient who now has her life back.

Gina is another 40 year old on disability, has multiple psych medications, and again, we tried her on all medical management, physical therapy, and despite that, she was going to the bathroom over 30 times a day. For years, she hadn't gotten any more than an hour's worth of sleep at one time. And we did her test stimulation, she came back in the office a new person. She had actually slept seven hours in a row, the first time in 20 years. And she's an artist. She came back with drawings that she had drawn 15 years ago, and it basically was really

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dramatic about how it demonstrated the pelvis and all the pain and discomfort her pelvis and her bladder were causing her.

She was my very first implant. She didn't get the success she got with the test stimulation, and she was willing to undergo another surgical procedure to readjust the lead placement because she knew what was possible. And now she is much better off and in fact, she's riding a bicycle and just fell off her bicycle.

Another patient was a back injury patient who, my one goal in life was to come into the exam room and see her sitting down. And when I first mentioned the Inter-stim to her, she said no way, I don't want a foreign device in my body. I said well, just look at the videotape, and she saw the videotape, I walked into the room, she was crying and said when can I sign up.

She hadn't been able to sit through a movie, her family was constantly giving her grief about what she drank, didn't want to travel with her because they had to stop so much, and with the Inter-stim, her life has really changed around as well. She can now sit through a movie without having to go to the bathroom.

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So, this has dramatically increased my practice. As far as patient satisfaction, I have something to offer them that I never had before. It's a breakthrough procedure and there really is nothing that compares it to that has the outcome that

I found. Thank you.

MS. CONRAD: Thank you, Dr. Smith. Let's do one more before we take a break. Kimberly Oleson.

DR. OLESON: Good morning. My name is Kimberly Oleson and I am an employee of Medtronic. Until July of this year I was the principal clinical programs manager for the Medtronic functional stimulation business. Currently I am the director of clinical operations for Medtronic's E/T systems business.

In collaboration with the global study investigators, the design of an FDA regulated multicenter trial began in 1992. The purpose of this trial was to evaluate the safety and effectiveness of sacral nerve stimulation therapy for the treatment of specific voiding disorders. It gives me great pleasure to provide with you with background information on this study. It looks like I may be missing a slide.

In terms of background, the genesis of

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sacral nerve stimulation therapy was born out of early work by Schmidt, Tanagho and others at the University of California San Francisco, in connection with the NIH neuroprosthesis program. This group explored the complex innervation of the sacral nerves as they innervate the pelvic floor and the viscera, including the bladder. They hypothesized that stimulation of the sacral nerves would modulate dysfunctional and organ behavior. They explored this work in animal and cadaveric models, and trial stimulation of the sacral nerves in human feasibility studies was accomplished via percutaneous access through foramen or existing holes located in the sacrum to access the sacral nerves.

In all cases when we talk about sacral nerve stimulation, it's important to note that we mean that this is transforamenal sacral nerve stimulation therapy. Success with trial stimulation and early feasibility studies in humans resulted into the development and the need for more long-term therapy. Therefore, implantable systems were developed.

Today the Inter-stim system, as seen on the screen, is comprised of a lead, a neurostimulator, and an extension that connects those two devices. This is the same technology that has been commercially available in the United States since the mid 1980s for the indication of spinal cord stimulation to treat trunk and limb pain.

In this presentation, my task is threefold. First, I will present what is sacral nerve stimulation; secondly, provide key definitions used in the clinical study; and third, review the clinical study design. This presentation is intended to set the stage for Dr. Steven Siegel as he presents results from clinical study, and for Dr. Thomas Benson as he defines more clinical applications of sacral nerve stimulation therapy.

Medtronic had sponsored a multi-center randomized trial in December of 1993. This trial involved 22 global investigative sites and the purpose of this study was to evaluate safety and effectiveness of SNS therapy for the indications of urge incontinence, urinary urgency frequency, and nonobstructive retention. As defined in the study protocol, urge incontinence is defined as an involuntary loss of urine associated with the strong urge or desire to void. Urgency frequency is defined in the study as an uncontrollable urge to urinate, resulting in very frequent and small volume voids.

And nonobstructive retention is comprised of partial retention or complete retention. And in all these cases, mechanical obstructions have been ruled out before entry into the trial.

SNS therapy is delivered in two different stages. The first is test stimulation, and the second is surgical implantation.

Test stimulation is a procedure that is intended to evaluate SNS therapy on a trial basis in patients before they are considered for surgical implantation. In this procedure, a needle, a foramen needle is used to percutaneously access the sacral nerves, to provide acute stimulation in the

physician's office under local anesthetic. Once the stimulation location is identified, acute stimulation is applied to the subject, and the physician learns how to optimize location by looking for very specific motor and sensory responses to acute stimulation. Once these locations are you identified, a test stimulation lead is passed through the cannula of the needle, percutaneously placed, and the patient is actually sent home for a trial period of three to seven days.

During this time patients will fill out in the baseline and test period entries in a diary in an

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effort to quantify the effects of stimulation on their voiding pattern. The data collected at baseline and during the test stimulation period, consistent with standard urologic research, only patients with a 50 percent or greater improvement as documented in order to consider a subject for a long-term therapy or surgical implantation.

And as advocated by the medical community and the AHCPR guideline, voiding diaries comprise the primary outcome parameter in this particular study. For each of the three indications, we selected key parameters relevant for that condition in order to determine success or efficacy of the therapy. For example, for urge incontinence, we look at the number of leaking episodes per day, the severity ranking of those leaks, and those are ranked by patients as mild, which means drops or urine; moderate, which means one to two tablespoons of urine leaked; and a severe leak or heavy leaking, which is defined as soaking the pad, diaper or patient's outer garments. And finally, we recorded the absorbent and pad diaper usage because of leaking episodes in this study.

For the indication of urgency frequency, we looked at frequency of voids, volumes voided, and the perceived degree of urgency prior to voiding.

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And finally, for retention we looked at catheter volumes in this study.

Study enrollment was based on very specific inclusion an exclusion criteria in this

trial. It is important to note that in this study, as noted in the inclusion side, patients must have demonstrated failure of conservative therapy or conservative therapy was deemed medically inappropriate for that patient before entry. And although the literature may suggest that SNS therapy may be beneficial for other subpopulations or indications, we purposely excluded neurogenic conditions, primary pelvic pain and primary stress incontinence in order to minimize the potential for confounding factors for this particular study.

And here's how the clinical study design worked. Within each of the three indications that we studied, all patients underwent test stimulation. A positive response to test stimulation, meaning a 50 percent or greater reduction in their primary symptoms resulted in randomization in the study to one of two treatment arms. In the first arm, control, the control group patients did not receive SNS therapy; they were allowed to continue standard medical care for a period of six months. The

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standard of care included treatment such as pharmacologics, biofeedback, et cetera. At the end of the six-month waiting period without stimulation, if appropriate, they were allowed to cross over to the treatment arm of the study.

In the treatment arm of this study, subjects were immediately implanted with the SNS system and were followed then post-implant through a period of six months. After the six-month implant visit, subjects returned to the clinician's office and underwent as part of the patient consent what's known as a therapy evaluation test, in that the investigator deactivated the stimulator and over a period of several days documented the voiding diaries that patients filled out to see what happened to their behavior with stimulation off. After returning, if they wished, they may have the device reactivated, and they're followed every six months until the study was terminated.

In this particular design, this randomized design, efficacy was evaluated at three points: Six

months, treatment versus control stim on versus no stimulation; at therapy evaluation, stim on versus stim off; and then of course on chronic follow-up, stim on long term versus no stimulation at baseline.

Safety was prospectively documented throughout the follow-up period. Now, the investigators were successful in designing a study protocol that was randomized that could document the effects of SNS therapy, however, long debated the issue of incorporating a placebo control. The investigators, the FDA, Medtronic agreed that a sham implant was not merited in this highly refractory population. And more importantly, because patients during test simulation become very attuned to the sensations of stimulation, which involves sensations of pulling in the rectum, of tingling or vibration in the perineal or genital region, it logically follows that in an implant setting, these feelings are nearly impossible to mask. Therefore, alternative study designs such as randomizing to on-off, or suboptimal versus optimal, were reviewed but rejected by the study investigators.

We received FDA clearance for three different indications, but these indications followed the same protocol, used the same devices, the same outcome measurements. And because of rapid enrollment, an FDA expedited review of Medtronic's PMA application, Medtronic received clearance in September of '97 for the indication of urge

incontinence. Shortly thereafter, in April of '99, the additional indications of urge frequency and retention also received FDA clearance.

And to characterize the chronic safety and effectiveness of SNS therapy, Medtronic continues to sponsor an ongoing five-year post-approval study, and those results are still being collected. I am available for questions and I thank you for your attention.

MS. CONRAD: Thank you, Dr. Oleson. I have been asked to continue with the public presentations and skip the break; just leave the room

as you wish to. This will move the HCFA and Blue Cross presentation back just a little but, but I think the panel meeting will flow smoothly. I also wish to tell you that we are going to have a working lunch, in that the panelists will be leaving around noontime, getting their lunch and bringing it back here. They will reconvene at 12:30, not one o'clock. At 12:30 we will start with the additional public presentations, if there are any, and then open panel deliberations. Okay.

Having said that, Dr. Steven Siegel, followed by Dr. Thomas Benson.

DR. SIEGEL: Hello, panel members, and

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thank you for the opportunity to present this information to you. My name is Dr. Steve Siegel, and I am a practicing urologist from St. Paul, Minnesota. And I have been a paid investigator by Medtronic, I'm a proctor, I provide educational courses for them, and my travel to this meeting has been paid for by Medtronic.

My interest in sacral nerve stimulation for voiding complaints developed from my areas of subspecialization in female urology and neurourology. This form of treatment has made a huge difference in the quality of life of my patients, and you have heard this again and again from the people that have spoken ahead of me. These are patients who otherwise would have had no satisfactory alternatives, and that's why I've been involved now for over 12 years in all aspects of this therapy, including participation in multi-center clinical trials in the 1980s, before Medtronic became involved with the therapy.

I helped to convince Medtronic to sponsor further trials, I participated in those trials, and I presented the clinical data to help gain FDA approval for this therapy in 1997. Since 1997, I have dedicated much of my personal and professional time

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to teaching and training my urologic and urogynecologic colleagues about SNS in order to help them provide the treatment for their patients. It's

been a great pleasure for me to sit here and listen to all the physicians who I either had an opportunity to train in formal didactic sessions, or in the majority, to participate hands on in one or two of the initial phases of their first patients.

I see this meeting as another opportunity to document the effectiveness of the therapy for my patients. My presentation today will provide information in five areas, the results of the clinical study, the safety, the impact on quality of life, the long-term results, and the results of a 65 and older patient survey for patient satisfaction. I have a lot of information to cover, so please bear with me if I speed along through it.

The study enrolled 581 patients for all three indications combined. The age range was very wide, averaging 43 years. The demographics basically reflect that which is seen in our clinical practice. And it's amazing to note that the average duration of symptoms of these patients was eight years. Out of the 581 patients, 260 experienced at least a 50 percent improvement in one of the primary voiding

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measures during the test stimulation, and as Kim showed you, were randomized into the trial. In total, 219 patients were ultimately implanted with the neurostimulation system at the time of database analysis.

It's important to note that the patients in this study were extensively treated for their voiding dysfunction, and almost a hundred percent had some previous form of intervention. The vast majority had tried and failed multiple drug regimens. About half had some nonsurgical treatment such as biofeedback and as you see, the frequency of this treatment went as high as 147 individual treatment episodes for a single patient. Almost 60 percent had some surgical intervention that ranged from a low of one to a high of 41 procedures for one patient.

So it's accurate to say this population was refractory to traditional treatment approaches, and had no other treatment alternative other than nonreversible surgery.

Let's talk about the results for urge incontinence. As indicated, there were 184 patients. At baseline these patients had an average of 8.9 leaks per day and 2.7 heavy leaks, and those were defined as saturating pads or diapers, or their

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clothing. They used an average of 4.8 pads or diapers per day, and they had a symptom duration of over nine years.

This is the data that compares those patients randomized to the control group for a delay of six months to those with an implanted sacral nerve stimulation system for six months. In all cases, the control group is in the darker color and the implant or treatment group is in the lighter color. As Kim described, the primary measures were the number of leaking episodes, the severity of the leaking and use of pads. As you will see for all the measures, sacral nerve stimulation produced statistically significant changes compared to control.

For the implant group, 47 percent were dry, and another 29 percent had at least a 50 percent improvement in their leaking. So in total, 76 percent were considered clinically successful, while 74 percent of the control group had no reduction in their leaks.

As you recall from our definition of heavy leaking, which was soaked pads or diapers or undergarments. For heavy leaking, 92 percent of the treatment group were considered clinical success, while the control group witnessed few reductions.

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The implant group showed a statistically significant improvement in the number of leaks and number of pads compared to the control group as well.

Just like the preceding slides, the implant group shows statistically significant improvements. Here, 50 percent of the implant group eliminated the need for absorbent pads, and an additional 37 percent had at least a 50 percent reduction in pad usage. And as you can see, there is no corresponding change in the control group.

The second population study was the

urgency frequency group, of whom there were 220 patients. Their average number of voids per day were about 13, and they had about 160 cc per void average voiding volume. Their degree of urgency was a 2 on a scale of 1, which was least severe, to 3, which was most severe. And they had an average symptom duration of about eight years.

Just like the previous data, the urgency frequency implant group data is very positive and goes in the same direction compared to the control. For the number of voids per day, 56 percent of the implant group experienced a significant reduction in the number of voids. 64 percent of the implant group experienced a significant increase in the average

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volume per void. The implant group was also clinically successful, with 52 percent experiencing lower urgency and higher volumes, and 36 percent experiencing the same urgency but at higher volumes. Obviously for these patients, the optimal outcome is to have a lower degree of urgency and a higher voided volume.

For the retention group, there were 177 patients who had nonobstructive retention. These patients were basically dependent on a catheter in order to empty their bladder, and they averaged about 335 cc's per catheterization, and they catheterized almost five times per day, and they had a symptom duration of about seven years.

As in the preceding populations, the implant group experienced statistically significant changes. 69 percent of the retention group no longer needed to use catheters. An additional 14 percent experienced a significant reduction in the catheter volume per catheterization and again, you can see virtually no change in the control group. With the sacral nerve stimulation therapy, retention patients voided significantly more and correspondingly, catheterized less.

To document the efficacy of the

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stimulation on versus off and further document the effectiveness of SNS on voiding function, a therapy

evaluation test was conducted at six months post-implant. The stimulation was temporarily turned off for three to seven days, and voiding diaries were again collected to compare the effects of the therapy. Results during the therapy evaluation test demonstrated a return towards baseline symptoms for all three groups when the stimulation was turned off. In all three groups, these changes were statistically and clinically significant and were similar to symptoms exhibited at baseline. This clearly indicates that the reduction of urinary symptoms observed with stimulation turned on is attributable to the therapy itself and the therapy is clearly reversible.

Here are the results for the urge incontinent group, where you can see that at baseline, they voided almost 11, had 11 episodes of incontinence per day, versus 2.9 with stimulation on. And then with it off, went back up towards the baseline. The results for the urgency frequency group shows the number of voids at baseline of 16, down to less than nine, and then pack towards baseline with stimulation turned off. And lastly,

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retention, volumes per catheterization decreased markedly with stimulation on, and increased toward baseline with stimulation turned off.

Next, I want to talk about the safety data. Safety results were based on a combination of information from all three study groups, including urge incontinence, urgency frequency, and retention. This was permitted as the identical devices and protocols were used for all three groups. For the test stimulation procedure, there were 181 adverse events out of the 914 test stimulation procedures. The most common event was migration of the lead, resulting in loss of stimulation during the test period. This frequently resulted in a repeat of the procedure so that a solid determination could be made about any change in symptoms from stimulation.

Since the study, the test lead has been redesigned to a coil design, which is intended to minimize the potential for lead migration. There

were no long-term clinical sequelae from any of the events, and all adverse events were resolved with no permanent injury to nerves.

Of our 219 implanted patients, 52 percent experienced an adverse event, which ranged from pain at the site of the neurostimulator, infection or skin

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problems, to minor concerns such as skin irritation. 91 percent of the events were resolved at the time of original study database closure. It's important to note that no event resulted in a permanent nerve injury.

A little more than half of the adverse events required some surgical intervention. This included repositioning of the neurostimulator due to pain. It's now most often implanted in the upper buttock instead of the lower abdomen in order to reduce this risk, and also, revisits included repositioning of the lead due to migration. The lead was redesigned to permanently attach the anchor to the lead body, which is intended to reduce lead migration. I will discuss a little bit more about that in a moment.

Next I want to emphasize the quality of life data. We used the SF-36 Health Outcomes Survey, which as you know, is a validated measurement tool for collection of quality of life information. The following three charts compare the implant group which is in blue, with the control group in red, and US normative data is on the top in light green. For each of the eight scores, the range is between 0 and 100, and as you can see from the normative data, even

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a healthy person doesn't rate everything at a hundred percent.

For urge incontinent patients there were significant improvements reported in several of the categories. You can note the differences between the implant group and control group that were statistically significant in both physical functioning, general health and vitality.

The most dramatic changes were seen in the urgency frequency patients, and they had significant

improvements in many of the categories. These patients showed scores that were significantly higher than the control group on seven of the eight variables. For all three populations studied, this was clearly the group that was most negatively impacted by the baseline symptoms and most dramatically improved with sacral nerve stimulation.

For retention patients, there were statistically significant differences seen in the scores for bodily pain.

Overall, the clinical study showed that sacral nerve stimulation provided to a refractory group of patients resulted in a statistically significant improvement in primary voiding measures. And these improvements were also accompanied by

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significant improvements in the various domains of the SF-36 outcome survey.

While I mentioned device improvements during the adverse events information, I want to recount the specific device advancements that have been made as a result of the clinical study. Difficulty with migration of the test lead during the test stimulation period led to development of a coiled wire design for the lead. The intention of the design is that it uncoils to stretch before displacing. The new test stimulation lead design uses a nondiscrete electrode, which eliminates the possibility of separation by advancing the foramen needle over the lead after it's been inserted. Additionally, adverse events experienced led to the development of a change in the implant lead. Originally, the anchor used was separate from the implant lead, and now we use a preattached fixation point to avoid snaking of the lead or lead migration.

Next, I want to show you the long-term results from all three study populations. Consistently, there were sustained clinical results for urge incontinence. These are the percentage of patients who have a greater than 50 percent reduction in leaks per day as you can see now, out to 48

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months. For urgency frequency, over half the

patients have a 50 percent or greater increase in the volume voided per void now followed out to 36 months. And for the retention patients, more than 70 percent of the population have eliminated catheterizations or are experiencing a 50 percent or greater reduction in the residual catheterized volume, now out to 36 months.

By way of summarizing the study, sacral nerve stimulation is providing sustained efficacy for all indications in populations of patients who were refractory to all other treatment. Sacral nerve stimulation is safe, it's reversible, and it doesn't preclude alternative treatment.

I know that the panel will want to focus on how this therapy works for patients over 65 years of age. To augment the clinical study and long-term data we just reviewed, a survey of patients 65 and over was undertaken. 140 patients in Medtronic's device registry over 65 years were sent a survey about their experiences with SNS, and 68 provided responses, and here's what was learned. The median age of the respondents was 73, and over 90 percent reported that they had urgency frequency or urge incontinence as the reason for the SNS implant. Like

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patients in the clinical study, the responders had experienced voiding dysfunction symptoms for a median of eight years. Nearly 100 percent indicated that their physician recommended over treatments prior to SNS implant, and about 60 percent had some type of surgery for their bladder problem. They indicate the following. 93 percent are using the implanted system. 75 percent are satisfied with the results. The median improvement in symptoms was 70 percent. 87 percent would recommend the therapy to others. And 84 percent would repeat the surgery. Overall, two-thirds of them are using the system, are satisfied, would recommend it to others, and would repeat the surgery. Clearly, there are substantial results and satisfaction among Medicare aged patients regarding sacral nerve stimulation.

In conclusion, I would like to point out that this is a very clinical presentation of a

scientific study that I think shows that there were dramatic and positive results in the management of these patients' refractory clinical syndromes and that impact their quality of life greatly. You've heard many of the physician presenters who are motivated to come here on their own behalf, speak of specific clinical instances from their own practices,

which are very compelling, and that's what I would like to point out to you, that each one of these data points discussed today represent an individual who has had their great suffering alleviated dramatically by this therapy. And I appreciate very much the opportunity to bring this to your attention in the hopes that it will become available for patients in the Medicare age population. Thank you.

MS. CONRAD: Thank you, Dr. Siegel.

DR. MAVES: Dr. Siegel, this is a very well done study. Can you help me with some numbers, because I'm having a little trouble following some of the patient numbers, and just sort of help me with this.

DR. SIEGEL: Sure.

DR. MAVES: You start out saying you have 581 patients total involved in the study, of which 219 received implants. But then when we go back through, for instance when you look at the urge incontinence, for instance, I think it's hard to sort of say that the number of implants that you were looking at when you said there's a 76 percent clinical success, there's only 34. And similarly, when you go back through the other categories, retention, I think there was 29 implanted, and for

the urge frequency, 25 implanted. So the numbers sort of deteriorate.

And then when we get back to looking at some of the other factors in the end, such as the long-term results of urge, urge frequency and retention, the numbers seem to go back up. Explain to me sort of the rationale and how to follow that, because you sort of start out with a big N and you go gee, you've got some real power here. It seems to go

down when you're looking at the categories and then reappears.

DR. SIEGEL: That's an accurate observation, and basically it has to do with the design of the study. We had the large number of 500 some odd patients to begin with. Those were all the patients who underwent a test stimulation. Of that group of patients, roughly 50 percent, or 260, actually had at least a 50 percent improvement in one of the key symptom variables for whatever category they were being enrolled in the study in, so that's where that half of the patients went.

Now, in the study design where there is a control arm and an immediate implant arm, in each individual category, the total pool of patients that were going into the urgency frequency group were

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split in half again, and so you're looking at the half of the patients that were implanted versus the half of the patients that served as control. So there again is where that N decreases.

Now, in the longer term study arms, what's happening is that some of those patients that were in the control arm, actually virtually all of those patients were then given the option to go on to implantation, so they matriculated into the implantation arm and you're seeing those patients again in terms of the long-term study.

DR. OLECK: I have I guess a follow-up question on that, and I have a couple of other questions. Beyond what you describe here though, when I was looking, and some of these numbers come from the TEC assessment, I guess they had looked at more things that were just in the articles there. It looked like there were a number of case, for example in the urge incontinence, I think they had said there were 98 patients that were randomized and yet, the report was only on 76 of them. In the urge frequency study, there were 80 eligible and the report was only on 51 of them.

In going through the report, well, primarily the TEC assessment, it looks like, first of

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all, there were some people who were randomized, a good number of people who were randomized to the implant group who didn't have the implant. There were also a number of people who said well, they didn't have data at six month because the study was closed out before they reached that six months. I mean, that is really surprising to me that in a study which is supposed to define the usefulness of this, that the study was closed out before the six-month variable or the six-month end point for such a large number of people. Can you explain that?

DR. SIEGEL: That is what happened, in the sense that when this data was presented to the FDA in 1997 and that data was used as a basis for some of the initial publications for the efficacy in urge incontinence, not all the patients had been implanted and followed out to six months, and therefore, they were not included in that database analysis, so that's what that statement meant.

And as far as other patients that were randomized to the implant phase that did not go on to implant, I am not aware of what the specific percentage of patients that represented, but my honest impression is that it was a very minute percentage and indeed as I emphasized, virtually all

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of the patients who were randomized to the control arm ultimately went on to be implanted.

DR. OLECK: I guess the other question I had concerns the exclusion for the neurological patient, in terms of why those were excluded, whether there was some idea those people would respond differently to that. Apparently there wasn't any formal mention made of that exclusion in the FDA approval. Does that mean this shouldn't be used in those patients, or can you explain that.

DR. SIEGEL: Well, that has to do with the strategy of the study to gain FDA approval. In other words, we want to pick cherries and show that we can bake a cherry pie. And so what we wanted to do is pick the most clear-cut individuals that would have the greatest chance of success. That doesn't mean that individuals who have an underlying neurological

disorder might not improve, but say for example patients with M.S., which is a disease that the symptoms may wax and wane, if we implant the patient who had M.S. And then the therapy became less effective for that patient, does that represent a primary failure of the therapy or does it represent the fact that the target disorder is changing. And we didn't want to have to answer those questions in

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order to gain the FDA approval.

At this point, there is good clinical expectation that those patients would improve and they should be the subject of further study to document the effectiveness in specific patient populations, like partial spinal cord injury, or M.S., Parkinson's, et cetera.

DR. OLECK: It seems if we're talking about neruomodulation to people who have neurological diseases, if it doesn't apply to them, that would seem to be a significant group to raise a number of questions about whether it would or it wouldn't be effective or as effective in that group of people.

DR. SIEGEL: What I would say again as an answer to that question is that I believe personally that this therapy would help a significant proportion of those patients. And as a scientist, I believe that it needs to be demonstrated with well designed clinical studies that those patients are impacted with the therapy.

DR. GARBER: Ken?

DR. BRIN: I wonder if we could focus for a minute on the Medicare population. How many of the patients in the original study were of age 65 or older, have you done a subgroup analysis, did these

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patients tend to be the ones who had greater complication rates, were the success rates identical, worse, better, can you share with us some of that date?

DR. SIEGEL: I think I can share with you that data. We had -- I believe there were eight patients?

DR. GARBER: Yeah. Miss Oleson, you can

respond if you'd like.

MS. OLESON: There were nine subjects who had 12-month follow-up in the clinical study who were age 65 years and older. And I believe at the most recent administrative closure, we have about 50 percent of those patients demonstrating a 50 percent or greater improvement in their symptoms, so it appears to be consistent. If you look at other prognostic factors, just by looking at age categories, we found that age is not a prognostic factor in terms of potential for success, so we have concluded from looking at that factor as well as others, including potential for revision surgery, duration of symptoms, number of test stimulations, et cetera, that basically test stimulation appears to be the one factor that helps to select patients which are more amenable to surgery.

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DR. GARBER: Well, maybe I could ask Ken's question in a slightly different way. Two of your slides, Dr. Siegel, were about the safety data, the test stimulation based on implantation. There were 914 patients in the test stimulation phase and you didn't give the number for implantation, but presumably this is larger than the clinical trial because there were more people in the implantation test.

DR. SIEGEL: No, I didn't mean to represent it in that way. There were 914 test simulations performed on the 500 patients.

DR. GARBER: On the same sample.

DR. SIEGEL: Right. So it means that some of the patients had two test stimulations.

DR. GARBER: Do you happen to have the data that appear in the (inaudible) follow-up implantation stratified by age. The subsequent table is the one that said 15.3 percent had pain at neurostimulator site, 9 percent in pain, et cetera.

MS. OLESON: I'm trying to understand.

DR. GARBER: Divided by age above or below 65, for example.

MS. OLESON: We have looked at as a cutoff age of 59 because we had so few patients who were 65

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and older.
DR. GARBER: That's fine.
MS. OLESON: And are you looking at the potential for efficacy?
DR. GARBER: No, this is only safety data, so it's the adverse effects associated with the implantation. I'm just curious if the rates differed in any systematic way.
MS. OLESON: No, they did not.
DR. GARBER: Okay, thank you.
DR. OLECK: And commenting further on the age thing, I guess, we've heard a lot about how this does seem to be a problem affecting, urinary incontinence affecting the Medicare age population. I guess I'm just surprised that, why the study population was then so heavily weighted or was more heavily weighted to a younger population rather than to the Medicare age population.
DR. SIEGEL: Well, this is a classic catch-22 in the sense that we were expected in performing this clinical study to obtain insurance reimbursement for the patients that participated in the study, and patients that were 65 years of age or older were not allowed to participate in a clinical experiment. So for that issue, we didn't enroll
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those patients and that was basically the reason.
DR. GARBER: Ken.
DR. BRIN: Just a question with regard to learning curve and complication rates. Have you analyzed your study data to take a look at whether complication rates decrease substantially with number of procedures by the surgeon performing this, or is it randomly distributed?
MS. OLESON: The revision rates were equally distributed amongst investigative sites. We also looked at the early implants versus the later implants, and there was no statistical difference observed.
DR. SIEGEL: I can just say from my own clinical experience now with over 12 years of this therapy, and witnessing many of my colleagues getting

started with the therapy, that there is a substantial learning curve and that both issues of patient selection and the risk of complications associated decrease with the experience of the physician.

MS. CONRAD: Thank you, Dr. Siegel. Dr. Benson, please, followed by Martha Goldberg Aronson.

DR. BENSON: Good morning. My name is J. Thomas Benson. I'm a urogynecologist in Indianapolis, Indiana. I'm at the University of Indiana and I direct a urogynecology fellowship. The fellowship is actually in female pelvic medicine and reconstructive surgery. This fellowship is three years in duration and it's accredited by the American Board of Obstetrics and Gynecology, and by the American Board of Urology, I think probably the first time a fellowship has had double board accreditation. It's open to graduates of either OB/Gyn residencies or urology residencies, and at the end of their four-year residency or five-year residency, they come and spend three more years in fellowship. So it's a lot of training. So our patient population are women with pelvic floor disorders. It's tertiary in that almost all of our patient have failed surgeries elsewhere and end up coming to us for care.

In this overview I would like to tell you how we select patients for sacral nerve stimulation therapy, describe three representative cases from our practice, and discuss what we can learn from these cases.

First off, when a patient comes to us with this problem, even though it's tertiary, we will still begin with the less interventional techniques. Diagnosis is established first to determine if the patient has stress incontinence, urge incontinence, or a combination or some other disorder. Then behavior modification is employed, behavior modification including diary, examinations, examining what they take in, fluid intakes, et cetera, modifying caffeine intake, smoking, so forth. Then pelvic floor rehabilitation is carried out with

either biofeedback or functional electrical stimulation, and most of that care is performed by physical therapists that work with us in our group. Then the patients most often will go through pharmaceutical management if they have not had improvement with the behavior modification and pelvic floor rehabilitation efforts. And then pharmaceutical managements lead to a fair degree of success.

The ones that have failed all these then are candidates for sacral nerve stimulation testing. That is our algorithm for getting to these patients. Otherwise, these patients who have failed all these other therapies would be thinking of a very invasive surgery such as bladder augmentation.

Three examples of our patients: Patient HS, this person is a personal physical trainer. She's from Germany, very proud of her physique, she's

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41 years old, but she has severe disorder. Interstitial cystitis was her diagnosis, and she had had two bladder augmentation surgeries, trying to increase this. She had had several hospitalizations for bladder hyperdistention prior to the bladder augmentation surgeries. Because of the bladder augmentation surgeries, the detrusor muscle was removed, and so she was unable to void on her own, and so she had to self catheterize. She self catheterized 30 times a day, seven to eight times t night; she had never slept more than 45 minutes at this time.

She was so severely depressed by this, she could not work, could not do an activities, and seriously was contemplating suicide, was under psychiatric management for this. She learned about sacral nerve stimulation on the Internet and obtained a referral, and she had a dramatic response to the test stimulation. She went to seven voids per day, seven catheterizations per day. She had no nocturnal episodes of having to get up to catheterize. She of course cannot empty her bladder because she doesn't have a detrusor, but now she has a normal life with seven to nine self catheterizations per day.

Next patient, SH is a 28 year old female patient who had inability to urinate. She had nonobstructive urinary retention. She also had a severe constipation disorder that in this young 28 year old led to a colostomy. She would self catheterize for urinary retention beginning when she was 16 years old, had never voided on her own since that time. With her test stimulation results she was able to urinate voluntarily. We implanted her over two years ago and she has never self catheterized since that time. She even had the colostomy taken down.

The next patient is RE, which is sort of typical of the group over 65; a very frequent condition in people over 65 is a condition called DHIC, detrusor hyperreflexia with inadequate contractility. So these poor unfortunate ladies cannot empty their bladder well and yet it's constantly emptying on its own when they don't want it to. So they have both ends of the problem. This particular patient had a combination of the retention urge incontinence, and she'd had four surgeries for incontinence at various points in her life and had failed medical management. Her diary showed 14 voids per day, four self catheterizations, three to four heavy leaks requiring her to wear diapers.

With her test stimulation results, she went down to one leaking episode per day, did not have to self catheterize, and had a frequency of nine to ten voids per day. At 12 months post-implant, she has no accidents, does not have to self catheterize, and has nine voids per day.

We can learn a lot from these cases. We can even start getting an idea, and are doing a lot of investigational work trying to figure out why this therapy works so well. We still don't know the exact answers, but we do know that it has a lot to do with the reflex pathways in the pelvic floor, it has an awful lot to do with the afferent pathway, not just the motor pathway. And several studies are showing this and coming together to show how it changes

sensory thresholds, showing how it works better in people that have intact pelvic floor reflexes, et cetera.

The bottom line though for physicians and for the patients, is what a difference this makes in their lives. You have heard that over and over this morning and I would add to that, I have been doing this kind of work now almost 30 yours and I would have to say this is probably the single most gratifying therapy that I have been able to have to

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use for my patients, because this group is so difficult to treat otherwise. Thank you.

MS. CONRAD: Thank you, Dr. Benson. Okay, finally, Martha Goldberg Aronson.

MS. ARONSON: My name is Martha Goldberg Aronson and I am the general manager of Medtronic functional stimulation. I want to very briefly review several important topics, including physician training, evaluation and adoption of sacral nerve stimulation.

As you have already heard this morning, as part of the FDA approval, Medtronic is required to thoroughly train physicians in the use of SNS. The approval requires that SNS be prescribed only by physicians experienced in the diagnosis and treatment of lower urinary tract symptoms, or urologists and urogynecologists. Medtronic trains these physicians through a didactic one and a half day classroom training course which includes cadaver work, and that is then followed by the proctorship process, whereby a proctor stands next to the physician for their first two test stimulation procedures and then again is proctored for the first two implant procedures. And this is done, performed by a physician who is experienced in utilizing sacral nerve stimulation.

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Additionally, we have on-site training centers available if a physician requires or requests additional training on the therapy. So far, 538 physicians have attended a workshop. We estimate that we will continue our training efforts with an anticipated 200 additional physicians to be trained

each year. Currently, 189 have fully completed the proctoring program and are actively using the therapy in their practice, and 88 physicians are in the process of proctorship.

We are very pleased with the enthusiastic adoption of sacral nerve stimulation by the physician community. Later today you will be hearing from Dr. Lefevre from the Blue Cross/Blue Shield Technology Evaluation Center on reported evidence on sacral nerve stimulation. I think it's also important to know about the level of scientific scrutiny by other technology assessment organizations. In addition to Blue Cross/Blue Shield assessments, SNS has been evaluated by Hayes, ECRI, and numerous payor organizations.

For the record, Medtronic requested that the panel address all three indications. We acknowledge that HCFA has only asked the panel to address two indications, urge incontinence and

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urgency frequency. Our understanding and our request is that HCFA consider all three indications, urge incontinence, urgency frequency, and retention in its coverage policy considerations. This substantial level of evaluation has been fueled by a high level of publication. Since early 1999, 19 peer review articles have been published or accepted for publication. SNS has also been the subject of numerous abstracts, posters, and presentations at scientific meetings. This has served to increase awareness as well as adoption of the therapy.

As evidence of this, you can see that commercial payors have made positive coverage decisions on hundreds of SNS cases. Over 60 have issued a written coverage policy. Further, local medicare jurisdictions have been active in providing coverage, 34 have issued positive coverage policies, 13 provide individual case coverage, and three jurisdictions are developing coverage policies, for a total of 50 out of 52 jurisdictions. Almost all Medicare beneficiaries have access to this therapy. Thank you very much for your time and attention.

MS. CONRAD: Thank you, Miss Aronson.

DR. OLECK: Question. I don't know if you can answer or one of the other people. In terms of other conditions that are being looked at now besides the three that are listed, are there active studies looking at this for other conditions, particularly, it was mentioned to me before, the neurological patients, but I was wondering for stress incontinence or the primary pelvic pain patients that were one of the exclusions, or other things.

MS. ARONSON: The most active trial going on right now is utilizing sacral nerve stimulation for bowel disorders. There is an active study group underway with that and in fact we do have CE mark approval for that device to be utilized for that in Europe, so that is underway. There are also other, we have a small study underway to look at the effectiveness of sacral nerve stimulation in the multiple sclerosis population, and in addition, we are aware of some additional physician sponsored work that is going on, but those would be the two main areas that Medtronic is involved in.

DR. OLECK: Thank you.

MS. CONRAD: Thank you. Continuing with the program, Dr. Mitch Burken.

DR. BURKEN: Good morning. My name is Mitchell Burken and I'm a medical officer with the HCFA coverage and analysis group. I'd just like to say, or I'd like to embellish some of Ms. Doherty's earlier points before turning the program over to Dr. Frank Lefevre of the Blue Cross/Blue Shield Association, however, the intervening public speaker have also included this information.

I think we've seen this diagram earlier in some slightly different forms, but here we go, here we have the pulse generator that's implanted subcutaneously, wire passing through the sacral foramen and enervating the sacral nerve roots, and there's multiple points of enervation, but most notably the bladder.

Urge incontinence, as we have discussed earlier, is the involuntary loss of urine associated

with a strong desire to void, and this is urgency, and it's usually associated with involuntary contractions of the detrusor muscle. Such detrusor instability can occur in both individuals with and without specific neurological disorders.

The urgency frequency syndrome is well described in the article by Brubaker and Sand from 1989. Urgency frequency syndrome is the multifactorial presentation of urinary frequency, that is, voiding intervals of two hours or less, or more than seven times per day, combined with urgency,

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which is a powerful sensation to void regardless of bladder volume. Patients may have easily treatable causes such as uncomplicated cystitis. However, bladder neoplasm or interstitial cystitis may have the same presenting symptoms. The increasing incidence and prevalence with age is due to several factors such as atrophic changes in the epithelium and the muscle composition of the urethra, as well as the predilection for iatrogenic causes such as catheterization and other instrumentation.

Now, I have a working definition of refractory. It's important to note that this term refractory is very central to the charge of the MCAC today, and as a working definition, the patient has already failed an attempt at one or more of the following modalities: Behavioral therapy such as prompted voiding or pelvic muscle exercises; pharmacology such as anticholinergics; and surgery. And earlier speakers have gone into these therapies in more detail.

Finally, I just wanted to make the point that the MCAC packet includes different types of evidence, it includes the clinical trials data which has been described and which Dr. Lefevre will also go into. But there is also case series data which is in

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your packet, along with some tables which summarize those case series reports. On the right-hand side of the diagram is an alternative approach where clinical trials data is used only and other approaches are set aside and not reviewed.

Thank you, and Dr. Lefevre will follow.

MS. CONRAD: I invite Frank Lefevre to the microphone please. Thank you, Dr. Burken.

DR. LEFEVRE: I want to thank the panel for the opportunity to present our assessment of this technology today. My name is Frank Lefevre from Blue Cross/Blue Shield Technology Evaluation Center, and also from Northwestern University.

The objective of our assessment was to determine whether sacral nerve stimulation improves health outcomes for patients with refractory urge incontinence and urgency frequency syndrome. We used an evidence based approach to perform this objective and we will look today at the adequacy of the evidence, both considering the methodological quality of the evidence and the magnitude of effect, and we will also consider the relevance to the Medicare population.

Just a brief word about the Blue Cross TEC center. It's one of the longest standing and most

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well established technology assessment bodies. Established in 1985, has to date performed over 400 full length technology assessment reports, and follows established rigorous methodology for evidence based medicine, which includes external review by our medical advisory panel, and this assessment has been reviewed and approved by our medical advisory panel. The TEC program has established partnerships with Blue Cross plans as well as with Kaiser Permanente since 1993, and since 1997 has been one of the 12 evidence based practice centers of the AHRQ. This reflect an evolution of the TEC program from an entirely proprietary organization in the 80s to a more publicly available program, and in fact the TEC program will in the next year or two become entirely publicly available and all the TEC assessments will be available to the public and to consumers as well as physicians outside of the TEC program.

We used systematic review methodology for approaching this question and these are the steps that we follow in this methodology. The first step is to establish a problem formulation, and the

problem formulation in essence will define for us what are the patient indications for this procedure, what is exactly the intervention that we are talking about, what are the outcomes that we will be interested in, and then finally, what are the comparison technologies that we want to compare this to.

Following the problem formulation, we would develop a priori study selection criteria which will define what types of study will be adequate for answering our question that we posed. Then we would systematically search the literature for any studies which meet this selection criteria, we would abstract the outcome data that we have decided is relevant to the assessment, and then go ahead and synthesize the data, either qualitatively or quantitatively, depending on the data available.

The problem formulation for this assessment includes first of all, the patient indications and as was stated before, refractory urge incontinence and refractory urgency frequency syndrome. We define refractory as patients who had failed conservative treatment, and under conservative treatment we would place both behavioral modalities and drugs. The issue of whether someone should fail surgery prior to this is questionable, but we didn't feel that was an appropriate indication to include, so we defined conservative treatment as drugs and/or behavioral therapies, although many patients who end up getting this technology have already went through surgical procedures.

The intervention was defined as an implantable device that delivers controlled electrical impulses to the sacral nerve roots with the intent of modulating the neurological input to the genital urinary system.

Now the outcomes we considered important are listed here. Now the main outcomes in urinary incontinence are derived from patient recorded diaries, and when patients mainly record the number of incontinent episodes or the number of times that

they void and then starting from this data, you can calculate the outcome measures that we have here. First of all, what's the percent change in the frequency of incontinence and/or the frequency of voiding. And this a prepost kind of measure as to the percentage of change overall.

The percentage of patients improved is often used as another outcome measure, and a 50 percent improvement in incontinence has been defined by urological societies as a clinically significant improvement. And so we would agree that percentage of patients with a 50 percent improvement is a

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clinically important measure which can also be looked at.

And lastly and perhaps the most important measure, the percent of patients who are cured. And when we're talking about urge incontinence, the percent of patients who are cured are those who have no further incontinence. When you're talking about urgency frequency syndrome, the percentage of patients who are cured are those that go below a predefined threshold of what's normal voiding, and that is typically defined as seven or less episodes per day.

The second category of outcomes, which may be very important, are quality of measures, and we will talk about some quality of life measures, the SF-36 that are included here. And then finally, we will compare these beneficial outcomes with adverse events outcomes to determine the net risk-benefit ratio.

The comparison treatments are a bit problematic in this assessment because of the issue of the definition of refractory and what are the appropriate comparisons. For someone who has gone through all the available treatments, including surgery, then the appropriate comparison is really no

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further treatment, because they really have no alternatives. However, for patients who have only completed conservative treatments, meaning behavioral and pharmacological therapy, then surgical

alternatives are an appropriate comparison group.

Under surgical alternatives there are quite a number of different variations of surgery and I've listed three for here. For urge incontinence particularly, there's the enterocystoplasty, this was referred to as an augmentation cystoplasty. There's also bladder denervation procedures, where the nerve impulses to the bladder are interrupted. And also a newer procedure called detrusor myeloectomy, where part of the detrusor muscle is taken out. Any of these could be considered a viable alternative to sacral nerve stimulation for certain patients.

Finally, urinary diversion can't be considered a comparison treatment. This is a permanent catheterization or cystectomy with permanent suprapubic catheterization, but this is really not an acceptable alternative for the majority of patients that we will be considering for this treatment.

So, our study selection criteria was full length published literature in the English language,

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and it was refractory urge incontinence or urgency frequency patients, and we did require that we would want to see a concurrent comparison group which was not treated with sacral nerve stimulation. This was important because it did exclude many of the case series or clinical series of this technology which are available, but we did not feel that offered strong evidence as to the true efficacy of the procedure. And finally, the reports would have to report on at least one of the relevant outcome measures that we talked about.

And then our key question, just to repeat, is for patients with refractory urge incontinence or urgency frequency syndrome, does treatment with the sacral nerve stimulation improve health outcomes?

Now, there were two articles about the selection criteria, one in each category, and these were both populations drawn from the same multi-center study sponsored by Medtronic. Now we've heard a lot about this study today and I think what I'll try to do in the interest of time is not to

spend a lot of time on the results per se; the results that have been presented are very much the same as what I have, but try to focus more on the interpretation of the results from our perspective,

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and are they valid and what do they mean.

There were several stages to this study, as was mentioned. First, the test stimulation, the peripheral nerve evaluation test. Secondly, the randomized portion, in which sacral nerve stimulation was compared to a control group, a waiting list control. This was supplemented with the cohort analysis, which was a longer follow-up of all patients who received the technology. And finally, the therapy evaluation test where the stimulation was turned off and outcomes were reevaluated at that point.

The patient population defined here, we've seen some of this data before. Evidence that there has been extensive prior treatment in these patients, although the exact prior treatment is not standardized. Patients may or may not have had either or any of these treatments. For example, most patients had drug treatment, almost all the patients had drug treatment. Somewhat over half had prior surgical procedures. Somewhat less than half overall had had nonsurgical procedures, which would include the behavioral treatment. And the number of prior procedures are listed here for each of the categories, an average of over one surgical procedure

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per patient in the urge incontinence, and over two surgical procedures per patient in the urgency frequency group. And also, a significant number of nonsurgical procedures.

The average length of time of symptoms was between seven and nine years, and the baseline amount of incontinence or degree of severity of illness was actually quite high. So I think there is evidence that this is a severely ill population with extensive and longstanding prior treatment, even though it's not totally standardized as to what that was.

This was also discussed previously, sort

of the flow of the patients through the study, and I just listed here for each of the categories again, the urge incontinence and the urgency frequency, the number of patients who enrolled in this study; this is the number of patients who were eligible by the eligibility criteria of the study in each category, 155 in the urge incontinence, and 222 in the urgency frequency syndrome. Of these, the second line gives you the number of patients who passed the test, the peripheral nerve test phase, and were randomized. Of the 155 urge incontinence patients, 63 percent of them passed the peripheral nerve test; a total of 98 were eligible for randomization.

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And in the urgency frequency group, it was somewhat less. A little more than a third of the patients in this group passed the peripheral nerve test and were eligible for randomization. A total of 80 were eligible for randomization in this group.

And finally, the patients evaluated at six months. This was again, mentioned before, and somewhat less than the number of patients who were randomized. Most of the patients who were randomized but were not evaluated at six months had not reached the six-month time point at the time of the study reporting. It was not truly dropouts; the number of dropouts was somewhat less, I believe it was about 10 percent overall that were true dropouts. So this number of patients evaluated is a subset of the number of patients implanted but it is more a function of who reached the time point at the time the study results were reported.

These were results we have seen before. This is the percent change in incontinence or in voids. For the urge incontinence group it's the percent change in incontinent episodes, number of leaks per day. For the urgency frequency group, it's the change in the number of voids per day. A 73 percent reduction for the urge incontinence group in

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the number of leaks per day, compared to a 22 percent worsening in the control group, statistically significant at 0.00 -- less that 0.0001. Somewhat

less impressive results for the urgency frequency group, with a 45 percent overall reduction in the number of voids per day compared to virtually no change in the control group, again, statistically significant at the same level.

The two other outcomes, the percent of patients improved, again meaning the percentage of patients with a greater than 50 percent improvement, percentage of patients cured, 76 percent of the patients urge incontinence had a 50 percent improvement, 47 percent cured. Again, the 47 percent who are cured are perhaps the single most important outcome that we would consider in the urge incontinence group; half of the patients were cured, compared to zero percent in the control group.

In the urgency frequency group, again, not quite as impressive results, but also statistically significant. 15 percent of patients were cured, meaning they had less than seven episodes per day, seven voids per day, and 40 percent of them had a greater than 50 percent improvement.

The quality of life outcomes, again, we

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have seen these before. For the urge incontinence group, there were improvements on virtually all of the measures of quality of life, the SF-36 measures. Two of these reached statistical significance, the physical functioning and the general health. For the urgency frequency group, in contrast to the previous outcomes, these outcomes were actually much more impressive for the urgency frequency group, where there was a greater magnitude of improvement in the urgency frequency group, sometimes as high as 20 to 30 points on the SF-36 which is a very clinically significant improvement, and seven of the eight measures were statistically significant compared to the control group.

Now when we look at the RCT portion of this study, this basically is a positive study, so we would next look at, are these results internally valid, or could these results potentially be explained by systematic bias, and we would choose major areas of bias to look at, and to look at each

of these areas and the probability, the potential that these biases are present, and then also the likelihood that these biases, if they're present, might invalidate the results of the study.

As far as selection bias goes, it was a

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randomized study, well randomized. There was no indication that the groups were not comparable. A very low problem of selection bias.

Withdrawal bias, I think this is important to talk about, because of the diminishing numbers at each stage of the study. And even though the numbers were diminished, we don't think there was really much likelihood for withdrawal bias because as I said, the actual number of dropouts were actually low, and even though the final number of patients is much lower, we don't feel this is a problem for internal validity. It's more a problem for generalizability of the results. But as far as the internal validity of the RCT portion, we feel withdrawal bias was not a concern.

The main concern for bias was performance bias in this study, and performance bias means the equality of the intensity of treatment between the experimental group and the control group. And in this case of course, the implanted group had a much higher intensity of treatment. And so you can ask, was performance bias a big concern, was the placebo effect a big concern? And there was a high potential for performance bias in this study, and I'll address this in a minute.

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I think there are some other aspects of the follow-up that sort of minimize the probability that performance bias explains the results. But there is a potential for performance bias in this study.

Ascertainment bias refers to ascertainment of the outcomes and are the outcomes ascertained in an objective way, and ideally in a way in which there's no knowledge of treatment assignment in ascertaining the outcomes. And we place the potential for this bias at moderate, and this is more

a function of the type of outcomes that are used in incontinence, the fact that these are self reported outcomes, they're usually patient diaries that are used to report incontinence. And even the quality of life data is patient reported data. And of course the patients know which group they are in so there is some possibility for ascertainment bias but as I said, it's more a function of the types of outcomes that are used in studies of incontinence rather than a function of the study itself.

Now, the next thing we looked at was the adverse events, adverse effects of the procedure. And listed here, these have been talked about again, and are a relatively high rate of adverse effects

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overall, a total of over 50 percent of the patients had experienced at least one of these adverse events. The most common adverse event was pain at the implant site, and often pain at the implant site was corrected either by modulation of the stimuli or by modulation of the device itself. None of these events that were reported were considered real serious and most of them as stated previously, were resolved either with modulation of the impulse or modulation of the device.

There were in the group of urge incontinence, there were a total of six patients that required permanent explantation of the device and following explantation, the adverse effects were resolved. But it did require taking out the device in a subset, a small subset of patients.

Now the cohort analysis, I bring in here mainly as a factor to look at in terms of the randomized control trial in terms of looking at the durability of the effect and also the possibility that the difference that we saw in the randomized trial might be due to performance bias and/or placebo effect. And as stated previously, the cohort analysis shows that these effects, this percentage of patients improved is maintained over at least an 18

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to 24-month period with really no diminution of effect. Now if performance bias or placebo effect

was operating there, you would expect that there would be a fall-off in effect. Usually placebo effects are short lived and will usually either diminish greatly or disappear by six months, and certainly by longer periods of time than that. So this was taken as evidence, corroborating evidence to the RCT that the effect is durable and also that the possibility of performance bias explaining the results is lessened.

The therapy evaluation test also gives further evidence that the effect is truly due to the device itself. Where the device is turned off and the number of leaks or voids per day returns roughly to baseline, and goes back to the previous level after it's turned on again. This was also used as evidence that the effect is reversible.

Now the comparisons to alternatives, I think as I mentioned before, is somewhat problematic, and the comparisons to alternatives, especially for the urgency frequency syndrome are really lacking, although I think we can say in the case of urgency frequency, there's probably less good alternatives than in the case of urge incontinence. And the

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available treatments here, no treatment, surgical alternatives, or urinary diversion. The results of the RCT really only allow us direct comparison to the alternative of no further treatment. And this might be the appropriate comparison group for those patients who have gone through all available alternative, including surgery, but it may not apply to patients who still have a surgical alternative.

As I mentioned, urinary diversion is not really an acceptable alternative in most cases and we won't focus on that. So what about the comparison to surgery? And this would apply primarily to the urge incontinence patients but also to the urgency frequency patients, but the data, any data on this surgical alternative is really in the urge incontinence patients. So we searched for evidence of comparison in these patients, and in the AHCPR guidelines they did a pooled analysis of enterocystoplasty in patients with urge incontinence.

And of 10 studies that they looked at, they estimated that there was a rate of continence without catheterization of 38 percent. There was a higher rate of continence, I think it was more in the 50 to 60 percent range, but these patients may require intermittent catheterization to manage chronic

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voiding dysfunction as a result of the surgery itself. And another thing to mention about this comparison, it's not directly applicable, because it would include many patients with neurological origins of their urge incontinence and really what we're concerned with are patients with a nonneurological alternative.

We did find one rather large clinical series of idiopathic detrusor instability, which is more comparable to the patients with urge incontinence or approximately 42 patients in which there was a total of approximately 50 percent of the patients reported they were either cured or greatly improved. And this 50 percent could be compared to the sacral nerve stimulation population, to those who have a greater than 50 percent improvement, as probably the most relevant comparison, and there we have approximately 75 percent of patients who have improvement, compared to this 50 percent for surgery.

So as far as we can make the comparison to surgery, we can say that it looks like the sacral nerve stimulation is probably at least as good in terms of benefit if not better, and certainly, I think the case is that the surgical alternatives have higher morbidity, including significant rates of

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serious morbidity, including death and more serious morbidity.

As far as the relevance to the Medicare population, this was also discussed previously. The mean age in the population was 46 years of age in the urge incontinence and 38 years of age in the urgency frequency syndrome. We don't really have any data to say whether or not this is generalizable to the Medicare population, we don't have any subgroup analysis or stratification by age. We don't think

there's any evidence that treatment effect differs by age for any of these incontinence treatments, and there is no physiological rationale why elderly patients would respond differently. That's about all we can say about the generalizability to the Medicare population.

So in summary, the strengths of the data are listed here. The strengths of the data are that this is a well done methodologically strong study; it's a multi-center randomized control trial. It's a carefully selected population. The protocol and the outcomes are well described and well reported. I think it deserves reiterating, the prior selection of the patients, meaning the selection by the peripheral nerve evaluation test, is likely to benefit the, or

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likely to benefit, likely to maximize the benefit-risk ratio. This is sort of a choose the winner approach, you know, choose who's going to benefit, and I think you could look at this in two ways.

In terms of when you're looking at the magnitude of effect of the study in a scientific sense, it may amplify the magnitude of effect. You might reasonable decide that the denominator of patients that you want to look at would be all patients who are eligible for the device, and then the numerator would be all patients who actually end up benefitting from the device. That would give you a much smaller magnitude of effect. However, the other way to look at it is from a clinical perspective, you're not exposing patients who may not benefit to a potentially invasive procedure where they're not benefitting.

So there's pluses and minuses to it. I think from a scientific perspective, it may somewhat overestimate the magnitude of effect, but from a clinical perspective, it's certainly a good thing.

As far as the benefit, there is positive outcomes and there is a relatively large magnitude of effect on these implanted patients and the numerator

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and denominator are relatively large, but in a

statistical sense in comparison with the other studies, there is a large magnitude of effect compared to other treatments.

The results of the cohort analysis and the therapy evaluation test minimize the possibility that the results of the RCT are due to bias. And the adverse effects in the study are not serious ones. This doesn't rule out the fact that there might be serious adverse effects, I think that's important to say. A study of this type, of this duration and number of patients, is not adequate for fully determining the true rates of adverse effects and the true rates of serious adverse effects, and I think it will be important in the follow-up Medtronic study, the five-year study with larger number of patients, to better define what the true rate of adverse effects is and whether or not there are serious effects that might occur.

The weaknesses of the data, the obvious weakness is that there's only one study, only one randomized control study. There are the clinical series, but there's only one RCT. And as mentioned previously, there is only a subset of enrolled patients who achieved benefits. And if you look at

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the number of patients who actually achieved benefit to the total number of patients who are eligible, it is a minority and I think that need to be taken into account, primarily for the generalizability of the results.

The definition of refractory is not standardized and all patients did not go through the exact same prior treatment prior to the procedure. It's possible that some of the patients may have benefitted from another type of therapy prior to getting this, but we don't know that.

And then finally, the adverse effect rate is high. Even though we said it was not serious, it is high.

So in conclusions, we can say that for patients with refractory urge incontinence or urgency frequency syndrome, who have a successful peripheral nerve evaluation test, that sacral nerve stimulation

is effective in reducing incontinence or reducing the frequency of voiding and improving the quality of life. The magnitude of effect is reasonably large. We feel this is likely to be more effective than available alternatives, although this is not supported by evidence, direct evidence. And it's also likely to have similar efficacy in the Medicare

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population, although again, not supported by direct evidence. Thank you.

DR. GARBER: Thank you, Frank. Les?

DR. ZENDLE: Frank, I have two questions, and I don't know if you can answer both of them. First is, why wasn't retention addressed like the other two conditions, urge incontinence and frequency.

DR. LEFEVRE: Well, the retention data was longer getting through the pipeline than the other data, and at the time that we had done the assessment, there was no data on retention published. We had looked at the unpublished data on retention as part of our evaluation here, and decided we would like to see it go through the peer review process before we would include that in the formal review.

DR. ZENDLE: My second question is, I'm getting the sense that everybody loves this treatment and I'm wondering, is there any group that doesn't think this is a worthwhile treatment? I realize you can't get, necessarily come here and tell us, but in your looking through the literature and talking to the clinical experts, did you hear any reluctance by some to embrace it, and if you did, could you or maybe some of the people that support the therapy

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explain maybe their motivation?

DR. LEFEVRE: I am probably not the best one to answer that. I mean, I can probably comment more on the literature than the experts I've talked to, which is a subset of experts. I think of the experts I talked to, most of them were positive. I think there may have been one out of group of five or six who had greater reservations in terms of the technology had not fully evolved, we didn't know

really why it worked, we didn't know fully the mechanisms, and he wanted to see a more complete understanding of the technology prior to adoption.

As far as the evidence in the literature, I don't think there is really much dissenting view that I've seen or read.

DR. ZENDLE: There are no negative editorials.

THE WITNESS: I don't recall any, no.

DR. GARBER: Maybe -- I don't mean this to be a segue into the committee deliberations, but Frank, while you're here, there is a question I'm sure will come up in our panel deliberations and that is something you touched upon. How do you define refractory and what's a reasonable definition for the panel to use based on the data that you have

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presented? The slide that you showed that gave the percentages of different types prior to treatment showed that virtually everybody received drugs, a majority had received surgery, and then a minority behavioral therapy, but a substantial minority. And there will be a reasonable question that even though the majority had received surgery, it sounded from the tenor of all the comments that we heard today that this would be an alternative to consider before surgery in people who had failed noninvasive therapies.

How reasonable is it to draw the conclusion that refractory could be defined as something like having failed drugs and/or behavioral therapy? Would that fit with the data that you have analyzed?

DR. LEFEVRE: Well, I think that would fit with the definition that we had decided upon as refractory, as what is clinically appropriate for a definition of refractory, meaning failed both behavioral and drug therapy. I don't think you can say it really fits with the data per se, because the population that we have here, a large number of them had surgery, but I think that could only probably be in favor of the data, because the population in the

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data would be more refractory than the population that we would consider.

Although having already said that, there is a mix of that, there is a mix because there is less, you know -- I think it's hard to say, because the population is really mixed and it's not standardized as to who got the sacral nerve stimulation, what they had had previously. I think clinically it does make sense to make the definition as having failed behavioral and drug therapy.

DR. GARBER: Clinically it does?

THE WITNESS: It does make sense I think, yes.

DR. GARBER: Thank you. If there are no further questions for Frank or for Mitch Burken, we can proceed to open panel deliberations.

DR. TUNIS: I was going to make just one more comment on the question regarding retention, and I think it was mostly clarified, but we had been discussing this with the folks from Medtronic and the publication I believe is in press now for the retention data, and it hasn't actually come out yet. And so for us to provide the panel with the unpublished data would actually put it in the public domain, which we obviously couldn't do. So since the

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panel couldn't possibly discuss the data on retention, we decided that we would address that internally within HCFA, since it should come out in the time frame that we have available to us before we have to do our final decision, and we will certainly take the comments of the panel regarding this other data into account as we interpret the retention data.

DR. HOLTGREWE: Would a motion be appropriate at this juncture?

DR. GARBER: It depends on what the motion is.

DR. HOLTGREWE: I move that the committee recognize there is adequate evidence to draw conclusions about the effectiveness of sacral nerve stimulation in the Medicare population for two indications, refractory urinary urge incontinence, and refractory urge frequency syndrome.

DR. GARBER: Okay. Is there a second to that motion?
DR. SIGSBEE: Second.
DR. GARBER: Discussion? Yes, Adrian.
DR. OLECK: I just wonder whether there's any concern from the other panel members about this issue of the neurological patients. I still, neurological conditions seem to be underlying cause

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for some of these people with incontinence, and this is a treatment that is aimed at neuromodulation, and I guess I'm a little uncomfortable with the fact that those people were specifically excluded from the study and yet the recommendations we're proposing don't address that at all. Is that a concern to anyone else?
DR. HOLTGREWE: The problem you have when you include neurological disorders is it is such a mixed bag. You can't even say that multiple sclerosis patients all act the same; they're all different. And I think that it was appropriate in the studies that were constructed here to exclude these people, because it would be a confounding factor to an enormous degree. Now this doesn't mean that this might not be an acceptable technology, but I think it awaits further study.
DR. GARBER: Adrian, as I understand the way that the questions were formulated, they adhere closely, perhaps not perfectly, to the way the studies were designed, so that the indications closely correspond to the randomized trials, and I think that's perhaps one of the reasons people don't feel uncomfortable about that issue. Les?
DR. ZENDLE: I thought maybe I would just

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address two of the follow-up points that go along with that question, because I think it probably needs to be reiterated, and it came up in both the testimony and the assessment, and that's that although it is reasonable to say that the results are applicable to the Medicare population, that's not from direct evidence, it's probably from indirect evidence. And again, that doesn't in any way make me

reluctant to approve this, but I just think it should be noted.

And secondly, although this should be generalizable beyond the research setting, many people stressed the importance of training and adequate proctoring and all that, and I think the fact that Medtronic has such a good program is to be commended, but I also think we ought to state that there is a learning curve and that, I don't know how to state some concern, that only those who are appropriately trained do this procedure.

DR. GARBER: That's something you can do internally at HCFA?

MS. CONRAD: Yes.

DR. GARBER: In fact, you might want to take your point to say this is how you address whether this generalizes beyond the research setting,

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since they have instituted a training program, so under those conditions, that's how it generalizes.

DR. ZENDLE: Yes. And I don't think it needs to be in the motion but I wanted it to be in the discussion, that we agree that it should be part of, or that I agree anyway, that it should be part of the training program and that helps me feel comfortable that there's enough evidence that this is worthwhile.

DR. SIGSBEE: Just a point of clarification, I at least had understood that under the FDA approval process, this device could be sold only to physicians who met the criteria of going through the training program, so there is that barrier already in place. And so, somebody can't just decide that they're going to start implanting.

DR. TUNIS: Just also to further explore that, if any of the folk from Medtronic could comment on this. It would be helpful for us to understand a little bit more about how much of the training is required to get the typical practitioner up to speed in terms of being able to do not only the implantation, but the test procedures, et cetera? Is there any kind of comments on that in terms of the proctoring program?

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DR. GARBER: Sorry, Connie. We have to take roll call.
MS. CONRAD: Excuse me. For today's panel meeting, voting members present are Michael Maves, Kenneth Brin, Logan Holtgrewe, Angus McBryde, Bruce Sigsbee, and Les Zendle. A quorum is present. No one has been recused because of conflicts of interest. Thank you.
DR. GARBER: Sorry. You can go ahead now.
MS. ARONSON: The question is, what's really involved and how can we -- can you restate the question one more time for me?
DR. TUNIS: I'm trying to get a sense of how in any way we would be able to understand what sort of adequate training to get people who are learning this procedure up to the point where they are competent by some measure.
MS. ARONSON: Right. Well as we mentioned, the process is first the day and a half didactic course, which includes a cadaver work shop. Then the proctorship on the first two stimulations, and another proctorship on the first two implants. Following each one of those steps, it's reviewed by both proctor and the person being proctored and at that upon, if it's felt buy either party that
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additional training may be required, or if the proctor would get in and say for example, I really didn't feel comfortable that this physician was comfortable doing the therapy, as I mentioned before, we have established sites across the country of our experienced implanters, where this person can then go to one of the on-site locations and get additional training. So we really do take it to all the steps to make sure that both parties feel as though we have a proficient test stimulator and implanting physician.
DR. TUNIS: Just, I've learned for the first time that there is an FDA requirement that this training be in place.
MS. ARONSON: That's correct. When we received the initial FDA approval in September of

1997, the FDA did mandate that as a condition of approval, we would establish a training program. So this is the training program that we discussed and agreed upon with the FDA.

DR. TUNIS: Okay. So the FDA actually reviewed the contents of the training program?

MS. ARONSON: That's correct.

SPEAKER: I took the course in November, Dr. Siegel came and proctored me in February, and we

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did the first implants in March. The rep from the company still comes for all our test implants, he still comes for all my surgical implants, because I still feel like I need that feedback. It's not that he's showing me how to do anything, but he's there in case I have questions. If he doesn't know, he calls the company or Dr. Siegel, and he will actually be there until I tell him I don't want him anymore.

The other thing is not just the surgical implant of it, it's also doing the fine tuning when the patients come in to get activated, and it's not unusual to need to fine tune them several times in the first six months to 12 months. And again, the sales rep comes back for all the activations. My nurse, they went to a course to learn how to do the activations, but a lot of it is not just you push this button and this button, but it's a lot of clinical playing around and again, there are very supportive.

DR. GARBER: Do any of the panelists want to address this issue about how we define refractory, or would you rather leave the language just refractory, without a definition? I think HCFA would probably -- would you like somewhat more guidance than just refractory or not, from the panel?

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DR. ZENDLE: Really, the question is do you include surgical in refractory, and I think people want to avoid, one, many people want to avoid it, and two, it's an alternative, and it appears this has better outcomes than surgical, so why would we want to include that as a definition?

DR. GARBER: Right. You could define

refractory without requiring prior surgery to be part of refractory, if that's the way you feel.

DR. ZENDLE: Do we really need to though?

DR. HOLTGREWE: The surgical procedures that are used here are, number one, virtually irreversible and carry with them substantial risks far in excess of what we have looked at here this morning in terms of sacral nerve stimulation, so I think the algorithm would be failure of medical management and behavioral therapy, and then you go to SNS rather than going to surgery. Surgery was used because there was no other alternative at that time.

DR. GARBER: Bruce?

DR. SIGSBEE: It's been said.

DR. GARBER: I think we're all in agreement about the circumstances in which it should be used. The question is, do you want to have language to the effect that refractory means failure

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of, you might call it conservative measures, i.e., drugs and/or behavioral therapy?

DR. ZENDLE: What would the purpose of that be? Are we afraid that somehow HCFA is going to require someone to have surgical before they get this?

DR. GARBER: Well, that's certainly -- if you go straight from the studies, where you have the majority of people getting surgery, that is an inference that's possible to draw. So if you felt strongly that you didn't want to require surgery, you might want to define refractory.

DR. ZENDLE: Again, I don't think we are addressing coverage here, so I don't see a need to be really stating that.

DR. GARBER: I'm just trying to make sure we have this issue covered, so if you want to say anything, it's the sense of the panel that you don't want to define refractory?

DR. McBRYDE: It seems to me that if you do, you would have to include a time limitation too, that ought to be one of the requirements, and then define surgery, because all of them virtually I'm sure have had cystoscopy and some other procedural

stuff, so are we talking about those major surgeries.

DR. GARBER: Okay. So, the motion on the floor is the language as stated in the questions posed to the panel and the answer to the question -- Logan, you were the one who made the motion?

Dr. HOLTGREWE: I made the motion.

DR. GARBER: And it was to answer it yes, correct?

DR. HOLTGREWE: Correct.

DR. GARBER: Any further discussion?

Dr. McBRYDE: While we're waiting, can I ask two small points related to Medicare population? First of all, did any of the Medicare population in any of the studies get dry, in other words, they got a total hundred percent cure? I remember some of them did in the younger population. Did they, Dr. Siegel?

DR. SIEGEL: Yes.

DR. McBRYDE: Okay. And secondly, were any of the patients involved, even though initially they weren't suspect for any neurological disease, did any of them turn out or have they turned out in any of the studies to have some M.S. Or some sort of neurological problem?

DR. SIEGEL: I am not aware of any.

DR. GARBER: Are there any members of the public who have not spoken, or who have spoken and would like to speak now?

MS. OLESON: I would just like to address the question on defining what refractory means, and if -- the subjects in the study were indeed refractory to all forms of therapy, including surgery in 58 percent of the subjects. We also did follow after implant the use of concomitant therapies, including drugs, interventions and surgeries. And what we had seen with long-term follow-up past 24 months, the use of non-Inter-stim related surgeries dropped from a baseline of 58 percent of patients down to less than 3 percent through several years of follow-up, so that might help you to address the issue of defining refractory.

DR. GARBER: Thank you, although we have already decided not to define it, but HCFA should take that into account. Yes.

DR. BENSON: I would also like to address the question about surgery as a prerequisite. These patients have a combination of symptoms, stress incontinence and urge incontinence. Most of the surgical procedures were stress incontinence procedures, which are sort of done as the last resort in patients before you had other modalities of

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therapy. Nothing else has worked, so I'll try my stress incontinence procedure. So requiring surgery to be failed in this group would be self defeating, so it should not be a prerequisite before they go to this kind of therapy. The only real surgery for the urge incontinence group are denervation procedures or bladder augmentation procedures or shunting.

DR. GARBER: Thank you.

DR. TUNIS: Maybe this is a question for Dr. Siegal or other folks involved in the trial, but when Dr. Lefevre was reviewing some of the information about the prior therapies that patients had had, it looked like something on the order of 50 percent overall for the two indications had had prior behavioral therapy. And I guess the question to you is given the relatively high rate of adverse events, why wasn't the behavioral therapy sort of a required prior intervention.

DR. SIEGEL: This is a factor of the fact that the study took place in 22 centers, in several different countries, and the standards of therapy available to the patients differed greatly. For example in our center, 100 percent of the patients enrolled had conservative therapy including biofeedback and other interventions. And in some

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centers where this was not routinely offered, maybe none of the patients did. So I think the problem has to do with the number of study centers throughout the world that were enrolled, and I would continue to encourage my colleagues here in the United States at least to follow the standard that was discussed

today, which is some sort of trial of behavioral therapies and drug therapies before consideration of sacral nerve stimulation.

DR. TUNIS: So maybe then, and this is more in the form of badgering the panel, but they don't have to respond if they don't want to, but kind of along these same lines is that one way clearly we will be internally thinking about this whole notion of refractory therapy is whether to approach this as patient should have failed adequate behavioral therapy and drug therapy prior to going to sacral nerve stimulation, the logic of that being this relatively high rate of adverse events. That's what I would throw on the table. I'd just like to get some feedback from either the panel or the audience on the wisdom or lack of wisdom of that, given that we're going to have to talk about it internally.

DR. BENSON: When you say and there, there are some patients who cannot use the drug therapy

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where it's contraindicated.

DR. ZENDLE: I think it's common sense to say that they have to fail those two therapies, but I include failed therapy as a patient that is not able to take it or whatever, I include that as a failure. So I don't think we need to go beyond that, just because it's so common sense, but if you want us to, we could.

DR. GARBER: Yes, Mike.

DR. MAVES: You know, Sean, I think your point is a good one and it actually is something that I sat and wrestled with a little bit. I think the question is how to select the patients that receive this treatment. I think the refractory language will give the Agency guidance on that with the sense that the panel feels that ought to be, and I think, you know, how that actually gets implemented into a coverage decision is clearly in the purview of you and the rest of the folks at HCFA.

So, those are two things that I sort of thought a little bit about, but I think again, the sort of coverage itself is not our purview, and I think the refractory language helps me at least to

say, yes, I think there needs to be some sort of a selection that goes on in these patients, I have

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several questions about that, but I'm satisfied that this is not something that gets offered to patients a priori without having some, it sounds like everybody had something done in some form, and for any variety of reasons, they may or may not be able to tolerate it, and I think the refractory language captures that for me.

DR. GARBER: Bruce?

DR. SIGSBEE: Plus, I think that we have to avoid trying to micromanage clinical practice. If the clinician has an algorithm and decision process, and new information may come forward next year that modifies the sequence of how the procedures are offered the patients, and I'm not sure it's worth trying to codify regulations in this specific sequence this morning.

DR. TUNIS: Okay. I think just to further express at least the concern that I'm laying on the table is that I'm imagining that should coverage be provided for this procedure, that the number of practitioners offering it will be much higher, whether or not Medtronic has the infrastructure to provide the same level of attention and training to a much broader group of practitioners is unknown, and so the adverse event rates that are reported in these

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trials are likely to go up substantially.

And so, you know, I don't think we spent a lot of time talking about the adverse events, but that's the issue and why I'm kind of pressing on this issue.

DR. GARBER: Well, I think you have the clear understanding from the panel that first of all, this was done in a multi-institutional trial, so it is not all of one site, one person operating or anything like that. And I think if I'm correctly reporting the sense of the panel, the assumption is that this would only, that our conclusion about adequacy and presumably effectiveness, presumes that they get training similar to the training of the

physicians participating in the trials. And I don't know how reassured you should feel by the fact that that's a condition for FDA approval, but in fact that is what our discussion is predicated on, that they will get comparable training. So, that's actually better than is typical for surgical procedures. Ken?

DR. BRIN: Just to address that very directly, in my area, particularly in interventional cardiology, most new technologies that come out, there is a very formal training period. The formal training period is mandated in essence by the FDA

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through how they approve that device or that technique, but it is also mandate by each individual's hospital's credentialing committee, which requires that. And I say that both in terms of trying to reassure HCFA that these mechanisms are set up, but also with the hope that the HCFA final ruling does not address, other than to mention appropriate training, because if in fact we have to as practitioners provide evidence to our local intermediary that we have gone through the training, this is going to add yet another level of administrative difficulty that is already being met by at least two other levels.

DR. GARBER: Okay.

DR. McBRYDE: I have one other thought. It is worth thinking about that in a little more depth, because much of your information about the initial diagnoses, not the Steves of the world, but in urology, there are a number of people I'm sure that have psychological problems that have this type of thing, it's all subjective, most of your outcome as well as your income, if you will, is subjective. So it is important to step back even one step further. You can always document treatment, but you can't always document, is this really the problem, so

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the diagnosis itself becomes really important too, not to have it mixed on the front end even one step back from the treatment documentation.

DR. GARBER: Okay. Anybody else from the public want to speak. If not, does anybody from the

panel want to raise further discussion? If not, we're ready to take a vote.

The motion on the floor is to answer yes to question one about adequacy of evidence. All those in favor?

Unanimous.

I'm going to ask you to quickly, we don't need to spend a lot of time, go through the reasons for your vote, preferably addressing the consistency of the results, the applicability to the Medicare population, generalizability beyond the research setting. Start with --

DR. ZENDLE: I thought we did this already.

DR. GARBER: It's implicit in your comments, but not everybody spoke on all of these points, and you can say you agree with the person before you. So Les, you can start off.

DR. ZENDLE: I think I already stated my opinion and the reasons why I support it.

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DR. GARBER: Okay, Ken?

DR. BRIN: I already said my bit previously. Let me address, consistency when there is one study is relatively irrelevant. Applicability, I think we have discussed that already. It would be nice to have more data and I presume with time we'll get more data, but we can only use what our experts have otherwise mentioned which is, it is highly likely, and then watch the outcomes here.

As far as generalizability, I think that many of the settings in which it has been used are what one would call routine clinical settings, so I think it is generalizable.

DR. GARBER: Thanks. Angus?

DR. McBRYDE: My vote is yes. I do think there are, and I don't know enough about the potential for abuse, and it's not our purview in this committee to talk about CPT codes and how many would be used, and what the accelerated usage of the implant would be, but it's something to keep in mind. It's efficacious in my opinion.

DR. GARBER: Logan?
DR. HOLTGREWE: I felt that the two randomized prospective trials that were presented

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were rather compelling, and I feel that they demonstrate without question that this is a valuable technology, in the absence of anything else as good.
DR. GARBER: Thank you. Mike?
DR. MAVES: I will echo Dr. Brin's comments.
DR. GARBER: Okay, ditto. Bruce?
DR. SIGSBEE: As a neurologist, I think I would like to comment a little bit about the concern with neurological procedures, particularly M.S. I would probably have done the same thing in setting up the research protocol to exclude particularly patients with M.S. The underlying physiology of this methodology is not known, there is an important afferent arc, M.S. Patients have lesions spread throughout the nervous system, and a failure in that patient, it's not known whether it would be due to a failure of the technique, or was it because there is in that particular patient interference with the appropriate arc. We're talking about a contin level vectoration center, and obviously a lot of lesions could exist between the stimulation site. So I think that it was very appropriate to have as clean a study population with as few variables as possible to demonstrate to try to demonstrate whether the

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technique works or not. But also in my view, I think it is probably entirely generalizable to neurologic patients and their problems and we will get more data.
DR. GARBER: Okay, thank you. Is the panel ready to tackle the second question? Les?
Dr. ZENDLE: Yeah. I'd like to move that we answer the second question as fitting the category of more effective, and I will state why after somebody seconds.
DR. GARBER: Is there a second to that motion?
DR. McBRYDE: Second.

DR. GARBER: Okay.
DR. ZENDLE: I think, as was discussed when we were talking about the first motion, and as the case was presented, there are some problems with the results, and I think what it leads me to believe is that I'm not so sure -- I don't think it's a small effect, I don't think it's a large effect, it's somewhere in between, and I think to have to say something is a breakthrough technology is maybe just the semantics of the word. I don't know that there's enough evidence to support that. But I also don't think it's relevant to the information that HCFA

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needs, and we have all stated that we are going to have to see how the results keep coming in, especially in regards to the Medicare population. So I have no trouble supporting more effective at this point.
Dr. GARBER: Logan?
DR. HOLTGREWE: I would concur. I think that part of the definition we've been given by HCFA that the outcome is so large that the intervention becomes a quote, standard of care, closed quote, and I'm not convinced at this juncture that that this is quote, standard of care, closed quote, where you really have to do it or you're guilty of malpractice, which is the definition of standard of care, so I think more effective is the proper category.
DR. GARBER: Further discussion? So the motion on the floor is to assign it Category 2, more effective.
All those that in favor?
Unanimous.
Well, I think that ends our business. Connie?
MS. CONRAD: To conclude today's panel meeting, I would like to announce that the Executive Committee is scheduled to meet November 7th, here in

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the Convention Center. And I would like to thank all the panelists and participants, and could I have a motion that the meeting be adjourned?
DR. GARBER: Actually, before we have that

motion, let me also thank the people who spoke on behalf of the public. I think you could see that there were a lot of questions for you, the information was very helpful to the panel in its deliberations.

I will now entertain a motion for adjournment.

DR. HOLTGREWE: So moved.

DR. SIGSBEE: Second.

DR. GARBER: All in favor?

(The meeting adjourned at 11:57 a.m.)