

*ACTION - IMPACT Research Design Considerations for  
Randomized Clinical Trials of SCS for Pain*

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*November 16, 2018*

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*A Matter of Record  
(301) 890-4188*

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| 16 Friday, November 16, 2018                    | 16  |
| 17 7:59 a.m. to 2:52 p.m.                       | 17  |
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| 1 C O N T E N T S                               | 1 P R O C E E D I N G S                               |
| 2 AGENDA ITEM PAGE                              | 2 (7:59 a.m.)   |
| 3 Study Execution (e.g., Controlling            | 3 Presentation - Simon Thomson                        |
| 4 Non-Specific Factors; Programming Standards;  | 4 DR. THOMSON: So welcome back, everybody, to         |
| 5 Sponsor Involvement; Site and Patient         | 5 day 2. Just a little bit of housekeeping, when it   |
| 6 Training; Outcome Assessment Procedures)      | 6 gets to the discussion, and we've got a lot of      |
| 7 Simon Thomson, MD 4                           | 7 hours of discussion later, could you try and        |
| 8 Data Analysis, Interpretation, and Reporting  | 8 remember to lean forward and announce your name for |
| 9 (e.g., Pre-Specification; Estimands,          | 9 the transcripters. We sort of lost it last night,   |
| 10 Missing Data, Multiplicity, Clinical         | 10 yesterday evening, although I think some people's  |
| 11 Meaningfulness; Responder Definitions;       | 11 accents are probably recognizable.                 |
| 12 Discerning Hype from Substance)              | 12 The other thing is if you are leaving today,       |
| 13 Jennifer Gewandter, PhD 30                   | 13 just remember that checkout time is 12:00;         |
| 14 Economic Outcomes and Cost-Effectiveness     | 14 otherwise your key card doesn't work. So that's    |
| 15 Analyses                                     | 15 that.  |
| 16 Brian Kopell, MD 56                          | 16 My task is to talk about study execution,          |
| 17 Methodological Quality of SCS                | 17 and I think you'll find this as a little bit of a  |
| 18 Cost-Effectiveness Analyses                  | 18 revision of some of the points that we started     |
| 19 Rod Taylor, MSc, PhD 70                      | 19 discussing yesterday.                              |
| 20 Special Issues in RCTs of SCS, including     | 20 (Pause.)   |
| 21 Sham Stimulation and Programming Comparisons | 21 DR. THOMSON: Spinal cord stimulation, and I        |
| 22 Sam Eldabe, MD 82                            | 22 know we're talking about randomized-controlled     |

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1 studies for pain. We tend to think of this as a  
 2 treatment for neuropathic pain, but I think the  
 3 clinical distinction between mechanisms of  
 4 neuropathic and nociceptive get a bit blurry, and  
 5 at the end of the day, it is a clinical  
 6 differentiation. It's also a treatment for  
 7 visceral pain, although it has not enough clinical  
 8 science to support it.

9 It's a treatment for ischemic pain syndrome,  
 10 chronic critical limb ischemia, vasospastic  
 11 disorders, cardiac ischemia, and mesenteric  
 12 ischemia. Then it's also used in other conditions.  
 13 It can be used in stabilizing ventricular  
 14 dysrhythmias in heart failure; spinal cord injury,  
 15 as has hit the news recently; persistent vegetative  
 16 states it's been used in; and even augmenting brain  
 17 tumor chemotherapy.

18 Now, when it comes to study and design, I  
 19 use two phrases there, the devil is in the detail  
 20 and the word "equipoise." And we're going to be  
 21 talking about these titles. We're going to talk  
 22 about recruitment, recruitment of centers and

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1 recruitment of patients. We're going to be talking  
 2 about patient information, written website and  
 3 social media. We're going to talk about  
 4 randomization and patient education and training in  
 5 the outcome measures. We're going to be talking  
 6 about efforts at blinding and reporting on  
 7 blinding. We talked briefly about programming.  
 8 We're going to talk about the sham and generally  
 9 about outcome measures; how do we actually measure  
 10 our primary outcome?

11 This is one of Sam's slides on equipoise.  
 12 He found this, and it turns out it is a drug for  
 13 horses, but basically, it's a principle of  
 14 research, genuine uncertainty whether a treatment  
 15 will be beneficial. And that should be the  
 16 position of not only the investigator, the staff,  
 17 but also even the patients.[indiscernible]

18 Sources of bias, I think this will probably  
 19 be one of Nate Katz's slides. Subject expectation  
 20 comes from research staff who are overly  
 21 enthusiastic about one treatment over another. It  
 22 will come from looking at the patient information

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1 sheets, what's available online about one treatment  
 2 or another, and even subjects' word of mouth.

3 I think as we've heard, expectation bias can  
 4 be very destructive and bias studies to the null,  
 5 bias one treatment over another, and be at least as  
 6 large as any treatment effect. And I think there's  
 7 evidence to show it can be long lasting and in some  
 8 circumstances even indefinite.

9 Recruitment in the research center, somebody  
 10 mentioned about good clinical practice training,  
 11 and that should be, of course, a standard for  
 12 anybody. And if they are doing their training  
 13 properly, they will understand many of the  
 14 principles about clinical research that we've  
 15 talked about.

16 I briefly mentioned how in Cambridge they  
 17 started doing a spinal cord stimulation trial in  
 18 refractory angina, but really they had no training  
 19 in how to do spinal cord stimulation or look after  
 20 their patients. But what we often don't think about  
 21 is what about the comparator treatment.

22 It may not be necessarily another SCS

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1 device, but even then, they need to be skilled,  
 2 that that has different programming opportunities,  
 3 different lead positions. But it's often if you're  
 4 comparing against an alternative treatment, have  
 5 they skills providing the comparator treatment and  
 6 if it's a more pragmatic study with usual care, can  
 7 they provide a broad range of usual care  
 8 treatments?

9 Similarly, what about the outcome measures?  
 10 Because they're not just pain scores and tick  
 11 boxes. It might be exercise, the 6-minute walk  
 12 test. It might be other outcome measures that are  
 13 specific to the disease that you're researching.

14 As I say, the second bit is actually what  
 15 I've just said.

16 When it comes to patient recruitment, I  
 17 think it's important that the referrer -- so if  
 18 you've got people referring to your center for  
 19 research, when that interaction they have with the  
 20 patient might be, "I know just the treatment for  
 21 you. They're doing this really interesting study  
 22 on this brand new treatment that's just come over

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1 from Europe, and it's wonderful; you should go to  
 2 that center" and then you get randomized to the  
 3 non-treatment group.  
 4       So it extends even beyond the referral  
 5 center, and everything is all about trying to  
 6 manage expectation bias. The care that the patient  
 7 should receive should not be dependent upon  
 8 research participation. I think we often find that  
 9 if they are going to get this wonderful device,  
 10 then they will only get that wonderful device if  
 11 they're part of the research study. And it goes  
 12 further that they may not even get spinal cord  
 13 stimulation because they don't have the insurance  
 14 cover unless they're in a research study.  
 15       The SCS should be universally available if  
 16 you are taking them into a study. The patients  
 17 should be equipoised. They shouldn't come with  
 18 pre-conceived ideas that the investigator treatment  
 19 is going to be better than the comparator  
 20 treatment.  
 21       Ideally, the situation is that you're  
 22 referring the patients to the center for a second

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1 opinion, not specifically for SCS nor this  
 2 interesting new treatment. And as I say, SCS  
 3 should be available, and patients should be  
 4 provided with factual and equipoised information,  
 5 and be indifferent to treatment randomization.  
 6       The patient information sheets and the  
 7 literature available should not just be about the  
 8 investigator treatment but also the comparator  
 9 treatments, and that should be explained with rates  
 10 of success and complications. But what about that  
 11 that's present in the public domain? What about on  
 12 the website? What about social media? Should, for  
 13 example, industry websites be suspended during the  
 14 time of a recruitment; patient information sheets  
 15 examined by a third party, and we're going to be  
 16 talking about a case example soon. Can you control  
 17 social media? Obviously, we all know we can't.  
 18       Here's an example of a patient information  
 19 sheet, and apologies that it has to be a named  
 20 company, but this was what was given to patients.  
 21 The clinical study says that Senza is designed to  
 22 treat chronic pain in the trunk and limbs at least

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1 as effectively and without some of the potential  
 2 side effects associated with currently available  
 3 SCS systems. The Senza system is designed to treat  
 4 chronic pain in the trunk or limbs without the need  
 5 for a buzzing sensation. So we've got sort of a  
 6 placebo statement and a nocebo statement.  
 7       Then if you turn to the website that was  
 8 available during patient recruitment, conventional  
 9 SCS provides considerably less relief for chronic  
 10 back pain for most patients. So you've just now  
 11 told the patient that they're going to be  
 12 randomized to the control group and it's going to  
 13 be less good.  
 14       Parasthesia. In fact, 71 percent of  
 15 patients reported uncomfortable stimulation on a  
 16 large survey, a nocebo statement. Process study  
 17 results, poor back pain relief. The study is about  
 18 the relief of back pain as the primary outcome.  
 19       Although SCS provides meaningful relief for  
 20 leg pain, back pain relief is still a challenge for  
 21 most SCS patients. The goal is to provide superior  
 22 efficacy without the uncomfortable stimulation

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1 commonly experienced with conventional SCS therapy.  
 2 Only the Nevro system delivers the unique waveforms  
 3 designed to offer compelling back pain relief and  
 4 avoid the side effects commonly associated with  
 5 conventional SCS. So you get the idea.  
 6       Here's an example of an equipoise statement.  
 7 Do you remember writing that? I'm sure you thought  
 8 a lot about it, Richard. The study was presented  
 9 to candidates as a comparison of two standard,  
 10 non-experimental procedures, SCS and reoperation,  
 11 to determine whether SCS should be offered as an  
 12 FBSS treatment before or after exhausting all  
 13 reoperation treatment options.  
 14       In our own PROCO study, standard SCS uses  
 15 stimulation frequency between 40 and 100. "In  
 16 recent years, and SCS device capable of giving  
 17 frequencies of stimulation as high as 10K has been  
 18 used with claims of improved back pain relief and  
 19 without the patient being aware of the stimulation.  
 20 However, the science to support this claim is not  
 21 adequate. Furthermore, it is not known as such  
 22 high frequencies are required to achieve the pain

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1 relief."

2       So when it comes to consideration for our

3 guidelines, I think the important thing is to be

4 transparent. We have to document our efforts to

5 balance research and subject expectation between

6 groups and measure expectation. We can actually

7 measure it of patients both at baseline and the en

8 point for researchers and subjects.

9       We have to be absolutely transparent with

10 making available the patient information sheets and

11 what was available on websites at the time. So

12 that's when it comes to reporting.

13       The randomization process, this is probably

14 the one bit that we are quite good at because we do

15 realize that we use mostly computer-based systems

16 to generate some randomizations, although not all

17 as we heard. The recruit has to feel equipped

18 about what group they've ended up in.

19       Now, there were reports -- and I haven't got

20 this in the public domain, but having been around a

21 number of the centers, I remember being told of how

22 patients would sometimes be weeping that they'd

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1 been randomized to the non-Senza group. So they

2 weren't in different to which treatment they ended

3 up in. We need to also look at maybe surveying the

4 satisfaction patients have with their

5 randomization.

6       When it comes to patient education, it's

7 difficult enough to educate people firstly about

8 chronic pain; secondly, about this complex

9 treatment; and then thirdly, what are the

10 comparator treatments that are available; and then

11 the outcome measures for a clinical study. It's an

12 awful burden for patients to take on when they're

13 coming into a study, so is sufficient time and

14 learning experiences available to patients when

15 they come in for this study?

16       There is also the physical burden. In the

17 PROCO study, as you see, we collected real-time

18 pain schools. The patients had to wear this watch

19 for 9 months, inputting this data 3 times a day,

20 every day. Then we talked about blinding. It's

21 true to say that most RCTs in SCS don't have any

22 blinding. And what's worse is not only do they

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1 know what the treatment is but also its effect,

2 either positive or negative. So when they end up in

3 that group, there's extraordinary expectation.

4       As we heard earlier, yes, we all know it's

5 difficult to double blind, but it doesn't mean you

6 can't single blind, at least the data collectors.

7 We've been working on studies where we have

8 clinical teams and research teams, and one is

9 unblinded and one is blinded in order to be able to

10 carry out the therapy, but the people who matter

11 when it comes to data collection are blinded. But

12 then everybody has to maintain that blinding

13 discipline; not least the patients as well.

14       These are the statements that we've heard,

15 and this is one of Sam's slides; subjects and

16 investigators. So these are quotes the write up of

17 a variety of different recent studies where there's

18 always a statement about the blinding, in other

19 words, why they've not done it. Subjects,

20 investigators, and study site were not blinded to

21 subjects assigned therapy. And that can be even

22 within. So like with the SUNBURST study, it was

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1 within device but two different modes, subsection

2 and parasthesia-based programming.

3       Due to practical considerations, study

4 subjects and investigators were not masked to the

5 assigned treatment group. Given the nature of the

6 intervention, it was impossible to blind patients

7 and difficult to blind investigators during this

8 trial; and this is why we get such a low

9 recommendation from those outside our field.

10       There are a few studies double blind, not

11 least the PROCO RCT I was involved in. Then people

12 will put forward the Alkaisy study, which although

13 the work was done before ours, it was published

14 after, actually when you read it, a third of the

15 patients had a perception of parasthesia of

16 1 kilohertz. But as I say, there could be a single

17 blind, and in Jose De Andres' study, they that were

18 single blinded to the observers.

19       I think there is also this concept of having

20 interactions scripted or monitored. Often with our

21 interactions with the field engineer programmer,

22 there was always a research nurse monitoring the

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1 interactions, and then again, that can be  
 2 documented.  
 3 We talked briefly about the programming.  
 4 And yes, there are advantages of why you want your  
 5 expert programmer being able to use that technology  
 6 to the best degree, and I understand that. We  
 7 talked about how long will that go on and how many  
 8 visits that will take. And again, I think that  
 9 should be protocolized to some degree or at least  
 10 reported on.  
 11 Particularly when some of the studies -- so  
 12 if you're, say, doing an angina study with maybe a  
 13 6-minute walk test, traditionally you would always  
 14 have your research nurse walking with that patient.  
 15 What might be the interaction that's going on? The  
 16 patient will know that they've got a device in. So  
 17 what encouragement is being made to -- "Come on.  
 18 Let's keep going" is that different, too, at the  
 19 baseline, for example.  
 20 We talked about the dichotomy of  
 21 programming. Yes, we want the clinical team. If  
 22 you have the clinical team doing it, you might have

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1 suboptimal programming, but we talked about  
 2 training. Do you use the industry research  
 3 scientists? We keep banging on about industry, but  
 4 essentially we got together our clinical scientists  
 5 leadership from the large industry -- that's just  
 6 their employer -- but first off, they're actually  
 7 into the research. They're not marketers; they're  
 8 into the research. And that's what they tend to  
 9 provide when they are supporting products in the  
 10 field, people who are into the research.  
 11 So we could make it explicit that that's  
 12 good practice, but what we don't want is them to be  
 13 contaminated by marketing objectives.  
 14 Or do you use the commercial team? Or as  
 15 what happened in the Senza study, you had the  
 16 research scientists, who actually had an office  
 17 within the hospitals, versus the normal commercial  
 18 team who might visit every 3 months to reprogram a  
 19 patient. There should be efforts to control the  
 20 interaction, monitoring by the research team, and  
 21 scripting maybe. We talked about the duration and  
 22 frequency of programming sessions.

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1 What about the sham? What's the purpose of  
 2 a sham? The purpose of a sham I think is twofold,  
 3 and I'm sure I'll be told otherwise. One is you  
 4 need this to look for the treatment effects over  
 5 the non-treatment effects. But also, when it comes  
 6 to things like inferiority, if you've got both A  
 7 versus B being the same, does that mean they're  
 8 both as good or both as bad? That's one of the  
 9 reasons.  
 10 What about sham in parasthesia based? Well,  
 11 you could do investigatory surgery, and an awful  
 12 lot of people outside our field would love us to do  
 13 this, is to be able to look at unilateral treatment  
 14 for bilateral pain, unilateral stimulation for  
 15 bilateral pain. Then I think it was Solomon  
 16 Tesfaye -- I said 1998, but Liverpool, who in  
 17 diabetic neuropathy, they had a red box. It was an  
 18 external connected to stimulator, and they had a  
 19 red box that came on even when it was a sham  
 20 stimulation. Then they surveyed the patients who  
 21 all apparently believed that they were having the  
 22 active treatment.

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1 Then there's this idea of the ultra low-dose  
 2 SCS, one stimulation like they did in an angina  
 3 study, Zipe's study. But then we heard, "Well,  
 4 actually, is that an active treatment?" Then what  
 5 about subperception program? And as I mentioned,  
 6 that can go awry because sometimes these patients'  
 7 different positions, if they start to activate,  
 8 then turn up the amplitude, they start getting  
 9 sensation.  
 10 Also, there are problems with draining the  
 11 battery because if you're using rechargeable  
 12 systems, there are fears that if the patient  
 13 notices they don't have to recharge their device,  
 14 they know that they've been on a sham. And the  
 15 issue of whether a patient can tell whether they've  
 16 been on a slightly different current consumption;  
 17 if only patients were that clever that they could  
 18 actually tell, and therefore, "Oh, I know. I've  
 19 only had to charge once today. I must have been on  
 20 1K." That's not what happens; I can tell you that.  
 21 Let's get on to the interesting bit on  
 22 outcome measurements. Obviously, what we choose,

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1 it really depends on what is the research question  
2 we're trying to answer and who is asking that  
3 question. As far as I'm concerned, as a clinician,  
4 I'm treating long-term conditions, and I'm not a  
5 believer in the pain score as being a useful  
6 measure for long-term conditions. I'm much more  
7 interested in health-related quality of life and  
8 improving that long term. Others are interested in  
9 function. Others might be interested in medication  
10 reduction.  
11 Of course, we have to select. This is a  
12 single primary outcome measure. And we always  
13 dutifully collect the secondary outcome measures.  
14 And as you'll see, it's important to be able to  
15 blend the two because what happens in secondary  
16 outcomes might actually explain the validity of  
17 your primary outcome.  
18 So when we choose the primary outcome -- and  
19 we talk a lot about regulation, but, hey, we're  
20 beyond regulation in Europe. It's now about  
21 reimbursement. This is a wave that's going to hit  
22 you in the U.S. As you're starting to notice, it's

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1 not about the regulatory bodies; it's about the  
2 reimbursement. It's about CMS.  
3 So what is the actual answer to the question  
4 that you want? Is it to satisfy regulatory  
5 demands? And they're going to say your device, you  
6 say it's a treat pain, tell me about pain. But to  
7 satisfy your reimbursement people, they don't want  
8 to know about a pain score. It means nothing to  
9 them. They want to know about return to work, or  
10 function, or quality of life.  
11 Anyway, let's talk about the pain score.  
12 We hear a lot of this percentage pain relief. This  
13 is what we use clinically, isn't it, in the clinic.  
14 We say, "Look, you've had this stimulator on now.  
15 What percentage pain relief have you got? 100 is  
16 complete, zero not at all." And they give you a  
17 figure. And you know and I know that always  
18 exaggerates; anything you can measure with an NRSPI  
19 difference. That's the other way we do. Sometimes  
20 we use a VAS scale, actually a proper VAS scale  
21 with a mark on a piece of paper, on a line, or more  
22 typically we use NRSPI and express it as a

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1 percentage change.  
2 Now what do we do? Actually, what happens  
3 in a lot of these studies -- and I'm going to get  
4 onto this -- is it's a single point. Looking back  
5 over the week, the patient [sic] said, "Here you  
6 are, now. This is your data collection time.  
7 What's been your pain like over the last week?"  
8 You might divide it up at worst and average  
9 or best, and generate 3 scores. You might do that  
10 or you might just do one. What is one after? Are  
11 you after the worst or are you after the usual?  
12 It's often not explained. And the diabetic  
13 neuropathy ones, often pain worse at night, they  
14 did a day-night one.  
15 Or are you going to measure a mean pain  
16 score multiple times of the days over 5 or 7 days?  
17 And if you're going to do that, are you going to  
18 use a pain diary which notoriously are incomplete,  
19 or are you going to use -- one of the ways we got  
20 around it was a watch strap, and they had a sliding  
21 scale, and it beeped at them every 8 hours, and  
22 they inputted a data point.

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1 Then the other thing is we have to have a  
2 strategy of what do you do when they don't put the  
3 pain score in? We had a paper diary backup, for  
4 example. And often the patients with that device,  
5 they knew if they had done it wrong, and they just  
6 jot it down. Paper diaries, there's data to show  
7 that they're only in 11 percent of cases complete.  
8 They're often done in the car park at the data time  
9 collection points. So often their memory of their  
10 pain over that previous week might be unreliable.  
11 As I said, this is what we did with the  
12 PROCO, and it does at least take the observer out  
13 of it. These are just a little private moment they  
14 have with their watch strap as they input their  
15 pain score. And it does mean we can monitor  
16 throughout several days. But one of the things the  
17 Alkaisy study did is they used the pain scores over  
18 the whole period, whereas in the PROCO study, we  
19 were doing, if you like, our optimization. And it  
20 was only in the last 5 days where that was the data  
21 collection period, and there's the watch strap we  
22 used. That was the PROCO study, which basically

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1 went to show that the determinant of outcome was  
 2 not the kilohertz frequency.  
 3 So let's have a look and see if we can be  
 4 informed as to what might be important how we  
 5 measure the pain score. This is actually the SSED,  
 6 which you and McNicol, I think you should somehow  
 7 include in your literature search because there is  
 8 so much more data -- I don't know whether you're  
 9 allowed to do it, but anyway -- in those to explain  
 10 what's going on.  
 11 This is the Senza study at the primary  
 12 endpoint looking at the responder rate and this  
 13 fantastic figure of 78.3 percent, which took our  
 14 field by storm. But they did do a diary. It's not  
 15 in the write-up. They did do a diary. And there's  
 16 an 11.6 percent change in their primary outcome  
 17 measure, 11.6 percent difference in responder rate,  
 18 just simply dependent upon the methodology that was  
 19 used for measuring the primary outcome. It was the  
 20 same in both groups, but if you like, the marketing  
 21 message has been to say what a wonderful responder  
 22 rate we've got, and that's been waved in our faces

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1 quite a lot.  
 2 Let's look in more detail and look at the  
 3 other secondary outcome measures. Which one  
 4 correlates? Is it 78 percent? If we look at  
 5 global impression of change, this is the percentage  
 6 of patients who would describe themselves as better  
 7 or a great deal better.  
 8 Now, if you had a responder rate of greater  
 9 than 50 percent reduction, I would expect that to  
 10 be near the 78 percent mark. So what's better? If  
 11 the subject expectation is 52.8, 2 percent subject  
 12 global impression change, is it the responder rate  
 13 or is it the pain diary? So we need to describe  
 14 what scores actually best describe the outcome.  
 15 Let's look at the ACCURATE study, and here,  
 16 this is the composite outcome of the two groups.  
 17 81.2 percent achieved this composite outcome, which  
 18 I think was 50 percent pain reduction and no  
 19 neurological change, versus in the control group,  
 20 55.7 percent, actually both quite good results,  
 21 exceptionally good on the DRG. That was the  
 22 composite responder rate.

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1 But if you just look at the pain scores  
 2 themselves at 12 months, you'll see that it's not  
 3 quite so impressive. With a single point looking  
 4 back, it's only 10 percentage points of the VAS  
 5 score. If you look at the diary at the mean data  
 6 endpoint, it's only 5 points on the VAS score using  
 7 the diary.  
 8 Then if we then look at other secondary  
 9 outcome measures, one would expect satisfaction.  
 10 How likely would you undergo this therapy again? I  
 11 know there are other things other than just pain,  
 12 but look, really, between control, not a lot of  
 13 difference; not something that I think justifies  
 14 that big composite pain difference. And then if  
 15 you looked at other things as well, there's not  
 16 that much difference.  
 17 Then the other problem with the DRG it is  
 18 actually reported in the write-up, but it's never  
 19 by their speakers. They never mention this, the  
 20 adverse events. I always get told by their  
 21 speakers, no, there were no differences in adverse  
 22 events between the two groups. And we all know in

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1 Europe that's not going to be true. And in fact,  
 2 even in the ACCURATE study, there is a big  
 3 difference, statistical difference in adverse  
 4 events that were related to the implant procedure.  
 5 Why is all this important? Let's be  
 6 realistic. I'm delighted that new products come to  
 7 the market. Nobody minds that. Well, I don't mind  
 8 it. And that's the regulators are interested in.  
 9 Is it safe? Does it do what it says on the tin?  
 10 But remember, they're always going to be funded by  
 11 the sponsor. They're often start-ups. They live  
 12 and die by the study. They're always  
 13 noninferiority designed. Most of them have been  
 14 unblinded. I think we're going to have a new one  
 15 coming which is blinded.  
 16 They come with massive expectation bias.  
 17 Possibly there's observation bias. I commend you  
 18 to read the SSEDs, summary of safety and  
 19 effectiveness data. And of course, remember when  
 20 you go to meetings, the messages one hear are not  
 21 necessarily scientific, but they are marketing  
 22 messages. And I think we haven't talked about this



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1 today, but Eric Buchser and Sam, we've often quoted  
 2 the Flacco [ph] thing on randomized studies, and  
 3 the literature of head-to-head RCTs is dominated by  
 4 the industry.  
 5 Industry sponsored, comparative assessments  
 6 systematically yield favorable results for the  
 7 sponsors, even more so when noninferiority designs  
 8 are involved. And I think if you're a  
 9 noninferiority design and you're industry  
 10 sponsored, there's a 97 percent chance that your  
 11 study will show favorability or at least  
 12 noninferiority.  
 13 Study execution should include transparent  
 14 methods to reduce expectation and observer bias.  
 15 We know that, but how do we actually implement that  
 16 and give guidance? The role of the clinical  
 17 research and sponsor teams must be documented and  
 18 managed by the trial management group with  
 19 independent members. Will a pain score always be  
 20 the primary outcome? Depending on the question.  
 21 There are lots of ways of measuring the pain score,  
 22 and I think we've got to decide which one. Thank

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1 you very much.  
 2 (Applause.)  
 3 So I finished exactly on time, which is  
 4 pretty good for a blabber mouth. I'd like to now  
 5 welcome to the stage Jennifer Gewandter I'm going  
 6 to say.  
 7 DR. GEWANDTER: Yes.  
 8 DR. THOMSON: Okay. She's going to talk on  
 9 data analysis, interpretations, and reporting. So  
 10 hopefully it will be a good follow-on. Thanks,  
 11 Jennifer.  
 12 Presentation - Jennifer Gewandter  
 13 DR. GEWANDTER: Good morning. Thanks to Bob  
 14 and Dennis for inviting me to talk today. With my  
 15 talk, I'm going to try to talk a little bit  
 16 about -- follow-up what Nate said about RCTs being  
 17 the gold standard of evidence, depending a lot on  
 18 how they're done and how they're reported to the  
 19 consumer or the reader.  
 20 We've talked a lot about different things  
 21 that can affect the validity of trial results, so  
 22 I'm going to try to talk about things that are a

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1 little bit different from what we've covered  
 2 already today. Just as disclosure, I'm not a  
 3 statistician, so I'll try to answer all your  
 4 questions but might not be able to answer  
 5 everything.  
 6 It really depends on a lot of different  
 7 things. These are the types of things I'm going to  
 8 cover today. I'm going to talk a little bit about  
 9 minimizing type 1 error or the false positive rate  
 10 by prespecifying and limiting multiple testing.  
 11 I'm going to talk about designing trials from the  
 12 perspective of an estimand, which is a relatively  
 13 new concept in clinical trial design.  
 14 I'm going to talk about clinical  
 15 meaningfulness, the difference between within  
 16 patient and between group and what that means for  
 17 the design and interpretation of trials, and  
 18 looking at the confidence intervals to inform  
 19 interpretation of non-significant superiority  
 20 trials. So it's pretty similar concepts to  
 21 designing and interpreting noninferiority trials,  
 22 but how we would apply them to superiority trials.

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1 I'm going to go through this quickly because  
 2 I think a lot of you probably know a lot of this  
 3 already, that we want to prespecify as much as  
 4 possible, we want to be specific, and we want to  
 5 keep it to a minimum. Multiple statistical test  
 6 can inflate type 1 error. If you have an alpha of  
 7 0.05, that means that your false positive rate is  
 8 about -- oh, sorry, that should be 5 percent;  
 9 sorry, 5 percent.  
 10 If you do 8 different tests at an alpha of  
 11 point 0.05, the potential false positive rate is as  
 12 high as potentially 40 percent. So this is what we  
 13 call the family-wise type 1 error. This is really  
 14 most important to think about when we're defining  
 15 our primary analysis, but it's also important for  
 16 key secondary analyses.  
 17 This is just an example of a lot of the  
 18 different things you have to think about. You have  
 19 to think about what is the primary outcome measure.  
 20 You have to be really specific about that. You  
 21 can't just say pain. You have to say pain with a  
 22 diary. You have to say what instructions you're

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1 going to give the patients. You have to decide  
 2 what's your primary time point is going to be; what  
 3 statistical tests are you going to use; and what's  
 4 the model; what are the different factors you're  
 5 going to put in the model; what should the  
 6 population be for the analyses, are you going to  
 7 include all randomized subjects or just the ones  
 8 who finished; and then what method are you going to  
 9 use to accommodate missing data?  
 10 So all these things should be specified  
 11 upfront so that at the end of the day you can't  
 12 make a few little changes, and cherry-pick, and  
 13 report what you find to be the "positive"  
 14 quote/unquote or p less than 0.5 analysis.  
 15 The other thing I would say is we all like  
 16 to collect a ton of stuff for RCTs, and that's  
 17 really great. We want to get as much data as we  
 18 can from the patient's time. But it's also  
 19 important to prespecify just a few secondary  
 20 analyses so that the results of those analyses are  
 21 actually more reliable, and you don't again do 20  
 22 secondary analyses and just pick the few that were

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1 positive and support your hypothesis.  
 2 I just want to draw your attention to this  
 3 manuscript. This was led by Dennis on different  
 4 ways you can adjust for multiplicity. If you  
 5 really can't choose just one for your primary, you  
 6 can do things like making multiple co-primary  
 7 endpoints where you split the alpha. Both of the  
 8 primary endpoints, if let's say it was pain and  
 9 physical function, have to reach significance of  
 10 0.025 for the trial to be considered positive.  
 11 In this case, unfortunately, if only one of  
 12 the analyses doesn't reach 0.05, your trial would  
 13 lose and not be considered evidence for the  
 14 treatment. But then again, if you do get both, you  
 15 can claim that it does both in your primary  
 16 analysis.  
 17 The other thing you can do is something that  
 18 we call hierarchal gatekeeping approach. You don't  
 19 have to adjust alpha, which is great, but you do  
 20 have to prospectively decide which is more  
 21 important to you. For instance, let's say we  
 22 decide that pain is the most important thing, that

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1 would be prospectively put as the first outcome,  
 2 and if that hits at .05, you could then go to do  
 3 your second outcome.  
 4 In that case, as long as pain hits at 0.5,  
 5 the trial can be considered a success no matter  
 6 what happens with physical function. But you have  
 7 to be really sure that you want pain to be your  
 8 most important because if physical function hits  
 9 and pain doesn't, you can't call the trial a  
 10 success.  
 11 Then there are other things to think about  
 12 for the secondary analyses. In general, you want  
 13 to think about limiting the family-wise or overall  
 14 type 1 error of the trial. One way to do that is  
 15 to prospectively decide how much more alpha am I  
 16 okay with or false positive rate am I okay with for  
 17 the whole trial?  
 18 Let's say you decide that's 10 percent, then  
 19 your 0.05 would be left for your secondary  
 20 outcomes, and then you could split that between  
 21 those secondary outcomes using things like  
 22 Bonferroni correction or other related step-wise

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1 procedures that are a little bit less conservative.  
 2 Again, I'm not expecting you to remember all of  
 3 that. If you are interested, you can read this  
 4 paper.  
 5 The next thing I'm going to talk about is  
 6 estimands and how we can you use estimands to  
 7 better design our trials and also interpret what  
 8 the actual effect estimate really means. From a  
 9 historical perspective, RCTs would have an  
 10 objective. You would say, I want to estimate the  
 11 effect of the treatment compared to the placebo.  
 12 It's very general.  
 13 Then conventionally what we would do is we  
 14 would design a trial in a specific population. It  
 15 would have an active and placebo group. We would  
 16 pick a method to accommodate missing data. We  
 17 wouldn't really think about what exactly that means  
 18 for the resulting estimate. Even now, but  
 19 definitely up until fairly recently, generally that  
 20 would be things like an LOCF or a BOCF analysis,  
 21 where you carry forward the last observation or the  
 22 first observation.

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1 More recently after the NRC report, that  
2 would be things like doing multiple imputation,  
3 some more sophisticated methods; but again, just  
4 kind of picking them off the shelf because they are  
5 quote/unquote "the better thing to do" without  
6 really thinking about what does that mean for my  
7 effect estimate.  
8 Because of this, we would decide on the fly,  
9 or after the fact, what would we do with  
10 intercurrent events? And what I mean by  
11 intercurrent events are things like rescue  
12 medication usage or maybe even use of disallowed  
13 medications. A new push by statisticians is to  
14 kind of think about this a little bit differently  
15 by using the thing called estimands.  
16 This is a definition from this reference,  
17 which is really helpful if you want to learn more  
18 about this, about all different things that the  
19 estimand includes, things that we already think  
20 about like the population of interest; what's our  
21 endpoint variable; and what kind of summary are we  
22 going to use or statistic for our data. But really

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1 the important thing that's different about this way  
2 of thinking is that we specify how intercurrent  
3 events are reflected in the scientific question of  
4 interest. And I think the easiest way to think  
5 about this is to just look at some different  
6 examples of estimands.  
7 So estimand 1 is we're trying to estimate  
8 the effect of being randomized to the active  
9 treatment compared to placebo, regardless of  
10 whether intercurrent events occur. This is what we  
11 call a pure ITT estimand. This is really  
12 appropriate when your goal is effectiveness.  
13 One thing that's important to note about  
14 this estimand is that it's really impossible  
15 actually if you have a lot of dropout that you  
16 can't follow up because you can't really impute  
17 people's data for what actually happened to them  
18 because you really don't know what actually  
19 happened to them based on the other people in the  
20 trial, which is generally how we impute data in the  
21 more sophisticated methods.  
22 Estimand 2 would be the effect of the

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1 treatment compared to placebo that would have been  
2 obtained if all participants tolerated and complied  
3 with the treatment and protocol. This is what I  
4 call the efficacy of estimand. This is really for  
5 efficacy instead of effectiveness, and it's really  
6 assuming that everyone can take the drug or, sorry,  
7 use the device, and they are going to do it exactly  
8 how you ask them to.  
9 Estimand 3 is the effect of the treatment  
10 that is actually attributable to the randomized  
11 treatment. This seems very similar to estimand 2,  
12 but the difference is that, for example, if someone  
13 drops out early for an AE, you're not going to give  
14 them credit that the drug or the device worked for  
15 them because it's really not effectively  
16 attributable to the actual drug because that person  
17 was not able to take it anymore.  
18 So these are three different things that  
19 you're estimating, and how you handle missing data,  
20 either data that you can't find or data that  
21 happens after these intercurrent events will affect  
22 whether you're asking the question in the vein of

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1 estimand 1, 2, or 3.  
2 I want to define intercurrent events for  
3 finishing this conversation. There are two types.  
4 One, the data are potentially available, and one,  
5 they're not available. Data are potentially  
6 available for things like someone took an allowed  
7 rescue medication or someone took a forbidden  
8 medication that they weren't supposed to take. The  
9 participant wants to stop using the therapy, but  
10 they're willing to provide primary endpoint data  
11 anyway. They'll come back.  
12 With these type of data, you have two  
13 questions. One, should data after these  
14 intercurrent events be included in my trial, and if  
15 not, how should they be imputed? For data that are  
16 not available, this is things like participants can  
17 no longer be contacted, completely lost to follow  
18 up, and you have no idea what's going on with them;  
19 or the participant decides to withdraw from the  
20 study, they're unwilling to be contacted further,  
21 and they don't want to hear from you again. Then  
22 you might know, hopefully, you've done a good job

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1 and you know why they're dropping out. It could be  
2 they didn't get efficacy from the treatment, so  
3 it's not worth showing up anymore. They don't like  
4 the treatment. They have AEs or maybe just  
5 completely random, they moved away and they can't  
6 come anymore.

7 For this type of data, intercurrent events,  
8 you don't have a choice. All you can choose is how  
9 should I impute these data and should it be  
10 different depending on the reason that the data are  
11 missing? These are your two questions now.

12 So let's talk again. Let's bring it back to  
13 what the estimands are. For the first estimand,  
14 you want to follow participants and use their  
15 observed data whenever you possibly can because  
16 that's really the only way you can actually  
17 calculate this estimand.

18 For estimand 2, you really don't actually  
19 need to follow up patients after intercurrent  
20 events, at least for the primary analysis, because  
21 you're not going to use their data anyway. You're  
22 going to impute their data after they're observed

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1 and only use their observed data. And it's the  
2 same for estimand 3. It's not necessary to follow  
3 them up because you won't use those data anyway.  
4 And then the question with the estimand 2 and  
5 estimand 3 becomes how do you actually accommodate  
6 missing data so that you are answering the question  
7 in the vein of estimand 2 or estimand 3.

8 This slide is really busy -- sorry -- and  
9 it's kind of complicated. I'm not sure how much  
10 you can actually take away from this in a couple  
11 minutes, but I just wanted to introduce these  
12 terms, and you can learn more about them if you're  
13 interested.

14 When choosing what method to use for  
15 accommodating missing data, we think about the  
16 assumptions regarding the pattern of missingness.  
17 And formally what that means is the probability  
18 that the values are missing given the values of the  
19 outcomes, either observed or unobserved, and the  
20 statistical model.

21 For missing completely at random, this  
22 probability does not depend at all on any outcome.

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1 This is something like the person was in a bus  
2 crash on the way to the appointment, so they didn't  
3 give you their endpoint. It has nothing to do with  
4 how they're doing on the drug or whether they had  
5 an adverse event at all. The probability of being  
6 missing is completely random.

7 Then there's a term called "missing at  
8 random," which I will give you is misleading  
9 because this probability depends on observed  
10 outcomes but not unobserved outcomes. An example  
11 would be at the final visit where you were able to  
12 observe them, they report that they're not  
13 experiencing great pain relief, and they decide  
14 before the next visit that the study isn't worth  
15 their time because their pain relief is just not  
16 good and they just don't come back.

17 So you knew at their last study visit that  
18 they weren't getting great pain relief, and that is  
19 why they decided not to come back. We call that  
20 missing at random because you have an inkling of  
21 why their data are missing and the probability of  
22 their data being missing.

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1 For missing not at random, the probability  
2 of their data being missing depends on unobserved  
3 outcomes. An example would be you have a  
4 flexible-dose trial. The participant's last visit,  
5 they're getting only mild relief but they're  
6 reporting no AEs, and you decide to up their dose.  
7 They go away. Actually, their pain spikes, so they  
8 decide they don't want to come back, and they never  
9 contact you. You have no idea that their pain  
10 spiked because before they were getting mild pain  
11 relief. And in fact you might assume that maybe  
12 they had an AE because you upped their dose. So  
13 the reason that their data are missing, you don't  
14 have any idea. It's dependent on unobserved  
15 outcomes.

16 Those are the three different assumptions  
17 that we make when we make models to accommodate  
18 missing data. I'm going to talk about two of those  
19 and how we might think about what we choose to  
20 accommodate missing data based on the estimand we  
21 want.

22 For estimand 2, again, let me just remind

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1 you that the efficacy estimand, you're interested  
 2 in knowing how the treatment actually works' if  
 3 everyone can take it and everyone can tolerate it.  
 4 What I'm showing here is these black boxes, which  
 5 is the average trajectory for the group that's  
 6 taking placebo, and this is the average trajectory  
 7 for the group that's taking active.  
 8       These purple dots are one patient or one  
 9 participant, and the first two of these dots are  
 10 observed. You know those data. You got them from  
 11 the patient. This is the pain score. If you  
 12 impute their data using missing at random, what  
 13 that means is you base the imputation of these new  
 14 data on the trajectory in the active group because  
 15 this participant is in the active group, and they  
 16 come in slightly higher than the average because  
 17 they started out slightly higher. You use their  
 18 baseline data as part of that model.  
 19       This is how this patient's data would be  
 20 imputed with some uncertainty, which is a really  
 21 important point. You don't want to just impute a  
 22 single point because that can inflate type 1 error.

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1 This is what their data would look like. But if we  
 2 have the exact same scenario -- oh, and by the way,  
 3 this person dropped out because they had an AE.  
 4       If we have this same exact scenario but  
 5 we're interested in estimand 3, we want to know  
 6 what the effect of the treatment is only if they  
 7 can actually take it, then we would do something  
 8 maybe called jump to reference, which is a missing  
 9 not at random assumption.  
 10       In this case, again, we have the same exact  
 11 observed values. The person drops out for an AE,  
 12 and now instead of imputing their data putting in  
 13 the model the average from the active group, we use  
 14 the average from the placebo group, or the  
 15 reference group, to impute their data. And again,  
 16 their data jumps up here, and it's a little bit  
 17 higher than the average placebo person because they  
 18 started out a little bit higher, and this is how we  
 19 impute their data.  
 20       We've decided a different method to impute  
 21 their data with a different assumption because of  
 22 the estimand that we are trying to estimate. So

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1 now it makes the decision of whether we want to use  
 2 missing at random, multiple imputation, something  
 3 like jump to reference easier because we're  
 4 deciding that based on what question do we really  
 5 want to know.  
 6       Not only does it make it easier for us when  
 7 we're designing, it makes it easier for us when  
 8 we're reporting our trials because we can explain  
 9 to readers better what actually our estimate means.  
 10 So I would argue that when you report your trials,  
 11 you should be upfront and say this is the estimand  
 12 and this is what our data are estimating. And  
 13 therefore, we accommodated missing data using this  
 14 method. So that's all I'm going to say about  
 15 estimands.  
 16       DR. FIORE: May I ask a question  
 17 [inaudible - off mic].  
 18       DR. GEWANDTER: Sure.  
 19       DR. FIORE: Greg Fiore. A question is about  
 20 who makes those determinations of what might have  
 21 driven the patient to drop out. Is that a  
 22 statistician who's making that, typically?

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1       DR. GEWANDTER: No. Actually, this is a  
 2 very important point. These information obviously  
 3 are only available for people who told you why  
 4 they're dropping out. So unfortunately, people who  
 5 are lost to follow up for no reason and they don't  
 6 give you any reason, in the jump-to-reference  
 7 scenario, estimand 3, you can't put them in the AE  
 8 group because you just don't know.  
 9       ACTTION is actually working on a  
 10 demonstration of this using some data from the FDA  
 11 database. And what we ended up doing was if it was  
 12 recorded as an AE, we put them in the  
 13 jump-to-reference group, and if it wasn't recorded  
 14 at all, unfortunately, they had to go in the  
 15 missing at random imputation.  
 16       So I think the moral to that story is, as  
 17 well as you possibly can collect reasons for  
 18 missing data, the better off you'll be later when  
 19 you're trying to impute your data.  
 20       Next, I'm going to talk a little bit about  
 21 clinical meaningfulness and the difference between  
 22 inpatient and between group, which is challenging,

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1 to say the least. This comes a little bit off of  
2 what Dr. Thomson was saying.  
3 We think a lot in the pain field. We say,  
4 oh, a 30 percent or 50 percent difference is  
5 clinically meaningful. Where did that come from?  
6 This was I think one of the first studies that did  
7 this. It's the one that I am most familiar with,  
8 so I chose it to demonstrate to you.  
9 This study looked at a bunch of different  
10 trials and compared the changes in the NRS pain  
11 scores to a PGIC where patients told you how much  
12 improved they felt. And what they found was  
13 that -- know also that these are a lot of different  
14 conditions, so it's not just one condition, so it's  
15 pretty generalizable results.  
16 They found that in about 30 percent, or even  
17 less, people said they were minimally improved. So  
18 that's where this minimally clinically important  
19 difference from baseline for within patient comes  
20 from. Then if you go to about 50 percent, you get  
21 people who are saying they're much improved or very  
22 much improved. So that's where these numbers come

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1 from, and that can be very useful for defining  
2 treatment responders. You can say that X percent  
3 of patients responded to treatment.  
4 Now just as a caveat, my statistician would  
5 say you don't really know they're responding to  
6 treatment. They can be regressing to the mean and  
7 doing all these things, but regardless, that's, if  
8 you want to do a responder analysis, where those  
9 numbers might come from.  
10 Then there's this idea of a difference  
11 between groups. A lot of times people don't want  
12 to do a responder analysis for the very reason I  
13 just said or also because a dichotomous analysis  
14 has lower power. So we often are interested in,  
15 well, I would like to do a continuous analysis and  
16 get more power.  
17 Let's say I start at 6.5 or at the average  
18 participant, the people in the placebo group go  
19 down to 3.5 and the people in the treatment group  
20 go down to 3. So everyone's had a clinically  
21 meaningful difference, or not everyone; like the  
22 average person in both groups has had a clinically

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1 meaningful difference for themselves.  
2 So the question is now, let's say this is  
3 statistically significant, is this meaningful?  
4 It's hard to decide that because you have a large  
5 placebo effect, but there is a real effect of this  
6 treatment. It's statistically significant, but is  
7 it big enough? So I would argue that it's  
8 different depending on your perspective. So the  
9 NCD will be different depending on the risk  
10 associated with the treatment.  
11 If the risk is small, then maybe we don't  
12 need to see as big of a difference between the two  
13 groups as we would otherwise, especially because  
14 there's a lot of variability. These are averages.  
15 Also, it will be different depending on the  
16 perspective of the interpreter.  
17 If I'm a drug or device developer and its  
18 early stages, and I have a small difference that is  
19 statistically significant, which may be because  
20 you're really good at picking a super homogenous  
21 population, you might be skeptical to take it  
22 forward because you know that once your population

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1 becomes more heterogeneous, your difference is  
2 going to get even smaller, and it might be hard to  
3 show a difference in a trial.  
4 If you're a policymaker, let's say you're  
5 someone who is writing treatment guidelines, or  
6 you're a payer deciding whether you should pay for  
7 this drug, you might want to see a bigger  
8 difference, and you might want to see a bigger bang  
9 for your buck. We don't know.  
10 But if you're a clinician or a patient who  
11 has tried everything else, nothing works for you,  
12 and this treatment has low risks, you might look at  
13 this be like, hmm, this looks pretty good to me. I  
14 don't really care how much more of a benefit the  
15 people in the active group got over the placebo  
16 group; I want to try this.  
17 So I would argue that -- I know it's  
18 contentious; I can see people going like this. I  
19 would argue that this takes a little bit more  
20 thought than slap 20 percent change on it and go  
21 with that, especially when you're powering a trial,  
22 because at the end of the day, whether we like it

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1 or not, we all know we're supposed to power trials  
 2 on what's important. At the end of the day, you  
 3 might not see a significant difference, so are we  
 4 doing anyone any favors by underpowering our  
 5 trials?  
 6 I know you guys are device people. I'm  
 7 mostly thinking about drugs, so maybe these large  
 8 trials are not feasible. I'm just laying it out  
 9 there. You can take what you want from it.  
 10 I thought about you guys, and you might want  
 11 a bigger difference for things that are permanently  
 12 implantable. As a patient, I'm going to be like,  
 13 "Oh, I'll try pregabalin for 6 weeks and see what  
 14 happens; whatever, no big deal." But you're going  
 15 to undergo surgery, and you're going to have this  
 16 thing permanently in your body, so you might want a  
 17 little better chance that it's going to actually  
 18 work well for you or there's a bigger difference  
 19 between placebo and active when this type of  
 20 treatment is being used. And Bob has written a lot  
 21 about this. If you're interested, you can take it  
 22 up with him and read these.

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1 The last thing I'm going to talk about is  
 2 confidence intervals to inform interpretation of  
 3 non-significant superiority trials. I think we've  
 4 thought about this a lot because we've been talking  
 5 about noninferiority trials. Oh, sorry. Did I say  
 6 noninferiority? I think I did. I meant  
 7 superiority.  
 8 All I'm really going to say about this is if  
 9 you decide a superiority trial and at the end of  
 10 the day, you don't get p less than 0.05, you cannot  
 11 say that things are similar; you just can't. You  
 12 can use the confidence intervals, though, to  
 13 comment in the discussion, not in the results,  
 14 about how likely it is that these data actually  
 15 support a true negative, meaning one treatment is  
 16 no better than the other, or the data are  
 17 inconclusive.  
 18 So I would just say, let's say you've  
 19 decided what does MCD is, and we're not going to  
 20 debate that anymore, so this dot is the effect  
 21 estimate, so the average mean between groups or  
 22 whatever statistic you're using, and these small

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1 bars are the confidence intervals.  
 2 For this top one, I would argue that even if  
 3 you didn't plan this study as a noninferiority  
 4 study, it gives fairly good support to the fact  
 5 that these two treatments, whether it's placebo or  
 6 two active treatments, are fairly similar in  
 7 activity, because the reason you got p greater than  
 8 0.05 isn't because there was just a ton of  
 9 variability and it's all over the place, which is  
 10 this scenario, where you really can't rule out a  
 11 treatment that's in favor of active or of control.  
 12 I'm just giving a plug for if you do a  
 13 superiority trial or you're reading a superiority  
 14 trial where the p value is greater than 0.05, don't  
 15 just assume that means they're the same. You  
 16 really have to do some due diligence.  
 17 I didn't put the data here in the interest  
 18 of time, but we did a review looking at how authors  
 19 interpret these confidence intervals, and they're  
 20 very rarely actually interpreted by authors, at  
 21 least in 2015, so you as consumers of these papers  
 22 need to really think about it yourself.

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1 My conclusions, to ensure the RCTs provide  
 2 the gold standard of evidence, investigators,  
 3 authors, and readers must pay attention to many  
 4 trial design details. The topics in this  
 5 presentation represent only a few important aspects  
 6 of RCTs that we have to consider when we're  
 7 designing and interpreting our trials. Paying  
 8 attention to these details will increase the  
 9 reliability of our results, and thus their  
 10 acceptance by important stakeholders, including  
 11 regulators, policymakers, and payers. That's all I  
 12 have. Thanks.  
 13 (Applause.)  
 14 DR. THOMSON: Okay. We're doing a fabulous  
 15 job keeping to time, so our New Yorker is going to  
 16 hustle us through.  
 17 Presentation - Brian Kopell  
 18 DR. KOPELL: First of all, again, thank you  
 19 for inviting me. The last day and a half has been  
 20 just really terrific in terms of the quality of the  
 21 back and forth discussions. I really love the  
 22 opportunity to interact with people on sort of a

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1 more personal intimate manner as opposed to some of  
 2 these bigger meetings, where you don't really get  
 3 to have an in-depth conversation, a nuanced  
 4 conversation.  
 5 As everybody surmised from my discussions  
 6 yesterday, my interest in this particular realm in  
 7 terms of what this body could do to recommend for  
 8 trial design centers around economic outcomes and  
 9 cost effective analyses, mainly because I think  
 10 that when we begin to see how difficult it is to  
 11 absolutely determine efficacy in a convincing  
 12 fashion and so forth and plus the cost of these  
 13 devices, we really are going to run into a  
 14 situation where we're not going to be able to  
 15 provide this really life-changing therapy for our  
 16 patients, and that's going to be a real shame.  
 17 Rod is going to give an update on this.  
 18 It's probably better than I will be since two of  
 19 the papers that I'm presenting are actually his.  
 20 And not surprisingly, most of the cost  
 21 effectiveness data comes from our European  
 22 colleagues. We don't really in this country do a

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1 very good job at looking at cost effectiveness. It  
 2 is partially a cultural thing, but it's not  
 3 something that we have the luxury of ignoring any  
 4 further.  
 5 These are my disclosures.  
 6 Probably in his greatest book, Tom Wolfe,  
 7 "The Right Stuff," attributes a quote to Gus  
 8 Grissom, one of the Mercury 7 astronauts. And Gus  
 9 was basically remarking that without any sort of  
 10 real funding, as cool of a project might be, you  
 11 can't do it unless you have the money. He said  
 12 very eloquently, "No bucks, no Buck Rogers." And I  
 13 think that when it comes to neuromodulation and  
 14 neurostimulation technologies, which are  
 15 undoubtedly cool, undoubtedly have incredible  
 16 potential for our patients, it costs a lot of  
 17 money, both on the development side and the  
 18 deployment side. And we don't show the milieu the  
 19 bucks in this, we won't have our Buck Rogers.  
 20 I'm going to start by just doing a quick  
 21 review of the literature and then give some  
 22 thoughts about economics in trial design not to

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1 prescribe what I think that we should recommend per  
 2 se, but maybe hopefully stir some discussion for  
 3 our discussion period in just a little bit.  
 4 Review of the literature. What's  
 5 interesting is that the average U.S. patient  
 6 changes health coverage every approximately three  
 7 years. Most of the measures in the United States  
 8 studies basically are measures that involve  
 9 break-even points beyond the three-year mark, and  
 10 that may not be very attractive to payers because  
 11 they want to see the payoff right away. So I just  
 12 want to kind of put that in your perspective.  
 13 Again, in my opinion, probably the best  
 14 measurement is what we've already referenced, the  
 15 so-called quality measurement, the quality-adjusted  
 16 life year. And most of you probably know this, but  
 17 whoever doesn't, the concept is a year where  
 18 somebody is in essentially perfect health is  
 19 considered a quality life year. Then you can begin  
 20 to take a look at a treatment and determine its  
 21 costs effectiveness by determining how much does it  
 22 cost for one year of this perfect life.

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1 If you look at the literature -- and this  
 2 was a really good review of this from the New  
 3 England Journal a few years ago -- there's this  
 4 rough sort of agreement across the board in various  
 5 different fields that about \$50,000 per  
 6 quality-life year is a very reasonable number to  
 7 attribute to any sort of therapy, whether it be a  
 8 pill, whether it be a device, 50 grand for every  
 9 quality-adjusted life year. That's probably the  
 10 best way that we could probably dive into this.  
 11 There are other ways, obviously, we could  
 12 probably show this: reduction in physician visits;  
 13 reduction in hospitalization and ER utilization.  
 14 Obviously, this kind of goes into it. If you're  
 15 having a perfect quality life year, you're not  
 16 going to the doctor. That makes sense.  
 17 Perhaps the lowest hanging fruit is the  
 18 reduction of medications. This is definitely  
 19 something that we see for DBS for movement  
 20 disorders, that the number one reason why DBS for  
 21 movement disorders is absolutely cost effective is  
 22 that we can reduce the meds. It's very simple, and



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1 it's probably going to be the same in this realm as  
 2 well. I don't have to tell this audience that  
 3 drugs are expensive. Many patients are on 5, 6  
 4 drugs per month. That's a lot of money over the  
 5 course of a year.  
 6 This is probably the lowest hanging fruit  
 7 where we could potentially show the impact of where  
 8 spinal cord stimulation can be cost effective. And  
 9 remember, if we all believe that spinal cord  
 10 stimulation has a large effect on our patients, we  
 11 should be able to reduce their medications. We  
 12 should be able to do that.  
 13 Just going through some of the studies in a  
 14 chronological order, in 2002, this was a study  
 15 looking at spinal cord stim, and this is basically  
 16 demonstrating cost effectiveness breakout point at  
 17 5 years post-implant. Now sure, that's great, but  
 18 that determines whether -- or that's predicated on  
 19 whether a patient stays within one payer for  
 20 5 years. If they have commercial insurance, Aetna  
 21 might kind of go, "Yeah, that's okay. I guess," so  
 22 just consider that.

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1 Rod, this is one of your studies from, I  
 2 believe, 2004, Spinal Cord Stimulation Cost  
 3 Effective Within Three Years Across the Board for  
 4 Failed Back Syndrome, Angina, and CRPS. What is  
 5 interesting is most of the cost effectiveness data  
 6 are for indications that are not available in the  
 7 United States, basically, but there is some for  
 8 CRPS and failed back syndrome. And again, the  
 9 reduction is in, not surprisingly, cost of drugs,  
 10 physician visits, and hospitalization. Here, this  
 11 study found that for the CRPS indication, it's  
 12 about \$22,500 per quality, well under the 50,000.  
 13 Richard, your paper here demonstrated the  
 14 difference between crossover from spinal cord stim  
 15 to surgery, and obviously crossing over to surgery  
 16 adds costs, and if we can prevent that sort of  
 17 situation, by definition we're going to reduce  
 18 costs.  
 19 Again, in 2010, Rod, another one of your  
 20 papers, An Advantage of Spinal Cord Stimulation  
 21 Over Conventional Medical Management to the tune of  
 22 about 3500 pounds for CRPS. And overall, spinal

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1 cord stimulation is cost effective at \$30,000 per  
 2 quality. What's also interesting is that the  
 3 rechargeable IPG tends to be more cost effective  
 4 than a primary cell that last 4 years or less. So  
 5 there's another example of how some of the specific  
 6 technologies can become cost effective.  
 7 Here's one that I found that basically  
 8 demonstrated that spinal cord stimulation is not in  
 9 fact cost effective. And it's very interesting.  
 10 It's mostly for failed back surgery syndrome for  
 11 workers compensation. Failed back surgery may be  
 12 the most difficult patient population to  
 13 demonstrate this cost effectiveness. And  
 14 ironically enough, that's probably the most  
 15 indication in the U.S.  
 16 I think that this to some degree touches on  
 17 what you said yesterday, which is when you're sent  
 18 a set of records, you can almost kind of read the  
 19 story and kind of determine this is not a good  
 20 candidate for this particular type of procedure.  
 21 And in this particular group of workers comp  
 22 patients, spinal cord stim was by far more

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1 expensive treatment.  
 2 What was also interesting across the board  
 3 for this patient population, whether it be spinal  
 4 cord stim, conventional management, optimize  
 5 management, only 10 percent achieved any  
 6 significant pain relief, so that says something  
 7 about the patient population, doesn't it? That's  
 8 all it is.  
 9 In 2013, this was another study looking at  
 10 various spinal cord stimulation patients in Canada  
 11 across the board for failed back surgery, CRPS,  
 12 angina, and PVD, and again, throughout this, once  
 13 again, very cost effective treatment.  
 14 In 2017, my colleague Ash Sharan did a  
 15 meta-analysis of 21 studies looking at cost  
 16 effectiveness of spinal cord stimulation for back  
 17 pain. What's interesting in this study is the  
 18 large majority of the spinal cord stimulation  
 19 studies demonstrated cost effectiveness. So it  
 20 really does beg the question why can't we do this  
 21 in a way that really makes our payers compelled to  
 22 pay for this?

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1 As I said, there's this increasing  
 2 resistance from third-party payers despite FDA  
 3 approval of these devices. Year after year when I  
 4 go to these meetings, when I sit on boards of  
 5 societies, one of the biggest things that come up  
 6 over and over and over again is the fact that we're  
 7 getting such pushback from payers basically for  
 8 these therapies.

9 A hallmark of this -- I alluded to this  
 10 yesterday -- is in 2005, VNS for depression was  
 11 approved by the FDA. It was approved. And then in  
 12 2007, CMS basically said it was not necessary and  
 13 won't pay for it. The result of that is that  
 14 nobody pays for it or very, very few pays for it.  
 15 So I would just submit to you, what's the point of  
 16 having a trial that gets regulatory approval that  
 17 we can't get into our patients? It's literally the  
 18 most Sisyphean, basically, tasks that we could  
 19 possibly do. We'll just roll the rock up the hill  
 20 for no darn good reason. So we have to basically  
 21 demonstrate that in addition to reducing pain, we  
 22 are unburdening the system of this huge economic

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1 cost of pain.

2 Another example, DRG-stim, which has come on  
 3 the market, doesn't even have its own code. We  
 4 have to kind of call it spinal cord stimulation.  
 5 It is sort of spinal cord stimulation. I guess in  
 6 some sort of philosophical discussion, you could  
 7 probably determine that. So many have deemed  
 8 investigational. What good is it if we can't get  
 9 it into our patients?

10 How many here are still from industry?  
 11 Raise your hand.

12 (Hands raised.)

13 DR. KOPELL: Okay. How many of you are  
 14 aware that under the current Medicare payment  
 15 scheme, not one hospital can actually break even on  
 16 your devices? Not one company offers a spinal cord  
 17 stimulation that basically Medicare will give a  
 18 lump sum and that they can at least break even on?  
 19 Everyone loses money. How many of you are aware of  
 20 that?

21 (No response.)

22 DR. KOPELL: None of you. Obviously, none

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1 of your companies would be in business if you can't  
 2 make a profit. We want you to make a profit  
 3 because we want you to continue to develop these  
 4 things. But in the same way, the hospitals are not  
 5 going to be able to continue this way. It's simply  
 6 impossible. It's just simply impossible. Not my  
 7 law; law of the universe, basically.

8 So we have to address this. If there is  
 9 high upfront cost, there has to be a payoff for  
 10 this system. Maybe the hospitals won't see these  
 11 patients in ER down the line for the next several  
 12 years. Then all of a sudden, it makes sense for a  
 13 hospital to have at least that initial investment  
 14 into these patients. Otherwise, I don't see how  
 15 they're going to be able to do it.

16 The last point has been touched and probably  
 17 will continue to be touched on. Most of the  
 18 pivotal trials are essentially 510(k)s; they're not  
 19 PMAs. So that's the lowest hanging fruit of  
 20 regulatory approval in the U.S. And then on top of  
 21 that, they're noninferiority studies.

22 Now again, I'm very happy to let the

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1 companies come to market as quickly as they can  
 2 because I want to see better devices. I'm a  
 3 technophile. I like to see this. I want them to  
 4 thrive. But if you're going to have that  
 5 low-hanging bar to get into the market, you have to  
 6 do something for our patients and us to show that  
 7 your devices aren't just continually burdening the  
 8 system. That's not going to work.

9 As I said, what's the rationale for  
 10 third-party payers, or even CMS for that matter, to  
 11 pay for treatments that reach market merely by  
 12 superseding a noninferiority threshold and don't  
 13 demonstrate any incremental, true economic benefit?  
 14 What's the point of it? They're there for profit.  
 15 Whether we like it -- we could have a debate about  
 16 whether for-profit insurance is the right thing,  
 17 but we do have basically a for-profit insurance  
 18 milieu in this country. They're there to make  
 19 money. So if you basically offer them a device  
 20 that costs them more money and doesn't do more, I'm  
 21 sorry, you will run into the laws of economics, and  
 22 you will see what will happen eventually.

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1 So again, if the vast majority of the  
 2 literature suggests that spinal cord stim is cost  
 3 effective, then why aren't the payers tripping over  
 4 themselves to pay for this? Well, probably it is  
 5 because probably the quality of the data that we  
 6 have is probably on the poor side. It's  
 7 retrospective. It's observational. And I would  
 8 argue that if our endpoints, perspective when we  
 9 are trying to come to market, include this cost  
 10 savings data, not only would this facilitate  
 11 reimbursement without the need for postmarket  
 12 studies, I believe it would accelerate the actual  
 13 growth of this field because it will become very  
 14 apparent that this is the right way to go and the  
 15 right thing to do for our patients.

16 So again, in summary, I think that one of  
 17 the most important things that this body might be  
 18 able to do is make a recommendation of how we can  
 19 get some of this data into these pivotal trial  
 20 designs so that we don't have to continually fight  
 21 this uphill battle, and that's it.

22 Rod, you're going to do a much better job

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1 than me in about two seconds.  
 2 (Laughter.)  
 3 DR. THOMSON: Thanks, Brian.  
 4 DR. KOPELL: You bet.  
 5 (Applause.)  
 6 DR. THOMSON: As Brian has alluded to, we  
 7 have an extra session to the program. I think Rod  
 8 Taylor is going to be talking about cost  
 9 effectiveness from somebody's perspective; payer  
 10 perspective, obviously.

11 Presentation - Rod Taylor

12 DR. TAYLOR: Thanks, Simon. This is sort of  
 13 unplanned. And I've got to say, Brian, that was a  
 14 great presentation. I think everything I've said,  
 15 you've captured. This was a piece of work that I  
 16 think I managed to twist Bob's arm to agree that we  
 17 might do. The usual thing, I'm up here getting all  
 18 the glory, but the person who's done all the hard  
 19 work is a guy called Rui Duarte. Rui's actually in  
 20 Rwanda, of all places at the moment, so he can't be  
 21 here with us, but Rui's helped me do this.

22 Effectively what I twisted Bob's arm to do

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1 is to do an updated review of the evidence for cost  
 2 effectiveness for spinal cord stim with a  
 3 particular focus on methodology, which is what this  
 4 meeting's all about. So I'm not going to present  
 5 any results. Brian's done that and gave you a  
 6 flavor. But what I want to talk about is are there  
 7 any particular recommendations we might want to put  
 8 in our paper around not just a collection of  
 9 clinical data but also the collection of economic  
 10 data and how we might use that data to make  
 11 economic decisions, if you like, around SCS.

12 So again, we've heard a little bit about  
 13 this. There are actually three formal systematic  
 14 reviews of SCS cost effectiveness, the most recent  
 15 one by Hoelscher and colleagues. But what's  
 16 interesting, including our own, is that none of  
 17 these reviews have really focused on methodology.  
 18 They've been really all about know, what are the  
 19 results. And as Brian was saying, results are all  
 20 pretty positive, but is the reason that the result  
 21 is positive because of poor methodology?

22 So what we aimed to do in this review was to

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1 focus on the research methods employed. We've also  
 2 collected the outcomes. We've also collected the  
 3 results. And actually, we will hopefully have a  
 4 separate publication on this review, but I think  
 5 it's the methodological piece that Bob was  
 6 particularly keen we focus on.

7 So again, Ewan, a huge thanks. We've  
 8 piggybacked on Ewan's review, and Ewan and his team  
 9 ran some additional economic search terms. If I  
 10 understand it right, you basically just  
 11 grafted [ph] these on the SCS generic terms. But I  
 12 think what's important here is that we didn't just  
 13 limit ourselves to what are called trial-based  
 14 analyses because many analyses in this area are  
 15 what are called model-based analyses.

16 Sometimes with clinicians, I get a little  
 17 bit of skepticism about model based because  
 18 essentially clinicians say you've taken the data  
 19 from a real trial, and then you make it up, you  
 20 extrapolate it, you manipulate it, you've  
 21 bastardize it, and then you come up with some other  
 22 figure.

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1 Well, I'd put it to you that's maybe a bit  
 2 cynical about models. Models are very, very  
 3 helpful. And one of the reasons that they're  
 4 helpful is that by definition, when we do trials,  
 5 our follow-up is finite in our area for maybe up to  
 6 two years, typically in a randomized-controlled  
 7 trial.

8 How long does pain lasts for, chronic pain  
 9 last for? Well, the answer is it's lifetime. So  
 10 we've got to take the results of clinical trials  
 11 and then extrapolate them over what is the  
 12 appropriate time horizon for the patient. If we  
 13 were dealing with an acute disease, that would be  
 14 fine, two years, but we need to think in a longer  
 15 timeline.

16 So what we did here -- and as I say, two  
 17 reviewers reviewed all the titles; it was really  
 18 one. Rui's done all the hard work. I've been kind  
 19 of carrying his shopping bags for him, but doing  
 20 the checking. But this is just to summarize what  
 21 our inclusion and exclusion criteria were, and I  
 22 think nothing more to say other than that they had

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1 in the literature. Jane and I had a bit of a  
 2 discussion about this yesterday. We do need to  
 3 look at quality, but effectively, we're looking at  
 4 the quality of reporting.

5 How many cost-effectiveness studies full  
 6 economic evaluations in spinal cord stim are there?  
 7 And the answer is 14. At this moment in time,  
 8 there are 14, and this is them. I've summarize the  
 9 population, population RA, for instance. So  
 10 Andres, the first line, RA's refractory angina;  
 11 FBSS; CRPS; CMIC [ph], complex, reflex, pain  
 12 syndrome; CLI, chronic limb ischemia; and then DN,  
 13 diabetic neuropathy, so quite a few different  
 14 indications here, but you can see by far and away,  
 15 the most evaluation has been in FBSS, and of course  
 16 that is an indication recommended on both sides of  
 17 the pond.

18 Comparisons are interesting, aren't they,  
 19 that you can have anything, believe it or not,  
 20 from -- I think as I mentioned yesterday, in  
 21 refractory angina comparing spinal cord stim with  
 22 coronary artery bypass grafting, Simon talked

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1 to be full economic evaluations. So studies like  
 2 the BUD [ph] analysis that Brian showed initially,  
 3 which was just a cost analysis, we excluded.

4 How do you assess quality here? This is one  
 5 of the best named quality checklists you can come  
 6 across. This is the CHEERS checklist. CHEERS is a  
 7 group, the Consolidated Health Economic Evaluation  
 8 Reporting Standards. And if you like, this is  
 9 CONSORT from cost-effectiveness studies. Everybody  
 10 knows CONSORT.

11 This is a good group of people called the  
 12 ISPOR Collaboration. ISPOR is very predominant. I  
 13 guess they're the IMMPACT of the health economics  
 14 world. They published this guideline led by Don  
 15 Husereau, but then the second author here, Mike  
 16 Drummond, is sort of the grandfather of the whole  
 17 area of health economics, so that's a good  
 18 pedigree.

19 Twenty-four questions, and what this focuses  
 20 on is the quality of reporting. Remember when we  
 21 look at quality, we do have a challenge that what  
 22 we can only do is judge what we see people writing

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1 yesterday about percutaneous myocardial  
 2 revascularization. But again, a lot of these are,  
 3 again, what we call CMM or conventional medical  
 4 management.

5 I just wanted to focus on the fact that you  
 6 can see that although some of these analyses are  
 7 trial based -- in other words, the time horizon of  
 8 the analysis is exactly the same as the trial -- a  
 9 number of them are model based. But just to pick  
 10 up on Brian's point, I thought I might,  
 11 particularly for the model-based analysis, look at  
 12 where their primary source of effectiveness or  
 13 efficacy data came from. And I think just picking  
 14 up on Brian's comment, how useful is it to have a  
 15 cost-effectiveness model where the data is  
 16 effectively predicated on non-randomized  
 17 literature? I would perhaps say that it's going to  
 18 be less helpful, and that will be one of the  
 19 comments I'll come back to.

20 This is a death-by [ph] slide, so this is  
 21 just to show you that Rui really did do some very  
 22 hard work here. These are all the studies. This

|  |   |
|--|---|
| <p style="text-align: right;">Page 77</p> <p>1 is the first 8 or 9 questions, so these are the<br/> 2 various questions that CHEERS asked. And then we<br/> 3 looked to see did they fulfill that question; did<br/> 4 they fulfill that criteria. If so, a yes; if not,<br/> 5 a no. And I think these are all yeses, but as you<br/> 6 go through later, some of them are nos, or some of<br/> 7 them are actually not applicable, but 24 questions<br/> 8 across 14 studies.</p> <p>9 What was the headline here? If you total<br/> 10 the CHEERS scores, as I said, normally it's 24. So<br/> 11 the denominator here is 24, so if you fulfill all<br/> 12 the criteria of reporting, it will be 24 out of 24.<br/> 13 The slight wrinkle is that up to 3 questions here<br/> 14 are not applicable. So if you're doing a<br/> 15 trial-based analysis, one of the questions says,<br/> 16 "Was your model an appropriate one?" Well, clearly<br/> 17 that's not applicable to our trial.</p> <p>18 So the denominator here for some analyses is<br/> 19 as low as 21, if you're following me so far, and<br/> 20 what I've therefore done is just to express how<br/> 21 many of these studies achieved the reporting<br/> 22 criteria. And I think what is quite</p>         | <p style="text-align: right;">Page 79</p> <p>1 be explicit about those conflicts and who's in<br/> 2 there, and that hasn't always happened with at<br/> 3 least a couple of these analyses.</p> <p>4 A couple of maybe suggestions, Bob and<br/> 5 others, to what this might mean if we're going to<br/> 6 use any of this information in terms of our<br/> 7 write-up. I think if we use the CHEERS quality of<br/> 8 reporting checklist, I think, as you hopefully<br/> 9 agree with me, the quality is actually generally<br/> 10 quite high. But I would say the real big caveat<br/> 11 here is we're looking at the quality of reporting,<br/> 12 but that's not necessarily the appropriateness of<br/> 13 what they've done.</p> <p>14 So you might say, "Well, what do you mean by<br/> 15 appropriateness, Rod?" Well, for instance, did<br/> 16 they choose the appropriate cost? You didn't look<br/> 17 at that. Did they make the appropriate modeling<br/> 18 assumptions? Was their model structure<br/> 19 appropriate? Did the model structure reflect the<br/> 20 clinical disease process? None of those questions<br/> 21 are tested here. This is just purely about<br/> 22 reporting.</p> |
| <p style="text-align: right;">Page 78</p> <p>1 interesting -- and I need to be careful here<br/> 2 because a couple of these are mine, so you might<br/> 3 say, "Well, yes, of course you said that, Professor<br/> 4 Taylor." But actually, the quality of reporting<br/> 5 here looks pretty good, doesn't it, by and large.<br/> 6 Most of them are fulfilling.</p> <p>7 A couple didn't do quite so well, so I just<br/> 8 thought I'd pull out what the main issues were.<br/> 9 The Andrell study didn't state the perspective.<br/> 10 Perspective means did they look at it only from a<br/> 11 healthcare perspective or did they take a broader<br/> 12 societal perspective and, for instance, look at the<br/> 13 cost of return to work. They didn't state the<br/> 14 discounting rate.</p> <p>15 Handling uncertainty is really, really<br/> 16 critical, not only in clinical trials as we heard<br/> 17 from our previous speakers, but also an economic<br/> 18 evaluation clearly also dealing with heterogeneity,<br/> 19 and we can do that by presenting cost-effectiveness<br/> 20 ratios for subgroups. Then again -- and I'm guilty<br/> 21 of this as well -- many of these analyses are<br/> 22 funded by industry, and that's okay, but we need to</p> | <p style="text-align: right;">Page 80</p> <p>1 Just to make the point I guess is we've got<br/> 2 the same problem with the Cochrane risk of bias,<br/> 3 too, haven't we? Basically, it's just looking at<br/> 4 quality of reporting. So we shouldn't beat<br/> 5 ourselves up, but at the same time I think we just<br/> 6 need to be cautious that this is a caveat here.</p> <p>7 What would I say my recommendations are?<br/> 8 And I'll blend these in with Brian's. I think we<br/> 9 should be really trying to encourage, wherever<br/> 10 possible, any analyses, particularly model based,<br/> 11 to be based on randomized-controlled trial<br/> 12 evidence. And know, going back to Nate's point,<br/> 13 not every randomized-controlled trial is one that<br/> 14 we might want to talk about, so they've got to be<br/> 15 those -- what were we calling them?</p> <p>16 DR. DWORKIN: Level zero.</p> <p>17 DR. TAYLOR: Level zero, our new term.<br/> 18 That's got to be in the manuscript. Bob doesn't<br/> 19 like that. You're going to have to work it out,<br/> 20 guys.</p> <p>21 Clearly, the other issue we need to be<br/> 22 careful about is when we are doing modeling, it's</p>  |

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1 very easy to cherry-pick, isn't it, the trial that  
 2 shows the best results clinically, and then you  
 3 pull that through. But should we be doing that?  
 4 Well again, like any area of evidence review, we  
 5 should be basing that on a systematic review and  
 6 not cherry-picking.

7       Then I think, clearly, as I've mentioned,  
 8 there are a couple of analyses where we could do  
 9 better, clearly being explicit about perspective,  
 10 why we're choosing certain comparators, discount  
 11 rates, and the time horizon. And I think probably  
 12 the biggest one that we have here is this issue  
 13 about -- FBSS, for instance, is a tremendously  
 14 heterogeneous population, and I think it's one of  
 15 the issues for actually trial reporting as well as  
 16 economic reporting, is can we start to  
 17 differentiate the baseline characteristics of those  
 18 individuals and even begin to power the study so  
 19 that we can begin to examine whether the treatment  
 20 effects are consistent across different baseline  
 21 characteristics.

22       That was my additional tuppence worth,

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1 Simon, so thanks for your attention.  
 2       (Applause.)  
 3       DR. THOMSON: Thanks very much, Rod.  
 4       I think our last talk is going to be from  
 5 Sam Eldabe.  
 6       Presentation - Sam Eldabe  
 7       DR. ELDABE: Thank you very much, Simon.  
 8 I've been drafted in to talk to you about special  
 9 issues to do with programming and the sham  
 10 stimulation. It is perhaps a serendipitous choice,  
 11 as I'm one of these physicians who still insist on  
 12 programming his own patients in the clinic. So it  
 13 is  
 14 a subject I'm familiar with.  
 15       For the purpose of this, I will take you  
 16 through a number of studies, and I'll show you what  
 17 is being reported on programming, how it's being  
 18 reported, and how much is being reported. In order  
 19 to do that, I decided to look at the studies in  
 20 terms of whether they are an effectiveness study  
 21 that's looking at the effect of spinal cord  
 22 stimulation in any pain indication, or whether it's

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1 a study that compares devices, or whether it's a  
 2 study that investigates modes, parameters of  
 3 stimulation, or is it a sham-controlled trial.  
 4 We'll look at those, and we'll see how the  
 5 reporting differs from one type of study to  
 6 another.

7       We will then -- as Nate asked me  
 8 yesterday -- aim to come up with a list of possibly  
 9 what we may recommend in the manuscript that can be  
 10 done about the issue of programming, so to make  
 11 your life easier.

12       Let's delve a bit under the bonnet of  
 13 programming. The question is why does it matter?  
 14 It matters because the outcomes are dependent on  
 15 programming. If you implant the device, and you  
 16 don't program it, you get absolutely nothing, or  
 17 theoretically you shouldn't. The Alkaisy study  
 18 shows that this is not indeed the case, but there  
 19 you go.

20       There is no consensus on what constitutes  
 21 appropriate programming. There is no standard for  
 22 programming SCS in a conventional way. We don't

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1 have a standard algorithm. We do have a partial  
 2 standard algorithm for programming high frequency,  
 3 we do have the same for burst, and we may have  
 4 something for other modes of stimulation, high  
 5 density or the subparasthesia stimulation.

6       It all sounds far too complex when you look  
 7 at it from the outside, but actually, the  
 8 parameters we're playing with are simply three  
 9 parameters: frequency, pulse width, and amplitude.  
 10 My premise is that if you know that these are the  
 11 three parameters you're playing with, you can  
 12 program any device. It does look a bit like a  
 13 complicated story, but it isn't.

14       The other parameters that we need to look at  
 15 is the position of the cathode that we are  
 16 importing this current to, and as you can see here,  
 17 I've shown you an x-ray, and the cathode is at T9.  
 18 The other thing that is sometimes reported is the  
 19 position of the lead. And the position of the lead  
 20 is inferred from the position of its tip. So here,  
 21 that lead is at the T8-9 disk.  
 22       Let's take a look under the bonnet of the

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1 device programming and see whether we end up  
 2 saying, yes, there is an engine all right or  
 3 whether we find something like this. Before we  
 4 move on to look at how programming is happening,  
 5 we'll take another look as to why it matters. I  
 6 think you are a very enlightened audience. You  
 7 probably know this more than I do.  
 8 This paper summarizes the placebo and the  
 9 nocebo effects in neuropathic pain and is a very  
 10 interesting publication. What the authors come up  
 11 with is a list of the predictors of a high placebo  
 12 response. I just want you to look at this bold  
 13 one, which is the number of face-to-face visits  
 14 predicts a high placebo response. Now, programming  
 15 is a face-to-face visit. That is never mentioned  
 16 and never talked about in trials.  
 17 You've seen this slide before. This is a  
 18 typical pragmatic approach in reporting programming  
 19 in a trial. They are programmed by a separate  
 20 technician and so on and so on. This is the  
 21 programmer that I started with when we started  
 22 doing neurostimulation. It was a suitcase that you

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1 had to carry around. I don't think you need it to  
 2 plug it into the wall, but I think there existed  
 3 the parallel to that, that you needed to plug into  
 4 the wall.  
 5 Why does it matter? I think we mentioned  
 6 that it is usually delegated to industry  
 7 representatives, and sometimes these industry  
 8 representatives are operating in isolation from the  
 9 clinical staff and in isolation from the study  
 10 staff. So you'll get a rep who comes in, takes the  
 11 patient, goes into a room, spends a couple of hours  
 12 with them, and you have absolutely no insight into  
 13 what happened there, what conversation occurred,  
 14 what information was given, and that is part of  
 15 your intervention in the study.  
 16 There is also the issue of the reporting of  
 17 SCS failures and explants. If you look at our  
 18 trials in the general, you will find that the rate  
 19 of explants of SCS in the trials is zero percent.  
 20 There are very, very few patients who are explanted  
 21 because of failure of the therapy within a trial,  
 22 whereas when you look at the real-world data,

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1 you'll find that for most of us, it's around 20  
 2 percent. Half of this is because of lack of  
 3 efficacy.  
 4 So you do ask the question, what actually  
 5 happens? What's so special about patients who are  
 6 included in the trials? And the answers must be,  
 7 at least partially, that because we have no insight  
 8 into this interaction and the patient is not going  
 9 to request the device be removed until someone  
 10 tells them that we've run out of options.  
 11 If you lock them up in a room with an  
 12 industry rep whose job it is to come up with  
 13 another option, we may go on forever, and that's  
 14 probably what happens, and that probably has an  
 15 impact on the failure rates that we report in  
 16 trials.  
 17 There are very few reporting of frequency of  
 18 the programming across groups, and of course these  
 19 frequent visits focused attention can have an  
 20 impact on pain and satisfaction of the patient.  
 21 The programming reporting sometimes happens in the  
 22 methods, sometimes happens in the results, and we

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1 look at that, and nobody thinks about whether these  
 2 visits have a cost attached to them, nobody  
 3 actually appropriates that cost, and it does not  
 4 appear in cost evaluation.  
 5 Just to give you an example, this is an  
 6 extract from the Senza study, and that is what the  
 7 Senza study tells you about programming in its  
 8 totality. Have a read of this. This is an extract  
 9 from the methods section. We're saying that for  
 10 traditional SCS, subject parameters were adjusted  
 11 to optimally overlap parasthesia and so on and so  
 12 on, until you get to suddenly hear, you're getting  
 13 results. This is no longer methodology; this is  
 14 results.  
 15 When you read it, it is quite difficult to  
 16 comprehend. You need a translator to understand  
 17 what these figures are, and I haven't actually  
 18 worked out where they are yet. What is the meaning  
 19 of an average and standard deviation of the minimum  
 20 and the maximum program parameters frequency, blah,  
 21 blah, blah? What does that mean? I have no idea.  
 22 I took it to mean that you have two groups where

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1 you have high values and low values, and they group  
2 the high values together and the low values  
3 together, and this is the mean of all the  
4 programming values throughout the study. It could  
5 be that, but it could be anything else as well.  
6 This is from the study by Jose De Andres  
7 colleagues, and he gave us a very good way of  
8 programming devices. Even with conventional  
9 stimulation where we say there is no way you can  
10 produce an algorithm, he gave us an algorithm. I  
11 want to go into that in great detail because it is  
12 somewhat technical. But it goes to show that if  
13 you put your mind to it, you can produce an  
14 algorithm to program a device in conventional  
15 stimulation, and there it is. And he applied that  
16 in his study, and it worked.  
17 He also gave us a very clear approach to  
18 reporting on programming, or a better approach to  
19 reporting on programming, in that he told us the  
20 devices were programmed in a session run by a staff  
21 physician and an industry representative; that  
22 systems were reviewed at all the study assessment

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1 points and if the patient reported a change in  
2 parasthesia. However, he failed to tell us how  
3 often did this report change in parasthesia happen.  
4 So we don't have an idea of what is the total  
5 number of visits that occurred to do with  
6 programming.  
7 Now these are the effectiveness studies that  
8 I told you about earlier on. What I will do is  
9 just take you through who reports what and in which  
10 part of the manuscript. Here is the population:  
11 critical limb ischemia, complex regional pain  
12 syndrome, failed back surgery syndrome, diabetic  
13 neuropathy, and the refractory angina.  
14 As you can see, the programming method is  
15 reported in one study, and here they give us a  
16 glimpse of what the programming methodology may be,  
17 but the rest do not, much to my shame, including  
18 one of my studies. Surgical procedure, every study  
19 describes the surgical procedure in great detail,  
20 but no study describes the programming methodology  
21 in such a detail.  
22 The programming results. Now, this study is

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1 an old study by comparison, 1995, but they do a  
2 fantastic job of reporting on the programming  
3 results. They actually had a full technical  
4 publication in 2000 where they reported on every  
5 single piece of detail on the programming and how  
6 it was done, the lead position, the cathode  
7 position, everything that we've looked at.  
8 Apart from that, there is only a report from  
9 the PROCESS study 2007 about mean and standard  
10 deviations of the values, and that is in one of the  
11 appendices of the paper. Otherwise, most tell you  
12 that we adjusted amplitude to suit patients, and  
13 that's about all you're getting. How many tell us  
14 about the frequency of the programming? None.  
15 Who's programming? None; nothing.  
16 Conclusions. Effectiveness studies do not  
17 report on programming. There are no reports on  
18 who's programming, and the reporting is variably  
19 presented, sometimes in the methodology, sometimes  
20 in the results, and sometimes there's a mixture.  
21 This no doubt affects the quality and the  
22 reproducibility and the generalizability of these

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1 findings in the long term.  
2 So when we think about it, this is a complex  
3 intervention. The outcome of this complex  
4 intervention is dependent upon a lot of factors,  
5 including the competence of the implanter, the  
6 competence of the person programming the devices,  
7 the instructions given to the patients, and their  
8 adherence to these instructions.  
9 So despite this complexity, there are very  
10 few studies that have accounted for the potential  
11 variability of such a complex intervention. We  
12 have no idea what the impact of that variability  
13 may be. Because of the concept of the rep in a  
14 closed room and a patient, we have no insight in  
15 one, two, and three.  
16 Nobody has actually given us a glimpse that  
17 this intervention needs to be quality controlled.  
18 The quality control on the surgical part of the  
19 intervention is fantastic and is present in every  
20 study. The quality control on this part of the  
21 intervention, the programming, which is the  
22 long-term one, which is the one that matters, is



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1 absent.

2 This is a bunch of device comparison studies

3 that you have seen before. A lot of these you've

4 seen before. And basically what I'm doing here is

5 showing you who's reported on programming method,

6 who's reported on programming in the results

7 section, whether the frequency of programming was

8 mentioned at all, not reported, and whether the

9 personnel was mentioned.

10 You'll find that the picture here is a

11 little bit better. In Senza, I've showed you what

12 was reported. In ACCURATE, there is a table that

13 gives you all the values of programming with mean

14 standard deviations and ranges. In SUNBURST, it's

15 not so clear. We were told that the frequency of

16 programming is as needed.

17 De Andres' study I've talked about, and it

18 does give us a very clear view of what happens.

19 This is a smaller study that compares conventional

20 stimulation to burst and low burst, which the

21 authors initially called sham, but when it turned

22 out to perform as well as burst, they called it

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1 something else. And what they do here is they tell

2 us that we used a broad range of parameters,

3 multiple programs, and they mention some ranges.

4 That's as far as they go about telling us what

5 actually happened.

6 Conclusions about device comparison studies,

7 you have marginally better reporting. The

8 reporting is mostly in the methodology. There is

9 very little reporting in the results section where

10 it is reported. It is mostly reported as mean and

11 standard deviation and ranges of the three values

12 that we play with. There is very little in the way

13 of reporting of cathode position and non-report on

14 personnel or frequency of programming.

15 Moving on, these are your parameter studies,

16 and there are quite a few of them. And again, you

17 will find that in the methodology here, we have

18 quite a bit of reporting because it is the essence

19 of this study. You can't do a parameter study

20 without reporting on the methodology. However, the

21 story becomes quite different when you get to the

22 results section.

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1 So you're telling us you intend to do X, Y,

2 and zed. In the methodology, did this actually

3 happen? There is always a parameter that is

4 variable that you can increase or decrease, so you

5 might as well give us what is the average or what

6 is the range of this parameter. And you'll find

7 that the reporting in the results section is by no

8 means uniform, but is much better than what we saw

9 earlier on. The reports on the personnel remains

10 quite poor. The reports on number of visits

11 remains completely absent.

12 Conclusions about parameter studies, you

13 have better programming method reporting. The

14 results section reporting remains quite poor, and

15 the commonest reporting is mean standard deviation

16 and ranges of the values of amplitude, frequency,

17 and pulse width. The majority do not report all

18 the programming parameters; they report only the

19 ones that are of interest to that particular study,

20 so you may find there is quite a big emphasis on

21 the frequency, whereas when it comes to amplitude

22 and pulse width, you're left guessing as to what

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1 actually happened here. And none provide a report

2 on personnel or the number of sessions.

3 So if we were to think about

4 recommendations, I'll give you some potential

5 recommendations. You may agree or you may

6 disagree. I may end up in the position of Mrs. May

7 in Parliament, and you may shoot me down.

8 (Laughter.)

9 DR. ELDABE: -- but I'm hoping not.

10 So we would recommend that in an RCT,

11 programming is an integral part of the intervention

12 and should be quality controlled. The personnel

13 programming in an RCT should be provided with

14 study-specific training; that industry does utilize

15 best practice algorithm, and there is no reason why

16 they don't share these with investigators. They do

17 share them with us in clinical practice, so it

18 shouldn't be any different in an investigation.

19 Best practice algorithms are currently

20 applied available for HF10, for burst, for HD, and

21 for subparasthesia. There are scripted programs

22 for conventional stimulation as used by Jose De

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1 Andres. The investigators should make attempts to  
 2 strip the programming where possible, so it  
 3 shouldn't be a free for all. I recall one of the  
 4 reps who used to turn up in our hospital; buy two  
 5 coffees, one for him, one for the patient; lock  
 6 himself with the patient in the room for 4 hours,  
 7 and that was it. Once he left, our results  
 8 nosedived.  
 9 Investigators also should ensure that the  
 10 site staff training on the programming script does  
 11 occur. Where site staff training is not feasible,  
 12 industry representatives may program the study  
 13 according to the study algorithm in the presence of  
 14 site staff. We have to acknowledge that the idea  
 15 of site staff programming is not going to be  
 16 feasible across everywhere. But if you were doing  
 17 a cognitive behavioral intervention, you would not  
 18 actually release it in the study without quality  
 19 controlling it.  
 20 The questions that we need answers to are  
 21 who, where, how often, and for how long. Other  
 22 recommendations about the reporting of programming,

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1 if you are describing a programming algorithm in  
 2 the methods sections, what do we want from you? We  
 3 want what do you intend to use? What's the script  
 4 that you're intending to use? What ranges are you  
 5 going to? Are you intending to put your cathode?  
 6 Who's going to program it, and how often do you  
 7 intend to do that?  
 8 If you're reporting this in the results  
 9 section, we want to know what is the mean standard  
 10 deviation ranges of the three values. Where did  
 11 the cathode positions actually happen or where the  
 12 lead positions were? Who programmed it? What was  
 13 the frequency and intensity? What was the setting  
 14 of the programming? I'm not sure that you can  
 15 insist on an outcome in every case, but it is very  
 16 helpful to know what was the outcome of that  
 17 particular session.  
 18 If we move a little bit from programming to  
 19 the placebo-controlled trials in spinal cord  
 20 stimulation, we have a few. And this is a very  
 21 interesting part of spinal cord stimulation. It's  
 22 one where most of my interest lies; how much of the

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1 impact of this intervention is actually what we  
 2 call nonspecific effects?  
 3 This you can buy from Amazon, Zeebo. It's a  
 4 very good product. When I clicked on it, there's  
 5 frequently both together, and you can see that you  
 6 obtain this for princely sum of \$32. It's very  
 7 cheap.  
 8 What are the barriers to placebo-controlled  
 9 trials in SCS? The placebo-controlled trials in  
 10 SCS are a little bit more complex than in pharma.  
 11 Why? Because patients feel paresthesias with  
 12 conventional stimulations. They also carry this  
 13 thing about, which is their hand-held programmer.  
 14 If you want to give them sham stimulation, you're  
 15 going to have to do something about this or you can  
 16 take it away. But if you take it away, you have to  
 17 give them a mechanism to switch off their device in  
 18 case of a problem. All of these are an issue.  
 19 Patients who have a rechargeable device will  
 20 need to recharge their devices, and they have a  
 21 certain frequency, and if you're recruiting  
 22 patients who have had spinal cord stimulation for a

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1 while, they will have a fair idea of how long it  
 2 takes them between sessions to recharge and how  
 3 long it takes for their battery to deplete.  
 4 So if they are in the sham group, they will  
 5 know instantly that they're in the sham group,  
 6 unless you program their battery to leak the  
 7 current somehow. There are consent issues, which  
 8 we're not going to talk about. Device programming,  
 9 it's a question of what do you program in order to  
 10 get to a placebo?  
 11 These are most of the studies that have used  
 12 a placebo control in spinal cord stimulation.  
 13 Here, the top three are refractory angina studies,  
 14 and they are all a bit from the last 10 years.  
 15 What they have done here is they have used a  
 16 placebo against a parasthesia stimulation, which is  
 17 quite difficult, but they seem to have achieved it.  
 18 This gentleman here programmed patients on  
 19 the placebo arm to 0.1 volt, and he informed them  
 20 that they may or may not feel stimulation within  
 21 his study. Gaetano Lanza and his colleagues, they  
 22 did something similar but in a sense very

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1 different. They set the device to produce  
 2 stimulation for 1 hour a day; whereas here, it was  
 3 point 0.1 volt for the whole day.  
 4 So these guys assumed that a very low  
 5 threshold stimulation makes no difference. Here,  
 6 the assumption is a very low threshold stimulation  
 7 delivered for a short period of time makes no  
 8 difference.  
 9 This is the largest of the three studies and  
 10 is quite interesting because they came up with,  
 11 again, a different placebo. Their placebo was  
 12 super-threshold stimulation, so the patients would  
 13 feel parasthesia, but that was delivered 1 minute  
 14 in 24 hours, which is an interesting concept  
 15 because if you tell the patients that you may or  
 16 may not feel paresthesia, for 1 or 2 minutes a day,  
 17 or 3 minutes a day, they will feel parasthesia, and  
 18 that's fine. Interestingly, this study found no  
 19 difference between what is high stimulation and low  
 20 stimulation as they call it.  
 21 I put this one in yellow because this is a  
 22 study that was done during the trial period, and

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1 the setting for this is much easier than if you  
 2 have someone who's implanted already with a device,  
 3 so these guys were not implanted yet. This is a  
 4 study that we did with Professor Buchser there.  
 5 This is the first one that was to be done in a  
 6 rechargeable device, and what we did there was to  
 7 make the device in the sham period discharge  
 8 current. And because it was a crossover, you had  
 9 to make the device discharge current at the same  
 10 rate as it was using current in the previous  
 11 session.  
 12 So how did we do that? The patient came in.  
 13 Whether they were in the sham arm or whether they  
 14 were in the control arm, we actually measured their  
 15 perception threshold in various positions. When we  
 16 measured their perception threshold, we knew how  
 17 much the current utilization would be. We then  
 18 rang the company who gave us how much current  
 19 leakage.  
 20 So if they went into the active program, we  
 21 programmed them to the active program. If they  
 22 went into the sham, we programmed the current

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1 leakage that was based on the parameters of active  
 2 programming.  
 3 Therefore, it was quite difficult for a  
 4 person crossing over to discern whether they're  
 5 current utilization was different or not. And Eric  
 6 Buchser had the foresight to ask the company to  
 7 give us a time stamp on whether the device had been  
 8 switched off by the patient, because this is an  
 9 issue with these. It's a question of who gets a  
 10 patient programmer and when.  
 11 Here you can see that, in these, there is no  
 12 comment on whether these patients got a patient  
 13 programmer or not. The question is how do you  
 14 manage to maintain people at 0.1 volt when they  
 15 have a programmer that tells them that they can't  
 16 increase the current? It stands to reason that you  
 17 must take away their programmer, but the manuscript  
 18 doesn't tell you that. You just have to conclude  
 19 it yourself. It's the same here. We don't know  
 20 anything about the patient programmer; same here.  
 21 Most of these manuscripts also rely on the  
 22 perception threshold, the perception at which the

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1 patient starts to feel paresthesia. Because of the  
 2 movement to the spinal cord, we know that to be  
 3 different in different positions. So a patient's  
 4 perception threshold in the supine position is at  
 5 its lowest. You stand them up or sit them, the  
 6 difference can be about 5 volts. Yet, most  
 7 manuscripts tell you we program these patients to  
 8 the perception threshold, but they never tell you  
 9 which position was that perception threshold  
 10 detected in.  
 11 Here, in the comments section, the  
 12 manuscript tells you whether the patient was  
 13 programmed in a particular position. Here for  
 14 example, the perception threshold was done in the  
 15 supine position. The authors tell you that we took  
 16 away the patient programmer. The patients were  
 17 allowed to switch off their device using the  
 18 charging belt. They can do that.  
 19 Here, for example, in this study they took a  
 20 very interesting approach to how to deal with a  
 21 patient programmer. They gave the patients their  
 22 programmer, but they gave it to them in a sealed

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1 envelope. And that sealed envelope, when it was  
2 opened, you knew that the was unblinded; so a very  
3 interesting approach to that.

4 Here you can see in the sham there are a  
5 number of comparisons, and most of the comparisons  
6 are with device switch off except for this study  
7 that we've mentioned before, where they did burst  
8 at 0.1 milliamps. Again, the position wasn't  
9 mentioned. This is an interesting study because  
10 it's the largest study that has a placebo control.  
11 Again, it's a crossover, and the placebo here is  
12 device off.

13 In a subparesthesia stimulation, device off  
14 is very easy to work through. In a parasthesia  
15 stimulation, if you want to convince patients that  
16 they are getting some paresthesia, then you would  
17 need to look at some of these modes.

18 Conclusions and what can we recommend? As  
19 you can see, sham stimulation in spinal cord  
20 stimulation studies is a variable entity. Sham is  
21 not the same thing across all studies. That is  
22 because of the fact that some patients feel

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1 parasthesia and others do not. In parasthesia  
2 stimulation, as we've seen, the sham can consist of  
3 very low amplitude continuous through stimulation,  
4 short duration of superior threshold stimulation,  
5 or no stimulation at all.

6 All of these carry and inherent risk. The  
7 risk in numbers 1 and 2 is that we don't really  
8 know that stimulating people for 1 minute at 0.1 or  
9 super threshold stimulation for 1 minute today does  
10 not have an effect on the central nervous system,  
11 and the authors in this particular refractory  
12 angina study did argue that the two groups were  
13 equivalent because their sham was not a sham. The  
14 same applies to this one. When you run no  
15 stimulation at all in a paresthesias study, you run  
16 the risk of unblinding your patients.

17 Your sham complexity increases with the use  
18 of rechargeable systems. Therefore, in champs  
19 stimulation, you need a rechargeable device that  
20 accounts for the risk of unblinding by virtue of  
21 the patient finding out how often are they needing  
22 to recharge their device. So in this study, we set

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1 the maximum as twice-daily recharging.

2 If you have a patient who is on the higher  
3 frequency and is recharging twice daily, they move  
4 to the sham, and the current leakage is lower.

5 They find out they're recharging once a day, they  
6 might guess. So they had to have a frequency that  
7 allowed them to recharge twice a day.

8 Self-discharging IPGs need to consider the  
9 current use in the active arm, particularly in  
10 crossover studies. The patient programmer status  
11 needs to be reported. What have we done with the  
12 patient programmer? Do they have it? Did they  
13 take it home or has it been taken off? Without  
14 that, you can't have a sham.

15 We need to confirm adequacy of the blinding.  
16 I think most studies have done that. Most studies  
17 have asked the patient, which group do you think  
18 you're in? The studies that are using perception  
19 threshold need to report on which positions did you  
20 do your perception threshold measurement in.

21 With that, I think that's my last slide.  
22 Thank you very much.

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1 (Applause.)

2 DR. THOMSON: Well, thanks to all our  
3 speakers. I think we've got a break now, and then  
4 I think we've got a whole afternoon of discussion.  
5 So that will be the good bit. Remember to lean  
6 forward and announce your name. It's easy.

7 (Whereupon, at 9:59 a.m., a recess was  
8 taken.)

9 Group Discussion

10 DR. KATZ: If all of the speakers from this  
11 morning could come up and sit on the panel, please:  
12 Simon, Sam Eldabe, Jennifer Gewandter, and Rod,  
13 please, as well. You spoke, you qualify. Thanks,  
14 everyone. We still have more people sitting in the  
15 audience than on the panel, so it's okay.

16 (Laughter.)

17 DR. KATZ: I just counted. It's close, but  
18 I don't think we need a recount.

19 First, I want to just say that I thought the  
20 presentations this morning were really fabulous,  
21 were really particularly lucid and important for  
22 the goal that we're trying to accomplish. So I

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1 want to thank all the speakers, again, for their  
 2 effort to bring these complex ideas to a place  
 3 where they're lucid and understandable.  
 4 Since everybody took the trouble to fill out  
 5 that survey, I thought I would show what the  
 6 results are, and just take a few minutes on that.  
 7 Then once we're done with that, I think it will  
 8 help set up the rest of the day's conversations.  
 9 Then once we're done with that, we can then go  
 10 through questions and answers about this morning's  
 11 presentations.  
 12 You'll recall that you filled out a survey  
 13 yesterday. It was a free-hand entry. The results  
 14 were really incredibly convergent. People as a  
 15 group really felt similarly about most of the key  
 16 issues, which I was a little surprised and  
 17 gratified to see. I did my best to compile them.  
 18 Of course, with a free-hand survey, let me start  
 19 out by saying not everybody's handwriting is that  
 20 good --  
 21 (Laughter.)  
 22 DR. KATZ: -- my own included. So I had to

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1 take some liberties in deciphering what people were  
 2 actually trying to write. And then, of course,  
 3 people used different words for the same thing and  
 4 the same words for different things, as you could  
 5 expect. So I had to take some liberties and  
 6 understanding not only what people were writing but  
 7 what they actually meant.  
 8 So you'll forgive me. This is not a  
 9 precision survey, but I think it will give a rough  
 10 idea of what people felt about the key issues.  
 11 DR. NORTH: How many votes for Al Gore did  
 12 you find?  
 13 (Laughter.)  
 14 DR. KATZ: He's still getting votes.  
 15 The first question that I asked is what is  
 16 the key scientific question that you think needs to  
 17 be answered? As I mentioned yesterday, there's no  
 18 point in talking about study design until you know  
 19 what question you're study is trying to answer.  
 20 Again, the other comment I want to make is  
 21 that I don't think we should take these votes too  
 22 seriously because actually things that were

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1 mentioned by only one or two people I think were  
 2 critically important. The difference between a 4  
 3 and a 3 is not really relevant. This is just to  
 4 give people a sense of what the ideas were.  
 5 The most common idea was we need to know the  
 6 efficacy of any waveform versus sham. That came  
 7 through pretty clearly, virtually or equally  
 8 represented were comparing one waveform to another,  
 9 preferably in the context of a comparison to  
 10 placebo. So those ideas came through front and  
 11 center as being key scientific goals.  
 12 Then there were things that were really more  
 13 focused on impact on the patient, impact on the  
 14 totality of the patient over time. That came  
 15 through in terms of a lot of mentions on measuring  
 16 impact of pain and function; pain reduction;  
 17 long-term cost effectiveness; efficacy on multiple  
 18 clinical domains; pain function, quality of life  
 19 was mentioned. Here, it looks like only one, but  
 20 it actually came through a lot, in a lot of  
 21 people's comments.  
 22 Another thing came through, which is

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1 predictors of benefit. Now, I took the liberty of  
 2 calling a lot of different things predictors of  
 3 benefit. Some people said biomarkers. Some people  
 4 said phenotypes. Some people said baseline  
 5 characteristics. But it all amounts to the same  
 6 thing. How do we know in an individual patient,  
 7 whether spinal cord stimulation will work for them?  
 8 And if it does, what kind of spinal cord  
 9 stimulation might work best for them based on what  
 10 disease they have, what kind of person they are,  
 11 whatever it is? So those were the key scientific  
 12 questions. That was item 1 on this survey.  
 13 Then I asked about what study design  
 14 elements do you think should be utilized in order  
 15 to accomplish that goal? I'll share all these  
 16 slides with everyone, too, if anybody's interested.  
 17 Those will be posted with everything else, and it's  
 18 all anonymized and will be posted.  
 19 Of course, it's a little bit silly to ask  
 20 people for a smorgasbord of study hypotheses, and  
 21 then ask for a smorgasbord of study design elements  
 22 because there was no easy way for me to match one

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1 to the other. But I just thought I would throw out  
 2 what the key study design elements were that kept  
 3 on coming up.  
 4 Number 1 was sham controls. Some people  
 5 recommended crossover and some people recommended  
 6 parallel. But I think that there's actually  
 7 meaning in those differences that I'm going to get  
 8 to on my conclusion slide. So don't take this as  
 9 an endorsement of crossovers is parallel. It's  
 10 more about what kind of design would be best  
 11 supported by a crossover study and what kind of  
 12 design would be best supported by a parallel.  
 13 Double-blinding was mentioned. Standard of  
 14 care controls were mentioned by a number of  
 15 different people. That's what SOC means here. A  
 16 number of people spoke about the need to explore  
 17 the usefulness of doing a trial; what kind of  
 18 trial. Should it be a sham-controlled trial?  
 19 Should you try multiple waveforms? Do you need a  
 20 trial at all?  
 21 So people mentioned trial in a few different  
 22 a ways. There were a few interesting comments

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1 about the need for pragmatic designs or potentially  
 2 the value of registries rather than  
 3 randomized-controlled trials. So I don't want to  
 4 ignore those comments.  
 5 I asked about what people thought the  
 6 primary endpoint should be. Interestingly, quality  
 7 of life was number one. Of course, that that would  
 8 never fly from a regulatory perspective in the  
 9 United States. If you want your thing to be  
 10 indicated for pain, your primary endpoint has to be  
 11 pain. Sorry. That's just the way the world works.  
 12 But in terms of what actually interested me, it was  
 13 quality of life. It was function. That came  
 14 through again and again and again. Pain of course  
 15 was still mentioned.  
 16 I think the reason pain wasn't mentioned  
 17 more is because it was sort of taken as  
 18 self-evident, and these comments were really meant  
 19 to say, gee, don't just think about pain; think  
 20 about these other things as well.  
 21 There were a number of comments about the  
 22 usefulness of composite endpoints, if a patient has

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1 great pain control, but they've had terrible safety  
 2 events. For example, do we really count that as a  
 3 success of therapy? Or if their pain is down by  
 4 1 point on a 0 to 10 scale, but globally they don't  
 5 feel like they're any better, is that really a  
 6 success?  
 7 Or conversely, if someone's pain is not  
 8 discernibly improved, but they've improved in their  
 9 quality of life and their function and their global  
 10 evaluation, and they haven't had any major safety  
 11 events, should we not count that as a success of  
 12 therapy?  
 13 So the limitation of focusing only on pain  
 14 came through in a number of different ways,  
 15 including in an interest in composite endpoints,  
 16 global response and safety.  
 17 I asked people, well, what other scientific  
 18 questions you think are important, and not  
 19 surprisingly, I got a smorgasbord of different  
 20 ideas. I'm not going to go through all these, but  
 21 comparing waveforms to another came through. There  
 22 was a lot of emphasis on long-term -- some people

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1 said I want to know more about long-term benefit.  
 2 Some people said I want to know more about  
 3 long-term risk. Some people said I want to know  
 4 about long-term benefit and the risk, and I  
 5 collapsed that all in this single line.  
 6 Cost effectiveness came through. Again,  
 7 predictors of response, who gets better, who  
 8 doesn't, who's going to get better on what kind of  
 9 spinal cord stimulation came through.  
 10 There were a lot of comments about  
 11 comparative research, but comparative what? And  
 12 what I want to say is that most people thought that  
 13 the key question, in terms of comparison, was  
 14 comparative waveforms, and that came through in a  
 15 variety of different ways. What waveform works  
 16 best for this. What waveform works best for that?  
 17 What waveform works best overall? However, there  
 18 were a few people who were interested in  
 19 comparative product information, so I just want to  
 20 draw that distinction.  
 21 Durability, if it works, does it work for a  
 22 long time? There were a few methodological

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1 comments. How do we balance these nonspecific  
 2 factors that I spoke about yesterday and others  
 3 have spoken about; Simon spoke about this morning.  
 4 How do we improve recur of design, conduct, and  
 5 monitoring? Something about opioid use. I think  
 6 those were the main secondary scientific questions  
 7 that came through.

8 I just thought I would pull out one quote,  
 9 which I really liked. There were a lot of  
 10 interesting quotes that I liked, but one question  
 11 that somebody asked was, "Can we measure whether  
 12 the extent to which the treatment brings the  
 13 patients reasonably closer to their life condition  
 14 prior to the onset of their pain condition?" I  
 15 thought that was just a beautiful way of talking  
 16 about what we're really trying to accomplish with  
 17 these treatments, but that we never really ask  
 18 about, at least not in a formal way.

19 This is my conclusion slide. When you take  
 20 all these various sorts of comments that people  
 21 made, it really does boil down to a few things;  
 22 that the critical scientific questions were

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1 comparison of any waveform to sham. And if you're  
 2 going to do a trial comparing a waveform to sham,  
 3 and you're agnostic about which waveform you're  
 4 most interested in, then obviously the  
 5 non-perceived waveforms make it easier to blind a  
 6 study like that. And I think Rick has been trying  
 7 to push us towards that kind of a study yesterday.

8 Set comparison of waveforms to each other;  
 9 long-term efficacy and safety and cost benefit and  
 10 predictors of benefit. Those were really the four  
 11 key scientific questions that everybody converged  
 12 on. Then you might say, well, gee, obviously it's  
 13 not going to be the same kind of study that's going  
 14 to answer all these questions, so it makes things  
 15 much more intelligible to think about what kind of  
 16 study design would help address this question and  
 17 what kind of study design would help address that  
 18 question. And that really falls into two groups,  
 19 and maybe I'll just focus down here.

20 So whether you like a crossover or whether  
 21 you like a parallel design really depends upon the  
 22 goals of the study. And if you're interested in

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1 the questions about does any waveform work compared  
 2 to sham, or how do waveforms compared to each  
 3 other, one could imagine a relatively short-term  
 4 crossover study, potentially with multiple periods,  
 5 2, 3, 4, periods.

6 That's probably the most efficient way of  
 7 answering that question; whereas if you're  
 8 interested in this other big picture or question,  
 9 long-term safety, efficacy, cost benefit, et  
 10 cetera, then a long-term parallel study, where  
 11 harms and benefits are carefully ascertained and  
 12 quality of life and health economics issues are  
 13 measured, that's probably the optimal way to answer  
 14 that question.

15 It doesn't preclude pasting an optional  
 16 crossover at the end of a long-term parallel study,  
 17 but the key here is long-term follow-up. And of  
 18 course the longer you have to follow a patient, the  
 19 less practical a crossover design becomes. If you  
 20 need two years of follow-up to answer that  
 21 question, you're not going to do a crossover study.  
 22 Even a year would be probably impossible or at

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1 least very difficult.

2 Once you kind of get what the key scientific  
 3 questions are, and then you start marrying that up  
 4 to a clinical trial design, then all of a sudden  
 5 the importance of various key study design elements  
 6 become much more clear, blinding, et cetera,  
 7 et cetera. The only other point I'll add is that  
 8 people did emphasize the need for transparency and  
 9 balance of these nonspecific factors regardless  
 10 which question you're trying to answer or which  
 11 study design would be most appropriate to answer  
 12 that question.

13 So that's what you guys said. I'm just  
 14 distilling it down and presenting it back to you.

15 Does anyone have any comments or questions  
 16 on that before we go into discussion of this  
 17 morning's presentations?

18 Rick, do you have any questions or comments  
 19 about that?

20 DR. NORTH: I think that's a very nice  
 21 summary. By the way, the program says Ali Rezaei.  
 22 Ali has not put on weight. It's Rick pinch-hitting

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1 at Ali's request.  
 2 I'm a big fan of blinded,  
 3 randomized-controlled trials, and until recently,  
 4 we haven't had a good way to do them. I think it  
 5 is really incumbent on us now that we have  
 6 parasthesia waveforms, for which major benefit is  
 7 claimed that we demonstrate that at last.  
 8 I think that conventional SCS, which is  
 9 unblinded, can go along for the ride in a crossover  
 10 study; that is it can be one of the waveforms that  
 11 is tested in the usual fashion. And its  
 12 comparative results, however they compare, even if  
 13 inferior, allow the conventional to remain on the  
 14 menu. So I think it's good for everybody.  
 15 DR. KOPELL: Richard, I'm curious, and  
 16 unfortunately our American regulatory people aren't  
 17 here. But to the question that you said, for  
 18 years, when I was training to do spinal cord stim,  
 19 it was like, gosh, if we could only have a  
 20 parasthesia-free, we could finally do that  
 21 randomized-controlled trial. And all of a sudden,  
 22 you had a company come to market, or

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1 [indiscernible] to come to market, how did the FDA  
 2 allow them to do a noninferiority first?  
 3 I mean, when they sat up here and they were  
 4 like, "Hey, well that's not our purview." What is  
 5 your purview, then? If it's not going to be that,  
 6 then just be a safety body, basically.  
 7 DR. NORTH: Can we speculate?  
 8 DR. KOPELL: Yeah, sure.  
 9 DR. NORTH: Nevro is not represented here,  
 10 and the FDA is no longer represented.  
 11 DR. KOPELL: Right.  
 12 DR. NORTH: And no one was talking about it  
 13 at the time, nor have they since to my knowledge.  
 14 But what I inferred was going on was that the FDA  
 15 responded to a simple argument that you have a  
 16 device that is grandfathered in and/or approved,  
 17 and how can you keep us off the market if we show  
 18 that we are noninferior? It's that simple. So  
 19 while the FDA might have asked them, politely even,  
 20 to do a sham-controlled trial, I think it would be  
 21 hard for them to compel it.  
 22 DR. THOMSON: I think we're a little

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1 over -- I think if we can use subperception as a  
 2 way of proving efficacy, everything is one thing.  
 3 But I think we're a little over-obsessed with the  
 4 waveform thing. And I think there's more of a  
 5 need -- I'm a predictor-of-benefit man because I  
 6 think we've got to make it a much more simple  
 7 pathway for referral through to treatment.  
 8 I think we are -- with the trial period,  
 9 which we've actually never shown to predict  
 10 long-term outcome, it costs a lot of money, so it  
 11 increases the overall health economic cost. And  
 12 what we should be concentrating on is basically  
 13 improving our selection criteria so that we are  
 14 almost certain that we're going to have a  
 15 responder.  
 16 But where we're held back is the economic  
 17 system of healthcare delivery in the U.S. because  
 18 we've already heard that it's uneconomic for most  
 19 hospitals to implant devices, even with the two  
 20 bites of the cherry, the trial and the implant.  
 21 Organizations like Kaiser Permanente and our  
 22 British NHS, which actually looks more at the cost

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1 of the whole healthcare system, would be quite  
 2 attracted to taking cost out of the delivery of the  
 3 thing.  
 4 The other problem we have is the  
 5 non-believers, NSCS, the people who we need our  
 6 pain colleagues to refer, they're very unclear as  
 7 to what patients to refer and what patients do  
 8 benefit. Then I think there is some exciting stuff  
 9 going on with cytokines and other potential  
 10 biomarkers, which is an area of research that I  
 11 think we should be in.  
 12 DR. KATZ: Great. I'm not sure if we should  
 13 depart from this topic yet or not. Any other  
 14 comments about these, like what are the big-picture  
 15 scientific questions and what are the kind of big  
 16 frameworks of study design for how we would address  
 17 those questions before we dive into more detail on  
 18 this morning's presentations? Sam?  
 19 DR. ELDABE: I think you nailed it in your  
 20 presentation. The central question that we need an  
 21 answer to is how does our original intervention  
 22 compare to sham. And it's not impossible to answer



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1 that question. As I've showed, some studies have  
2 done that. And without the answer to that  
3 question, we are floating in a sea of uncertainty.  
4 That's a problem. And whatever comes after  
5 that is irrelevant because, as we've seen from the  
6 sham-control trials, if your effect size of SCS is  
7 that big, about two-thirds of it is non-specific  
8 effect; in the short term, I hasten to add. I  
9 don't know what it's like in the long term, but in  
10 my mind, unless we answer the question, how big are  
11 the non-specific effects of SCS and how long do  
12 they last for, we will never be taken seriously.  
13 DR. NORTH: Sam, do you think that one of  
14 the reasons that no one has done a sham-controlled  
15 trial of their wonderful new parasthesia free  
16 waveform is that foreseeably, there will be a  
17 substantial placebo effect, and there's reluctance  
18 to bring that out.  
19 DR. ELDABE: Well, you're absolutely right.  
20 An industry would not have a vested interest in  
21 doing that, but we would have a vested interest in  
22 doing that. So that's not --

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1 DR. KOPELL: We sort of do. Right? From a  
2 scientific, we have a vested interest, but here's  
3 the domino effect. You have a parasthesia-free  
4 device that has now a superiority labeling. FDA  
5 has given that to standard spinal cord stim. If  
6 you now say that your superior treatment is no  
7 better than placebo, the entire industry gets  
8 decimated overnight because you basically have now  
9 proven --  
10 DR. NORTH: Conventional therefore is worse  
11 than placebo.  
12 DR. KOPELL: That's exactly right? So then  
13 what do we do? I mean, then we're really up --  
14 MALE VOICE: I'll stop doing spinal cord  
15 stimulation.  
16 DR. KOPELL: Right.  
17 DR. ELDABE: I think you're asking a very  
18 good question, and you can only answer this  
19 question if you're about two or three years away  
20 from retirement.  
21 (Laughter.)  
22 DR. ELDABE: I don't expect you to answer

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1 this question, but I should.  
2 (Laughter.)  
3 DR. KATZ: Howard Fields?  
4 DR. FIELDS: Since I'm 11 months  
5 post-retirement, I can definitely give my unbiased  
6 opinion. I came across a paper. I've been  
7 searching around for a little science here. And  
8 this is a paper that was published in  
9 neuromodulation July of 2015. The title of the  
10 paper is Effects of Spinal Cord Stimulation on Pain  
11 Thresholds and Sensory Perceptions in Chronic Pain  
12 Patients.  
13 Now, this is a beautiful paper. Now, I  
14 haven't seen the paper; I just have the abstract  
15 here. But what they did was they had people who  
16 were already implanted, and they tested for changes  
17 in pain threshold both in the area where there were  
18 parasthesias and in areas outside where there were  
19 parasthesias. There were consistent and  
20 significant increases in pain threshold.  
21 Now, there's no reason why you couldn't  
22 easily do that prior to entry of a patient into a

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1 study. And then you could say, well, if they don't  
2 get an effect on pain threshold with spinal cord  
3 stimulation, we don't enter them into the study.  
4 The other thing you could do is you could adjust  
5 your parameters based on whatever ones gave you the  
6 greatest analgesia, and then you don't have to  
7 reprogram once the person's entered into the study.  
8 So I would say that there is a value to  
9 actually doing science, and here you have it. So  
10 everybody in this room has convinced, and I'm  
11 persuaded, that spinal cord stimulation does  
12 produce analgesia. So it gets back to which  
13 patients benefit the most. It gets back to patient  
14 selection and how do you design a trial. And I  
15 feel like there is a way to design a trial to get  
16 rid of many of the pestering problems of  
17 reprogramming.  
18 DR. THOMSON: So if you were able to look at  
19 the early view in your modulation, you'd see that  
20 actually we've just done a QST looking at pain  
21 pressure thresholds, and we found that there is a  
22 predictor of success with spinal cord stimulation.

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1 DR. FIELDS: That was in that paper, too,  
 2 that it correlated with success. So you have a  
 3 way. It seems to me you have a way out of the  
 4 woods. You have to have a device to do the  
 5 quantitative stimulation, but once you've made that  
 6 investment, you have it, and it's an interesting  
 7 biomarker.  
 8 DR. NORTH: Years ago, Mark Sendu's [ph]  
 9 group reported using the R100, which is sort of  
 10 H-reflex measure, to identify patients who are  
 11 going to respond to SCS.  
 12 DR. FIELDS: But if it's a reflex, then you  
 13 don't know whether the effect is motor or sensory.  
 14 That's a problem.  
 15 DR. THOMSON: Right.  
 16 DR. KATZ: Just a quick housekeeping  
 17 announcement. People, when you start speaking just  
 18 say your name, then it's --  
 19 DR. FIELDS: Howard Fields.  
 20 DR. KATZ: Thank you, Howard.  
 21 DR. FIELDS: San Francisco.  
 22 DR. KATZ: What I didn't fully understand is

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1 that this meeting is being transcribed. So when  
 2 people say things, the transcriptionist wants to  
 3 put their name, so you can have some idea who's  
 4 making what comments. So otherwise, the transcript  
 5 will be completely unintelligible. So if you could  
 6 say your name, that would be great.  
 7 Yes?  
 8 DR. VAN DONGEN: Could I make a comment.  
 9 Robert van Dongen from Nijmegen, The Netherlands.  
 10 DR. KATZ: Don't forget to say your name.  
 11 DR. VAN DONGEN: Robert van Dongen, yes.  
 12 Considering the QST data, we did a lot of QST  
 13 measurements in Holland on patients for chronic  
 14 pain, seeing in the outpatient clinic, and we would  
 15 follow them during spinal cord stimulation. We did  
 16 beforehand, during, and after. But the main  
 17 problem we saw is when you decrease the medication  
 18 due to the efficacy of the spinal cord stimulation,  
 19 you also change your QST measurements.  
 20 So it's a dynamic process, which you don't  
 21 really know what you're tweeting. So your QST  
 22 measurement might be objective to prevent or to

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1 predict which patient might respond, but on the  
 2 other hand, you change your medication during their  
 3 follow-up and it also changed the QST measurement.  
 4 So it's not as simple as we initially thought, and  
 5 especially when they use opioids or  
 6 anti-neuropathic pain drugs, then you get a  
 7 different effect of the QST measurement afterwards.  
 8 DR. NORTH: Back in 1977, we tabulated  
 9 reductions in medication, and it was our assumption  
 10 that a reduction in medication attributable to the  
 11 pain relieving effects of the stimulator was a good  
 12 thing, and that a change in medication couldn't  
 13 possibly confound the results of the trial. But  
 14 that of course is simplistic.  
 15 DR. FIORE: Nate, a comment, if I may? Greg  
 16 Fiore.  
 17 DR. KATZ: Please.  
 18 DR. FIORE: I sit and think about the  
 19 validity of sham as a comparator. When the data I  
 20 think is widely accepted, the sham is an effective  
 21 treatment. But it's not really a treatment that is  
 22 available to these subjects or to these patients.

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1 So why is sham such a valid comparator in that  
 2 context? Because there's nothing better  
 3 potentially?  
 4 DR. THOMSON: Simon Thomson. I kind of  
 5 agree with you because when I hear people say we'll  
 6 just have to stop doing it, I have to think of all  
 7 of those patients who clearly benefited from these  
 8 interventions. I don't know a better way of  
 9 turning on a sham for this particular patient  
 10 group, is really what I'm saying. And I think  
 11 that's what you're saying.  
 12 DR. NORTH: Send them to your competitor who  
 13 does a technically inadequate job --  
 14 (Laughter.)  
 15 DR. NORTH: -- and they benefit anyway.  
 16 (Laughter.)  
 17 DR. KATZ: Brian, I have a question for you.  
 18 So why don't we start moving into talking about the  
 19 specific presentations. And, Brian, maybe I'll  
 20 start with asking you a question since you're very  
 21 focused on the payers, and it seems like that's  
 22 going to end up being a driver of more rigor in our

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1 research.

2 I guess my question is what type of study

3 design do you think would be -- if that's our

4 stakeholder group that we're focusing on, at least

5 for the moment, what type of study design do you

6 think would most persuade that audience that the

7 treatment is worth paying for?

8 DR. KOPELL: Now, I understand that there's

9 going to be problems with what I'm about to say,

10 but it would seem that, like other device studies,

11 a reduction in medication is the lowest-hanging

12 fruit in terms of showing reductions of costs; the

13 way it is in DBS for movement disorders, and they

14 are absolutely depleted with dopamine. So there is

15 no doubt that they need dopamine, and that is the

16 way that we have demonstrated, essentially, cost

17 effectiveness of that therapy. I think you're

18 probably going to be forced to do the same here.

19 DR. KATZ: I do want to say that I've been

20 involved in a lot of health economic studies of

21 chronic pain populations of one kind or another:

22 back pain, osteoarthritis, neuropathic pain. In

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1 the U.S., medication costs tend to be a relatively

2 small percentage of their overall costs because

3 things like Vicodin and Percocet and ibuprofen, and

4 now generic gabapentin and tricyclic

5 antidepressants, those are all generic now. So

6 even if you add up two or three of those

7 medications, at least from the data that I've been

8 involved with, they tend to be relatively small.

9 DR. KOPELL: It's still a reduction in cost,

10 though.

11 DR. KATZ: Yes.

12 Andrea and then John.

13 DR. TRESKOT: Andrea Trescot. We talked a

14 little bit about this last night, too, and I didn't

15 go forward with it. But it occurs to me that what

16 you're saying is absolutely right. The medicines

17 are the least -- if you listed all the costs of a

18 low-back pain patient, the medicines are the least

19 of them. So what we need to be looking at is a

20 much more global -- the ER visits, the physical

21 therapy visits, the return to work, the overall

22 consumption of resources.

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1 The problem comes in is that right now the

2 insurance companies are not prepared to do that. I

3 actually was threatened with being removed from

4 Blue Cross from an economic credentialing because

5 they said, "My goodness. You see these patients 11

6 times, and your competitors see them 3." And I

7 said, "Well, my competitors are doing procedures in

8 the surgery center, and I'm doing them in the

9 office. I bring the patients in for a ketorolac

10 injection instead of them going into the emergency

11 room. We're doing the neurodiagnostics here in the

12 office." And the response was, "Well, those are

13 all different pockets and different buckets, and we

14 can't look at that."

15 Now, that was several years ago. I didn't

16 get de-credentialed, and that's where something like

17 the National Health Service or Kaiser or one of the

18 self-insured groups would be I think -- and the

19 military is another place where we might be able to

20 look at this in terms of DoD, where they're

21 covering all the costs in pretty much one bucket.

22 But to my mind, it's absolutely clear that if we

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1 can't show to the insurers that this saves them

2 money instead of being a cost setter, they will not

3 do it.

4 DR. KOPELL: I love the idea of being able

5 to show reduced other utilizations of healthcare.

6 I now think -- because again, I've had two years of

7 experience as a chief medical officer of a public

8 medical device company, and when I think about it,

9 I how long would a trial have to be to demonstrate

10 what you just said? See, the thing is, they still

11 have to run their trials. So if all of a sudden

12 you're saddling them with a five-year trial, that's

13 a nonstarter, too, guys. So you've got a good

14 baseline and that's

15 DR. TRESKOT: A year, if you've got a good

16 baseline. And that's the key. You have to be able

17 to start with patients that you can identify what

18 their baseline costs are.

19 DR. KOPELL: I'm just saying that's a

20 challenge in a relatively short-term trial. Now

21 again, I'm not an expert in quality analysis, but

22 can you do a quality analysis that's valid in a

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1 one-year study?  
 2 DR. TAYLOR: So simple answer, yes.  
 3 DR. KOPELL: Okay. So that's what I would  
 4 recommend, basically.  
 5 DR. THOMSON: And indeed, I think one of the  
 6 things that was striking to me -- so I'm a health  
 7 economist who normally lives in a cardiovascular  
 8 cave who's come out and played with some of the  
 9 chronic pain area. The thing that struck me  
 10 as -- and it's true in all of chronic pain, that  
 11 the levels of disutility that people with chronic  
 12 pain have are equivalent to end-stage cancer and  
 13 NYHA4 heart failure.  
 14 Now you might say, well that's a problem for  
 15 the patient. Actually, it's an opportunity. Your  
 16 ability to improve quality of life because the  
 17 baseline effect is so low is huge. So going back  
 18 to Brian's point, one of the reasons that payers  
 19 have gone here is that the quality gains you get,  
 20 because of the improvements in quality of life,  
 21 from randomized controlled trials with follow-up,  
 22 using the EQ5D up to 12 months, are stunning.

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1 So you don't have to demonstrate cost  
 2 savings. For the extra cost to the healthcare  
 3 system, because of the qualities you gain, you're  
 4 less than the magic \$50,000 per quality or 20,000  
 5 to 30,000 pounds per quality in UK, and that's why  
 6 you've been successful; just an observation.  
 7 I think, Nate, going back to your question,  
 8 what would payers be wanting in terms of a design,  
 9 I think actually the PROCESS study is not perfect,  
 10 but I think was a very important exemplar to help  
 11 UK say that they wanted to fund spinal cord  
 12 stimulation. If we hadn't had PROCESS and we  
 13 didn't do modeling, we wouldn't have got, I think,  
 14 approval.  
 15 I think that the cost [indiscernible], if I  
 16 may very quickly now, is that payers are beginning  
 17 to get a bit suspicious, and they're hearing about  
 18 this placebo problem. And because we've now got  
 19 the technological ability to do the sham  
 20 trial -- for instance, NICE recently looked at  
 21 Nevro. The guidance will be out on a website near  
 22 you very soon. I can't tell you what the guidance

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1 says, but what I can tell you is there's a research  
 2 recommendation saying we need a placebo-controlled  
 3 trial here. So they're not saying we won't cover  
 4 it, but they're putting down a marker for the  
 5 future.  
 6 DR. KATZ: Thank you, Rod.  
 7 DR. THOMSON: Simon Thomson. Just to add, I  
 8 think derived from the PROCESS study and the  
 9 economic evaluation, we did show that the  
 10 sensitivity analysis, as far as what were the main  
 11 drivers of cost and how to reduce them, one of them  
 12 was being able to reduce, in the non-treatment  
 13 group, the medication -- Oh, no, in the treated  
 14 group, the medication. And the other is device  
 15 longevity and initial device cost, and of course  
 16 complications. I think those are the four things  
 17 which warrant research, basically.  
 18 DR. KATZ: John?  
 19 DR. MARKMAN: John Markman, Rochester. I  
 20 wanted to make two comments; one risky and one  
 21 safe. The risky comment is risky because I'm going  
 22 to disagree with Brian. I think that with regard

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1 to value in economic outcomes, it's hard to be in a  
 2 position in a field where the measure of quality of  
 3 care for many of the practitioners is multimodal  
 4 care: the physical therapy visits, the cognitive  
 5 behavioral therapy, the drug therapy, the  
 6 integration of those with the procedures and their  
 7 devices.  
 8 I think that if our position is we're going  
 9 to show value by showing how we take away or reduce  
 10 the need for the multimodal way of delivering care,  
 11 which they're is the highest standard of care in  
 12 this country, I think there's a tension there that  
 13 we would have to resolve because all of our lead  
 14 organizations are constantly touting the fact that  
 15 the more multidisciplinary care there is, and the  
 16 more of it you give in a more integrated way --  
 17 I think this is a point of contrast with  
 18 Parkinsonism, as an example, like in movement  
 19 disorders. If you cure someone with DYT1 from  
 20 their dystonia, nobody cares about  
 21 multidisciplinary care. They care about the fact  
 22 that the dystonia is gone. And I think for pain

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1 care, there's a cultural acceptance that it's going  
 2 to have to be multidisciplinary because there's an  
 3 intractability to it no matter how good your  
 4 therapies are, and I think we're in a weird tension  
 5 to be arguing against that.  
 6 My second point, less risky because I'm  
 7 agreeing with Howard Fields --  
 8 (Laughter.)  
 9 DR. MARKMAN: -- which is always a safe  
 10 place to be.  
 11 (Laughter.)  
 12 DR. MARKMAN: There are a quarter million or  
 13 more cardiac pacemakers implanted in the United  
 14 States. Obviously, third-degree heart block and  
 15 tachy-brady syndrome are bulletproof indications  
 16 for those devices. You cannot say no. If you want  
 17 to put those in, it's because we have a biomarker  
 18 which says this is a biomarker which matters. We  
 19 have this rhythm. And if you have this rhythm, you  
 20 get the device.  
 21 The closest we could come to that is a QST  
 22 signature just like the one that was described,

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1 which would be if you have this pattern, then you  
 2 get this device. And again, that would be  
 3 something which we could articulate and say, this  
 4 is our understanding of the nervous system in 2022.  
 5 Let's be honest. We've got a new drug for  
 6 transthyretin and amyloid neuropathy, which is  
 7 \$450,000 a year; \$450,000 for one drug, for one  
 8 neuropathy. And those patients don't just have  
 9 neuropathy, by the way. When you have an  
 10 amyloid-related neuropathy, you've got a lot of  
 11 other medical problems, and the drug is over  
 12 \$400,000 a year.  
 13 So the idea is there is a lot of merit to  
 14 really refining the neurobiological basis for why  
 15 you're putting this in because it completely  
 16 recalibrates the value proposition.  
 17 DR. KATZ: Just a quick plug. In terms of  
 18 biomarkers, for those of you who do research, I was  
 19 just at an NIH meeting -- what day is today,  
 20 Friday? -- on Wednesday, on biomarkers. The new  
 21 NIH HEAL Initiative, they have \$500 million that  
 22 they said needs to be completely committed by

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1 September of 2019, \$500 million dollars. They  
 2 outlined the major focuses of their funding plans,  
 3 and one of the major focuses is biomarkers for  
 4 treatments for pain.  
 5 So if anybody's interested in doing studies  
 6 on biomarkers to predict efficacy of spinal cord  
 7 stimulation, now's your chance.  
 8 Brian, do you want to comment on John's  
 9 comments?  
 10 DR. KOPELL: I hear what you're saying, but  
 11 I am a big believer in multidisciplinary care.  
 12 Even doing DBS for movement disorders requires  
 13 multidisciplinary care. But still  
 14 multidisciplinary care, by definition, is more  
 15 resourceful than streamlined or very simple care,  
 16 basically, by definition. So if we use less of it,  
 17 it's less of a burden.  
 18 If we have a patient -- I agree with you, a  
 19 complex inpatient requires multidisciplinary care  
 20 to get the best treatment. That I will never  
 21 debate you on. But if that patient is the same way  
 22 10 years from now versus a patient that doesn't

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1 need that multidisciplinary care anymore, I would  
 2 argue that patient that doesn't need it anymore,  
 3 that's the success.  
 4 DR. MARKMAN: No. But I don't think this  
 5 is -- in my hands, at least, this is not a  
 6 technology which -- if I don't see the patient for  
 7 10 years and I put one of these in, my assumption  
 8 is not that I've cured them and they're just coming  
 9 back for a battery replacement in another decade.  
 10 My assumption is -- I think someone said  
 11 this -- they've probably gone somewhere else,  
 12 because I don't see the ablation of pain. I don't  
 13 see this as the treatment of DYT1. I think there's  
 14 efficacy. I just don't think it's that.  
 15 DR. KOPELL: Yea, I get it. So then as a  
 16 payer, if I'm a payer, and I'm a for-profit payer,  
 17 I'm going to look at that and say, "Well, gee, is  
 18 it really worth us to be putting in a few hundred  
 19 grand into this patient if we're no better off than  
 20 where we were before?" I'm sorry, but they're  
 21 going to make that their argument, and they're  
 22 going to win that battle.

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1 DR. LOESER: I don't think they will.  
 2 DR. MARKMAN: I don't think they win it.  
 3 And we don't win it in an age -- the unmet need --  
 4 DR. LOESER: It's a chronic disease --  
 5 DR. MARKMAN: Yeah.  
 6 DR. LOESER: -- and chronic pain is a  
 7 chronic disease. And we need to use the chronic  
 8 disease model, which is not one of an episodic  
 9 care, and then you're done with the patient. And I  
 10 think that's an important point we need to keep in  
 11 mind when we deal with those who pay for care, that  
 12 this is a chronic disease, and we do not have a  
 13 cure for this chronic disease.  
 14 DR. KOPELL: Okay. To that same token, any  
 15 chronic disease will have a certain slope of cost  
 16 for that care. If you do not change that slope in  
 17 any intervention, it doesn't matter whether it's  
 18 chronic or acute, the payers are going to say  
 19 that's not worth it.  
 20 DR. LOESER: The slope of care cost needs to  
 21 include not only the cost of the healthcare but the  
 22 cost of the disability the patient may have. And

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1 if you are capable of restoring someone to gainful  
 2 employment, you have made a huge contribution.  
 3 DR. KOPELL: Sure. I give you that, but  
 4 that's hard to demonstrate in a small trial,  
 5 basically.  
 6 DR. KATZ: I have a quick comment on that,  
 7 on the debate between John and Brian. And then I  
 8 need to go to Jane; and then I need to go to  
 9 Howard; and then I need to go to Andrea. So there  
 10 is a method to this madness.  
 11 In terms of the cost effectiveness, I do  
 12 want to say, just again from my own experience with  
 13 looking at cost data and chronic pain, and looking  
 14 at where costs savings do actually come when  
 15 they're assessed in patients based on, treatments  
 16 for pain, when you do see cost savings, it's  
 17 usually not from reducing -- mostly from reducing  
 18 medication, so there's certainly a component.  
 19 It's usually not from the multidisciplinary  
 20 care either. It's not because you're reducing  
 21 physical therapy or acupuncture. If you do save  
 22 costs, it's because of things that the patients

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1 don't want. It's emergency room visits. It's  
 2 hospitalizations. Often those ER visits and  
 3 hospitalizations can't even be tied directly to  
 4 what the patient's pain syndrome is, but yet you  
 5 still see them there, and they're attributable  
 6 because they're accessing the pain patients  
 7 compared to a control population.  
 8 So I think there is a common ground here,  
 9 where if an effective treatment does reduce ER  
 10 visits and hospitalizations and additional  
 11 surgeries, and management of complications and  
 12 things like that, then it's a win-win for  
 13 everybody, especially if you combine that with what  
 14 Rod said, which is that if we're improving quality  
 15 of life, then the pressure on actually decreasing  
 16 dollar cost is less potent.  
 17 All right. So that's my comment.  
 18 Jane, it was your turn.  
 19 MS. SHIPLEY: Thank you. Jane Shipley from  
 20 Baltimore. First of all, thank you all. I learned  
 21 a lot this morning, and it's not every day when I  
 22 learn a lot, so I appreciate your presentations.

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1 One thing bothered me, however -- since we're  
 2 talking about cost effectiveness and study  
 3 design -- and that is that two presentations  
 4 mentioned the Hollingsworth cost- effectiveness  
 5 study.  
 6 I would like to point out that that was  
 7 based on clinical results from Judith Turner's  
 8 study. There were those of us who considered  
 9 Judith Turner's study so fundamentally flawed that  
 10 we suspect that it might have been a deliberate  
 11 attempt at policy-based evidence making.  
 12 MALE VOICE: I think that's not acceptable  
 13 to make that statement.  
 14 MS. SHIPLEY: I just said some of us think  
 15 that -- I didn't say that it actually was. I  
 16 certainly have --  
 17 DR. KATZ: Jane, do you want to explain why?  
 18 MS. SHIPLEY: Well, the sponsor was involved  
 19 in which patients got the therapy. They presented  
 20 it as if it were an RCT, and it wasn't an RCT.  
 21 We've written about this. We've written a letter  
 22 to Pain. We've presented on this. We've made our

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1 objections to the study public.  
2 At any rate, my point I'm trying to make,  
3 that aside, is that if you're going -- the CHEERS  
4 checklist Rod talked about, and he said we can't  
5 cherry-pick, but we also have to remember that junk  
6 in is junk out. And if no one is looking at the  
7 validity of a study with clinical results upon  
8 which another study is based for cost  
9 effectiveness, and they're taking the results of  
10 the cost-effectiveness study without determining  
11 whether the clinical study could be, in fact,  
12 considered accurate, and beneficial, and something  
13 we should pay attention to, then I think that's a  
14 mistake. So I just want to put that out there.  
15 DR. KATZ: Rod, do you want to comment on  
16 that from a methodological perspective?  
17 DR. TAYLOR: Yeah. I'll keep it apolitical.  
18 I think there are a couple of problems with the  
19 study that at least I'm aware of the scientists,  
20 regardless of the setting of Washington State that  
21 did the study. One was just the population. Brian  
22 said that it's worker's compensation, and I think

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1 there are so many perverse incentives there that  
2 really biases what the outcomes might be. It's  
3 almost to the point that could we rely on the  
4 outcomes at all.  
5 That's the big issue, Jane, isn't it? It's  
6 the patient selection. Then the other one, as you  
7 said, it was a non-randomized study. So yeah. I  
8 do cock-a-snook, as we say in Scotland.  
9 Cock-a-snook? Have you heard that?  
10 DR. KATZ: No. What does that mean?  
11 DR. TAYLOR: If somebody says to you, "Oh,  
12 cock-a-snook," what they're doing is they're  
13 ignoring you.  
14 (Laughter.)  
15 DR. TAYLOR: So I cock-a-snook to that  
16 study.  
17 DR. KATZ: Andrea, I think you were next.  
18 DR. TRESKOT: I think it is important to  
19 look at chronic pain the same way that we look at  
20 diabetes, in that early intervention has the  
21 potential for preventing long-term consequences.  
22 And unfortunately, we get the patient when they

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1 have gangrene, and then all of a sudden, it's  
2 surprising that we're not able to salvage these  
3 patients.  
4 So perhaps looking at these stimulators not  
5 in failed back, which is -- we've already said a  
6 totally amorphous group of patients and not a  
7 diagnosis, but rather in those patients who have a  
8 more defined pathology earlier in their care, not  
9 as an end therapy but as a modulator of care,  
10 comparing them perhaps to an untreated group, which  
11 I'm not sure that is actually ethical -- but the  
12 idea of this early intervention, the fact that if  
13 we're using spinal cord status stimulation as a  
14 salvage, we are going to have to accept much  
15 smaller improvements than if we looked at it as a  
16 primary therapy.  
17 DR. KATZ: So let's actually pivot on that  
18 topic for a moment because we have to come up with  
19 the research recommendations. We have on that  
20 slide a list of key questions that we all brought  
21 forward, but what we didn't get at in that survey  
22 is what pain syndrome would be the best one to test

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1 these hypotheses on. I think maybe there's an  
2 assumption because there's been a lot of discussion  
3 that lumbar radiculopathy in the setting of a  
4 failed back surgery syndrome, since it's the most  
5 common indication, might be the best place to do  
6 that, but we haven't really talked about that  
7 explicitly.  
8 So what do people think would be the best  
9 pain syndrome to test these hypotheses on?  
10 Simon, do you want to start us off?  
11 DR. THOMSON: Yeah, I'll just kick off with  
12 that because we say chronic radiculopathy, as you  
13 said, in the context of failed back surgery  
14 syndrome, we're working on it, trying to redefine  
15 the phrase And again, a lot of this is all to do  
16 with the reimbursement.  
17 In the UK, we manage to make it so that SCS  
18 is available for all patients with refractory  
19 neuropathic pain. It's not a requirement that they  
20 have to have had surgery before you can prescribe  
21 spinal cord stimulation. But I think in the U.S.,  
22 it is a requirement, is it, that they have to have

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1 had some spinal surgery before.  
2 DR. NORTH: Not an absolute one, but it is  
3 customary.  
4 MALE VOICE: I don't think so, not in the  
5 state of Washington.  
6 MALE VOICE: No, it's not.  
7 DR. EL DABE: Can I make a comment? I think  
8 given what Rod has told us about the baseline EQ5D  
9 of the population, the baseline EQ5D of the  
10 population Rod was referring to is specific to the  
11 failed back surgery syndrome population. It is not  
12 applicable to patients with low back pain. You go  
13 to low back pain, you'll find the baseline EQ5D  
14 around 0.4. If you go CRPS, you'll find the same.  
15 So if you want your best chance, it is with  
16 failed back surgery syndrome patients. There is  
17 nothing else that works for them. But the question  
18 is, which failed back surgery syndrome patients?  
19 It is such a heterogeneous population, we have to  
20 do a better job at defining these.  
21 DR. NORTH: Simon -- it's Rick -- picking up  
22 on your use of the word "radiculopathy," just as I

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1 did yesterday with neuropathy, that word means  
2 something wrong with the nerve root. And many  
3 failed back surgery patients have had nothing more  
4 than a fusion based on degenerative findings on  
5 imaging studies and whatever other incentives might  
6 be built into the system.  
7 But if you are careful to select  
8 patients -- and I'd go so far as to say you would  
9 want to have a spine surgeon review all the  
10 candidate's prior records to see whether there was  
11 a compelling case for their first surgery, that  
12 they had nerve root compression, even if they don't  
13 have it now, so there still is plausibly at least  
14 something residual still wrong with that nerve root  
15 or roots, that's the subset of people that we  
16 should have in this idealized study.  
17 DR. THOMSON: Whether they've had surgery or  
18 not.  
19 DR. NORTH: Well, I think if we limit  
20 ourselves to people who have surgery, it's a more  
21 straightforward homogeneous group; not to say that  
22 SCS is not a good choice, as an alternative to the

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1 first back surgery, if you will. But we do have  
2 one RCT that shows it's superior to repeat back  
3 surgery. It's very hard, by the way, to do and to  
4 repeat such a study. We tried with support of one  
5 of the companies, but couldn't enroll patients.  
6 DR. KOPELL: So you're basically saying  
7 limit this to patients that have had lumbar  
8 surgery, that had appropriate lumbar surgery in the  
9 first place, meaning reviewed by a spine surgeon  
10 and limit just to that patient population. When  
11 patients come to you with four or five surgeries,  
12 you'd have to vet every one of those five  
13 surgeries. In other words --  
14 DR. NORTH: You'd have to say that at least  
15 one of them was for nerve root.  
16 DR. KOPELL: Okay, fair enough.  
17 DR. KATZ: Howard?  
18 DR. FIELDS: I'm going to make a strong  
19 prediction, and maybe it's even helpful, that if  
20 you were able to have a way to assess small fiber  
21 function, let's just say thermal stimulation, if  
22 you find that there's an area where the initial

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1 stimulation is for a given stimulus intensity  
2 reported as less painful by the patient, and then  
3 with repeated stimulation, it becomes very, very  
4 painful, even more than the normal person, I've  
5 only seen that in patients who have nerve injury.  
6 So my guess would be, based on going back to  
7 Bishop and Landau [ph] the gate-control hypothesis,  
8 the fact that large diameter fibers have lower  
9 threshold, those are the patients that are going to  
10 get the biggest and most dramatic effect from  
11 spinal cord stimulation. So in addition to having  
12 Rick's criteria, I would say I'd like to have some  
13 objective evidence for a sensory abnormality in the  
14 distribution of their pain.  
15 I think if you had that, that's your ideal  
16 patient, and I predict that those patients as a  
17 group will do very well. And I would also say that  
18 if you had that evidence, you could go to the  
19 payers and say, "Look, we have something. This is  
20 the ideal scientifically based treatment for this  
21 condition. Nothing else does anything like this."  
22 The problem for the manufacturers is that's going



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1 to be a relatively small population of patients,  
2 which is why the payers will be more willing to  
3 cover it. So it's best for the patient.  
4 DR. NORTH: We've looked at that or tried to  
5 look at that, and for it, not as thoroughly as we  
6 might have done or as you might like. It was  
7 difficult to show any association with response to  
8 simulation.  
9 DR. KATZ: How was that done?  
10 DR. NORTH: But I'm with you. An objective  
11 basis for complaint of pain and an objectively  
12 demonstrable nerve abnormality would be nice to  
13 have.  
14 DR. KATZ: Any other thoughts about what  
15 painful disorder these idealized studies should be  
16 performed in? Andrea?  
17 DR. TRESCOT: Andrea Trescot. We were just  
18 talking about peripheral neuropathy as a treatment  
19 in that though 70 percent of them are idiopathic,  
20 you've at least got something that can be  
21 documented, and is debilitating, and potentially  
22 reversible. If what you think of the peripheral

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1 neuropathy as being an ischemic model, then this is  
2 a good way of potentially restoring blood flow, and  
3 therefore improving function. And for that, also  
4 looking at the peripheral vascular disease.  
5 DR. KATZ: Anyone have any thoughts on  
6 painful peripheral polyneuropathy, painful  
7 peripheral neuropathy, ischemic peripheral vascular  
8 disease as potential patient populations for such a  
9 study?  
10 DR. ELDABE: Sam Eldabe. I'm not sure about  
11 peripheral neuropathy. I can't really comment on  
12 that. But critical limb ischemia and ischemic  
13 diseases, there are more RCTs in that domain for  
14 SCS than any other domain. And the conclusion that  
15 you can draw from that is they're negative. You do  
16 not improve limb survival with SCS in critical limb  
17 ischemia, unfortunately, as much as we would like  
18 to believe otherwise.  
19 DR. TRESCOT: End stage. I'm sorry, but  
20 again, we're looking at end stage. If what you  
21 look at is not limb salvage, but improvement in  
22 perfusion, if you already have a patient who's got

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1 gangrene, that's one thing. But if you have  
2 somebody with intermittent claudication, then you  
3 can look at walking tolerance, transcutaneous PO2  
4 levels, healing of small ulcers. But again, once  
5 you have gangrene, if you're looking at it as an  
6 end-stage limb salvage, that would be like asking  
7 the diabetologists to now get their diabetes under  
8 control and see if that now fixes their gangrene.  
9 DR. KATZ: Sam or Simon or someone?  
10 DR. ELDABE: Sam Eldabe again. I think  
11 you're absolutely right, and therein you get into  
12 the problem that we have with refractory angina.  
13 You are not going to get vascular surgeons to refer  
14 you these patients at the appropriate timing. You  
15 will get them at a point where their transcutaneous  
16 PO2 is less than 10 millimeters mercury, and  
17 therein it becomes useless. This is why targeting  
18 a population that does not naturally turn up in  
19 your pain clinic poses a great difficulty in  
20 recruitment.  
21 DR. TRESCOT: Unless you go directly to the  
22 primary care.

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1 DR. ELDABE: Yes, that is correct. But I  
2 suppose for refractory angina and critical limb  
3 ischemia, that's not really possible.  
4 DR. KATZ: Sam, what does the literature on  
5 spinal cord stimulation say about efficacy in  
6 patients with ischemic claudication and not  
7 critical limb ischemia?  
8 DR. ELDABE: I think there's a whole  
9 literature about which stage you capture these  
10 patients at, and Angela's quite right. When you do  
11 transcutaneous PO2's, you get better results, but  
12 albeit, that study is non-randomized. So if that's  
13 the only positive study, but it's the only one  
14 that's non-randomized, that may tell you something  
15 in itself. But it's the only one that's captured  
16 patients at a stage that you can look at and say,  
17 yes, these are earlier stage patients.  
18 DR. NORTH: Importantly, I think that  
19 literature is based on conventional stimulation.  
20 I'm not aware of anything really with the new  
21 parasthesia-free waveforms, and that's what we need  
22 to use for our blinded trial.

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1 DR. KATZ: Eric and then John?  
 2 DR. BUCHSER: Eric Buchser. Studies on  
 3 peripheral vascular disease actually showed, under  
 4 certain circumstances, benefit at one year, not  
 5 beyond. So that might be a problem in terms of  
 6 cost effectiveness.  
 7 The other thing is that if you look  
 8 objectively at change in blood flow, nobody has  
 9 shown any change in blood flow except for  
 10 microcirculation. So actually, the objective  
 11 markers and criteria for spinal cord stimulation  
 12 and PVD actually are not there.  
 13 DR. KATZ: John?  
 14 DR. MARKMAN: John Markman, Rochester. I  
 15 think neuropathy is very intriguing. I don't think  
 16 a mixed basket of different neuropathies is very  
 17 promising at all. I think the assay sensitivity is  
 18 going to be vanished [indiscernible]. If you put  
 19 HIV neuropathy there, we know that there's never  
 20 been a positive trial ever for the drug conducted  
 21 in that group. We know that there's differential  
 22 treatment response across these different

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1 neuropathies for different anti-neuropathic pain  
 2 agents.  
 3 So there's a lot of evidence to suggest that  
 4 we can't mix and match and do all neuropathy, all  
 5 comers. Within specific neuropathies, I think what  
 6 it obligates us to do is use a parasthesia-free  
 7 system because I think historically, at least in my  
 8 hands and I think in others probably as well,  
 9 covering the distal feet, where oftentimes people  
 10 have the most severe spontaneous neuropathic pain,  
 11 is incredibly hard with a parasthesia-based system,  
 12 and to do it with great reliability.  
 13 So I do think it's a unique opportunity in  
 14 patients who have spontaneous pain syndrome, not  
 15 evoked, but who have a lot of spontaneous pain with  
 16 a parasthesia-free system in a single neuropathy,  
 17 potentially, with some sort of quantitative tests;  
 18 or even just to show sensory deficit as part of the  
 19 inclusion, I think that would be uniquely  
 20 promising.  
 21 DR. KATZ: John, you know what I'm going to  
 22 ask you.

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1 DR. NORTH: I have no plans for dinner.  
 2 (Laughter.)  
 3 DR. KATZ: Which neuropathy?  
 4 DR. MARKMAN: I think that -- well, that's a  
 5 great suggestion. Andrew just mentioned  
 6 alcohol-related neuropathy. It's one that's not  
 7 commonly studied in the drug world, but it is  
 8 ubiquitous. And it is one which I think is a very  
 9 attractive one. But the only thing that gives me  
 10 pause about that is that no drug company has ever  
 11 really sought to explore it, and I'm sure they've  
 12 thought about it.  
 13 So the options would be -- and as you know,  
 14 there are multiple neuropathy trials going on now  
 15 in phase 2 in the drug world for small fiber  
 16 neuropathy, which are largely based on punch  
 17 biopsy, and then there are several diabetic  
 18 peripheral neuropathy trials also ongoing.  
 19 My inclination is to avoid diabetic  
 20 peripheral neuropathy for two reasons. Number one  
 21 is many of these patients do not have a stable  
 22 underlying pain pattern in my experience; they have

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1 a variable pain pattern. And many of them really  
 2 have numbness more than pain, or by the time we see  
 3 them, they have numbness. So there's a lack of  
 4 stability to the underlying spontaneous pain  
 5 phenotype in the diabetic neuropathy population,  
 6 which I think adds an extra potential for  
 7 measurement error.  
 8 Second, obviously, is that for most of us  
 9 who implant on a regular basis, one of the only  
 10 times you really see infections in a way that you  
 11 can't minimize the risk is in patients with  
 12 diabetes, especially at the pocket. I think that's  
 13 the one group -- especially their HBA1c's are not  
 14 that well controlled. For me, that's been a  
 15 challenge in that population.  
 16 So I think that the infection risk as well  
 17 as the instability of the phenotype make diabetes  
 18 less attractive and push me more towards  
 19 chemotherapy-induced neuropathy or a very, very  
 20 esoteric -- maybe neuropathy in the setting of  
 21 monoclonal gammopathy, no immunocompromise,  
 22 relatively common, very easy to characterize in

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1 terms of laboratory studies, and not a lot of  
 2 treatments, so you kind of have a niche unto  
 3 yourself. So I would go for monoclonal gammopathy.  
 4 DR. KATZ: Rick?  
 5 DR. LOESER: I think that's going to be a  
 6 dead end; the numbers involved and the fact that we  
 7 are sitting here in the country with this immense  
 8 number of failed back surgery patients who are very  
 9 difficult to deal with. I think that it is  
 10 possible to characterize those who have had  
 11 surgery, who have a clear-cut neuropathic pain  
 12 within their pain syndrome, I think that's the  
 13 proper target for a study studies such as this. I  
 14 think going to arcane, rare neurologic disorders is  
 15 just the wrong way to go.  
 16 DR. KATZ: Brian, from a payer perspective,  
 17 it seems like the goal is to advance the  
 18 availability of this therapy for the most common  
 19 indication, which is failed back surgery syndrome.  
 20 Scientifically it may be super interesting to do  
 21 peripheral neuropathy, but from a payer  
 22 perspective, if that's our goal, how important is

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1 it actually to stick with the a syndrome that we're  
 2 trying to advance the therapy for?  
 3 DR. KOPELL: I think to stick with failed  
 4 back syndrome.  
 5 DR. THOMSON: Certainly in the UK, NICE  
 6 recommended spinal cord stim for FBSS CRPS, but  
 7 importantly indicated ischemic pain as being an  
 8 experimental indication, and therefore needed to  
 9 see more evidence. So I think if one of the  
 10 recommendations we want to make as part of this  
 11 get-together is where would one want to place your  
 12 bets on the roulette table to do a  
 13 placebo-controlled trial, I think what I'm hearing  
 14 is that that would be FBSS. Then the issue, as Sam  
 15 was saying, how do we best characterize those  
 16 patients within our heterogeneous space to maximize  
 17 the likelihood of a treatment effect?  
 18 DR. KOPELL: And I would go even further is  
 19 to kind of recapitulate a little bit about what you  
 20 did in '07, which is intervening before they get to  
 21 the fourth, fifth, and sixth surgery. So maybe one  
 22 single intervention, and then those patients and

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1 those patients only, because not only would you  
 2 basically show a cost benefit, but the implication  
 3 is if you can stop them from getting another  
 4 fusion, boy, now you're talking real cost savings  
 5 DR. TAYLOR: Yeah, and then that's much  
 6 better than medication.  
 7 DR. KATZ: Salim?  
 8 DR. HAYEK: I agree with John Markman.  
 9 Small fiber neuropathy is a great target  
 10 population. There's a high response rate. The  
 11 problem is it's hard for the average practitioner  
 12 to diagnose the condition because they have to do  
 13 the biopsy, and not all centers have biopsies. I  
 14 agree with him also on the diabetic neuropathy. A  
 15 lot of those patients go from having a mixed  
 16 neuropathy with small fiber, to becoming pure large  
 17 fiber, which is a non-painful neuropathy and they  
 18 have a high risk of infection and complications.  
 19 Therefore, I think failed back surgery  
 20 syndrome with predominant maybe leg pain component  
 21 and basically being neuropathic is the obvious  
 22 target. However, I cannot emphasize how it is

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1 important for our study going forward to make sure  
 2 that we exclude fibromyalgia, not based on history,  
 3 but based on actual investigators, screening the  
 4 patients with validated screens for fibromyalgia.  
 5 Because if you include those patients in your  
 6 study -- and a lot of the pain studies do not put  
 7 that as an exclusion criteria, especially with  
 8 failed back surgery patients -- we're going to see  
 9 a lot of failures, and that's because these  
 10 patients will complain every other day about new  
 11 pain syndrome.  
 12 DR. KATZ: Tell us your rule of thumb,  
 13 Salim. Tell us your rule of thumb for how you  
 14 select patients for treatment. Who do you rule  
 15 out?  
 16 DR. HAYEK: Beside fibromyalgia? Smokers,  
 17 worker compensation, fibromyalgia, active  
 18 litigation, pain in multiple areas besides  
 19 fibromyalgia.  
 20 DR. KATZ: One more.  
 21 DR. HAYEK: Opioids and unemployed on  
 22 disability? The list could keep going.

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1 DR. KOPELL: But patients that present to  
2 you with back and leg pain without any sort of  
3 surgery in the past or any sort of significant  
4 injury to them.  
5 DR. HAYEK: For our study purpose, I would  
6 stay away from it.  
7 DR. KOPELL: You do not.  
8 DR. HAYEK: I don't. I only have two  
9 patients in 20 years of practice that I implanted  
10 for radicular pain with not having had previous  
11 surgery.  
12 DR. THOMSON: Simon Thomson here. I think  
13 we're also missing out on some other things which  
14 would help us predict. I put quite a lot of  
15 store -- I mean, I hear what you're saying,  
16 everybody's signing. But also, those patients who  
17 respond well to a root block, they really do get  
18 good pain relief, and it last for a few weeks, few  
19 months, and they actually improve. But they keep  
20 getting recurrence and keep coming back, and you  
21 can't carry on forever doing it. They're, I think,  
22 always good candidates.

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1 DR. NORTH: All of these I think are very  
2 good potential indications. But again, we're  
3 talking about a blinded trial. That means  
4 parasthesia-free stimulation. And the evidence for  
5 the efficacy, that is basically in failed back and  
6 CRPS.  
7 DR. ELDABE: Can I ask a question?  
8 DR. NORTH: And I'm glad nobody's mentioned  
9 CRPS.  
10 DR. KATZ: You mentioned it just now.  
11 (Laughter.)  
12 DR. NORTH: Okay, fair enough. I think  
13 that's problematic. I always found it so  
14 clinically. They're basically two forms of it, the  
15 surgical standpoint. One, I think understand that  
16 I understand; the other, I have no clue.  
17 DR. THOMSON: Like diabetes, there are 5  
18 types of diabetes now, disease trajectories. And I  
19 think the CRPS story will be something like that.  
20 DR. NORTH: We need a marker for that.  
21 DR. THOMSON: And it won't be type 1 and  
22 type 2, a named nerve injury or not named injury.

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1 It's not going to be that.  
2 DR. KATZ: Eric?  
3 DR. BUCHSER: One question I have to the  
4 panel, what's your experience with pain in part of  
5 the leg or arm that has sensory deficit? Because  
6 my experience -- and that relates to  
7 polyneuropathy -- if you do have a significant  
8 sensory deficit, it simply doesn't work. So those  
9 should be exclusion criteria as well.  
10 DR. HAYEK: If it's complete  
11 deafferentation, I agree with you, but if it's  
12 partial deafferentation, I don't know. Perhaps our  
13 neurosurgery colleagues like Brian can comment on  
14 that. Maybe it's effective.  
15 MALE VOICE: Say this again.  
16 DR. HAYEK: I was referring to the question  
17 by Eric on deafferentation. He's saying if there's  
18 sensory loss, then perhaps we should not put a  
19 stimulator.  
20 MALE VOICE: I'm not sure. I guess the idea  
21 of a surgical question there. That's a --  
22 DR. HAYEK: I was just referring to the

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1 deafferentation, how much deafferentation there is  
2 in the extremity. If there's full deafferentation  
3 or complete deafferentation as in phantom limb  
4 pain, it's probably not effective. Maybe Sam  
5 published on this.  
6 MALE VOICE: It's sort of an ideology.  
7 DR. ELDABE: Sam Eldabe. I suppose if you  
8 look at the result of spinal cord stimulation in  
9 CRPS type 1, and you compare it to CRPS type 2, you  
10 end up with a completely different set of results  
11 because of what you say --  
12 DR. FIELDS: Which one does it work for?  
13 DR. ELDABE: It works well for type 1, but  
14 it doesn't work so well for type 2 where you have  
15 complete loss of nerve function.  
16 DR. BUCHSER: In all the studies that have  
17 been done in post-herpetic neuralgia, for instance,  
18 if you look at the results, there's no control size  
19 of course, but the case series show  
20 relatively miserable results, really.  
21 DR. KATZ: Eric, you're referring to -- your  
22 question is about complete the deafferentation in

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1 some named nerve segment --  
2 DR. BUCHSER: That's right.  
3 DR. KATZ: -- as opposed to just a minor  
4 sensory loss that you have work to detect.  
5 DR. BUCHSER: The only studies I know where  
6 minor sensory loss has been treated and has  
7 responded is actually in diabetic polyneuropathy,  
8 where the sensory loss is incomplete. But in my  
9 experience, at least, when you do -- I don't know  
10 exactly what that means, but a significant sensory  
11 loss where patients really have a loss of  
12 sensation, I have been very unsuccessful with those  
13 patients.  
14 DR. KATZ: Rick, do you have any comments on  
15 that?  
16 DR. NORTH: In some of our older papers that  
17 were large samples, not RCTs, we look specifically  
18 at sensory loss evident on clinical exam as a  
19 prognostic factor and saw no effect.  
20 DR. THOMSON: I concur. I know we're  
21 looking for the best model in which to do the  
22 perfect study. Maybe this isn't the perfect model,

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1 but I think we should be careful that -- I think  
2 we've all seen patients where spinal cord  
3 stimulations work nicely in people with sensory  
4 loss. Profound deafferentation, yes, it's less  
5 likely, but these things can happen.  
6 DR. KATZ: Howard?  
7 DR. FIELDS: Howard fields, San Francisco.  
8 I was very specific about my prediction. The  
9 prediction is that when you do the sensory testing,  
10 the initial stimuli are perceived as less intense.  
11 As you do repeated stimulation, it becomes more  
12 intense than normal. So what that suggests to me  
13 is that there is nerve injury in that part of the  
14 brain. There may be even hyperexcitability among  
15 the remaining fibers.  
16 The main change that's occurring is  
17 summation in the central nervous system. And if  
18 that's the case, and some aspects of the gate  
19 control hypothesis are correct, and what you think  
20 you're stimulating is what you're actually  
21 stimulating, the prediction would be those would be  
22 the ideal patients.

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1 So you have a thermal stimulus that only  
2 activates C fibers, nociceptors, and you show that  
3 they're still intact and contributing to the pain  
4 problem, those should be the patients in which it  
5 works. So a blanket statement about sensory loss  
6 is probably inadequate for the assessment of the  
7 patient.  
8 DR. NORTH: I think that's a great idea for  
9 optimizing patient selection, and that's part of  
10 what we're here to talk about. Then there is the  
11 generic study methodology to be applied for all  
12 conditions to avoid some of the problems with the  
13 research to date.  
14 DR. EL DABE: I have a question for you,  
15 Rick, based on the generic study methodology. You  
16 mentioned that if we run sham-controlled trial, we  
17 would have to exclude conventional stimulation.  
18 DR. NORTH: No. What I have in mind is the  
19 trial design coming out of the study would include  
20 conventional as one of the tunes that's in the  
21 jukebox, that each patient is going to successively  
22 try different forms of stimulation. My reference

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1 to conventional had to do with the fact that the  
2 claims for high-frequency burst and so forth, which  
3 are parasthesia free, are limited to a subset of  
4 common diagnoses at this point. So in planning the  
5 first ever study to show benefit over placebo, we  
6 probably should look at those.  
7 DR. EL DABE: I'm just trying to through if  
8 you were to randomize a population of whatever been  
9 condition to a number of stimulation parameters,  
10 including conventional stimulation, and high  
11 frequency, and something else, and you put a sham  
12 arm, there is no requirement for the people  
13 randomized in the sham arm to feel anything because  
14 they will be part of three groups who may or may  
15 not feel stimulation.  
16 So therefore, the idea of having a sham, we  
17 don't have to get into the complexities of the sham  
18 of conventional stimulation.  
19 DR. NORTH: But you're saying they might be  
20 randomized to that first. We haven't gotten into  
21 the details of implantation, but I would assume  
22 that we would put in the electrodes using

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1 parasthesia mapping. So when it came time to use  
2 conventional stimulation -- or for that matter  
3 burst for which the data have been gathered with  
4 electrodes placed using parasthesia mapping and a  
5 trial using parasthesia mapping -- that that would  
6 have been done. So everybody will get that on the  
7 way into the study, and then they'll be randomized.  
8 DR. ELDABE: That's a good point, but I  
9 suppose it forces you down the road of trialing,  
10 and it forces you down the road to parasthesia  
11 trialing, which may or may not be desirable. If  
12 you didn't want to do that, and you implanted  
13 everybody in the sham arm with a high-frequency  
14 stimulator, would that work?  
15 DR. NORTH: Is the question now are you  
16 going to screen patients for implantation using any  
17 one or all of the available tunes?  
18 DR. ELDABE: Assuming that you don't screen  
19 them because that adds a level of complexity into  
20 the story that is never ending, particularly when  
21 you get to a sham group.  
22 DR. THOMSON: I think there's an awful lot

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1 of plague on has the patient ever experienced a  
2 parasthesia or not. Well, that completely ruins  
3 the result for subthreshold stimulation or  
4 subperception. I think that's another of these  
5 things that's been made up, but I think it's true.  
6 Especially in this jukebox idea, I think it will be  
7 brilliant to have multiple opportunities where the  
8 patients don't feel anything, and then, oh, up pops  
9 one that you do feel. I think that would be fine.  
10 DR. NORTH: You might make it part of the  
11 routine follow-up visit for reprogramming, that  
12 there be a brief test of conventional stimulation.  
13 Verify the patient feels parasthesia. That  
14 reassures everybody that the system is working,  
15 whatever waveform you're delivering. And then you  
16 go on to do whatever you're going to do.  
17 DR. KATZ: Rod, did you have a comment?  
18 DR. TAYLOR: Just to help you bring us back  
19 to the task at hand, I think we're not here to  
20 design the perfect SCS study. We're here to  
21 hopefully present maybe a checklist of  
22 recommendations going forward for what a study

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1 would be. One of my observations is that we've got  
2 some really talented people in this room thinking  
3 about this question, so maybe one of the spin-offs  
4 of this meeting would be to bring together such a  
5 group to deliver such a trial.  
6 I think one of the observations from the UK  
7 is it's very hard to get NIHR to put their hands in  
8 the research pockets to fund neuromodulation  
9 research. But it sounds as though the NIH,  
10 particularly with this biomarkers call, there could  
11 be an opportunity there, and we might be able to  
12 grasp that.  
13 So here's a trial that would be done  
14 by -- investigator led. We would have all of the  
15 tunes and Rick's jukebox. It could be called the  
16 jukebox trial --  
17 (Laughter.)  
18 DR. TAYLOR: -- and we randomize people to  
19 it. And we do that definitive study. I know  
20 that's not the purpose of being here. I'm really  
21 enjoying the discussion, but I really wonder if  
22 that might be a useful ACTTION post of this

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1 meeting, is to follow that up. If anybody's  
2 interested, I would certainly be very interested in  
3 being part of that group.  
4 DR. KATZ: Bob, Dennis, what do you think  
5 about -- just to emphasize what you said, Rod, this  
6 is not a protocol design meeting. That would be a  
7 different kind of a meeting. It wouldn't have so  
8 many people, and it would be very focused on a  
9 specific hypothesis-driven protocol development  
10 approach; although it is part of this meeting to  
11 identify what the key scientific questions are and  
12 what general research consideration should be, and  
13 addressing any of these scientific questions.  
14 Bob, Dennis, what do you think about this  
15 spin-off where such a protocol would be advanced?  
16 DR. DWORKIN: I think potentially it's an  
17 interesting idea. My sense from having been at  
18 multiple NIH meetings over the past 18 months is  
19 they see the development of biomarkers as a kind of  
20 sequential process where you begin by identifying  
21 potential biomarkers, validating the biomarkers,  
22 going through the FDA hoops, and then at the end of

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1 this lengthy process doing a clinical trial to test  
2 whether the biomarker is either a pharmacodynamic  
3 biomarker or predictive biomarker.  
4 So I'm not sure -- though I completely agree  
5 with what you're suggesting, Rod -- that this can  
6 be done at one time rather than waiting for several  
7 steps. But I think their approach is this kind of  
8 very tortured, sequential approach rather than  
9 designing a clinical trial where we do it all at  
10 the same time. But we can look into this, and I  
11 think it would be a great question to send them.  
12 DR. KATZ: At this meeting on Wednesday, the  
13 way that they presented their approach to funding  
14 the biomarker initiative is that they presented two  
15 different pathways. The first pathway they called  
16 the discovery pathway, which was if you really  
17 don't have any preliminary data, well then, you can  
18 do a small little study and get some preliminary  
19 data. But if you already have what they consider  
20 to be adequate preliminary data, then they can jump  
21 you over that first step into the next step, which  
22 is a validation study.

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1 DR. DWORKIN: But of course, we're in the  
2 discovery phase. Howard had hypotheses, but Howard  
3 doesn't have hard data.  
4 DR. KATZ: I don't know to what extent there  
5 are data sitting in the literature or that people  
6 may have generated on the validity and reliability  
7 of various QST measures in patients with  
8 lumbosacral radiculopathy. That would be step one.  
9 My suspicion is that there's probably a lot of that  
10 kind of data sitting in the literature, and then  
11 maybe some pilot data or sub-studies that have  
12 looked at the relationship between that and  
13 outcome.  
14 So I wouldn't dismiss it offhand that there  
15 might be enough about pilot data sitting there.  
16 Dennis?  
17 DR. TURK: Dennis Turk. Let me agree with  
18 Rod about what the purpose of this meeting is and a  
19 potential detailed protocol design as another  
20 purpose. I think for the purpose of this  
21 particular meeting and this particular paper, what  
22 we're really looking for is essentially addressing

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1 some of the issues that we heard from Sam and that  
2 we heard from some other speakers, is what was Nate  
3 pulling together.  
4 So I think the nuances of which specific  
5 population is the best one or the idea one, or what  
6 exact experimental design you want to use to  
7 confirm something, that's fine. But I think for  
8 this purpose, we're trying to give -- imagine that  
9 the audience for this paper or from this meeting is  
10 somebody who's going to go back to their company,  
11 or clinic, or research center on Monday, and  
12 they're going to start thinking about how can we  
13 plan a study that investigates spinal cord  
14 stimulators as an effective treatment. What can we  
15 give them for guidance and not just wait for NIH to  
16 take as long as NIH will take for doing anything  
17 that they're going to do.  
18 So I think it's not an unimportant issue. I  
19 think it's just more in the weeds of detail that  
20 you have some people here who not easily, but who  
21 could sit together and craft a protocol, but I  
22 don't think that's the exact -- from my

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1 perspective, the purpose of this meeting.  
2 DR. KATZ: Yeah, I agree with that. So in  
3 the 8 minutes and 36 seconds that we have left in  
4 the session, I want to see if we can get at two  
5 targeted questions. The first is in relation to  
6 Sam's recommendations for how to deal with these  
7 programming issues in spinal cord stimulator  
8 studies, do people feel comfortable with those  
9 recommendations or does anybody have any  
10 additional -- would anybody propose any changes to  
11 what Sam has recommended?  
12 Eric?  
13 DR. BUCHSER: I totally agree with what Sam  
14 said. I'm just wondering how you should actually  
15 report those programming changing, and issues, and  
16 variability because it's so wide. It's so  
17 different from patient to patient, that I imagine  
18 the way it could look in a paper would be totally  
19 undigestible.  
20 DR. KATZ: Sam?  
21 DR. EL DABE: It's a very good point, and  
22 that's one of the reasons why people fail to report

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1 this, it's because of the limited space in a  
 2 publication, and it's not a priority. But some  
 3 people have done a very good job of doing that,  
 4 particularly the critical limb ischemia paper,  
 5 albeit what they did is they published a technical  
 6 paper.  
 7 But as a minimum, if you and I knew what was  
 8 the mean amplitude, what was the standard deviation  
 9 of the amplitude and what was the range, we could  
 10 have a stab at guessing where were these patients?  
 11 If we don't have any information, it's not  
 12 particularly useful. So I think as a minimum data  
 13 set, that's all we want in the main publication.  
 14 DR. BUCHSER: Would you stratify that by  
 15 lead positioning  
 16 or cathode positioning?  
 17 DR. THOMSON: The spatial target is very  
 18 important. You call it the cathode. Some others  
 19 might call it the central point of stimulation.  
 20 That's very important. Then I think the mode of  
 21 stimulation, so how you switch, whether you're  
 22 using, if you like, an anatomical target and a

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1 high-frequency thing, or whether you're using best  
 2 parasthesia position, and then a subperception  
 3 program.  
 4 I think I remember trying to do this for the  
 5 trial stim study. There are only a limited number  
 6 of, at the moment, categories, and we can define  
 7 those and make those our criteria for reporting.  
 8 DR. KATZ: Yes, Turo?  
 9 DR. NURMIKKO: Just briefly, about sham  
 10 stimulation, just thinking of what you were saying,  
 11 Simon, about the Alkaisy study, where 37 percent or  
 12 so, actually who were supposed to have a proper  
 13 sham didn't turn out to have that. And that was  
 14 then revealed after the study. So I just wonder  
 15 whether there should be something about indication  
 16 or some kind of an attempt by the investigators  
 17 prior to the study to ensure that the sham really  
 18 is sham.  
 19 We are taken it as a given, that high  
 20 frequency obviously has all these features that  
 21 would seem to make sham totally appropriate, but it  
 22 might be something to look into prior to so that

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1 you're absolutely sure, even if it was looking at  
 2 some patient samples to check that everything works  
 3 as planned.  
 4 DR. KATZ: Anyone have any thoughts on that?  
 5 Simon? Anyone?  
 6 DR. ELDABE: I think the 37 percent report  
 7 was in one of the stimulation arms of the study. I  
 8 suppose when they -- well, patients in the sham  
 9 group do report parasthesias. That's quite normal.  
 10 It's not unusual. I'm not sure it's not desirable.  
 11 It does happen, and I don't see the problem with  
 12 that at all.  
 13 DR. KATZ: Well, since it's good to end  
 14 every session with a little bit of statistics just  
 15 to work up our appetite for our lunch, Jen, first  
 16 of all, I want to say this is probably the only  
 17 presentation on causal estimands I have heard that  
 18 I actually feel like I understood.  
 19 (Laughter.)  
 20 DR. KATZ: And I've heard many of them, so  
 21 that's an accomplishment in and of itself.  
 22 Now that you've presented those options,

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1 what are your thoughts on what sort of estimand  
 2 approach will be appropriate and the sorts of  
 3 studies we're talking about here?  
 4 DR. GEWANDTER: I don't really like to be  
 5 prescriptive about what to choose. I like to let  
 6 you choose based on the explanation. For this  
 7 intervention, I think estimand 3 is good because  
 8 it's not like a drug, where if you have an AE, you  
 9 can just stop taking it. We really want to  
 10 know --  
 11 I feel like sometimes for drugs, I think,  
 12 well, as long as we know how well it works for the  
 13 people who can actually take it, that's a good  
 14 thing because people can kind of come and go as  
 15 they please; whereas this is more of a permanent  
 16 thing, so I would prefer I think to know the  
 17 estimate for the people that's actually  
 18 attributable to the treatment, and therefore  
 19 estimand 3, which would be more of a jump to  
 20 reference if you have to stop using the treatment  
 21 because of an AE.  
 22 DR. KATZ: Can you remind everybody what the



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1 implications would be for the design and conduct of  
2 the study if one were to use that approach?  
3 DR. GEWANDTER: The implication would be  
4 that -- so I made it simple by making the  
5 intercurrent event I was talking about  
6 discontinuation due to an AE, which is pretty  
7 serious. There are other more simple intercurrent  
8 events, like you took a rescue medication, or you  
9 took a medication that wasn't allowed in the study.  
10 So it's more nuance. You have to decide  
11 what to do with all those different types of  
12 intercurrent events. But the implication would be  
13 that if someone withdraws for an AE, you don't  
14 necessarily have to follow them or try to get their  
15 data. You can kind of just forget about them from  
16 a resource perspective. But the caveat to that  
17 is -- of Mike McDermott, he would say, well, you  
18 want to do sensitivity analyses, so you might want  
19 those data anyway. But from a primary analysis  
20 perspective, if that's your estimand, you don't  
21 necessarily have to work super hard to get those  
22 data.

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1 But with that said, if someone does drop  
2 out, you want to work really hard to figure out why  
3 and to know why in a good way. And what we found  
4 looking at the FDA database is that a lot of times  
5 it's protocol violation and patient withdrew. It's  
6 very well characterized, and that makes it really  
7 hard to do a targeted imputation that I've  
8 explained; so making sure in your trials that you  
9 really have a good exit interview, if you will,  
10 with the patients and a good understanding of why  
11 they decided they don't want to be in the trial  
12 anymore.  
13 DR. KATZ: I can say that we've sort of  
14 revised the dropout forms, and they're being used  
15 more and more in the pharmaceutical industry, where  
16 it's no longer sufficient to just check a box that  
17 says patient withdrew consent and see you later.  
18 So we're forcing investigators to have a more  
19 detailed set of checkboxes and then also to write a  
20 narrative. When a patient drops out, write a  
21 little story about why that patient dropped out so  
22 that a human being could look at that later and see

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1 if they agreed with where you put your checkbox.  
2 And FDA's pushing people, and we've provided some  
3 of those forms to different studies. So that seems  
4 like it would be important here.  
5 Rod, do you have any additional comments on  
6 that issue?  
7 DR. TAYLOR: No.  
8 DR. THOMSON: I've got a comment. One of  
9 the things that happens is that these are patients,  
10 particularly if you're doing the back pain dominant  
11 over leg pain, they end up with a lot of  
12 comorbidity and new onset pains, new onset  
13 diseases, and it's very common. So if you're  
14 trying to do -- you get to your data collection,  
15 the question I want to know is like they've got  
16 this new onset of pain or whatever, do you try and  
17 take a pain score of what their original pain was  
18 all about? And then you've got your quality of  
19 life measures, and yet they're ill because they've  
20 got pancreatitis or something.  
21 I find these things -- I'm just amazed at  
22 how ill these people get.

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1 DR. GEWANDTER: I think that's a very  
2 different question than the estimand question.  
3 That's a question of, if you enroll people in the  
4 study who have fibromyalgia, for example, can they  
5 distinguish between the pain that the spinal cord  
6 stimulator was for and the fibromyalgia pain. And  
7 I think that's depending on -- unless they're  
8 completely discrete, like John's patient in the  
9 video, they have completely discrete locations, I  
10 think that's very challenging.  
11 So I think that's more of maybe an  
12 inclusion/exclusion criteria. And I know that,  
13 like was said, the failed back surgery syndrome,  
14 people are the ones who are the sickest, so that's  
15 hard. But I don't think that's an estimand issue.  
16 The only thing I would say is if someone drops out  
17 for an AE that's not related to the treatment,  
18 that's related to something else, you might treat  
19 them differently in your imputation than you would  
20 for just like they got pancreatitis and they're not  
21 in the study anymore. That's not an AE related to  
22 the treatment. That would be more of a -- I would

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1 treat that person as a missing at random situation.  
 2 So whatever their pain experience, hopefully  
 3 they can distinguish in the leg or wherever you're  
 4 hoping the spinal cord stimulator is treating them,  
 5 at the time of their dropout, you impute their data  
 6 using the other people in that group, and you look  
 7 at their trajectory, and you don't consider that an  
 8 AE.  
 9 DR. KATZ: Let me change the subject. I  
 10 need to take a vote, so get your arm ready to vote.  
 11 There is an hour and a half lunch break right now,  
 12 and the schedule says that we're supposed to finish  
 13 at 4:00. It's Friday afternoon, and I'm not sure  
 14 if it takes people 90 minutes to eat. But I'm  
 15 going to take a vote, and I'm going to ask you to  
 16 raise your hand if you want to shorten the lunch  
 17 break to an hour instead of an hour and a half, and  
 18 then stop at 3:30.  
 19 (Hands raised.)  
 20 DR. KATZ: Well, I guess I don't really have  
 21 to take the answer for the other --  
 22 (Laughter.)

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1 DR. KATZ: -- so we'll break for lunch now,  
 2 and if people could return here at 1:00, we'll aim  
 3 to finish at 3:30.  
 4 (Whereupon, at 12:02 p.m., a lunch recess  
 5 was taken.)  
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1 AFTERNOON SESSION  
 2 (1:05 p.m.)  
 3 Group Discussion  
 4 DR. KATZ: Okay, everyone; homestretch. So  
 5 now is the time of the meeting where we start to  
 6 actually think about producing something out of  
 7 this discussion. So as all of you know, the intent  
 8 and the normal way that an IMMPACT meeting works is  
 9 that there's a summary paper that comes out  
 10 afterwards, in this particular case, that will  
 11 summarize the discussions that we've had over the  
 12 last 24 hours or so.  
 13 Jen was suggesting a separate paper on  
 14 reporting of clinical trials and spinal cord  
 15 stimulation. As you guys know, there are lots of  
 16 papers on how to report different kinds of trials.  
 17 And then, Ewan, your review what seem to logically  
 18 be, if we can get a third, a paper that would come  
 19 out of this meeting.  
 20 So that seems to be the current discussion.  
 21 Why don't we maybe begin by talking about that,  
 22 what the output could be, and then we'll move on

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1 from there to content.  
 2 Yes, Dennis?  
 3 DR. TURK: The way that IMMPACT meetings run  
 4 is that although Nate's going to draft the first  
 5 version of this manuscript, it will be circulated  
 6 to all of you and probably several times with the  
 7 comments. You should all realize, and we realize,  
 8 that you're going to think of things tonight, oh, I  
 9 wish I had said or I forgot to mention. So you'll  
 10 have a chance to see this. So you don't have to  
 11 assume that everything is in stone at the end of  
 12 today, but basically it's enough to give Nate a  
 13 first shot at this.  
 14 All of you will be invited to be authors,  
 15 and, obviously, it's your decision if you do want  
 16 to or don't want to be an author. And that  
 17 includes the industry people. Everybody's invited.  
 18 If for some reason you don't want to, that's fine,  
 19 as well. If you choose not to or your company  
 20 doesn't want you to, we will ask can we acknowledge  
 21 that you were at the meeting, just for that  
 22 reality.

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1 But just don't think that in the next two  
2 and a half hours, whatever it's going to be, that  
3 everything is going to be resolved; it's the final  
4 version; you're not going to see this again. And  
5 let me add to that a plea for Nate, which he hasn't  
6 made yet, which is when he drafts this up and  
7 circulates it, if you look at the number of people,  
8 if everybody sits on it for two or three months,  
9 this will take interminable to do. So the idea,  
10 typically, is to try to give you some reasonable  
11 time frame, like two weeks, or a month, or whatever  
12 Nate chooses to want to do.

13 Even if you want to say it looks good, fine  
14 with me, at least acknowledge that because the  
15 worst thing is we don't know. We send you an email  
16 with a draft, and we don't hear, and there's got to  
17 be multiple reminders and requests. So please try  
18 to be responsive either to just simply say you like  
19 it or you have some important points, or whatever  
20 you want to do, but don't just let it sit there in  
21 your 800th email, and poor Nate has to keep  
22 annoying you and nudging you.

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1 This will happen all the way from drafts to  
2 the submissions because a number of the journals  
3 require all the authors to acknowledge and give  
4 approval. Some IMMPACT papers takes forever just  
5 to get people to be willing to go to the website  
6 and do the two clicks that you have to do to say  
7 that, yes, you're an author and you agree to serve  
8 on this. So please be responsive.

9 DR. KATZ: Thank you, Dennis.

10 DR. NORTH: What is the rough timetable for  
11 first draft and ultimately submission?

12 DR. KATZ: I'm not sure. I think what I'll  
13 do is after this meeting is over and I can gather  
14 my wits and see what else is going on, I'll send an  
15 email out to everyone and let them know what the  
16 rough timelines are. I'd like to get everyone a  
17 draft within a month. That may feel ambitious, but  
18 give me a few days to get back to you on that.

19 DR. McNICOL: Can you just clarify what you  
20 think the two or the three papers will be? I think  
21 it will be between our paper and what Jennifer  
22 suggests, or would those be two distinct papers?

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1 DR. KATZ: Well, that's what I want to talk  
2 about now, actually. So it's open for discussion.  
3 It seems to me like the content of this meeting  
4 would be one paper, which would be something like  
5 research considerations in clinical trials, spinal  
6 cord stimulation for chronic pain, something like  
7 that, which is a very kind of typical IMMPACT style  
8 paper.

9 We could play a little bit with the language  
10 of that. Bob and I were having a little bit of a  
11 sidebar earlier; do we want it to be research  
12 considerations; do we want it to be research  
13 recommendations? But let's just put that in the  
14 world of detail for the moment.

15 Then, Ewan, it seems to me like your  
16 systematic review stands on its own two feet as a  
17 review of methodology in this area. And in some  
18 sense, as it did yesterday, would serve as a  
19 foundation for what we're doing here. That seems  
20 to be a coherent second paper. And I'm seeing a  
21 lot of heads go up and down with respect to that.

22 Then Jen and I just had a quick sidebar

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1 during lunch, which is by no means a formal  
2 discussion, about whether it would also make sense  
3 to do a separate paper on reporting  
4 recommendations. And I guess that would be based  
5 on your paper as well. You find the deficits, and  
6 then she leads the paper on reporting  
7 recommendations. But that's just something for  
8 discussion.

9 Do you think it's better to combine them or  
10 what do you two think?

11 DR. McNICOL: Jen's giving me a look that  
12 suggests no.

13 DR. GEWANDTER: No, no, no.  
14 (Laughter.)

15 DR. GEWANDTER: I was taking a look back  
16 [inaudible -off mic], and I was leading it.

17 DR. KATZ: Yes, that was skillfully done. I  
18 give myself credit for that.

19 (Laughter.)

20 DR. GEWANDTER: I think it would be easiest  
21 because you guys are done [inaudible - off mic].

22 DR. KATZ: Can you speak into your mic, Jen,

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1 please?

2 DR. GEWANDTER: Sorry. My name is Jen

3 Gewandter.

4 I think it just depends on how long it gets.

5 I think if you go back to Sam's talk, like all of

6 those different details that he talked about, I

7 don't know that they would necessarily naturally

8 come up in systematic review of results.

9 DR. TAYLOR: It wouldn't.

10 DR. GEWANDTER: So it might --

11 DR. McNICOL: I would certainly encourage

12 the separation.

13 Ewan McNicol, Tufts. If we're going to do

14 two separate papers or three separate papers, would

15 it make sense to submit all three papers to the

16 same journal, so there's a sort of continuum on

17 here, or do they not fit well together? Is one

18 journal going to be more about -- is one going to

19 be for neuromodulation, for example, and is one

20 more like what Jennifer's done in the past, where

21 she's done this sort of systematic review and I

22 think made some recommendations based on that

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1 review as well?

2 DR. GEWANDTER: Yeah. I usually do the

3 systematic review and make some very brief

4 recommendations in one paper. We did this with the

5 CIPN. I wrote a systematic review with a few

6 recommendations, and then we did the follow-up

7 paper on the design recommendations. They happen

8 to go to the same journal, but we didn't put them

9 in at the same time. It was just that the same

10 journal wanted them.

11 So it wasn't like they wanted a full

12 picture, if you will, altogether. I think your

13 manuscript would stand on its own. I think just

14 some of the more nuanced intricacies of all the

15 things that are important to report might not have

16 even been things that you looked for in your

17 systematic review. I don't remember what your

18 manual was like.

19 DR. McNICOL: We definitely missed some

20 stuff.

21 DR. GEWANDTER: I think, at least I've

22 found, it's kind of hard to comment on things you

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1 didn't actually look for in your systematic review.

2 So what I would advise is you write yours first and

3 just write whatever fits well and whatever you

4 think is good. And then if we still think after

5 that, that a more expanded thing is necessary, we

6 could do that. That's what I recommend.

7 DR. McNICOL: That's good. I have a

8 question since we're getting into the specifics of

9 publication here. During my talk, I mentioned that

10 we didn't incorporate extension studies and we

11 didn't incorporate angina studies. Do people have

12 a feeling for if we should incorporate them and how

13 we should incorporate them?

14 DR. KATZ: Anyone have any thoughts about

15 incorporation of angina studies?

16 What was the other thing, Ewan? I couldn't

17 quite hear you.

18 DR. McNICOL: Sorry. Extension studies.

19 DR. KATZ: Extension studies and angina

20 studies. Anyone have any feeling about whether

21 Ewan should incorporate that in his review? Sam?

22 DR. EL DABE: I think angina studies, it

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1 would be easy for you to incorporate those. There

2 are a number, I think 6 or 7 of them. I don't see

3 a reason why they should be treated differently.

4 DR. McNICOL: This may be a question more

5 for Jennifer.

6 Do you think we can use the same coding

7 manual for angina studies as we do for -- Rod,

8 you're nodding.

9 DR. TAYLOR: You can because dare I say,

10 we've had the pleasure of systematically reviewing

11 that literature. So there is a citation to Eldabe.

12 I think Sam was the first author or I was the first

13 author, doing the review you've done on angina.

14 But it's quite a date, so I think you bring

15 everything all together, including angina, would be

16 sensible. To leave angina out would seem a bit

17 perverse because actually, as we'll find, some of

18 the qualities of the trials and actually the

19 quality of the results is probably better than we

20 have in some of the rest of the literature. And

21 there are some lessons that we might learn from

22 that and that we would benefit from. At worse, I

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1 can understand you haven't included them, Ewan,  
2 [inaudible - mic fades].  
3 DR. McNICOL: We're happy to do that with  
4 the caveat that that's some extra work that we need  
5 to do that may add a few weeks on to the submission  
6 process. But I think if you feel it completes the  
7 process, we'd be happy to do it.  
8 Rod, a follow-up to that, do you think we  
9 should be out in the extension studies, then?  
10 DR. TAYLOR: I wasn't quite sure what you  
11 meant by extension studies. What do you mean by  
12 that?  
13 DR. McNICOL: Maybe that's not the correct  
14 term. I can't remember what --  
15 DR. ELDABE: I may be able to help you. I  
16 think you're talking about publications of a longer  
17 follow-up.  
18 DR. McNICOL: Exactly.  
19 DR. ELDABE: Yeah. So studies are published  
20 12 months, then they come back and publish it 24  
21 months.  
22 DR. McNICOL: Exactly.

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1 DR. GEWANDTER: In the past.  
2 MALE VOICE: Sorry. Can you please state  
3 your name?  
4 DR. GEWANDTER: Sorry. Jen Gewandter.  
5 In the past, I've only done the primary  
6 analysis, so that's how I handled that. And I  
7 don't know if maybe for this specific indication,  
8 it might be more interesting to keep them. But we  
9 were interested in things like did they identify  
10 the primary and how was it designed in the first  
11 place. So therefore, I don't know that putting  
12 another publication of the same trial would add a  
13 lot to it, and it might overly weight that trial in  
14 terms of the overall results.  
15 DR. McNICOL: Ewan McNicol, Tufts. I think  
16 Bob's suggestion fairly early on in this process  
17 was that we mentioned the extension studies as,  
18 hey, this is out here, but we don't actually make  
19 it part of the review or the systematic part of the  
20 review in of itself. Would that make sense?  
21 DR. KATZ: Nate Katz. The only question I  
22 would have about that, and this is just a question,

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1 is to what extent -- if somebody does a short-term  
2 randomized-controlled trial, and then does  
3 multi-year open-label extension, they may relegate  
4 their more detailed methods for evaluating safety,  
5 and they may push that into the open-label  
6 extension.  
7 So I don't know enough about this literature  
8 to know whether that happens here. But if part of  
9 your findings is going to be how well safety was  
10 reported. Then I wonder whether you'd need some of  
11 those open-label extension to see where the safety  
12 methods actually were implemented.  
13 That's just a question. Maybe some of you  
14 know whether that's an issue or not.  
15 DR. ELDABE: Sam Eldabe. I think most of  
16 the studies that Ewan is alluding to are following  
17 the same protocol, but for 24 months instead of 12  
18 months or so. It's not an open-label extension as  
19 you would find in drug trials. But you are  
20 absolutely spot-on in that there are some aspects  
21 of the study that are reported in 24 months  
22 extension that are not reported in the 12 months.

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1 And sometimes the safety is mainly reported in  
2 24 months.  
3 DR. KATZ: I guess what I would suggest,  
4 Ewan -- and this is just a suggestion -- is to  
5 maybe take a look at a couple of those studies and  
6 see if they do indeed seem to have safety  
7 methodology in what you're not calling the  
8 extension studies. And if there is really more  
9 meat on the bone in terms of how safety was  
10 assessed in these extension studies, that it may be  
11 worth pulling them in simply to be able to comment  
12 on strengths and weaknesses about how safety is  
13 reported.  
14 DR. McNICOL: I think Sam has quoted it  
15 correctly. I think there are there safety data  
16 quoted in these studies that aren't really looked  
17 at or maybe are not even valid for shorter term,  
18 3 months or 6 months.  
19 DR. NORTH: Rick North. Just as a practical  
20 matter -- you already spoke to this in another  
21 way -- I think it's important that you cite all  
22 these studies, include them in your bibliography,

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1 so that readers don't think you're unaware of them.  
2 DR. McNICOL: That's good. I was saying to  
3 Jane yesterday that in manuscripts, often it's  
4 stuck in an appendix somewhere that is really  
5 difficult for someone to access. When we do a  
6 Cochrane review, we list everything because  
7 Cochrane reviews are 200 pages long. So I want to  
8 balance practicality with completeness.  
9 DR. KATZ: Yes. Ewan, since we're on the  
10 topic of your paper, is there any other feedback  
11 you think would be helpful from this group today in  
12 terms of proceeding with that project?  
13 DR. McNICOL: I think those were my  
14 main -- and as you say, this isn't finalizing  
15 things. This is just giving us something to work  
16 with that we can send to you guys, and then we'll  
17 comment from there. But I just didn't want there  
18 to be some fundamental aspect of it, that we submit  
19 something to you and you're like, you should've  
20 thought about this. You're going to have to go  
21 back and start over. But I think everything else  
22 is details that we can iron out once we submit our

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1 first draft to you.  
2 DR. KATZ: In terms of who is involved with  
3 that paper, I don't know if Bob, Dennis, Ewan, if  
4 you had any -- were you thinking that everybody in  
5 this room would be an author?  
6 DR. DWORKIN: The commitment was already  
7 made. It was the steering committee for this  
8 meeting. So I think it's basically the speakers of  
9 this meeting. We had an email trail going back a  
10 year and a half, so that's been resolved.  
11 DR. KATZ: That will make it much easier.  
12 But I think, Ewan, if you feel like you need  
13 specific input from somebody in this room who's not  
14 on that list, I'm sure they'd be happy to  
15 correspond with you.  
16 DR. McNICOL: Yes. Sam's already offered.  
17 Thanks.  
18 DR. KATZ: And you can throw them any  
19 acknowledgements or whatever.  
20 DR. THOMSON: Simon Thomson here. Can I  
21 just say two things? One is this SSED, do you  
22 include that in a systematic review? Is it allowed

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1 to be included in there?  
2 DR. McNICOL: Just to clarify, the SSED is  
3 the safety and efficacy paper.  
4 MALE VOICE: Is this a British thing as  
5 opposed to an American thing?  
6 DR. THOMSON: It's American. It's an FDA  
7 thing.  
8 MS. LEITNER: It's a requirement  
9 [inaudible - off mic]. Sorry.  
10 DR. KATZ: And say your name.  
11 MS. LEITNER: Angela Leitner. SSED is a FDA  
12 requirement. When you submit a PMA, they go  
13 through it and say what you can and cannot say, and  
14 it's a basis for your claims that you can make for  
15 your product. So it usually provides a lot more  
16 complete information based on how you prespecified  
17 you would analyze your data. And you can look up  
18 the example of the Nevro one and see how complete  
19 it is, and make sure it is included.  
20 DR. McNICOL: Jennifer, have you done that  
21 for yours?  
22 DR. GEWANDTER: No, I have not. I think

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1 your review was of how these trials were reported  
2 in the peer-reviewed literature. I totally get  
3 your point that you get like all this extra  
4 interesting information from the SSEDs, but that  
5 was not necessarily the objective of what you were  
6 trying to do.  
7 So I think it would be a very interesting  
8 but different review of the literature. I think  
9 that would be interesting to kind of shed light on  
10 some of these issues that we're talking about in  
11 terms of the weaknesses of these studies, and  
12 actually maybe contrasting them to what was  
13 actually reported in the papers would be super  
14 interesting. But it's just I think a little bit  
15 outside of the scope of what Ewan was asked to do.  
16 DR. KATZ: Rod, did you have comment on  
17 that?  
18 DR. TAYLOR: I would just entirely agree  
19 with Jennifer. The equivalent in Europe is called  
20 an EPAR, European public assessment report. But  
21 again, in Cochrane reviews, we normally don't look  
22 at those. We use the published evidence.

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1 There is an interesting second review  
2 question, which is what is the disparity between  
3 EPARs and the American equivalent and the published  
4 paper? But I would encourage others to follow that  
5 up as a separate publication.  
6 DR. McNICOL: I will say that for the  
7 studies we looked at, if they were registered and  
8 there was information that we couldn't find in the  
9 preliminary or the published paper, we would look  
10 on clinicaltrials.gov, or whatever it was, for that  
11 extra information. So we did go into a little bit  
12 more depth, but I wonder if that's the limit of the  
13 depth that we should go into.  
14 DR. KATZ: Yes, I would say so.  
15 All great. So that's project number one, is  
16 the systematic review. I want to just take a step  
17 back out of this rabbit hole a little bit and just  
18 talk about the overall framework of what we're  
19 trying to accomplish. So I think we've settled  
20 that.  
21 Bob, I saw your hand up earlier when we were  
22 talking about just the overall set of papers we

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1 were thinking about publishing. Did you have  
2 something to say about that?  
3 DR. DWORKIN: Bob Dworkin. I think the  
4 primary paper from this meeting, having to do with  
5 recommendations, checklists for the design of  
6 randomized clinical trials of SCS, to me is also  
7 recommendations for reporting because we're going  
8 to have a bunch of recommendations about the best  
9 gold standard practices for these trials. And  
10 implicit in that is if you don't follow what we're  
11 suggesting, you really should kind of provide the  
12 rationale for not attending to our recommendations  
13 in your publication.  
14 So I see the possibility of a final table in  
15 this primary paper maybe being reporting  
16 recommendations, but I don't clearly see -- and  
17 maybe we should just defer it until the end of our  
18 discussion. I don't clearly see a third  
19 publication on reporting because it seems implicit  
20 in our design recommendations.  
21 DR. KATZ: Jen? Can you use your mic?  
22 DR. GEWANDTER: That's fair.

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1 DR. KATZ: Fair. That was Jen who said  
2 fair.  
3 So you are in agreement with folding that  
4 into this publication?  
5 DR. GEWANDTER: I think putting a final  
6 table that explicitly outlines what you'd want to  
7 see is a good idea, and just see how long it is.  
8 DR. KATZ: All right. I'm comfortable with  
9 that plan of trying to fold it all into one. If it  
10 turns out that that part of the paper becomes so  
11 bulky that it needs to give birth to a separate  
12 paper, we can make that decision as we go.  
13 Great.  
14 DR. THOMSON: Simon Thomson here. I put it  
15 in a symposia suggestion to the INS in Sydney,  
16 which is late May 2019, to really sort of -- I had  
17 a 2-hour symposium suggestion with various people  
18 about how we got to this place. And then Robert  
19 Dworkin would then present the findings of our  
20 group.  
21 They cherry-picked, and they've taken you  
22 for something, and they've taken Rod for something

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1 else, and they've invited me to present the  
2 findings of our group in a half-hour plenary. And  
3 I'm asking you is that okay and can you help me?  
4 DR. KATZ: Yes and yes. I think it's great,  
5 and certainly I'll be happy to help. Does anyone  
6 else have any other feelings about that symposium?  
7 DR. THOMSON: I was thinking I could do a  
8 double act with somebody. I think the trouble is  
9 they want to fund two speakers to fill one slot.  
10 But if you're already covered, that would be okay.  
11 I could reply back and say, yes, I accept, but we  
12 want to do a double act.  
13 DR. KATZ: We can talk more about that  
14 offline, but certainly in principle, I'll be happy  
15 to help with that process in whatever way makes  
16 sense.  
17 DR. TAYLOR: Nate, just on the publication  
18 specifically, in the spirit of transparency, again,  
19 because I've twisted their arm -- so I'm Rod  
20 Taylor, by the way, if you hadn't already guessed.  
21 Thanks. Sorry, folks.  
22 We will be taking the cost effectiveness

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1 review to publication as well, we being really  
2 myself, Sam's graciously signed up and so has  
3 Brian. But in the spirit of openness again, we  
4 will be writing that up for publication. If  
5 anybody in this room has a burning desire to be  
6 part of that, they'd be more than welcome to email  
7 me if you're comfortable with that, and we would  
8 add them into the authorship, obviously, with the  
9 normal expectations of what authorship would be  
10 here.

11 If I can just throw that out there, so  
12 people have got my email and want to follow up  
13 outside the meeting. But I would see this as being  
14 another paper that's kind of resulted from this  
15 get-together, if that's okay.

16 DR. KATZ: Thank you, Rod, for that. So if  
17 anybody's interested in being a co-author on the  
18 cost effectiveness publication, then shoot Rod an  
19 email.

20 All right. I think then that actually brings  
21 us to the topic at hand, which is what's going to  
22 go in this paper, research considerations,

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1 recommendations for RCTs of spinal cord stimulation  
2 for chronic pain.

3 Yes, Rick? Say your name.

4 DR. NORTH: Well, this is a subtopic.

5 DR. KATZ: That's Rick North.

6 DR. NORTH: We had a lot of discussions  
7 about specifics of study designs that might be  
8 adopted, and I wonder whether this group would be  
9 anything but complemented if the companies that are  
10 here, perhaps in conjunction with subgroups like  
11 IoN, were to pick up some of those ideas and run  
12 with them and get a trial going.

13 Were that to happen, what would be the  
14 proper way to acknowledge the genesis of the ideas?  
15 Waiting for the publication to come out so we could  
16 cite is not the American way.

17 (Laughter.)

18 MALE VOICE: Shoot first, yeah.

19 DR. KATZ: Go ahead, Bob.

20 DR. DWORKIN: Bob Dworkin. Typically  
21 within, I don't know, 6 to 8 weeks of the meeting,  
22 we on the IMMPACT website have all the slide

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1 presentations, the agenda, the list of  
2 participants, and then a full transcript,  
3 high-quality transcript of the meeting. So one  
4 possibility would be to cite that website that has  
5 essentially all of the meeting. And in fact, what  
6 I'm saying right now will be in the transcript.

7 (Laughter.)

8 DR. KATZ: Rick, does that meet that meet  
9 your needs?

10 DR. NORTH: Yes, good answer.

11 DR. KATZ: Great. So back to the content of  
12 this paper. As you heard from Bob, the current  
13 thinking is to summarize the presentations.  
14 Obviously, there are some redundancies, so  
15 reshuffle that into an order that makes sense and  
16 is cohesive. It's not going to be this talk was  
17 about this and that talk was about that. It's  
18 going to be obviously organized topically so that  
19 it flows in a way that makes sense.

20 Then presumably, the heart of that paper  
21 will be some sort of checklist of -- let's just  
22 call them recommendations for these sorts of

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1 clinical trials. So you can imagine in your mind's  
2 eye a table that has sections in it, and the  
3 sections have little check boxes in them, or things  
4 like that.

5 So let's put that all in on our mind's eye  
6 right now and open it up for discussion. What do  
7 people think should be in that checklist?

8 Now, we've been talking about this for 36  
9 hours now, so I think we all have a general sense  
10 of what those things are, but now in the last hour  
11 and a half or so is an opportunity for people to  
12 raise their hand and say, well, in case it wasn't  
13 clear, I really think this thing should be in the  
14 checklist, or in case it wasn't clear, I think this  
15 thing should not be in the checklist.

16 So I'll open up the floor for those sorts of  
17 comments. Rick?

18 DR. NORTH: Rick North, again. WikiStim,  
19 which Jane and I organized, already has in place a  
20 candidate checklist, if you will. And the SCS  
21 subsection of the site has a list of close to 200  
22 variables that potentially can be filled out for



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1 any research paper in the field. So I'd just offer  
2 that as a starting point.  
3 DR. KATZ: Great. Are those recommendations  
4 for research methods or are they checklists for  
5 what should be reported in a paper? What are they?  
6 Jane?  
7 MS. SHIPLEY: Jane Shipley. They're all of  
8 the above.  
9 And actually, I'm in the process of redoing this  
10 and elaborating, trying to keep the number of major  
11 checklists at 200, but offering but offering  
12 answers that can be easily copied and pasted into a  
13 sheet.  
14 For instance, on the analytical methods, for  
15 example, I'll list all the methods out and somebody  
16 can grab them. But right now, even in this format  
17 that I'm hoping to improve, it still should be  
18 useful as a starting point for you. There are  
19 200 -- and you can download the whole data category  
20 list. It's a CSV.  
21 If you search a paper that's not been  
22 completed -- that would be the best thing to

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1 do -- a completed one will have things filled out,  
2 but search one that's not completed and just hit  
3 CSV, and you'll get the citation, but you'll also  
4 get all the data categories.  
5 DR. NORTH: Or download the entry form,  
6 which has examples as well as definitions.  
7 MS. SHIPLEY: Yeah, yeah. There's a  
8 submission for it.  
9 DR. NORTH: Rather than characterize this as  
10 a potential guideline, it's more a database of what  
11 people have reported to date.  
12 DR. KATZ: I see. Okay, great. Thanks for  
13 that.  
14 MS. SHIPLEY: There's a lot that needs to be  
15 added, and I've been informed by this meeting. And  
16 I also was thinking about how to acknowledge that,  
17 and I was happy to hear about the URL because that  
18 will work for me, too.  
19 DR. KATZ: Okay. Wonderful. Thanks for  
20 that. I'll find you if I need you.  
21 Okay, great. Yes, Sam?  
22 DR. ELDADE: I appreciate we've had an

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1 excellent talk on outcome measures, but you guys  
2 have done quite detailed work on outcome measures.  
3 I'm not sure that there is anything specific about  
4 SCS that requires us to redo that.  
5 DR. KATZ: Well, we can make that a  
6 question. We can certainly refer to existing  
7 published guidelines on outcome measures for  
8 clinical trials of treatments for chronic pain and  
9 use that as a starting point. Dr. Dongen mentioned  
10 to me yesterday another website, a European  
11 website, that has its own consensus recommendations  
12 for outcome measures and various disorders,  
13 including chronic pain syndromes. I'd be surprised  
14 if there were any huge discrepancies, but that will  
15 be another place to go to and cite as a source.  
16 Yesterday, we began to have a discussion of,  
17 well, what else besides those are "peculiar" to use  
18 Rod's word, to spinal cord stimulation that we  
19 should think about including? And some did come up  
20 yesterday.  
21 DR. NORTH: I can give you a major example  
22 that been emphasized at all at this meeting. But

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1 for many, many years, the technical goal of spinal  
2 cord stimulation was to elicit parasthesia that  
3 overlapped a patient's area of pain, completely,  
4 with perhaps some extraneous areas of stimulation  
5 as well.  
6 There is a lot of literature dealing with  
7 that. You might call that a surrogate outcome  
8 measure, and it does certainly correlate with pain  
9 relief. It was felt to be, and still is to a large  
10 extent, a necessary condition for pain relief by  
11 conventional stimulation, to scratch where it  
12 itches, as it were.  
13 DR. KATZ: So are you saying that the extent  
14 to which the degree -- for that type of  
15 stimulation, the extent to which the parasthesias  
16 overlap the area of pain should be an outcome  
17 measure, should be reported?  
18 DR. NORTH: Over many years, it has been  
19 routinely reported as one of the outcome measures.  
20 DR. KATZ: Great. Any others?  
21 DR. THOMSON: Simon Thomson. We talk a lot  
22 about neuropathic pain. The systematic review is

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1 including ischemic pain syndromes. There are other  
2 outcomes other than pain measures in ischemic. And  
3 indeed with -- well, I'm going to call it angina.  
4 Actually, a pain score is almost a useless measure  
5 as an outcome. So we need to ask ourselves are we  
6 going to be advising in that, and the same with  
7 critical limb ischemia.  
8 DR. KATZ: That's a great question. Should  
9 we include consideration of chronic and angina or  
10 limb ischemia in this paper?  
11 DR. NORTH: Well, you certainly should  
12 mention them. This is Rick again. Are you going  
13 to get into them in detail? Because there are  
14 other applications ongoing and potential for SCS,  
15 and I think it would require a lot of effort to get  
16 into them all, and even then, to cover them  
17 adequately would be practically impossible.  
18 DR. KATZ: This is a chronic pain paper --  
19 DR. NORTH: Pain, the title.  
20 DR. KATZ: -- so your recommendation would  
21 be to indicate in the paper somewhere that this  
22 technology is used for angina and limb ischemia,

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1 but that the review will not focus on those areas.  
2 DR. NORTH: Each of those might have its own  
3 special outcome measures.  
4 DR. KATZ: I agree with that. Does  
5 everybody else agree with that? I'm seeing the  
6 heads go up and down.  
7 Ewan?  
8 DR. McNICOL: I just wanted to comment on  
9 that. When we were talking about the reporting  
10 paper, we agreed that it was important to include  
11 angina studies. But now we're saying for this we  
12 shouldn't include it. Do you not think we should  
13 be more consistent across the two publications?  
14 It's either important or it's not.  
15 DR. NORTH: It did include ischemia, if I  
16 remember correctly.  
17 DR. KATZ: Rod, I think you had advocated  
18 for including the angina, the vascular syndromes.  
19 What's your opinion on Ewan's question? Is it  
20 worth it? Should we pitch it to be consistent or  
21 keep it for completeness?  
22 DR. TAYLOR: Rod Taylor. If you're asking

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1 me, I think for comprehensiveness, I would suggest  
2 that we include the ischemic indications in the  
3 systematic review. But to keep this paper light  
4 touch, I think it's basically a statement,  
5 consideration of outcomes, and need to consider the  
6 specific indication, some of which will have their  
7 own core outcomes.  
8 I think part of this document is sign  
9 posting, isn't it, Nate? So it would be sign  
10 posting people to maybe whether those guidelines in  
11 those specific therapy areas already exists,  
12 assuming that they do. And there are certainly an  
13 area of angina that there's many recommendations of  
14 outcome measures. So we can just point people  
15 there, but we don't need to spend a lot of time in  
16 that space. I think that's what you're suggesting,  
17 Rick.  
18 DR. NORTH: I think you're making the point  
19 that many of the angina and limb ischemia papers  
20 were of pretty good quality. And to the extent  
21 they allow us to paint a better picture of the  
22 quality of this literature, it would make a lot of

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1 sense to include them as pain papers.  
2 DR. KATZ: In the systematic review, but not  
3 to deal with it specifically in the paper on  
4 research considerations.  
5 DR. NORTH: Right.  
6 DR. KATZ: So there will be a little bit of  
7 inconsistency, Ewan, but it sounds like there's a  
8 rationale for that inconsistency.  
9 Are you comfortable with that?  
10 DR. McNICOL: As long as we discussed it and  
11 there was a rationale for not being consistent,  
12 then I'm okay with it.  
13 DR. THOMSON: Simon Thomson. The counter,  
14 really, is the Europeans, we have quite a lot of  
15 experience with ischemic pain syndromes, and some  
16 of us -- I was involved in the early EPAR study on  
17 CCLI, and Sam and I on an incomplete feasibility  
18 study in angina, and Rod has done a systematic  
19 review, which has included those cases. I think we  
20 do between us have knowledge about these sort of  
21 outcome measures with a thought we could provide  
22 recommendations.

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1 DR. KATZ: Turo?  
 2 (Dr. North speaks instead.)  
 3 DR. NORTH: But they are peripheral, aren't  
 4 they, to the central theme here, which is research  
 5 design consideration design considerations, pain  
 6 trials. When the draft comes around, if somebody  
 7 wants to add a paragraph that says, by the way, in  
 8 limb ischemia, other outcomes salvage.  
 9 DR. KATZ: Yes, Turo and then Dennis.  
 10 DR. NURMIKKO: Turo Nurmikko, UK. You did  
 11 mention in the morning, and I think everybody  
 12 agrees, that as far as chronic pain is concerned,  
 13 pain measurement has to be the primary outcome  
 14 somehow. But at the same time, there all sorts of  
 15 issues related to that, and a paper of this kind  
 16 can be emphatic enough to actually start changing  
 17 minds.  
 18 It just occurred to me, to suggest that the  
 19 paper would indeed discuss this goes a little  
 20 beyond what the IMMPACT paper was saying and  
 21 underlining the importance, especially when you  
 22 deal with invasive treatment, the importance of

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1 such issues as quality of life and functionality,  
 2 et cetera, even perhaps going as far as suggesting  
 3 that in certain circumstances, you could consider  
 4 either one of them to be a co-primary outcome.  
 5 DR. KATZ: Yes. Dennis?  
 6 DR. TURK: In the first two IMMPACT papers,  
 7 the first one was looking at outcome domains and  
 8 the second was on specific measures. In the  
 9 domains, we were saying across the board in chronic  
 10 pain -- this was for chronic pain trials -- these  
 11 are the domains that should cover pain: physical  
 12 function, emotional function, et cetera.  
 13 In the second paper where we talked about  
 14 specific measures, we said there are many measures  
 15 that have been developed specifically for a  
 16 particular disease entity. When you want to be  
 17 looking at, for example, physical function, you  
 18 should be considering using those  
 19 well-established -- because if you have low back  
 20 pain versus upper neck and cervical pain, it may be  
 21 a very different physical function measure. When  
 22 they do not exist as any disease-specific measure,

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1 then we recommend some generic  
 2 So I think we got away from having to  
 3 discuss every one of the possibilities by either  
 4 referring by reference -- I think we did. We gave  
 5 a few examples of references. For back pain,  
 6 specifically we could use -- not the OMERACT, the  
 7 WOMAC, but we gave some examples.  
 8 The idea was that physical function is  
 9 important to consider. If in fact there are well  
 10 established measures for angina, if there are such  
 11 measures out there, then you would use those. If  
 12 in fact there were none, then you would default to  
 13 one of the more generic measures like the SF36 or  
 14 the BPI, or something else of that kind.  
 15 So I think you can get around  
 16 having -- because or else, my fear is -- at least  
 17 it was our fear that there are so many specific  
 18 disorders that have their already well established  
 19 measures, that for us to try to cover all of them  
 20 would make no sense.  
 21 DR. KATZ: Yeah. That feels like a big  
 22 project to me. And then do we have to talk about

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1 pancreatitis and interstitial cystitis, and chronic  
 2 testicular pain, and all sorts of other syndromes.  
 3 So I think I'm going to err on the side of, as you  
 4 said, follow the example of those papers and keep  
 5 it generic, and mention that there are specific  
 6 other syndromes which have their own measures and  
 7 their own considerations. And if that feels  
 8 inadequate to Simon or anybody else, then we can  
 9 always revisit that down the road.  
 10 Yes?  
 11 MS. LEITNER: Angela Leitner. One thing I  
 12 think is important is to address a nonbeliever like  
 13 Dr. Fields and open up the black box of SCS, and  
 14 what can we do to elevate the therapy?  
 15 (Laughter.)  
 16 MS. LEITNER: Is it FMRI, laser evoked  
 17 potentials?  
 18 Who's laughing? Anyway, I think what's the  
 19 best thinking on that and what can we recommend  
 20 controlled trials run for objective measures that  
 21 we can look at.  
 22 DR. KATZ: Do you mean objective measures of

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1 pain?

2 MS. LEITNER: Right. What's the next best

3 thing. What are other ways we can [inaudible - mic

4 fades] that information.

5 DR. KATZ: To be honest, the short answer is

6 that there aren't any that are useful in clinical

7 trials. Multi-day meetings just on this issue, and

8 every day, an email crosses my desk with yet

9 another paper/company/what have you. I don't know.

10 That feels like it would be a big job to try to put

11 that in this paper. I don't know.

12 Does anyone feel differently about it? Bob?

13 DR. DWORKIN: Bob Dworkin. It sounds to me

14 from this morning's discussion, there really was a

15 tacit consensus that when it's possible to do so,

16 that some kind of sensory phenotyping, sensory

17 profiling is done with a combination of

18 patient-reported symptom measures, and they exist

19 for neuropathic and non-neuropathic pain and

20 quantitative sensory testing.

21 So we could have a soft recommendation, that

22 in many circumstances, sensory phenotyping should

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1 be considered using a combination of

2 patient-reported outcomes and quantitative sensory

3 testing.

4 DR. KATZ: Howard, what do you think?

5 DR. FIELDS: Howard Fields, and I want to

6 stress that I'm not a nonbeliever, but I am a

7 practitioner of equipoise. That was so

8 articulately described earlier.

9 I think just a general push toward getting

10 more, what should I say, uniformity in a patient

11 group, prior to entry to the study. So you

12 wouldn't necessarily want to mix, let's say, angina

13 patients with diabetic neuropathy because that

14 introduces its own variability.

15 What I was pushing for was criteria for a

16 neuropathic component to the pain just on the off

17 chance that those patients might do better, so that

18 some sort of recommendation about grouping patients

19 or stratifying patients, if you will, selecting

20 patients, prior to the start of this study.

21 The other thing that I was pushing for was

22 we had a big discussion, and it turned out, I

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1 thought, fairly general agreement, that there was

2 this idea of reprogramming that was sort of not

3 unplanned and not scheduled, was a real hazard in

4 terms of the interpretation of the data. So if you

5 could have a way of doing the programming in

6 advance of study entry, that would be a major

7 advance in terms of the quality of the data that

8 you would get in your ability to interpret it.

9 DR. KATZ: We've got a few

10 different -- people have been advancing what I

11 think about as sections of this checklist. There

12 was a section on outcome measurement that we began

13 to discuss, and there's a section on patient

14 selection that we discussed in great detail earlier

15 today and that Howard has brought up now again for

16 further refinement, and one could imagine other

17 sections as well.

18 So maybe what I'll do is try to march

19 through these sections, or maybe I should just ask

20 explicitly, and start at that high level, and then

21 we can dig deeper in each one. So aside from a

22 section in our checklist on patient selection, a

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1 section on measurement of outcomes, we'll need to

2 have a section on this whole reprogramming issue,

3 which seems to have one foot in outcome

4 measurements, and one foot in patient selection,

5 and one foot in the trial. I'm not sure exactly

6 where to parse it out yet, but we don't have to

7 worry about that now.

8 What are the other high-level sections that

9 should be on this checklist? Something on study

10 objectives; I would imagine that's important.

11 Jane?

12 MS. SHIPLEY: [Inaudible - off

13 mic] -- biological complications, device

14 complication -- Jane Shipley; sorry -- stimulation

15 side effects; cost effectiveness; implantation;

16 description of the implantation procedure;

17 description of the screening trial; description of

18 stimulation parameters in mode and everything else

19 that's available now; pain location; pain

20 characteristics; demographic factors and study

21 population.

22 DR. KATZ: Something tells me if I look on

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1 your checklist, I'll find the answer to my  
2 question.  
3 MS. SHIPLEY: Yes. Thank you.  
4 DR. KATZ: You've got it.  
5 DR. TAYLOR: Rod Taylor. So going back to  
6 high level, I agree with Jane, many of these are  
7 what I would call reporting issues. But I think we  
8 had a cracking presentation from Sam today on  
9 considerations of how one might do placebo trials  
10 in this setting, and I think you gave us some  
11 recommendations based on the literature of how we  
12 might go about that. So I would definitely see  
13 that as being an important section.  
14 Then the other kind of peculiarity for me is  
15 how we bring in the learning curve issue. We  
16 didn't talk a lot about it, but basically for me,  
17 that's what might be an implanter and center  
18 selection issue. Again, we don't need to be  
19 definitive, but I think part of this document is  
20 just raising it as an issue and what the  
21 considerations might be for trialists to think  
22 about in this setting.

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1 Then the last one I've got, and I think it's  
2 peculiarity again, I don't know if it comes under  
3 programming, but it's what I would call in the  
4 complex intervention world of intervention  
5 fidelity; how do we know that the intervention was  
6 delivered as protocolized? And I genuinely don't  
7 really know the answer to that, but I think is  
8 tremendously important in this area. And part of  
9 that is the programming because the programming is  
10 all part of it. But I think there's more than just  
11 programming and fidelity.  
12 DR. KATZ: Right. Very good. Ro?  
13 MS. JAIN: Roshini Jain, Boston Scientific.  
14 This section on how to reduce bias perhaps,  
15 especially given these are all patient-reported  
16 outcomes, so reducing expectation bias; how do you  
17 frame these, say, programming paradigms; et cetera,  
18 et cetera.  
19 DR. KATZ: Thank you. I won't forget my own  
20 talk. I probably will, but thanks for the  
21 reminder.  
22 Greg?

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1 DR. FIORE: Greg Fiore. I just wanted to  
2 add onto that any measures taken to minimize  
3 likelihood of placebo response, so along the lines  
4 of sham response.  
5 DR. KATZ: Thanks. Sam?  
6 DR. ELDABE: Just to bring up Rod's point on  
7 intervention and fidelity, I think you have a  
8 number of components to this, and that's the  
9 surgery, and that's very well described in every  
10 publication, the programming and we've got a detail  
11 on how this is done. Then there is the  
12 instructions that are given to the patients as they  
13 leave the clinic, and finally the adherence to the  
14 therapy, and most devices will record when the  
15 device has been switched off inadvertently.  
16 DR. KATZ: Great. Any other high-level  
17 sections to this checklist?  
18 DR. THOMSON: Simon Thomson here. I think,  
19 Jen, the management of missing data because it's  
20 not just going to be pain scores missing; it will  
21 be all sorts of things, visits. Then I think the  
22 big thing is adverse event reporting and whether we

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1 can give advice as to what are classified as  
2 adverse events.  
3 DR. KATZ: Yes, Salim?  
4 DR. HAYEK: Salim Hayek. As long as we've  
5 had spinal cord stimulation, we've always felt  
6 that, well, it could be helpful in neuropathic more  
7 than nociceptive pain, but really, you can't find  
8 concrete evidence for either assumption. And the  
9 latest studies all say, well, for back pain or leg  
10 pain, which we know, at least for back pain, could  
11 be a component of nociceptive pain in addition to  
12 neuropathic pain.  
13 So I'm not sure if this is something that we  
14 should put in there, but perhaps for pain studies  
15 on spinal cord stimulation, we should make a  
16 recommendation that there may be some effort to try  
17 to identify the percent or the contribution of  
18 neuropathic pain to the overall pain of the  
19 patient.  
20 DR. KATZ: How would you do it?  
21 DR. HAYEK: There are neuropathic scales or  
22 validated questionnaires. For example, the one --

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1 MALE VOICE: DM4 [inaudible - off mic]?  
 2 DR. HAYEK: Yes, and then the one by Ralf  
 3 Baron.  
 4 MALE VOICE: Pain Detect.  
 5 DR. HAYEK: Pain Detect.  
 6 DR. KATZ: All right. And we have Howard's  
 7 suggestions from earlier. Actually, I had Andrea  
 8 in the back, and then I'll go to Robert.  
 9 DR. TRESKOT: Andrea Trescot. I'm not sure  
 10 I heard the functional outcomes evaluations,  
 11 Fitbits, iWatch, walking tolerance, the recognition  
 12 that we have to look at pain scores and we have to  
 13 look at global improved -- or global patient  
 14 perceived outcomes. We still have to look at  
 15 something that's objective. And if we're not going  
 16 to look at medicines per se, then we need to look  
 17 at something that is functional.  
 18 DR. KATZ: So just to respond to that, we  
 19 have to look at medicines.  
 20 DR. TRESKOT: And medicines as well, but  
 21 medicines, unfortunately, in this day and age, the  
 22 opioids are being taken down whether patients are

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1 hurting or not. They are being taken off their  
 2 opioids whether they're hurting or not. So to look  
 3 at the opioid level is not going to give you any  
 4 indication, today, of what their level of pain is.  
 5 DR. KATZ: They still need to be quantified  
 6 in any case, of course.  
 7 DR. TRESKOT: I agree.  
 8 DR. KATZ: Yes. I think we all agree that  
 9 there in this list of recommendations, we will  
 10 recommend that there needs to be, at minimum, a  
 11 patient-reported outcome measure related to  
 12 physical function; as Dennis just said, a generic  
 13 one if there's no disease-specific one available; a  
 14 disease-specific one if there is one available. I  
 15 think you're talking about performance-based  
 16 outcome measures where you actually have patients  
 17 do things, and you measure what it is that they do.  
 18 Maybe it's worth having a minute or two  
 19 discussion about that. What do people feel about  
 20 the role of performance-based outcome measures in  
 21 clinical trials with spinal cord stimulation?  
 22 DR. THOMSON: I thought we'd agreed

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1 that -- IMMPACT has done a lot on outcomes. We're  
 2 literally going to -- I mean, it's really, are  
 3 there any outcomes that are different because we're  
 4 treating people with spinal cord stimulation.  
 5 DR. KATZ: Are there?  
 6 DR. TRESKOT: Generalized activity. Sorry.  
 7 This is Andrea again. Generalized activity,  
 8 improvement in sleep, all of which can be measured  
 9 by an activity watch. So if they're getting up 4  
 10 and 5 times a night or they're sleeping through the  
 11 night; if they've increased their general level of  
 12 activity --  
 13 DR. THOMSON: But these are not particularly  
 14 new outcomes because of spinal cord stimulation.  
 15 DR. TRESKOT: Well, I would argue that they  
 16 would because you're now getting  
 17 people -- improvement in sleep is something we've  
 18 been able to show over and over again, is something  
 19 that the --  
 20 DR. THOMSON: Sorry, Andrea. These are  
 21 already outcomes that are measured in any pain  
 22 trial. They're recommended by the IMMPACT ACTTION

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1 group in any pain trial.  
 2 DR. TRESKOT: I see. I'm sorry.  
 3 DR. THOMSON: Do you see what I mean?  
 4 DR. TRESKOT: Okay.  
 5 DR. THOMSON: So it's like what are the  
 6 outcomes that are specific to our therapies, if  
 7 any, when treating pain?  
 8 DR. TRESKOT: Put them on their treadmill.  
 9 DR. NORTH: [Inaudible - off mic].  
 10 DR. KATZ: Can you speak in your mic,  
 11 please? Rick North.  
 12 DR. NORTH: Rick North. The watch than  
 13 Andrea refers to is a wonderful tool for measuring  
 14 an outcome, but it's common to stimulators and  
 15 other pain trials.  
 16 DR. THOMSON: It needs to be validated.  
 17 DR. NORTH: Yes, good point.  
 18 DR. KATZ: Yes, Robert?  
 19 DR. VAN DONGEN: Can I make one comment?  
 20 Robert van Dongen. Did we cover the psychosocial  
 21 aspects enough? I know it's common for the other  
 22 pain syndromes, but psychosocial existential

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1 problems can be a problem in these patients in  
2 treatment.  
3 DR. KATZ: Yes. Bob?  
4 DR. DWORKIN: I think Simon raises an  
5 important point, which is, shouldn't the bulk of  
6 this article be what is specific to spinal cord  
7 stimulation trials? We don't really need to talk  
8 about that it's important to capture adverse events  
9 using state-of-the-art methods, and that we need to  
10 report the patient's age and the patient's sex,  
11 et cetera.  
12 I think that so much of that already exists  
13 in the literature, that our contribution really can  
14 be to emphasize what's specific to these trials and  
15 not these generic questions. I mean, of course we  
16 want to get anxiety and depression as outcomes,  
17 maybe as moderators of treatment response, but  
18 that's true in every chronic pain trial, and we can  
19 cite all of that literature. But it's what doesn't  
20 exist in the literature or best practice  
21 recommendations for these clinical trials.  
22 DR. NORTH: Bob, I agree with you. Rick

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1 North again.  
2 This narrows things right down to a couple of SCS  
3 specific technology examples. There's an implant  
4 with accelerometers that can be used to measure  
5 activity. And one of the manufacturers is now  
6 using the aforementioned watch as part of the  
7 programming system. So SCS gives us opportunities  
8 to measure outcome that are specific to the  
9 modality.  
10 DR. KATZ: Yes, Eric?  
11 DR. BUCHSER: Eric Buchser. I think we  
12 should be very careful with the physical activity  
13 because the data that's out there does not actually  
14 support the fact that the level of physical  
15 activity is correlated with the intensity of pain.  
16 If you look at fibromyalgia, for instance, where  
17 it's been done extensively, it's how physical  
18 activity is distributed over the day that is  
19 different, but the total amount of walking distance  
20 and in those studies that have looked at the speed,  
21 the stride lines, and all that, actually do not  
22 correlate with the physical activity on the whole.

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1 So what's implanted in the stimulators, the  
2 way I see that is more of -- it's a marketing tool.  
3 You have this fantastic thing that shows you how  
4 much or less the patient's worked, how much they  
5 were sitting or lying, and I don't think there's  
6 any scientific support to that, so I would be very  
7 careful.  
8 DR. KATZ: Ewan?  
9 DR. McNICOL: Ewan McNicol, Tufts. I agree  
10 with Bob that if we just list off a bunch of  
11 outcomes that we need to look at, we're really just  
12 repeating the IMMPACT recommendations from the very  
13 first paper. I think we should focus more on what  
14 is peculiar to spinal cord stimulation and what of  
15 the recommendations that were made in that 2001  
16 paper are conversely what are not relevant to  
17 spinal cord stimulation. What things do we need to  
18 measure for drug trials that we don't need to  
19 measure for spinal cord stimulation?  
20 That could be nothing, but I'm just trying  
21 to think is there something that's not relevant to  
22 this literature.

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1 DR. THOMSON: Simon Thomson here. I think  
2 this is the right way to be thinking. So device  
3 usage, for example, it might be recharging  
4 intervals. It might be -- what else can we think  
5 of? Help me. Oh, device longevity, time to  
6 explant, because explant isn't always with  
7 non-rechargeables; it's a normal thing. You would  
8 expect to take it out and put a new one in.  
9 DR. KATZ: It seems to me that we're being  
10 somewhat idealistic about how faithful people who  
11 report trials and spinal cord stimulators are  
12 15-year old guidelines for what the basics are of  
13 reporting. It seems to be like --  
14 MALE VOICE: Maybe I can quote them and say  
15 refer to -- [inaudible - off mic].  
16 DR. KATZ: It seems to me a little refresher  
17 could come in handy for this research community, so  
18 I'm tempted to suggest that we -- how much real  
19 estate in a paper does it take to mention the  
20 6 core outcome domains? That's 6 words if I'm  
21 counting correctly. That's going to be okay. So I  
22 think we can very briefly highlight where there are

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1 standards, but then focus the majority of  
2 attention -- I think we can have our cake and eat  
3 it too a little bit in that way, and then focus the  
4 bulk of it on what's actually particular to spinal  
5 cord stimulation. I think I'll give that a shot  
6 and see how it comes out.  
7 Yes, Roshini?  
8 MS. JAIN: Roshini Jain, Boston Scientific.  
9 What about loss of therapy over time?  
10 DR. KATZ: Loss of efficacy over time?  
11 MS. JAIN: Correct, yes.  
12 MS. LEITNER: Angela Leitner. I think that  
13 we really need to then define loss of effect as a  
14 group for SCS because many people define it  
15 differently, so it'd be good to have a  
16 recommendation coming out of here.  
17 DR. KATZ: And this, of course is -- any  
18 treatment for chronic pain, the same issue, drug  
19 treatment, opioids, and loss of efficacy of  
20 opioids, as everyone knows, that's an enormous  
21 issue. As far as I know, there are no standard  
22 definitions for loss of efficacy of any type of

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1 chronic pain treatment, of any kind that I've ever  
2 seen.  
3 Anyone know different? It's kind of rules  
4 of thumb. Data's presented in every imaginable  
5 way. I think we could certainly talk about the  
6 importance of attempting to define it. For a  
7 one-week study, it may not matter, but for a  
8 one-year or two-year study, researchers should  
9 figure out some way of measuring that.  
10 Do we know enough now to be prescriptive  
11 about how that should be done?  
12 DR. NORTH: Rick North again. From the long  
13 perspective, going back to the '70s, some of our  
14 papers have reported like 20-year maximum  
15 follow-up. We have referred to a minimalist  
16 outcome measure, which is just patients still using  
17 stimulator as some reflection that it still is  
18 helpful.  
19 DR. FIELDS: Howard Fields. I want to pick  
20 up on what Rick just said. How many of the devices  
21 out there can subject turn on and off when they  
22 want to? Do we have that data?

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1 MALE VOICE: All of them.  
2 DR. FIELDS: All of them?  
3 DR. KATZ: All of them, I think.  
4 DR. FIELDS: So then the question becomes,  
5 in general, what's your impression about how  
6 patients actually use the stimulators? Do they use  
7 them all the time? Do they turn them off at night?  
8 If it turns out that they use them intermittently,  
9 you could ask them what is it that the stimulator  
10 is most helpful for, how often do you use it, and  
11 how effective is it for that?  
12 I don't know that you'd get a standard  
13 outcome measure, but you could begin to get a  
14 better idea of how the subjects actually use it  
15 now, and that way it's a lot like an analgesic  
16 drug, where somebody takes an ibuprofen when they  
17 have a headache and they don't take. And it could  
18 be very effective, but maybe they don't have a  
19 headache for 6 months. That would enter into their  
20 overall assessment of how helpful it is.  
21 So it might be interesting if there were  
22 some data on intermittent use and how helpful that

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1 was when they used it.  
2 DR. KATZ: That's interesting.  
3 DR. LOESER: John Loeser. Howard, you have  
4 to recognize that people are warned, "You don't  
5 want to use this too much because you'll run the  
6 battery down." So you end up then with a very  
7 complex pattern of how much the patient uses it  
8 versus how much their fear is the battery's going  
9 to decrease. It's not just their pain level, in  
10 other words, that determines how long they use it,  
11 how intensely they use it, and so forth. It's a  
12 very complex issue.  
13 DR. KATZ: Yes. I have to capture that.  
14 DR. THOMSON: Simon Thomson. Obviously, the  
15 battery issue was an issue in the past. Most of us  
16 use rechargeable devices. It's just become a  
17 non-issue. They toggle now between these different  
18 subperception and parasthesia-based programs  
19 nowadays.  
20 Howard, all of the above is how they use  
21 them. There will be some who will have it on all  
22 the time on subperception mode, and if they go out



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1 for a walk, they might put it on to parasthesia.  
 2 So it is fascinating how people use them, and then,  
 3 yes, there are people who basically their  
 4 background pain syndrome improves over time, then  
 5 they get stressed, or they do a lot of exercise,  
 6 and then they turn it on. So all of the above.  
 7 DR. FIELDS: Howard Fields. That's  
 8 absolutely fascinating, in a way, but it's not like  
 9 there's a Twitter post. There's not like there's a  
 10 way where somebody like me could look it over and  
 11 get a fuller picture.  
 12 Just like John Markman's videos, that would  
 13 never come out in any outcome measure, yet you hear  
 14 this person say it, and you're like, "Oh, my god.  
 15 This is phenomenal." All I'm asking is are we  
 16 losing something by giving general measures over  
 17 time when you've got something that used  
 18 intermittently and you'd like to know when it's  
 19 actually being used, how effective it is.  
 20 DR. KATZ: I'd like to follow up on that  
 21 point, and then get back to Angela's point about  
 22 measuring loss of therapeutic benefit because I

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1 think there's more to say about that.  
 2 Something that I've been doing a lot in the  
 3 last couple of years is convincing sponsors to bolt  
 4 a qualitative research component on the back of a  
 5 randomized-controlled trial. So you do your  
 6 randomized-controlled trial, everyone's filling out  
 7 forms, and obviously what the patients fill out is  
 8 limited by your imagination about what forms to  
 9 give them. But then at their termination visit,  
 10 have a semi-structured interview, where we ask the  
 11 patients questions like, "How was that treatment  
 12 for you?" and with a crossover study, "Why did you  
 13 like treatment A better than treatment B?" or "What  
 14 did you think about the way we designed this  
 15 clinical trial, and could we design this trial in a  
 16 way that might be more meaningful you?"  
 17 People say all sorts of interesting things  
 18 when you've give them an opportunity to talk and  
 19 you capture it. So it's qualitative data, but  
 20 qualitative data is the underpinning of most of  
 21 what we do. So I wonder if while we're all here,  
 22 do people think that there could be any value? I

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1 don't know that we could recommend it as a must-do  
 2 for every trial, but do people think there's any  
 3 value in bringing that research method to light in  
 4 the context of this paper?  
 5 DR. THOMSON: Simon Thomson here. Yes, I  
 6 think one of the failings of this meeting is we  
 7 haven't involved the patient voice. I think, one,  
 8 it should be in our recommendations that any trial  
 9 should involve some kind of patient-voice  
 10 consultation, anyway. And then Sam's group, which  
 11 I'm involved with, just had a qualitative study of  
 12 a bunch of randomized patients having qualitative  
 13 interviews. And I think it very much enriches what  
 14 we do. So as you say, not for every study maybe,  
 15 but I think it should be one of the  
 16 recommendations, yeah, I think.  
 17 DR. KATZ: Okay Thanks. Any other further  
 18 thoughts on that qualitative research angle before  
 19 we get back to Angela's point? Roshini?  
 20 MS. JAIN: Roshini, Boston Scientific. I  
 21 fully agree with the both of you, but just being on  
 22 the other side of also doing the analysis,

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1 sometimes when you keep a lot of open fields, we  
 2 get stories and stories, and then we're not able to  
 3 glean out. So I think yes and no questions were  
 4 fantastic, like would you want to do this again?  
 5 Would you recommend it to a friend? But when we  
 6 start going down the why, we do get lots of lengthy  
 7 stories that we find it hard to discern.  
 8 DR. KATZ: I'll be happy to help you with  
 9 that.  
 10 MS. JAIN: Yes, thank you.  
 11 DR. KATZ: There are all sorts of  
 12 qualitative research methods that can be used to  
 13 digest it, and then at least bring to light what  
 14 the major themes are. And that's not the whole  
 15 transcript, but it's the major themes.  
 16 Bob?  
 17 DR. DWORKIN: This goes back to Angela's  
 18 question. Bob Dworkin. Nat, I don't remember, but  
 19 I bet you do, how was time to loss of therapeutic  
 20 response defined in the randomized withdrawal  
 21 trials that had that kind of time-to-event  
 22 endpoint? Because that's in the literature, both

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1 for pregabalin and opioids.  
2 DR. KATZ: For those studies, it's been done  
3 in different ways, but the most common way  
4 is -- just to boil down to one thing would be time  
5 to 30 percent worsening. In pain intensity, there  
6 are composite approaches, too, so you could treat  
7 it as a time to event where if you lose 30 -- you  
8 get randomized when you have very little pain  
9 because you've responded to treatment, so maybe  
10 your pain score's a 3 or something like that.  
11 So if your pain score goes up by 30 percent,  
12 or you drop out due to lack of efficacy, or you  
13 take the forbidden rescue medication or something  
14 like that; so you can imagine composite approaches  
15 to that. That's been done also, which brings us  
16 back to Angela's point. I wonder whether there is  
17 actually more that we can say to people along those  
18 lines about loss of therapeutic efficacy.  
19 So obviously, if you drop out of the study  
20 because of lack of efficacy, well that's a  
21 no-brainer. If your stimulator is explanted  
22 because of lack of efficacy, which I guess is more

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1 or less the same thing, that's a no-brainer.  
2 In terms of peculiarities of the spinal cord  
3 stimulation world, if the patient is not using  
4 their stimulator anymore and the reason is lack of  
5 efficacy, I guess that would be another spinal cord  
6 stimulator specific type of loss of efficacy.  
7 Is there anything else that comes to mind  
8 that's specific to this area? Turo? Turo  
9 Nurmikko --  
10 DR. NURMIKKO: Turo Nurmikko, yeah.  
11 DR. KATZ: -- from the UK.  
12 DR. NURMIKKO: I'm not sure if this is still  
13 valid, but I used to have patients who complained  
14 of suspicion of the SCS losing its effect, and I  
15 put them on an SCS holiday for a couple of weeks.  
16 So you could actually measure that and see if  
17 indeed there's an impact or at least that could be  
18 one of those measures where you try and define loss  
19 of effect.  
20 DR. KATZ: Discontinuation. Great.  
21 Anything else on the issue of loss of efficacy?  
22 Sam?

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1 DR. ELDABE: Not particularly on the loss of  
2 efficacy, but on Dr. Fields; point, I think he  
3 makes a very good question about dosage. And the  
4 reality is that rather depends, as Dr. Loeser says,  
5 on what instructions you give the patient before  
6 they leave your clinic. However, all of this can  
7 be measured because all devices will give you a  
8 printout of when it was switched on and when it was  
9 switched off. This is not reported anywhere.  
10 DR. KATZ: What would be the best way to  
11 present that as an outcome measure?  
12 DR. ELDABE: Good point.  
13 DR. TAYLOR: It's effectively a process  
14 outcome here, isn't it? I would see it -- again,  
15 it's sort of going back to the fidelity of the  
16 intervention, really, isn't it? So I'd see it as  
17 just being a subheading within that.  
18 DR. KATZ: And what number would you report?  
19 DR. ELDABE: I think you can report the  
20 percentage of hours used. So if the person has had  
21 the device implanted 100 hours, they've used it 90  
22 hours, you can say 90 percent usage. Again, it

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1 ties into what instructions you give them because  
2 you might turn around and say, well, I want you to  
3 use this 20 percent of the time.  
4 DR. NORTH: Rick North. The implanted pulse  
5 generators routinely will display through the  
6 program total therapy hours, and that will tell you  
7 what percentage of the time, since the last  
8 interrogation, the device has been up and running.  
9 DR. KATZ: So it's essentially a percentage  
10 of your 24-hour day that you are using the  
11 stimulator.  
12 DR. NORTH: Yes. To Howard's point, back in  
13 '77, in that big, long report, I did an APL. There  
14 were several parameters like that, that we looked  
15 at, pertinent to designing a device. What controls  
16 did the patient need to have? How often would they  
17 be making adjustments? So there is literature out  
18 there, but it's not much reported.  
19 DR. THOMSON: Simon Thomson. Some of this  
20 business about the eye in the sky, as it were, or  
21 the spy in the can, some of the companies are much  
22 more sophisticated than others in that regard, so

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1 there are some that not only give you times of  
 2 usage, now they'll be imputing pain scores and  
 3 looking at the different modes of stimulation and  
 4 what the patients put in as their own pain score.  
 5 So this is very much one of those things. I think  
 6 there might be a minimal dataset that we should be  
 7 talking about maybe as an outcome, but reference  
 8 the fact that this is going to get more and more  
 9 sophisticated.

10 DR. NORTH: Simon, as you pointed out on a  
 11 sidebar moments ago, these things need to be  
 12 validated, too.

13 DR. KATZ: Great. Let's maybe channel the  
 14 conversation on a different issue that I think,  
 15 Simon, you and others have brought up already.  
 16 There are rechargeable and fully implanted spinal  
 17 cord stimulators. Does that have any impact on our  
 18 research design recommendations in any way, which  
 19 type of system is being utilized?

20 DR. THOMSON: Simon Thomson. I think the  
 21 duration of a randomized study is never going to go  
 22 more than two years. So in other words, I don't

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1 think it makes much difference, except for the fact  
 2 that there is the recharging burden. And that  
 3 can't be trivialized because for some it's a daily  
 4 thing. That can be a cause of giving up on the  
 5 treatment for some people. I suppose I'm saying,  
 6 yes, it does make a difference, but not because of  
 7 device longevity.

8 DR. KATZ: And what are we measuring there  
 9 exactly in terms of this recharging burden?

10 DR. THOMSON: Well, I think I said earlier,  
 11 it's like a recharging interval. What else would  
 12 you say?

13 DR. EL DABE: Sam Eldabe. You measure the  
 14 duration of time it takes a person to recharge the  
 15 device, and the recharge interval means the number  
 16 of days between one recharge and another, and the  
 17 strength of the coupling sometimes is displayed.

18 DR. NORTH: Rick North again. One of the  
 19 companies has introduced an externally powered  
 20 passive device, like the radio frequency devices  
 21 that I grew up with and used in preference to  
 22 primary cell devices for many years. And that

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1 changes the nature of trials, potentially, in a big  
 2 way. It in principle eliminates the need for  
 3 battery replacement because they're no  
 4 [indiscernible] components.

5 DR. KATZ: Is there anything else that we  
 6 would want to alert people doing studies using that  
 7 device, that they ought to be considering when they  
 8 design and carry out such studies?

9 DR. NORTH: Well, the main one that comes to  
 10 mind is that it lacks a pulse generator and can be  
 11 put in and tunneled as a trial device. But because  
 12 nothing emerges through the skin, when the patient  
 13 comes back and says, "Doctor, this is working just  
 14 fine; can't I keep it?" the answer is finally yes.

15 DR. HAYEK: The one downfall of this therapy  
 16 is that the patient has to wear an external  
 17 transmitter at all times when the patient desires  
 18 the therapy, which may be not convenient if the  
 19 patient is swimming or sleeping in bed. Sometimes  
 20 there are certain limitations to that therapy.

21 DR. THOMSON: Simon Thomson here. I think  
 22 there is this kind of patient satisfaction with the

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1 powering of the system measure because that would  
 2 be one, having to wear an external cloak in order  
 3 to provide energy to your implanted lead, and then  
 4 the difficulties some patients can get in with  
 5 centering their recharger over the implantable  
 6 device. So yeah, there needs to be some kind of  
 7 satisfaction measure with just the recharging  
 8 component.

9 DR. KATZ: Sorry, Angela, just one second.  
 10 Has anybody ever developed any patient satisfaction  
 11 instruments that are specific to spinal cord  
 12 stimulation?

13 (No response.)

14 DR. KATZ: No. Okay. Andrea?

15 DR. TRES COT: Andrea Trescot, Stimwave.  
 16 There are a couple of issues. One is that we have  
 17 been able to show a very prolonged effect from  
 18 short-term stimulation, so patients can wear this  
 19 for an hour or two, and they get long-term relief.

20 The second is that when they're doing the  
 21 recharging, some of the systems are requiring 2 and  
 22 3 hours of recharging sitting in a chair or

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1 connected to a wall socket, where with this  
 2 external device, they're wearing it in their  
 3 clothes; as long as they have their clothes on,  
 4 they're getting stimulation.  
 5 So yes, having also grown up with the old  
 6 ANS RF receivers, there are some issues, but if you  
 7 compare -- I think what will be interesting is  
 8 comparing the rechargeable IPG, not the  
 9 non-rechargeable. The non-rechargeable is a whole  
 10 different issue. And actually in Alaska, I put in  
 11 a lot of non-rechargeables because I have patients  
 12 who live in dry cabins. They don't have running  
 13 water. They don't have electricity. They want to  
 14 go off moose hunting for two weeks. So for those  
 15 patients, it's most important for them not to have  
 16 to be hooked up daily to a charging station.  
 17 DR. LOESER: There's a new outcome measure.  
 18 (Laughter.)  
 19 MALE VOICE: Moose hunting.  
 20 (Crosstalk.)  
 21 DR. TRESKOT: Are you able to moose hunt?  
 22 So yes, there is a mindset that has to change, but

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1 I would argue that most of us don't pay attention  
 2 to the time our patient has to be spending  
 3 recharging their systems. We've sort of ignored  
 4 that because it's not something that we're seeing.  
 5 But I think being able to develop some sort of  
 6 patient satisfaction would be huge because when  
 7 you're comparing a rechargeable system where you  
 8 have to physically sit in the chair for that period  
 9 of time, or you have to physically stay hooked up  
 10 to the wall unit for a period of time, it is  
 11 something that we don't really tell the patients  
 12 would be going on.  
 13 DR. KATZ: It's interesting that no one's  
 14 tried to turn that into a measure. With  
 15 medications, there's this measure, for example,  
 16 called the TSQM, the Treatment Satisfaction  
 17 Questionnaire for Medications, and it's like a  
 18 14-item questionnaire that gets at how convenient  
 19 it is to take your medication, and how much it  
 20 hurts when you get injected, and how big the pills  
 21 are. It gets at these patient-centric issues that  
 22 patients care a lot about, but you're not going to

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1 capture your 6 IMMPACT core outcome domains.  
 2 Roshini?  
 3 MS. JAIN: Roshini, Boston Scientific. For  
 4 our studies, typically we've adapted the TSQM.  
 5 DR. KATZ: Oh, okay.  
 6 MS. JAIN: Of course, it's not validated  
 7 because we've now modified it specifically for  
 8 devices, but we have an adapted version of TSQM  
 9 that we use as you're describing.  
 10 DR. KATZ: Have you thought about cleaning  
 11 it up and putting it out in the literature?  
 12 MS. JAIN: Roshini, Boston Scientific. I  
 13 have not, but we'll do so.  
 14 DR. KATZ: Maybe that will be an organized  
 15 way of capturing the patient's perception of these  
 16 issues that seem to be -- if I were hunting moose,  
 17 I wouldn't want to have to plug myself into a  
 18 tree --  
 19 (Laughter.)  
 20 DR. KATZ: -- and wait for a day or  
 21 whatever.  
 22 Great. So that gets at patient

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1 satisfaction. That gets up at rechargeable versus  
 2 non-rechargeable issue. Let's now rise back up to  
 3 the 50,000-foot level.  
 4 Are there any other sections -- can anyone  
 5 think of a section of this recommendations  
 6 checklist that's been left out?  
 7 DR. THOMSON: Simon Thomson, and I'm not  
 8 sure whether this is -- but patient-related outcome  
 9 measures, I'm not sure whether we've covered that  
 10 well enough, and I'm not quite sure whether the  
 11 IMMPACT thing covers it quite well enough, you  
 12 know, expectations met.  
 13 DR. KATZ: So do you mean measurement of  
 14 outcome?  
 15 DR. THOMSON: Yeah. So I'm back on outcome,  
 16 and I know this isn't what you wanted. But I just  
 17 feel we haven't completed that yet.  
 18 DR. KATZ: So I think where my thoughts are  
 19 about that right now is that we have the IMMPACT  
 20 core outcome domains for clinical trials. Then  
 21 there was a subsequent impact publication that  
 22 recommended some measures of those domains. I

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1 think we can just highlight the fact that those  
 2 exist. I don't think we need to relist all those  
 3 measures here.  
 4 Then we have some spinal cord stimulator  
 5 specific patient-reported outcome measures that I  
 6 think I have a little inventory of that I've been  
 7 taking notes on all along the way. And I think  
 8 that's where it sits right now.  
 9 Dennis?  
 10 DR. TURK: There is an IMMPACT paper that  
 11 reviewed all the physical function measures, both  
 12 from patient satisfaction, to family member  
 13 responses, to physical activity. Ann Taylor was  
 14 the first author; that it was about two or three  
 15 years ago. I can't remember which impact meeting  
 16 it was. So when you get to the physical function,  
 17 if you want to get a little more specific, then  
 18 just assess physical function.  
 19 We did review all of those, and importantly  
 20 we made a distinction between self-report measures  
 21 of physical function, performance measures of  
 22 physical function, and clinician or clinic-based

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1 physical function because we have subsequently  
 2 found that those don't correlate all that well. So  
 3 what patients tell you they can do, what they can  
 4 actually do and what they do in the clinic don't  
 5 necessarily tell us the same thing.  
 6 DR. KATZ: Dennis, who was the first author  
 7 of that again?  
 8 DR. TURK: Ann Taylor.  
 9 DR. DWORKIN: And there are also IMMPACT  
 10 articles on phenotyping. Rob Edwards is the first  
 11 author, and on biomarkers with Shannon Smith as the  
 12 first author.  
 13 DR. KATZ: Simon, was there anything else  
 14 that you think we've left out here?  
 15 DR. THOMSON: Are we at 50,000 feet?  
 16 DR. KATZ: Yes.  
 17 DR. THOMSON: All right.  
 18 DR. KATZ: Categories.  
 19 DR. THOMSON: Categories.  
 20 DR. TRESKOT: I'll take [inaudible - off  
 21 mic].  
 22 DR. KATZ: Can you speak into your mic,

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1 please?  
 2 DR. TRESKOT: Just a joke. And we'll take  
 3 history for 300.  
 4 (Laughter.)  
 5 DR. KATZ: Okay. So I'm not hearing anyone  
 6 thinking that there are some major chunks of this  
 7 research recommendations checklist that we've left  
 8 out, so we can dive down to 25,000 feet now. We've  
 9 got all the sections mapped out. Are there any  
 10 specific elements of this? I don't want to rehash  
 11 what we've been discussing over the last 36 hours.  
 12 Are there any specific -- and I will look at  
 13 your 200-item checklist. Are there any specific  
 14 recommendations for spinal cord stimulator trials  
 15 and chronic pain that have not been mentioned yet  
 16 that should be in this paper? Jane?  
 17 MS. SHIPLEY: Jane Shipley. This is a small  
 18 thing maybe, but I'm changing my system. I'm not  
 19 saying inclusion criteria and exclusion criteria  
 20 anymore; just patient selection criteria because  
 21 too often a study will say something in a positive  
 22 way, and then say the same thing in a negative way,

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1 and it's just plain stupid. So it should just  
 2 be -- that's a small thing.  
 3 DR. KATZ: That's a great point. I run into  
 4 that issue all the time. Excellent.  
 5 Yes, Eric?  
 6 DR. BUCHSER: Eric Buchser. Something  
 7 that's been diluted before, you can derive from the  
 8 parameter that you're using: frequency, voltage,  
 9 or intensity, and so on. And that would be the  
 10 charge per second because that could be something  
 11 that you could mention without people having to  
 12 work it out from the data they have. The charge  
 13 per second should actually be mentioned I think.  
 14 DR. KATZ: Charge per second  
 15 DR. BUCHSER: Charge per second.  
 16 DR. KATZ: Great. Anything else,  
 17 particularly if it's spinal cord stimulator  
 18 specific? Jane? Jane Shipley from Baltimore.  
 19 MS. SHIPLEY: Jane Shipley from Baltimore.  
 20 And I would say this should be for everybody. Now  
 21 my brain just died because you said "from  
 22 Baltimore."

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1 I think Sam brought this up. Too often,  
 2 people mix up methods and results. One of the  
 3 things I'm trying to do is say follow-up duration  
 4 planned, and then later on in methods, say  
 5 follow-up duration achieved.  
 6 MALE VOICE: That's result.  
 7 MS. SHIPLEY: I'm sorry, and result. So  
 8 method is follow-up duration plan and then  
 9 achieved. So I'm trying to push people to see that  
 10 there's an actual distinction, so they're not  
 11 putting results right in the methods. And there  
 12 are other places we can do that: programming  
 13 parameters planned, programming parameters  
 14 achieved. Papers are a mess right now, in general.  
 15 The literature's a mess.  
 16 DR. KATZ: Great. I want to revert back a  
 17 little bit to our recommendations on reporting of  
 18 safety. We did have a robust discussion of that,  
 19 really, throughout this meeting, but I want to see  
 20 if I can bring that down to what we think we're  
 21 actually going to recommend.  
 22 So capturing adverse events, we don't need

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1 to take up real estate in this paper about that.  
 2 It's a regulatory and universal requirement. Now,  
 3 whether there are any habitual gaps in how that's  
 4 reported in the spinal cord stimulator literature,  
 5 that might be worth attending to.  
 6 But what I really want to get at now is, is  
 7 there any template, for lack of a better word, any  
 8 specific list -- maybe the right way to ask this  
 9 question is, is there a list of adverse events of  
 10 special interest -- that's how I would think about  
 11 it in a drug trial -- where we can offer a  
 12 standardized set of terminology for adverse events  
 13 that occur, that are particular to spinal cord  
 14 stimulation, so people aren't using five different  
 15 words to mean the same thing or the same words to  
 16 mean different things?  
 17 Is this something that would be helpful? Is  
 18 there something like this out there? What do  
 19 people think about that? Salim?  
 20 DR. HAYEK: Salim Hayek, Cleveland. The  
 21 devil is in the details. You can make it as  
 22 extensive as you want. For example, lead

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1 migration, which is a very common occurrence,  
 2 especially with percutaneous leads, can be  
 3 clinically meaningful or clinically meaningless.  
 4 If a lead moves 2 or 3 millimeters, with current  
 5 stimulator devices, most of the time you're able to  
 6 recapture parasthesia if you're looking for  
 7 parasthesia, or pain relief if it's parasthesia  
 8 free, without the need for a revision.  
 9 So I think from a technical standpoint of  
 10 complications, the ones that are clinically  
 11 meaningful are the ones that result in revision or  
 12 loss of therapeutic efficacy. The biological  
 13 complications I think should be recorded as far as  
 14 infection. Again, if it's a deep infection, it  
 15 almost invariably results in an explant. Related  
 16 to that is adherence to previous guidelines that  
 17 that have been published, including the NAC  
 18 guidelines. Many of the people here were  
 19 co-authors on these.  
 20 So I guess you can be as extensive as  
 21 possible, but there are certain ones that we should  
 22 not miss in putting out a list, and I'll be happy

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1 to help with that.  
 2 DR. KATZ: Are there guidelines in the  
 3 literature now for how to report adverse events  
 4 specific to spinal cord stimulation?  
 5 MALE VOICE: No, not that I know of.  
 6 DR. KATZ: Would that be useful? And I'm  
 7 not talking about a 50-page guideline inside of a  
 8 5-page paper, but would it be useful even to  
 9 provide a little table that suggests a standardized  
 10 terminology for these particular sorts of adverse  
 11 events?  
 12 DR. NORTH: I would say there are  
 13 guidelines. Salim's paper, the Tim Deer intact  
 14 paper on complications, and Tracy Cameron's paper,  
 15 all use the same basic scheme: biological,  
 16 technical, et cetera, although not published as  
 17 guidelines. And WikiStim has a corresponding list.  
 18 DR. THOMSON: Simon Thomson here. There's  
 19 relatedness to the device, relatedness to the  
 20 procedure. Then there is the need for reoperation.  
 21 We struggle when we're doing studies because being  
 22 hospitalized in reoperation comes out as an SAE,

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1 whereas for us it's kind of a routine thing; okay,  
2 lead migrations. It's not a disaster but they need  
3 a reoperation. It's not really an SAE. So that  
4 would be helpful to the field. It needs to be  
5 recorded, but at least to take it down from being  
6 an SAE.  
7 Sam?  
8 DR. ELDADE: A couple of points. I think  
9 the SAE and AE classification is not ours to  
10 change. This is regulatory, and that remains where  
11 it is. It would be useful, as you say, to produce  
12 a list of stimulator-specific complications that we  
13 would like studies to report on specifically and in  
14 detail. The list is available in many  
15 publications. As Rick mentioned, there are a  
16 number of publications that are guidelines, but  
17 these guidelines are how to avoid complications.  
18 They're not guidelines on how to report them,  
19 because once you start issuing guidelines on how to  
20 report something, you have to define it. And none  
21 of these guidelines, to my mind, define what it is  
22 that we mean by lead migration.

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1 DR. KATZ: Rod?  
2 DR. TAYLOR: So just on this theme, and I  
3 guess as a generic comment, at the end of the day,  
4 you're in the chair, Nate. But I think one of the  
5 things we talked about over a beer last night was  
6 the CONSORT guidelines for reporting are quite  
7 useful because they often give you exemplars of  
8 good practice. They actually verbatim take bits of  
9 text out of papers and say this is how to do it.  
10 So I guess I might encourage that within the  
11 fight that it needs to be a manuscript that will  
12 fit in a journal. But I think illustrating, I find  
13 those as a trialist hugely helpful, not just saying  
14 do this, but here's an example of how you could do  
15 it well. And I think there are some examples of  
16 good practice here. So where they are there,  
17 again, I would just like to encourage we sign post,  
18 and obviously adverse events would be maybe one of  
19 those areas we've got some good practice.  
20 DR. NORTH: Rick North. The replacement of  
21 a primary cell implant is not generally reported as  
22 a complication. It's more like an expected end of

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1 battery life. But I think it deserves  
2 consideration, especially when there are externally  
3 powered alternatives, including rechargeables. So  
4 I wouldn't just sweep that under the rug and call  
5 it routine maintenance.  
6 DR. HAYEK: In some of the papers, it is  
7 reported as a complication, but you're right; it's  
8 something that is expected. However, if replacing  
9 the battery leads to an infection and an explant of  
10 the whole system, then it's also a potential  
11 complication because of that.  
12 DR. KATZ: Salim, how about if you help me  
13 come up with a table that lists a  
14 recommended -- preferably copies and paste, but  
15 these things always require some kind of clean-up.  
16 You think it's there and you can copy and paste it,  
17 and then you realize that there's something not  
18 quite applicable. So how about if you help me come  
19 up with that table?  
20 DR. HAYEK: Happy to do so and to share with  
21 everyone who has to edit it. But I'll circulate a  
22 draft.

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1 DR. KATZ: Oh, yes. Everyone will certainly  
2 have their thoughts about it, I'm sure.  
3 DR. SINGH: Rahul from MHRA, London. I  
4 think this is a problem throughout all research  
5 fields, whether it's oncology, orthopedics,  
6 whatever you want to say. Competent authorities  
7 actually have codes for adverse event reporting,  
8 which are usually adhered to when they're doing the  
9 clinical trials. But the issue is when a device is  
10 already CE marked and when clinicians do their own  
11 prospective, or even retrospective, studies that  
12 they want to publish, they don't adhere to these,  
13 or they don't know about these codes that are  
14 present.  
15 So if we did want to harmonize and have a  
16 common language, that would be good starting point.  
17 These codes are jargons to me, to be fair. They're  
18 numbers and letters and stuff, but if you follow  
19 the pathway of those codes, they do come down to a  
20 comment like dislocation. You can have a  
21 dislocation of a total hip replacement, or a  
22 dislocation or migration of a spinal cord

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1 stimulator, for example. So that's one way of  
2 looking at it as well I think.  
3 DR. KATZ: So I'll take that as an offer to  
4 look at whatever we come up with and provide  
5 comments.  
6 (Laughter.)  
7 DR. KATZ: Thank you for volunteering.  
8 DR. FIORE: It's Greg Fiore. I should  
9 probably also volunteer for that. I spent most of  
10 my career in pharmacovigilance and safety, and  
11 might as well put it to use.  
12 DR. KATZ: You're hired. Great.  
13 Great. Any other comments about this  
14 adverse event tracking? It sounds like we've  
15 agreed that it would be helpful to provide some  
16 kind of rubric. We've got a plan for working on  
17 it. Any other thoughts about that issue?  
18 DR. THOMSON: Simon Thomson here. There are  
19 going to be some things. I mean, we just touched  
20 on it talking about non-rechargeable; and is it  
21 after 5 years; is that an adverse event, that you  
22 have to change it? And there's an argument that it

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1 could be because you could have used a rechargeable  
2 system.  
3 But what if it didn't last 5 years, the  
4 premature exhaustion? Now that to me is an adverse  
5 event. But what is that? Is that 12 months? Is  
6 that 2 years? Probably 2 years I would have  
7 thought. Those sorts of things, we could usefully  
8 define.  
9 DR. KATZ: Yes, that seems really important  
10 to me because if you have to go to the operating  
11 room, that's part of the burden of therapy, whether  
12 it's expected or not. It reminds me almost of drug  
13 side effects, let's say opioid-induced  
14 constipation. Well, if you have to take a \$300 a  
15 month medication to reduce your constipation in  
16 half, but it's still a problem for you, yeah, it  
17 might be expected, but it's still a burden of  
18 therapy. So it seems like it ought to be tracked  
19 in some way.  
20 DR. HAYEK: Salim Hayek from Cleveland.  
21 Even among  
22 rechargeable devices, some of them are warranted

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1 for one year. Some of them commit suicide at  
2 9 years. Some of them go for 20 years. So should  
3 we say that the 9-year one is a complication  
4 compared to the one that goes for 20 years?  
5 There's a lot of gray zones in there.  
6 DR. KATZ: All right. Well, luckily we  
7 don't have to solve every problem, but if we can at  
8 least advance the agenda one step and provide a  
9 suggested template, then maybe that'll be helpful.  
10 Roshini?  
11 MS. JAIN: Roshini, Boston Scientific. Just  
12 two comments. Device complications, and especially  
13 those that result in an adverse event, just to be  
14 able to cull those out because each of them are  
15 different and significant. The second thing was,  
16 is there any thought on standardizing this with the  
17 MAUDE database that's out there? Just a thought.  
18 DR. KATZ: Yeah. That's a good question.  
19 Roshini, I think you're referring to the study we  
20 just did on the MAUDE. We just did a study on the  
21 MAUDE database, looking at spinal cord stimulator  
22 complications, and we spent a lot of time trying to

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1 make heads or tails out of what's in that database,  
2 which was not an easy task, and which left open a  
3 lot of questions.  
4 But maybe once Salim comes up with his  
5 suggested template, I can cross-check that with how  
6 the MAUDE database is, what the codes are, what the  
7 dropdown fields are the MAUDE database and make  
8 sure at least we try to pay attention to relating  
9 the two. Yeah, that's a great idea.  
10 MR. BOSLEY: Bernie Bosley from Nuvectra. I  
11 think this is also important to standardize this or  
12 at least communicate it more because the adverse  
13 events I see, some of them are defined in terms of  
14 harm; some are cause of harm. They're kind of  
15 mixed up a little bit. In Europe coming up, we're  
16 going to be asked to do active postmarket  
17 surveillance, and if the definitions in postmarket  
18 aren't the same as clinical, we're going to have  
19 trouble there, too.  
20 DR. KATZ: It's starting to feel to me like,  
21 although I don't want to -- it's starting to feel  
22 to me like this could be a separate project,



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1 figuring out what the classification system would  
2 be of adverse events in this area, and making sure  
3 that it makes sense on one side of the Atlantic,  
4 the other side of the Atlantic, and regulatory and  
5 clinical. That's not going to be part of this  
6 paper, but I don't know.  
7 Do others think that that would be a useful  
8 side project?  
9 DR. HAYEK: Salim Hayek. Should we assign  
10 numbers or points for severity of a complication,  
11 for example, if it's clinically meaningful or  
12 significant? Surgical revision, it gets higher  
13 points or is more serious than if it's a potential  
14 nuisance like pain over the generator -- or  
15 discomfort over the generator site; one that leads  
16 to surgery and one that doesn't lead to surgery.  
17 DR. KATZ: What we have now is you can be  
18 classified as an SAE. If it requires  
19 hospitalization, medical intervention to prevent  
20 serious harm, that's got its own list of regulatory  
21 definitions, so that obviously will need to be  
22 captured; it's a requirement. And then for adverse

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1 events that are not SAEs, we have regulatory  
2 definitions for what counts as mild, moderate, and  
3 severe, and every adverse events should be coded  
4 that way already.  
5 Do we need to go beyond that for this paper?  
6 DR. HAYEK: Is outpatient revision surgery  
7 of a generator a hospitalization? Would that be  
8 considered a hospitalization? Because the patient  
9 is not admitted in the hospital; that's an  
10 outpatient procedure.  
11 DR. FIORE: This is Greg Fiore. Nate, the  
12 way procedures are handled in the MedDRA coding  
13 schema that was referred to earlier is it's the  
14 diagnosis. The condition that led to the procedure  
15 is what is the adverse event, and the procedures  
16 can be captured separately. So if this group would  
17 want to recommend that investigators prespecify  
18 procedures that might be performed and list those  
19 not as adverse events but as procedures for  
20 treatment or for revision, that might be  
21 worthwhile.  
22 DR. KATZ: Greg, do you have a list of the

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1 MedDRA codes that are relevant to spinal cord  
2 stimulator complications? Actually, does MedDRA  
3 even apply here? Because it's supposed to be for  
4 drug adverse events. Isn't that what the D stands  
5 for?  
6 DR. FIORE: Dictionary for Drug  
7 Regulatory -- yeah.  
8 DR. KATZ: Drug, right?  
9 DR. FIORE: Yeah.  
10 MS. JAIN: Roshini, Boston Scientific. Yes,  
11 we use MedDRA coding.  
12 DR. KATZ: You do?  
13 MS. JAIN: Just because it's standardized as  
14 well.  
15 DR. KATZ: So you have a list of MedDRA  
16 codes that are applicable to this situation, so  
17 that once Salim comes up with his list, we can at  
18 least see where there's any relationship? Are  
19 there more than 10?  
20 MALE VOICE: [Inaudible - off mic].  
21 DR. KATZ: That's what I was afraid of.  
22 (Laughter.)

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1 DR. KATZ: All right. I'm willing to  
2 receive it. Let's put it that way.  
3 Greg?  
4 DR. FIORE: One more point on that if I can.  
5 Greg Fiore. What's very useful when analyzing  
6 safety information is that if somebody took the  
7 time up front to map the terms to categories that  
8 are useful for the indication. The dictionary  
9 has -- someone here probably knows -- hundreds of  
10 thousands of terms in it, and mapping up front.  
11 And then even letting investigators choose from a  
12 prespecified list is always helpful. Health  
13 authorities like it, and it allows us to really  
14 achieve meaning, because sometimes the terms are  
15 pretty esoteric.  
16 DR. KATZ: That's actually a really good  
17 point. With MedDRA, you could have the same event  
18 and see 6 different MedDRA preferred terms that  
19 it's coded to, which makes life very confusing for  
20 everybody. I don't know. I don't see us doing that  
21 mapping procedure in this paper; at least I don't  
22 see myself doing it, but let's see how far we get.

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1 All right. Any other comments on the issue  
 2 of safety for now?  
 3 (No response.)  
 4 DR. KATZ: All right. Well, are there any  
 5 topics, any recommendations that anybody feels  
 6 should be included in this list of recommendations  
 7 that have not been mentioned yesterday or today?  
 8 DR. SINGH: Rahul Singh, MHRA. We're  
 9 talking about -- I understand the scope of this  
 10 forum, but is there anyone innovating or trying to  
 11 amend, make changes to the spinal cord stimulators  
 12 to improve outcomes and reduce adverse events? Is  
 13 there anyone that you know of, apart from the  
 14 manufacturers -- obviously, they've got their own  
 15 R&D departments who are trying to excel in that  
 16 area, possibly.  
 17 Is there anyone in that area doing that that  
 18 you're aware of?  
 19 DR. KATZ: You mean in R&D not at a  
 20 manufacturer that's trying to improve upon the  
 21 technology?  
 22 DR. SINGH: Yes.

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1 DR. NORTH: Yes, anonymous.  
 2 DR. KATZ: Anonymous. Yes, anonymous.  
 3 Anyone else care to expand on that, on  
 4 Rahul's question? Any other units anybody knows  
 5 about that's working on this outside of  
 6 manufacturing?  
 7 DR. NORTH: Don't spill your IP.  
 8 DR. HAYEK: Salim Hayek, Cleveland. What  
 9 altitude are we at? You said any other questions,  
 10 any other comments. At what level? How granular  
 11 are we getting into? I mean, are we talking about  
 12 inclusion/exclusion criteria for studies?  
 13 DR. KATZ: I think we can be very granular  
 14 now, again, recognizing that we're not trying to  
 15 design every imaginable study now, but if anybody  
 16 feels that there is a general recommendation that  
 17 would apply across the board in spinal cord  
 18 stimulators studies for chronic pain, then now  
 19 would be the time to articulate it.  
 20 DR. THOMSON: Simon Thomson here. One of  
 21 the things that always vexes us is age.  
 22 DR. KATZ: Age.

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1 DR. THOMSON: We generally don't start doing  
 2 studies in children. Is that 16 or 18? And then  
 3 there's this top age, and we don't do -- it's  
 4 becoming politically incorrect to put a top age.  
 5 But obviously, the top age has comorbidities.  
 6 Is our recommendation that you have a top  
 7 age or do you just say stuff around cognitive  
 8 ability, and comorbidities that would make relevant  
 9 outcome measures difficult? These are the sorts of  
 10 things.  
 11 DR. KATZ: Of course that comes up in  
 12 virtually every clinical trial. Does anybody feel  
 13 like we should be advancing in this paper a  
 14 recommendation for a top age for spinal cord  
 15 stimulator studies?  
 16 (No audible response.)  
 17 DR. KATZ: I'm seeing heads shake in this  
 18 sideways direction, so it seems like people feel  
 19 like that should be up to the designer to struggle  
 20 with that.  
 21 DR. THOMSON: The other issues are around  
 22 pregnancy. IN other words, we wouldn't go out of

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1 our way -- we're not going to recruit pregnant  
 2 people, but what happens if they become pregnant  
 3 during the trial, and how do we manage that?  
 4 DR. KATZ: Is that a research design issue  
 5 or is that an issue of how to take care of patients  
 6 once they're in, if they're in clinical trials when  
 7 things happen to them?  
 8 Research design issue. Okay. Would anybody  
 9 be prepared to articulate a recommendation for how  
 10 to deal with pregnancy occurring during a clinical  
 11 trial in spinal cord stimulation? Should we be  
 12 doing that?  
 13 DR. THOMSON: Potential for pregnancy?  
 14 DR. NORTH: Rick North. I'd say not at this  
 15 level. I've been involved in cases where it's come  
 16 up, patients have gotten pregnant, during  
 17 pregnancy, and the pragmatic recommendation is,  
 18 well, what are the alternatives for managing your  
 19 pain, and has safety or efficacy been proven for  
 20 them. It hasn't been for the stimulator.  
 21 DR. KATZ: Yeah. Andrea, you had a comment  
 22 on that?

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1 DR. TRESKOT: Andrea Trescot. I was going  
 2 to recommend that the criteria be that if women are  
 3 of childbearing age or in the study, that there's a  
 4 survey being done asking them to avoid getting  
 5 pregnant for the period of the study because of the  
 6 unknown effects of stimulation on the baby, and the  
 7 potential that they would be dropped from the study  
 8 if they become pregnant because I think the  
 9 confounding issues of it can be a big problem.

10 Again, as my understanding, there is  
 11 currently no registry for women who become pregnant  
 12 during and have a spinal cord stimulator in place.  
 13 I don't know of that registry. We had it with  
 14 sumatriptan to monitor whether there was a problem.

15 DR. KATZ: Well, here's my sense of the room  
 16 right now. It feels like we're kind of done. You  
 17 sort of get the feeling after a while, all the big  
 18 issues have been covered, and to try to spend time  
 19 specifically to fill the time with more words, that  
 20 doesn't feel like it has a huge amount of value to  
 21 me.

22 So it's 2:45-ish, 2:48. So I feel that now

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1 is the time where you can spend a couple of  
 2 minutes, if anybody feels that we've missed  
 3 anything in terms of our big-picture plans, in  
 4 terms of the content of this paper -- obviously,  
 5 everybody's got plenty of time to look at revisions  
 6 of this paper and come up with all of the most  
 7 nuanced thoughts and recommendations that will come  
 8 up. It doesn't have to be today. There will be  
 9 plenty of shots on goal here.

10 Does anybody feel like we've missed anything  
 11 big in terms of the content of this paper?

12 DR. THOMSON: We've spent a lot of time over  
 13 the last 36 hours talking about blinding and single  
 14 blind and double blind. We're presumably going to  
 15 be making a recommendation position on that, aren't  
 16 we?

17 DR. KATZ: Yes.

18 DR. THOMSON: And all the things we've  
 19 talked about, we're going to be --

20 DR. KATZ: Yes. It seems like the wisdom  
 21 was to not make a strong recommendation that  
 22 there's only one way of dealing with that, but just

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1 to outline a number of different options, what  
 2 their pros and cons are, and then let the protocol  
 3 designer look at those and provide a rationale in  
 4 terms of why they chose one of those or chose not  
 5 to. And I feel like I've detailed enough notes to  
 6 at least write a draft and get people's feedback on  
 7 it.

8 Anything else that anybody thinks? Bob?

9 DR. DWORKIN: This is minor, but I'm going  
 10 to ask the group's permission for us to depart from  
 11 what's been a kind of unspoken IMMPACT-ACTION  
 12 policy. And that policy has been that everybody  
 13 who attends both days of the meeting is invited to  
 14 be a co-author on the manuscript that Nate is going  
 15 to be drafting. And really, the model has been  
 16 that people spend the bulk of their time; they  
 17 participate in the bulk of the meeting.

18 I'd like to ask for permission for an  
 19 exception, which is that we invite our two  
 20 colleagues from CDRH, who were here only for an  
 21 hour and a half yesterday, to be authors on this  
 22 manuscript. I think, for all sorts of reasons that

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1 don't have to be said out loud, it would be very  
 2 cool to have them involved in this process.

3 Does anyone disagree with that exception to  
 4 IMMPACT and ACTION's policy, that we invite our  
 5 two colleagues from CDRH to be authors? They of  
 6 course can decline.

7 (Affirmative nods of heads.)

8 DR. KATZ: The heads seem to be seem to be  
 9 going up and down.

10 MALE VOICE: I think that's a good idea.

11 DR. DWORKIN: So let's include them in the  
 12 process, and if they withdraw, that's up to them.

13 DR. KATZ: That's a great idea. Great.

14 Anything else? Bob? Dennis? Do you guys  
 15 want to make any closing comments of any type?

16 DR. DWORKIN: My closing comment is simply  
 17 thank you very, very much, Nate, for doing a  
 18 masterful job of sewing this altogether.

19 DR. KATZ: Well, thank you guys for making  
 20 it easy.

21 (Applause.)

22 DR. TURK: From ACTION and IMMPACT, I want

1 to thank our collaborators from the neuromodulation  
2 societies for their contributions. Those that  
3 don't know the background, there are lots of  
4 discussions and conversations going back for  
5 6 months, 8 months, a year, trying to set this up.  
6 There's a tremendous amount of work, and to also  
7 thank all the speakers who took the time, and to  
8 request that you'll be asked to allow us to put  
9 your slides up on our website.

10 If there are any slides within your set that  
11 are proprietary you don't want, you can remove  
12 those. But to the extent that you'll let -- people  
13 out there who might be interested in this meeting  
14 who aren't here would find those very interesting.  
15 So you will get an invitation or request to allow  
16 us to use your slides.

17 Adjournment

18 DR. KATZ: I'd like to finally thank Rahul  
19 from MHRA for coming because, first of all, you  
20 came a super long way, as did many others. And  
21 second of all, it's so critical for us to have  
22 people here who can provide a regulatory

1 perspective, so much appreciated.  
2 Alright. Well, happy trails, safe travels  
3 everyone. See you next time.  
4 (Whereupon, at 2:52 p.m., the meeting was  
5 adjourned.)

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