

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

November 15, 2018

*A Matter of Record
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1	ACTTION	1	Moderators: Salim Hayek, MD
2		2	Nathaniel Katz, MD
3		3	Systematic Review of Methodologic
4		4	Characteristics and Outcomes in
5	INITIATIVE ON METHODS, MEASUREMENT, AND PAIN	5	RCTs of SCS for Pain
6	ASSESSMENT IN CLINICAL TRIALS	6	Ewan McNicol, PharmD
7		7	Inclusion/Exclusion Criteria (e.g.,
8	Institute of Neuromodulation	8	Diagnoses, Pain Severity, Pain Duration
9	International Neuromodulation Society	9	Psychosocial Vulnerabilities, Treatment
10		10	History, Concomitant Analgesics)
11		11	John Markman, MD
12	Research Design Considerations for	12	Primary and Secondary Outcomes (e.g.,
13	Randomized Clinical Trials of	13	Pain, Function, Opioid Sparing,
14	Spinal Cord Stimulation for Pain	14	Duration of Follow-Up)
15		15	Ali Rezai, MD
16	Thursday, November 15, 2018	16	Adverse Events: Assessment and Reporting
17	8:05 a.m. to 5:29 p.m.	17	Salim Hayek, MD
18		18	Group Discussion: Inclusion/Exclusion
19		19	Criteria, Outcomes, and Safety
20	Westin Georgetown	20	Moderators: Nathaniel Katz, MD
21	Washington, DC	21	Richard North, MD
22		22	Adjournment
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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	2	(8:05 a.m.)
3	WELCOME AND INTRODUCTIONS	3	WELCOME AND INTRODUCTIONS
4	Dennis Turk, PhD	4	DR. TURK: Good morning. Thank you all for
5	Simon Thomson, MD	5	coming. My name is Dennis Turk, and I'm from the
6	The History of Research on the Mechanisms,	6	University of Washington, and I'm delighted to have
7	Efficacy, and Safety of Spinal Cord	7	all of you here for what I think is going to be not
8	Stimulation	8	only important but a very interesting and
9	Richard North, MD	9	productive meeting. And I'm looking forward to
10	SCS Clinical Trial Objectives and Research	10	learning a lot from you.
11	Designs, Including Comparison Groups and	11	I'm going to be introducing the conveners of
12	Testing Superiority vs. Non-Inferiority	12	the meeting first before we actually start the
13	Rod Taylor, PhD	13	formal presentations. There are a few housekeeping
14	Sources of Bias in RCTs of SCS and	14	details that we need to put up so you'll be aware
15	Their Mitigation	15	of those. Please put that slide up.
16	Nathaniel Katz, MD	16	When you registered, there's a sign-in desk.
17	Evidence Standards for Device Approval:	17	Please make sure you sign in and out. And I think
18	Regulatory Perspectives	18	you have to do that both days, if I'm correct.
19	Carlos Pena, PhD	19	MS. THOMPSON: Just sign in.
20	Rahul Singh, MD	20	DR. TURK: Just sign in?
21	Group Discussion: Study objectives,	21	MS. THOMPSON: Yes.
22	Designs, and Bias	22	DR. TURK: Okay. And silence your cell

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1 phones, which obviously goes without saying.
 2 This is being audiotaped, so be aware.
 3 Don't whisper any terrible things to anybody beside
 4 you. Speak directly into the microphone. These
 5 are voice activated, and that means that if four of
 6 you want to speak at the same time, it's going to
 7 be very difficult.
 8 So when one person is speaking, hopefully
 9 anybody else who wants to speak will let them and
 10 make sure that they finish up what they're going to
 11 be saying before. Since it is being recorded, when
 12 you have a question or you have a comment you want
 13 to make, please state your name and where you're
 14 from, just so the people who have the recording
 15 will have that information.
 16 The restrooms, if you haven't already
 17 identified them, are to the left of this room, my
 18 left walking out the door, and the WiFi, you can
 19 use. You select Western meeting rooms network on
 20 your browser, and then the access code is -- and
 21 make sure you use A-C-T-T -- two T's -- I-O-N,
 22 ACTTION. You'll understand what the two T's are

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1 for shortly.
 2 Lunch will be at 12:30 in the Mayfair Court,
 3 which for those that were here yesterday will know
 4 it's up two levels I think from here now.
 5 Valorie? Two levels up?
 6 MS. THOMPSON: Yes.
 7 DR. TURK: Then dinner tonight will be in
 8 the Thomas Board Room on the same level as the room
 9 as we're in right now.
 10 That's sort of the logistics of this. Any
 11 questions about any of those details before we get
 12 started officially?
 13 (No response.)
 14 DR. TURK: Okay. The person standing there
 15 in the back with the blonde hair is Valorie
 16 Thompson. Valorie is the organizer of this
 17 meeting, so if you have any questions and for some
 18 reason you need a snow plow to get you out --
 19 (Laughter.)
 20 DR. TURK: -- Valorie promised me that
 21 wouldn't happen. It would be out in the suburbs;
 22 no chance of it snowing in the city. At least in

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1 my room window, it looked like it was snowing.
 2 But Valorie is the person you can go to if
 3 you have any questions with logistics and any
 4 concerns about anything about the room, the
 5 meeting, anything that she can help you with.
 6 She's very good, and we're delighted. And we thank
 7 her for all the work that she puts into this to
 8 make it run as smoothly as we hope it has gone for
 9 you.
 10 You can put up my first slide. In case
 11 you're not familiar with where you are, this is the
 12 group that's having a meeting, and you'll
 13 understand why. It's being supported by ACTTION,
 14 or convened by ACTTION, and IMMPACT; International
 15 Neuromodulation Society; and North American
 16 Neuromodulation Society, and Institute of
 17 Neuromodulation.
 18 These are the organizations that are working
 19 together to create this particular meeting. As
 20 you'll learn about IMMPACT, we have had numbers of
 21 other meetings in the past, and we have had some
 22 other meetings in which we've arranged to work with

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1 other organizations; for example, with OMERACT. If
 2 you know the rheumatology area, you can understand
 3 that.
 4 So we're all working together. You'll be
 5 hearing from the other conveners. I'm going to be
 6 representing the ACTTION-IMMPACT. And I'll explain
 7 since many of you are not -- some of you are, but
 8 some of you are not familiar with ACTTION-IMMPACT.
 9 I'll just give a little teeny bit of background
 10 about that, what the letters stand for.
 11 For those that don't know, IMMPACT has been
 12 having meetings since 2001. This is the 22nd
 13 meeting. If you're saying, well, wait a second,
 14 that's too many meetings, there were some years we
 15 had more than one meeting. This particular
 16 meeting, so you know what you're here for, if
 17 you're not here for this, leave now; take some
 18 coffee. This is the time to do it.
 19 (Laughter.)
 20 DR. TURK: It's Research Design
 21 Considerations for Clinical Trials of Spinal Cord
 22 Stimulation. The emphasis on clinical trials, not

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1 on how effective they are, or not on things of that
 2 type. It's not a marketing meeting. It's totally
 3 designed to help us and help you come to agreement,
 4 and then help other people in the field design
 5 better studies to be able to answer the kinds of
 6 questions that you think are important to look at
 7 this particular type of intervention.

8 I want to thank the different device
 9 manufacturers who have supported this particular
 10 meeting. Their names and logos are up there, and
 11 we appreciate their assistance to us. Also to the
 12 FDA, ACTTION is a public-private partnership with
 13 the U.S. Food and Drug Administration. They
 14 provide some support to ACTTION, so therefore
 15 they're also supporters. But not only are they
 16 supporters; they're also heavily involved with us.

17 I don't see Allison right now, but we will
 18 have some people here from FDA, I believe.

19 Bob, is that still correct?
 20 (Dr. Dworkin gestures yes.)
 21 DR. TURK: Okay.
 22 What IMMPACT is not. In case you're

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1 wondering, the initials, it's not the International
 2 Micronutrient, Malnutrition Prevention and Control
 3 Program.

4 It's not the Interactive Massive Model
 5 Proximity Collision Tester. These are all available
 6 on the Web; you can go find them.

7 It's not the Immigrant's Public Action
 8 Coalition of Trenton, New Jersey.

9 It's not the International Maine Maritime
 10 Potato Action Team.

11 It's not Double Impact Taekwondo, although
 12 sometimes it feels that way as we have had to try
 13 to herd the cats are to deal with people. If
 14 you're not familiar with that gentleman on the top
 15 there, that's Dr. Bob Dworkin, who is the director
 16 of ACTTION.

17 So what is IMMPACT? It's the Initiative on
 18 Methods, Measurement, and Pain Assessment in
 19 Clinical Trials. The emphasis is on methods,
 20 procedures, and in clinical trials, so it's
 21 relevant for us. It's an international consortium
 22 of participants from academic research;

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1 governmental agencies; U.S. FDA; U.S. National
 2 Institutes of Health; U.S. VA; European Medicine
 3 administration; industry, consulting, and research
 4 organizations; and consumer advocates.

5 Those are the kinds of people who have been
 6 involved with this particular initiative. The
 7 mission is to suggest methods for improving the
 8 design, execution, and interpretation of clinical
 9 trials in treatment of pain. Now, we should be a
 10 little bit cautious about that because when you see
 11 the ACTTION acronym, and explain that to you, it's
 12 not just pain but some other topics as well. But
 13 IMMPACT is specifically focusing on these
 14 particular pain related areas.

15 IMMPACT is part of the analgesic,
 16 anesthetic, and addiction clinical trials
 17 translations; innovations; opportunities, and
 18 networks. Whew! That's a mouthful. The reason
 19 for the acronym, obviously to make it easier, is
 20 initially when ACTTION first began, it was just for
 21 the analgesic part there. The FDA asked us,
 22 because they're part of the public-private

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1 partnership, to also cover anesthetic and
 2 addiction, as well as peripheral neuropathy, which
 3 the acronym got to be ridiculous, so we're not
 4 adding any more letters.

5 Those are the kinds of things. So remember,
 6 IMMPACT is focusing exclusively on pain; ACTTION is
 7 broader.

8 What is ACTTION? Just so you know, I've
 9 already gave you the initials for it, it is a
 10 public-private partnership with the Food and Drug
 11 Administration. They have had important impact
 12 information provided to us, ideas, things that they
 13 want us to be looking at. They participate in
 14 meetings as much as they are able to. When we come
 15 up with manuscripts, on some of the manuscripts,
 16 they served as authors; and others, they've just
 17 been advisors to us. They, for legal purposes,
 18 can't serve as authors. You'll find out about
 19 authorship on papers shortly.

20 The mission of ACTTION, with all the
 21 initials, is to identify, prioritize, sponsor,
 22 coordinate, and promote innovative activities with

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1 a special interest on optimizing clinical trials,
 2 emphasis on research and clinical trials, that will
 3 expedite the discovery and development of improved
 4 analgesic, anesthetic, addiction, and peripheral
 5 neuropathy treatments for the benefits of the
 6 public health.

7 So the idea of this organization is to try
 8 to see if we can improve the quality of clinical
 9 trials, and that hopefully this will expedite the
 10 development of improved treatments, which
 11 ultimately is for the end user, which are the
 12 patients at the other end of the spectrum that we
 13 want to deal with. So that's what we're all about.

14 If you're interested in ACTTION and you want
 15 to find out more about it, you can go to the
 16 ACTTION website. It's A-C-T-I-O-N.org. If you
 17 put A-C-T-I-O-N, you're going to find all kinds of
 18 very unusual things, so make sure you put the
 19 double-T.

20 As I said, it's a public-private partnership
 21 with the FDA. We've also had representatives at
 22 different meetings over the years since 2001, from

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1 the Center for Drug Evaluation and Research, or
 2 CDER FDA; Division of Anesthetic, Analgesic, and
 3 Addiction Products; and Division of Bone and
 4 Reproductive and Urological Products. We've had
 5 meetings in which we've looked at pelvic pain and
 6 irritable bowel syndrome. The Division of
 7 Biometrics have been involved. The Center for
 8 Radiological Health, which is of particular
 9 interest to you, has been there, and people from
 10 the Office of the Commissioner.

11 So those are the kind of representation that
 12 we've received. And who comes from the FDA, as
 13 well as who comes for any of these meetings, is
 14 always dependent upon what the topic is going to
 15 be. So whereas some topics may be more appropriate
 16 for some individuals to attend, others may come to
 17 other meetings.

18 Who's participated? You know that over the
 19 years, we've had over 225 participants at the 22
 20 meetings, including this one. Some have attended
 21 more than one. They've come from 14 different
 22 countries. They're listed there. So we've had an

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1 international group. When we've had people from
 2 the EMA, especially, we've tried to make sure we
 3 could involve them to the extent it's possible.

4 For those that are not familiar with the EMA, it's
 5 run quite different from the FDA, so it's a little
 6 bit more complex in how to deal with them.

7 We represent over 96 different institutions,
 8 universities, academic centers, hospitals at these
 9 meetings. Participants have come from different
 10 governmental agencies that I've mentioned, as well
 11 as the Department of Defense, the Drug Enforcement
 12 Administration, SAMHSA, which is the mental health
 13 association, and the VA.

14 So we've had people from all those
 15 organizations come. Over time -- and again, if you
 16 want to know more about these things, you can find
 17 out more -- we've had support over the different
 18 meetings from 46 different pharmaceutical companies
 19 and 6 device manufacturers. So there have been
 20 lots of groups that have been interested in, and we
 21 thank them for their support.

22 There have also been consumer advocacy

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1 representatives from different organizations:
 2 American Chronic Pain Association, interstitial
 3 cystitis. We've had a whole range of people
 4 coming, depending upon the nature of the problem.

5 I don't think we have a consumer advocate
 6 here, do we, Bob?

7 (Dr. Dworkin gestures no.)

8 DR. TURK: No. Okay. We've also had some
 9 private consulting firms that have had
 10 representatives here who have brought particular
 11 expertise. It's been very helpful to us.

12 These are the different governmental
 13 agencies from NIH, and I'm not going to go over all
 14 these in more detail. You can see all of them
 15 listed there. You can see it's all the different
 16 institutes, or the majority of different institutes
 17 from NIH have been attending these meetings.

18 What do we do? Well, I'm not going to read
 19 these to you, but we've had different meetings each
 20 year. Just so you know, each year has had a
 21 particular topic. And based on the meetings, we
 22 make an effort to make sure that there are

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1 publications that come out of those. We also have
 2 on the IMMPACT website, if you're interested in any
 3 past meetings, who attended, the background
 4 presentations, the slides. We ask for permission,
 5 and if we get permission from these speakers, we've
 6 put those up there. They're available.
 7 Later meetings have been audiotaped, so
 8 those transcripts are available should you be
 9 interested in listening to us talk for two days.
 10 And to my knowledge, no one has ever requested or
 11 use those, but if you want one, or someone in your
 12 office wants to hear the details, they can read all
 13 that.
 14 These are just some more meetings. The last
 15 one that we had was on clinical trials for opioid
 16 sparing in patients with acute and chronic Pain,
 17 and the one before that was on pelvic pain and
 18 irritable bowel. So that's the most recent ones.
 19 We have another one that will be coming up
 20 in June, which we'll be looking at central
 21 sensitization syndromes and seeing how you would
 22 do -- remember, we're not looking at these from the

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1 standpoint of treatment and product. It's how
 2 would you do a study. If you wanted to study
 3 pelvic pain, for example, what would be the
 4 outcomes that you would use? How would you design
 5 the study? How would you analyze the data? How
 6 would you interpret the data? So that's what we're
 7 trying to do with these meetings. And you've
 8 already heard what this meeting is about.
 9 What else do we do? Well, in addition to
 10 the meetings, we also have commission papers. The
 11 commission paper that's going to be developed from
 12 this meeting specifically will be looking at
 13 meta-analysis. That will be coming out that you
 14 all will see. We conduct scientific studies. We
 15 develop some different measures.
 16 We support educational initiatives. The
 17 North American Pain -- Society. The North American
 18 Pain something meeting that goes on in Montreal
 19 brings in 50 young investigators from different
 20 areas and tries to educate them about doing
 21 research, so we support that. We also develop
 22 diagnostic criteria. I think you've got that on

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1 your table there.
 2 So we've done a lot of different things, and
 3 if you want to know more about, obviously you can
 4 go to the website. We've had over 7,600 different
 5 citations, and we've been cited in the papers in
 6 over 600 different journals ranging anywhere from
 7 addiction medicine, to women's health, to my
 8 favorite, veterinary medicine, which I would never
 9 have thought that anybody would find an interest.
 10 But I guess when you're talking about clinical
 11 trials, and data analysis, and how to interpret
 12 things, that would make some sense.
 13 So there's the website that you can go to.
 14 And you could see along the bottom, the
 15 publications, the background papers, the
 16 presentations, that's all available to you.
 17 What are the objectives of this meeting?
 18 And you're going to hear more about this. To
 19 discuss important considerations and provide
 20 suggestions regarding the design of clinical trials
 21 of spinal cord stimulators. That's what this is
 22 going to be all about; to disseminate these

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1 considerations, observations, suggestions, and
 2 peer-reviewed articles.
 3 The meeting is scheduled to end tomorrow at
 4 3:00, I believe, but if we don't have enough
 5 information for Dr. Nate Katz to develop the
 6 manuscript with the recommendations on that, then
 7 we could stay longer. We'd be more than happy to
 8 stay for forever if you want to keep talking. But
 9 an incentive to you will be that we will be pushing
 10 you to try to get to the point where we can do
 11 that.
 12 In order to do this, we've got to herd the
 13 cats. And you may note that we've learned this
 14 from trying to herd cats with IMMPACT members.
 15 Participants don't like to be herded. In fact, you
 16 can rarely herd participants, but that doesn't stop
 17 us from keeping to try to do this.
 18 Participants prefer to herd themselves, and
 19 they're not very good at it. Participants
 20 understand that they sometimes need to be herded,
 21 however, that doesn't make them any easier to be
 22 herded. Harsh herding usually has negative

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1 consequences, so coercing doesn't often work.
 2 Here's the group who are going to be herding
 3 you. And for those that are from Australia or UK,
 4 you may be familiar with rugby. Well, this is what
 5 it's like. And you've seen our other conveners
 6 there. In the center is the important person
 7 sitting right over here, Dr. Nathaniel Katz. He is
 8 really going to be shepherding and taking over this
 9 meeting and really pushing and driving and herding
 10 the cats.
 11 So I will get off the stage and let him,
 12 when he's ready to start doing that. But I just
 13 wanted you to have that background so you know what
 14 we're about and what the intent is, and what we're
 15 trying to accomplish from the standpoint of this
 16 particular meeting.
 17 Now, what I'd like to do is to have other
 18 conveners come up and give their welcoming comments
 19 to you for this meeting and their visions of what's
 20 there.
 21 DR. THOMSON: The big cat needs to be
 22 herded. We're behind already --

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1 (Laughter.)
 2 DR. THOMSON: -- but thank you.
 3 Just very quick, Dr. Simon Thomson. I was
 4 former president of the INS. In my role as past
 5 president, I recognize the need for, basically,
 6 this sort of initiative, but I didn't really know
 7 where to begin. I convened a meeting in Edinburgh
 8 in 2017 -- some of you may remember -- where we
 9 started thinking about how could we work together
 10 to improve the quality of our study design.
 11 Somebody mentioned IMMPACT and Robert Dworkin, and
 12 I met Robert in December 2017 at the first meeting
 13 of clinical trial studies -- do you remember? -- in
 14 London.
 15 That was in December 2017. Then when I was
 16 at in Las Vegas at NANS, Salim Hayek and others
 17 said, "You know, we've got this Institute of
 18 Neuromodulation, and we've just asked Nate Katz to
 19 help us with the manuscript." So they were
 20 thinking in the same lines as well.
 21 So this is really a natural coalition. It
 22 must mean that we know that there is a need to

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1 improve our clinical study design. So I'm very
 2 grateful to all of you, particularly to IMMPACT and
 3 ACTTION and Robert Dworkin, and Dennis, who've
 4 really taken over the leadership. I'm a working
 5 doctor. I'm not actually at a academic
 6 institution, but I try.
 7 I feel very well supported by my colleagues
 8 and friends from the U.S. and Europe. My first
 9 colleague, the other convener who is basically
 10 representing Institute of Neuromodulation, Richard
 11 North, would you like to just say a few brief words
 12 about why you're here or why ION are here? And
 13 then I'll introduce you for the first talk.
 14 DR. NORTH: Thank you, Simon for that kind
 15 introduction. The Institute of Neuromodulation,
 16 formerly known as the NANS Foundation, has taken on
 17 this and a couple of other initiatives, which we
 18 think are very important to the field. The
 19 president of ION, Ali Rezai, will be speaking and
 20 telling you more about ION. For now, let me just
 21 say on behalf of ION, that we're pleased to be
 22 involved in this important initiative, and we need

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1 to get on with the show.
 2 DR. SIMON: So now we've done our
 3 introductions, and I'm now going to just welcome
 4 Richard North, who is a retired professor of
 5 neurosurgery at the Johns Hopkins University,
 6 Baltimore, and also set up the Neuromodulation
 7 Foundation --
 8 DR. NORTH: Foundation, yes.
 9 DR. SIMON: -- which is a public
 10 organization, which also I think is involved
 11 WikiStim, which is a great resource for looking at
 12 data in our field.
 13 Richard, you'll probably say this more
 14 precisely, but thank you very much for kicking us
 15 off with the history of spinal cord stimulation
 16 research. Thank you.
 17 Presentation - Richard North
 18 DR. NORTH: Thank you, Simon, for that kind
 19 introduction. I believe I'm here now as the old
 20 guy who's asked to talk about the history of the
 21 field.
 22 (Laughter.)

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1 DR. NORTH: Increasingly, I find I'm asked
 2 to address that topic, but I think it's a nice
 3 opportunity. Here are my disclosures. You can
 4 see, they go back to 1974. And my previous
 5 employers, the nonprofit that I now head, have
 6 benefited from support from all of the important
 7 players in the field.
 8 My history with this goes back, I dare say
 9 farther than almost anybody else I see in the room,
 10 and I plan to take advantage of that perspective.
 11 Were I to cover the history of mechanisms,
 12 efficacy, and safety in detail, I would preempt a
 13 lot of what I know my colleagues are going to say.
 14 So I'm going to try to bring this
 15 perspective to my remarks, and I'm going to begin
 16 with mechanisms and talk about mechanisms as a
 17 rationale for what we do. "Mechanism-based
 18 medicine" is a fashionable term, and it's certainly
 19 an important idea. This is one of many statements,
 20 this one specific to our field, about how important
 21 it is to develop an understanding of what's behind
 22 what we do.

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1 This is wordier statement of the problem. I
 2 don't intend to e-read it, but rather that you step
 3 back and consider that the literature upon which
 4 rely is not always right. And if you consider that
 5 and then consider the fragility of any
 6 mechanism-based rationale, you end up here. And
 7 you could look at this dynamic as you honor this
 8 squared or cubed. So important as mechanisms are,
 9 I think it's important to keep an open mind because
 10 serendipity remains important.
 11 That said, spinal cord stimulation is a
 12 prime example of a therapy based on a theoretical
 13 mechanism. Back in 1965, Melzack and Wall
 14 published their seminal paper in science,
 15 hypothesizing that there was a central gating
 16 mechanism in the cord and that it determined
 17 whether neuroactivity signaling pain would be
 18 transmitted to the brain.
 19 It was hypothesized to be open by an excess
 20 of small fiber activity and closed by an excess of
 21 large fiber activity. And conveniently enough,
 22 large fibers can be selectively depolarized by an

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1 externally-applied electrical field. And at just
 2 the right amplitude, they can close the gate.
 3 Within a couple of years, Pat Wall, one of
 4 the co-authors of the gate theory, and Bill Sweet,
 5 a neurosurgeon at Harvard, tried this with
 6 percutaneous electrodes on peripheral nerves and
 7 found that, indeed, they were able to abolish pain,
 8 temporarily.
 9 Most peripheral nerves of course are mixed.
 10 They have sensory and motor fibers. Jay Law among
 11 others has pointed out that the thresholds for
 12 motor and sensory side effects are very close
 13 together, so it's easy to have uncomfortable motor
 14 effects occur at amplitudes near sensory threshold.
 15 The spinal cord, however, is organized in
 16 such a way as to encourage us to stimulate it
 17 because their primary efferents conveniently
 18 segregate it from motor fibers, and the dorsal
 19 columns in particular have collateral processes
 20 into the dorsal horn that can give access to the
 21 gate.
 22 This is a slide, one of a number in my

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1 presentation, that Bengt Linderöth was kind enough
 2 to provide. And this little cartoon shows that
 3 rostral electrodes will produce action potentials
 4 that are propagated and antidromically and then via
 5 collaterals into the dorsal horn. There are also
 6 propagated all the way out under the periphery.
 7 And furthermore, they are propagated centrally.
 8 Hence, the feeling of paresthesia.
 9 So it wasn't too long after Wall and Sweet
 10 reported peripheral nerve stimulation that Norm
 11 Shealy, then working in Cleveland as a
 12 neurosurgeon, reported the first spinal cord
 13 stimulator, and it's been 51 years now.
 14 Tom Mortimer, his collaborator, was a
 15 biomedical engineering doctoral student, and this
 16 was a successful project. However, the gate
 17 control theory came under criticism rather
 18 promptly, and that criticism has continued.
 19 However, some 25 years out, Anthony Dickenson
 20 published this editorial in the British Journal of
 21 Anesthesia to the effect that the gate control
 22 theory stands the test of time. You continue to

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1 hear it invoked routinely as the explanation for
 2 why spinal cord stimulation works, although it's
 3 more complicated than that, as I will try to
 4 explain in the available time.
 5 "Dorsal column stimulation" was the original
 6 term for spinal cord stimulation, which is now
 7 preferred. It is certainly topographically
 8 accurate, and it's been confirmed physiologically
 9 that dorsal column fibers are recruited. But it's
 10 simplistic as other structures are affected, too.
 11 Back when Bengt Linderöth published his PhD
 12 thesis in the early '90s, dorsal column stimulation
 13 was still preferred terminology. Bengt was working
 14 in Bjorn Meyerson's lab, and they developed little
 15 electrodes scaled to the animal model, and figured
 16 out how to scale stimulation parameters. They
 17 worked with a chronic pain model, which then was in
 18 its early stages looking at sciatic nerve ligation.
 19 They were able to show in one of their first
 20 projects that hyperactive flexion withdrawal
 21 reflex, as a model for allodynia, were attenuated
 22 my spinal cord stimulation. They have gone on to

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1 make a number of important findings, among them the
 2 neurochemistry underlying the effects, or at least
 3 some of the effects, of spinal cord stimulation.
 4 This slide shows percent changes from basal
 5 and levels of GABA and of glutamate, and here,
 6 spinal cord stimulation is administered. And as
 7 you can see, there's an increase in GABA and a
 8 corresponding decrease in glutamate. It occurs
 9 only in the animals that respond in the model,
 10 suggesting that this is a responsible mechanism.
 11 If the GABA-B receptor is blocked, then the
 12 glutamate effect goes away. That led, speaking
 13 again of mechanism-based medicine, to a new
 14 therapy, albeit a cumbersome one; that is putting
 15 in a pump along with a stimulator to administer
 16 intrathecal baclofen. And this showed, over a more
 17 than 5-year follow-up, that patients who were not
 18 responding well to spinal cord stimulation could be
 19 considerably improved by intrathecal baclofen.
 20 The neurochemistry is much more complicated
 21 than time permits me to explain, and it includes
 22 not only segmental spinal cord mechanisms, but

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1 rostral mechanisms. Recall, I showed the action
 2 potential propagation upward to the brain and the
 3 brain stem. So there are mechanisms in the rostral
 4 ventral medulla. 5-HT is implicated as an
 5 important transmitter there. And the locus
 6 coeruleus, which seems to be involved in
 7 everything, has been implicated, too.
 8 I put this up as a reminder that we're
 9 antidromically stimulating peripheral afferents.
 10 So when the patient reports paresthesias extending
 11 out into a limb, you can record activity in the
 12 limb. This was just a report of an unusual case,
 13 but it reminds me of something that I read back in
 14 '74, when I was getting started in the field, about
 15 afferent nerve impulses originating from neuroma,
 16 one of many neuropathic pain conditions, and at
 17 electrical stimulation propagates out into the
 18 periphery. That's not much talked about in our
 19 mechanisms literature, but we're still just getting
 20 started on explaining the underlying mechanisms.
 21 Let's back away for a moment and ask what we
 22 mean by the word "stimulation." So just thinking

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1 in terms of so-called conventional spinal cord
 2 stimulation at pulse rates on the order of 100 per
 3 second, we're talking about action potential
 4 propagation, which is achieved more easily in a
 5 cathode than in an anode. You can generate an
 6 action potential if you use an anode, turn the
 7 amplitude up high enough for a long time, and then
 8 shut it off, the so-called anodal break.
 9 This is one of many basic mechanisms. This
 10 goes back to 1975. James Ranck is still often
 11 quoted 10 days ago at a Cleveland meeting, which
 12 was more basic mechanisms oriented. Many of the
 13 engineers continued to quote him. We've moved on
 14 from these traditional stimulation parameters to
 15 play some new tunes through the spinal cord, and
 16 that requires that we rethink some of our premises.
 17 J. Law back in the '80s did a good job of
 18 articulating the technical requirements for spinal
 19 cord stimulation. It was understood from the mid
 20 '70s, Hosobuchi, among others, Nascholtz [ph], said
 21 that it was necessary that stimulation paresthesia
 22 overlap an area of pain if we were to expect pain

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1 relief. And Law defined the amplitude range within
2 which that needed to occur, founded below of course
3 by perceptual threshold and above by discomfort or
4 motor threshold, which can be synonymous.
5 But now we have paresthesia-free
6 stimulation. And so we've moved down into the range
7 below perceptual threshold. And at some of the
8 stimulation parameters that we're using, perception
9 is followed rather promptly by discomfort. So we
10 need to rethink what we're talking about here, and
11 we need to consider some other factors. One is
12 that we're stimulating a moving target, so when a
13 patient lies down supine, the spinal cord moves
14 close to the dorsal epidural space where our
15 electrode is, and then when they sit or stand or
16 assume a prone position, it moves away.
17 This is from a paper that we published back
18 in '98 showing a 25 percent average difference in
19 thresholds. This is from some still unpublished
20 work where we looked at voltage versus current
21 sources and found that the postural effect is more
22 than double for current sources.

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1 Current sources are becoming more
2 fashionable despite this disadvantage. It's what
3 you would expect from a model; that is the spinal
4 cord is higher impedance or electrical resistance
5 than the CSF that surrounds it. So when the cord
6 moves closer to the electrodes, the impedance or
7 resistance that the pulse generator sees goes up.
8 So a voltage generator will respond by doing
9 nothing, but a current generator will jack the
10 voltage up to maintain the current, which is quite
11 the opposite of what we might want to do.
12 Fortunately, there are automated ways of
13 adjusting amplitude compensate for that.
14 Another mechanistic approach to all of this
15 has been to model the structures in the electrical
16 fields in a finite element fashion. So this goes
17 back to Barry Coburn in the '80s, and Holsheimer
18 and his various collaborators have modeled this. I
19 refer to the variable conductivity.
20 White matter actually has different
21 impedance sideways than it does longitudinally, and
22 all of that needs to be considered in the model.

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1 Here is the segmentation that we're talking about,
2 and here are some of the model predictions that
3 shows isopotential lines going through the spinal
4 cord, and this shows the same thing. Note the
5 intense fields in the CSF.
6 So the models predict a number of things.
7 Recruitment threshold will vary as the spinal cord
8 moves closer to the dura and the electrodes. If
9 you want to minimize lateral recruitment, that is
10 dorsal root stimulation, which can be
11 uncomfortable, optimal longitudinal contact spacing
12 can be defined in the model. There are other
13 predictions, such as dual electrodes side by side
14 will be inferior to a midline position, and there
15 might be advantages for three columns, adding
16 lateral anodes to shield the roots from
17 recruitment. That's been called a transverse
18 tripole configuration.
19 Clinical corroboration of those modeling
20 predictions has come out. Our group did a trial
21 comparing dual with single electrodes and found
22 disadvantages for the dual electrodes. Konstantin

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1 Slavin and Kim Burchiel and the group at Oregon
2 studied the transverse tripole and found that
3 although they could steer using the lateral anodes,
4 that this was not the answer to chronic low back
5 pain.
6 Getting back to the alternative waveforms,
7 let's look at burst stimulation. Bursts resemble
8 normal neuronal activity. Single-unit recordings
9 from the nervous system in general and the pain
10 system in particular do show bursting activity.
11 Back when I started working with Fred Lenz who
12 records from the thalamus, we had a computer
13 controlled system, and we talked about playing back
14 his neuronal recordings through the system, but we
15 never got around to doing that.
16 Dirk De Ridder deserves a lot of credit for
17 pursuing this as he has. He's demonstrated by
18 source localized EEG that bursts activates dorsal
19 anterior cingulate and prefrontal cortex, which are
20 involved in emotion more than tonic SCS, and has
21 inferred that bursts might modulate attention to
22 pain. He's further hypothesized that burst has a

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1 differential effect on a medial pathway, which you
 2 can see here projects to DAC and can in turn affect
 3 a pain modulating pathways.
 4 This is from the animal literature, and this
 5 is one of the several slides that Bengt Linderoth
 6 provided. This shows that nucleus gracilis
 7 neurons, which are the first relay station from the
 8 dorsal columns, are not affected by bursts. This
 9 next slide shows, from a series of animal
 10 experiments, that serum GABA
 11 concentrations -- Bengt has these delightful built
 12 up slides -- burst effect not dependent on GABA
 13 receptor activation. And then in other
 14 experiments, that blocking the GABA-B receptor did
 15 not abolish the burst effect. So that's not the
 16 mechanism.
 17 Turning our attention to high frequency,
 18 specifically 10 kilo hertz stimulation, here is
 19 another cartoon showing the way this works. We're
 20 no longer propagating action potentials into the
 21 gate. We're stimulating the segments of the core,
 22 the same segments, by the way, that are targeted by

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1 conventional SCS indirectly. And this is where
 2 hyperactive wide dynamic range cells are located.
 3 This is a demonstration by Song et al. that
 4 there is no block or activation of dorsal column
 5 neurons by HF10. Here is 50 hertz stimulation,
 6 which will evoke parasthesia and is recruiting the
 7 dorsal columns. When you go to 10 kilo hertz,
 8 however, and 50 percent of motor threshold is
 9 pretty high, there's no recruitment of the dorsal
 10 columns. The same is seen even when this
 11 particular model is tested with application of a
 12 5-gram weigh.
 13 This is from Johns Hopkins where a Yun
 14 Guan's lab has generated a lot of important work.
 15 Here we are, 40 percent of motor threshold, which
 16 is supposed to be parasthesia free or below sensory
 17 threshold. And we're looking at the effects of SCS
 18 at a variety of frequencies starting at 50 hertz
 19 and going all the way up to 10 kilo hertz. And as
 20 you can see here, there are effects of SCS at all
 21 the frequencies studied, and they do not differ
 22 significantly.

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1 At 20 percent of the motor threshold, no
 2 differences are observed. When you go up to 80
 3 percent of motor threshold, which is higher than
 4 anyone would use clinically, the biggest
 5 differences were seen for a 1 kilo hertz, not for
 6 10. So this doesn't seem clinically relevant to
 7 high frequency.
 8 Here is another model. This is Song et al.,
 9 and they are looking at the behavior of a rat in a
 10 dark environment, which is when exploration and
 11 grooming behavior begins. So at
 12 40 percent -- sorry; motor responses are here at
 13 point 0.5, so it's a different scale. Behavior
 14 arrest and motor response delimit the clinically
 15 relevant range, so a sub-perceptive region of
 16 amplitude is chosen. And here's another study
 17 showing similar effects for all frequencies from 50
 18 hertz up to 10 kilohertz.
 19 What is 10 kilo hertz stimulation doing
 20 differently from conventional stimulation? Steve
 21 McMahon at King's College in London had a poster at
 22 NANS early this year. Here he's recording from

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1 superficial dorsal horn neurons. He is a patient
 2 fellow because you can see here, he waits
 3 90 minutes to see an effect by comparison with 45
 4 minutes.
 5 This is 10 kilo hertz sham. This is 10 kilo
 6 hertz at 20 percent of motor threshold. So we see
 7 a distinct effect of 10 kilohertz that does not
 8 occur at the lower frequencies. And here he's
 9 looking at wind-up and lamina 1 projection neurons,
 10 and this is sham. The next slide, 20 percent of
 11 motor threshold, and you can see that at these
 12 different time points, wind-up is attenuated to a
 13 significant degree.
 14 Sham-treated dorsal horn neurons show
 15 significantly increased fiber activity in their
 16 model with 10 kilohertz stimulation by comparison
 17 with sham. This is attenuated. McMahon went on to
 18 look at 1 kilohertz to see that this particular
 19 effect, although it was statistically significant,
 20 was nowhere near as pronounced as with 10
 21 kilohertz.
 22 This might or might not be relevant to the

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1 clinical situation, but at least it is a
 2 distinction for 10 kilohertz. So Dirk de Ridder,
 3 who's popularized verse stimulation came back
 4 around to suggest that maybe the mechanisms were
 5 fundamentally the same between 10 kilohertz and
 6 burst. This was a year ago where we're waiting to
 7 see whether performing EGs and functional imagings
 8 will show whether both schemes modulate the dorsal
 9 anterior cingulate.

10 This is 2010, but now we're in 2018. A
 11 couple of years ago, we began hearing about yet
 12 another new waveform; not really new because it's
 13 always been available from commercially available
 14 devices. That's so called high-density stimulation
 15 where one turns the frequency up to the kilohertz
 16 range and increases the pulse width to the highest
 17 level that the device will reasonably support.
 18 This is a placebo-controlled small trial that shows
 19 a significant effect in patients who had not
 20 responded well to conventional stimulation.

21 Wille in this paper suggested that what
 22 we're looking at here is simply a matter of dose,

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1 dose in the sense of total energy or power, if you
 2 will, delivered to the spinal cord. So you might
 3 look at this as just taking a conventional
 4 stimulator, which only goes up to 10, and turning
 5 the volume up to 11.

6 Harkening back to the 1960's, we knew back
 7 then that just turning the volume up all the
 8 way --
 9 (Laughter.)

10 DR. NORTH: -- was sometimes all that was
 11 necessary for an effect.

12 I'm going to move on to talk about efficacy.
 13 A full discussion of the history of efficacy
 14 research potentially would overlap all of these
 15 people, my friends and colleagues. So I'm going to
 16 harken back to 1973 when I was a new medical school
 17 graduate going into biomedical engineering post doc
 18 work and was introduced to Don Long, the new
 19 professor and chairman of neurosurgery.

20 At that time, there was a lot of enthusiasm
 21 for spinal cord stimulation. Like many new
 22 therapies, it was thought of as good for what ails

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1 you. Don had come from the University of
 2 Minnesota, where he had worked with Don Erickson,
 3 and Erickson inherited his patients. Although Long
 4 had observed really good results, Erickson reported
 5 to him after a while that only 15 percent of his
 6 original patients were considered successes. So
 7 they concluded that the methods of evaluating
 8 patients needed to be revised, and that one
 9 important thing was to have a third party do your
 10 follow-up.

11 Also at Minnesota, percutaneous methods of
 12 placing electrodes had been developed. This
 13 cartoon shows the approach. All of you who use the
 14 technique nowadays are using this method. So my
 15 job starting in '74 was to follow Don's patient.
 16 This is from a 77-page report that we put together
 17 where I was doing the third party follow-up.

18 This is one of the tables from the report
 19 that I submit, for your consideration, is part of
 20 the history of efficacy research. I was sitting in
 21 isolation in the applied physics lab, what we now
 22 have this whole committee doing, which is surveying

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1 the pain research methods, reading Sternbach and
 2 Melzack, McGill pain questionnaire, and other
 3 things, and putting together a test instrument to
 4 survey retrospectively this series.

5 We looked of course at percent pain relief.
 6 We continued to do that in a variety of ways. Bob
 7 Fischell said we really should ask patients whether
 8 if they had this to do over again, they would do it
 9 for the result they obtained. We've continued to
 10 ask that. That's not a common question that I see
 11 in contemporary instruments, but it does seem a
 12 scenic well known, if you're going to say you were
 13 successful, to get an affirmative answer to that.
 14 And comparison with relief by other methods is as
 15 you would expect in patients who failed everything
 16 else prior to stimulation.

17 This profile of adjectives comes out of the
 18 McGill questionnaire. We asked what percent of
 19 time patients spend in each of these levels and
 20 thought that allowed a useful comparison. We asked
 21 about latency to effect from the time the
 22 stimulator turned on until relief is achieved and

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1 persistence after it's turned off. That was
 2 important we thought to the design of a device. We
 3 were designing a rechargeable stimulator and
 4 actually implanted two prototypes in '79, but it
 5 wasn't until 2004 that the same group finally
 6 developed a commercially reasonable device.
 7 Of course we looked at drug usage. We
 8 didn't report this much detail in the scientific
 9 literature, but I think we would nowadays because
 10 there's increasing focus on this as an outcome
 11 measure. And indeed, the last IMMPACT meeting was
 12 devoted to opioid-sparing effects.
 13 We didn't have the tester instruments that
 14 we now have to look at indirect measures of pain
 15 relief, so we developed a grading scale for ability
 16 to perform various activities, and we asked
 17 patients to rate their degree of difficulty. And
 18 we ended up with this data. This is in our '77
 19 report in black and white. But in color, it lends
 20 itself to this stacked bar graph presentation.
 21 This is from our SCS versus repeat back
 22 surgery RCT in 2005. So we continued using this.

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1 There are other test measures that have been
 2 developed you'll be hearing about from other
 3 speakers, but this shows how many patients improve
 4 on these scales by comparison with how many in fact
 5 say they've been made worse.
 6 We published a short version of this in a
 7 dedicated issue in volume 1 of Neurosurgery. I've
 8 gone on, as all of you may know, to make a career
 9 out of reporting spinal cord stimulation clinical
 10 results and designing and developing new devices.
 11 The point of this is to show that as of 1991, the
 12 entire clinical literature in spinal cord
 13 stimulation would fit in one table on one page, but
 14 as of 2006, the last time we did this, Jane Shipley
 15 and I put together a table. And this was just the
 16 new literature since the last table.
 17 This was a cumbersome addition to a
 18 textbook, and that inspired WikiStim, which is a
 19 free online database. Many of you have signed up.
 20 I would urge the rest of you to do so. It's an
 21 extremely handy resource when one wants to look up
 22 any of the many references on clinical efficacy,

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1 which now number over a thousand.
 2 Moving on to safety and harkening back to
 3 our 1977 paper, Salim Hayek is going to talk about
 4 safety and complications as a dedicated lecture, so
 5 I'm going to skip over a lot of things. But I
 6 thought it would be interesting to him and to you
 7 to say that back in 1977, when percutaneous
 8 electrodes were brand new, electrode displacement
 9 or migration was a very common problem. That's
 10 since been substantially solved.
 11 I've remained active in the field of
 12 reporting complications and guidelines to try to
 13 minimize them and have made limited contributions.
 14 One is anchoring techniques for migration. This is
 15 another one that is in progress. There's one
 16 person in the audience who knows where this is
 17 from.
 18 It's from an RCT, and I might say that this
 19 is RCT evidence of an effect of trial duration on
 20 the rate of infection. What this shows is 10 times
 21 the incidence of infection in patients whose SCS
 22 trials go on for more than 10 days. But if you

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1 listen carefully to what I said, this is evidence
 2 from an RCT, but it was not among the study
 3 hypotheses. It was observed serendipitously. So I
 4 hasten to point out that this is a great example of
 5 confirmation bias.
 6 We happen to see something that was in
 7 accord with the long-held belief, and although it
 8 supports that belief, there were people who saw
 9 through this centuries ago, and all of us should
 10 continue to see through it.
 11 This is a poster that the SUNBURST group put
 12 up at the last NANS meeting. I put this up under
 13 the topic of safety in a deliberate attempt to be a
 14 little provocative. If you do a
 15 number-needed-to-treat analysis of spinal cord
 16 stimulation, like other surgical procedures, the
 17 NNT is very low. And if you look specifically at
 18 number needed to harm, it's very high indeed.
 19 Now, one might look at this and say, well,
 20 yeah, but SCS is invasive, and these drugs are not.
 21 But as a clinician, I've never seen a patient die
 22 from a stimulator procedure, but it's well

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1 publicized that patients all too often die from
 2 drug therapy for pain. That was the focus of the
 3 last IMMPACT meeting.

4 What conclusions do I presume to draw from
 5 this? One is as regards mechanisms. A lot of
 6 wonderful research has been done, but we should
 7 always bear in mind that our observations can be
 8 nonspecific. The nervous system, as was pointed
 9 out by Sherrington, who worked in this field a
 10 century ago, is capable of remarkable responses.
 11 And it can give a correct answer, so to say, to an
 12 improper or wrong question.

13 So we're still banging away at the nervous
 14 system rather crudely, and we're seeing some
 15 remarkable effects. But we should be careful in
 16 the inferences we draw as to the real underlying
 17 mechanisms.

18 From the perspective of a neurosurgeon, I've
 19 now had the 40-year experience that White and Sweet
 20 talked about when I was in medical school. Spinal
 21 cord stimulation is a wonderful alternative to the
 22 other procedures that are done. Augmentative

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1 procedures, one of the three A's here, are
 2 reversible. They act on the intact nervous system;
 3 whereas when we are so bold, as surgeons sometimes
 4 are, as to say I see what's causing the pain; I'm
 5 going to fix it, that can be a big presumption.

6 There's a lot to be said for reconstructive
 7 spine surgery, and remarkable advances have been
 8 made. But still, SCS is very attractive. And
 9 ablative procedures have a role, but more in cancer
 10 pain than in non-malignant pain.

11 I put this up at a spine meeting to be
 12 provocative and said, to point out to the
 13 neurosurgeons and spine surgeons, that what they
 14 were doing for the most part could be done perhaps
 15 better by a functional neurosurgeon or an
 16 interventional pain specialist. And I've already
 17 alluded to this NNT analysis by way of pointing out
 18 that by comparison with medical therapy, spinal
 19 cord stimulation is worth considering for its
 20 opioid sparing and other potential effects.

21 One last plug for WikiStim. I'm proud to me
 22 editor-in-chief of this. Jane Shipley, who is the

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1 brains of the outfit, is here. And if you have any
 2 questions about it, I'm sure she would welcome
 3 them. Thank you very much.

4 (Applause.)

5 DR. THOMSON: Thanks very much, Richard, and
 6 thank you for actually catching up and getting us
 7 back to time. There's certainly a point I want to
 8 raise from his talk, but I think this is now not
 9 the moment because we're going to have an
 10 opportunity a little bit later.

11 I'd like to introduce Professor Rod Taylor,
 12 who is a professor of trial design and
 13 biostatistics at Exeter Medical School, and has
 14 been a long-term collaborator with me, Samuel
 15 Darby, and others in helping to design some of the
 16 studies that we've been involved with in this
 17 field. I think you've sort of come back to spinal
 18 cord stimulation in recent years. He does a lot of
 19 other work in other fields.

20 So thank you very much indeed, Rod.

21 Presentation - Rod Taylor

22 DR. TAYLOR: Thank you, Simon; a very nice

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1 introduction. Thank you.

2 Wow! What a privilege. I've followed the
 3 IMMPACT group since I first came into the area of
 4 doing clinical trials.

5 Dennis and Bob, my sincere thanks for the
 6 opportunity, A, to be here. But B, also just the
 7 opportunity to actually speak in this setting
 8 because I think, genuinely, the IMMPACT group has
 9 made a tremendous difference in terms of the way
 10 that we've looked at our trial methods, which is
 11 one of my particular interests. And I think this
 12 meeting for the neuromodulation side of things,
 13 given that most of our concentration so far has
 14 been in the drug area, I think is strategically
 15 really important. So thank you very much for the
 16 opportunity.

17 Just in terms of housekeeping, my conflicts
 18 of interest, I haven't put them on a slide, but I
 19 think everybody's conflicts are already documented,
 20 so people have got them if they want to see them.

21 The other thing I'm also going to say in terms of
 22 introduction is that I'm going to really try and

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1 respond to Bob's challenges for me for this morning
 2 because clearly there's a lot of stuff that we need
 3 to cover over the next 36 hours.
 4 My particular things I've been asked to talk
 5 about are, first of all, the issue of superiority
 6 and noninferiority, which I've called hypothesis
 7 testing; reflect a little bit on study designs in
 8 this area; and then last but not least talk about
 9 comparators. I think, like Rick, there's going to
 10 be a lot of overlap. And I think not just overlap
 11 but also perhaps a difference in perspective and
 12 even a difference in views, which I think is really
 13 healthy and great.
 14 Now, I'm not going to try to steal the
 15 thunder of Ewan.
 16 Where are you, Ewan? You're here. Hi,
 17 Ewan. We haven't met I think
 18 taskingly [indiscernible] before. So I've had the
 19 benefit of having access to your database, Ewan,
 20 but I'm not going to steal your thunder.
 21 (Laughter.)
 22 Ewan and his group have done a huge amount

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1 of work, by the looks of it, in terms of doing a
 2 systematic review of the randomized controlled
 3 trials in the spinal cord stim space.
 4 But with your permission, Ewan, I'm going to
 5 use your database just to make a couple of
 6 reflections on these questions. But as I say, I'll
 7 really try not to steal your thunder for later, if
 8 that's all right.
 9 So hypothesis testing, I suspect much of
 10 this is familiar with you, but I think an important
 11 part of this morning is setting the scene. So for
 12 those of you who are trialists, again, just say to
 13 say, I'm not a clinician. I'm not an implanter.
 14 I'm just a humble statistician who's kind of
 15 bumbled into the pain space, but actually, as Simon
 16 was intimating, I do a lot of trials in the
 17 cardiovascular space. And I think pain is probably
 18 one of the more challenging areas. When I do my
 19 cardiovascular trials in pain, actually, I'm often
 20 scratching my head more in this space than I am in
 21 that space.
 22 So why is that? Well, certainly I think one

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1 of the commonalities of most trials that we do is
 2 that most of them are really about trying to show
 3 things are better. And of course we're all slaves
 4 to the p-value, not just statisticians, but as an
 5 interventionist, statistically better than the
 6 reference treatment.
 7 The invention of the randomized control
 8 trial and the superiority trial, the best thing
 9 since sliced bread. But of course one of the
 10 limitations of a superiority design is if you don't
 11 show a difference between the two groups, it
 12 doesn't mean the two therapies are equivalent. And
 13 for that reason, we need to think about other
 14 questions in the space.
 15 Clearly, if you like, the polarized opposite
 16 of superiority is equivalence. And in superiority,
 17 a null hypothesis says that the groups are the
 18 same, but actually in equivalence, the null
 19 hypothesis says the groups are different, and we're
 20 trying to test against that. What we're really
 21 trying to show is that a new intervention is the
 22 same as the reference.

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1 But actually, again, if you look at the
 2 trial, not just an in our space but in other areas
 3 of medicine, equivalence trials are pretty
 4 uncommon, certainly in the phase 3/phase 4 side of
 5 things. One of the main reasons for that, at least
 6 in my perception, is that, actually -- I'll go on
 7 and talk about it in a minute -- is we're often
 8 interested in noninferiority. And actually,
 9 equivalence is something that tends to be more
 10 actually in the pharmacokinetic space. So in other
 11 words, we might want to know whether there's a
 12 difference in either direction from the reference
 13 of importance.
 14 In my brief, I was asked to talk about
 15 noninferiority. So again, just to be clear, what
 16 is non inferiority? This is a situation where we
 17 seek to show that the new intervention is not worse
 18 than the reference. You might say to me, "Well
 19 look, Rod. In Washington, can we not be more
 20 ambitious than saying not worse than?" But I would
 21 put it to you that that's actually an important
 22 question. Many of the trials that I design are in

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1 the payer space, so we may be interested in
2 equivalence of clinical effect, but what we might
3 be interested in is the new intervention has some
4 other advantages.
5 Rick's already given some indication that
6 one of the things I think we should be particularly
7 interested in, in this space, is adverse effects
8 and harm. One of the big things in my area of
9 heart failure is actually a lot of our therapies
10 are evidence based, but none of them are actually
11 available to patients. So are some therapies more
12 applicable if they're in a home-based setting than
13 a hospital-based setting? Although they're
14 equivalent clinically, patients may be able to
15 access them better, so availability.
16 I'm a closet health economist for my sins,
17 so I often think about the economic impacts of
18 treatments. And maybe the two are equivalent
19 clinically, but economically, one offers benefits
20 over the other. Clearly, we've heard about
21 invasiveness again this morning and obviously, as I
22 said, fewer adverse effects.

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1 Sometimes I think those of us who work with
2 industry are maybe a little bit tough on those guys
3 and say, "Well, you know what guys? Doing
4 noninferiority studies, are you being a little bit
5 under-ambitious?" But I will put it to you that it
6 is an important trial design in our tool bag, and
7 we have to think about it, but clearly, something
8 quite different to superiority. And I want to
9 maybe walk you through why we need to think about
10 that methodological difference between superiority
11 and noninferiority.
12 Here's a classic picture. This actually
13 comes from the CONSORT guidelines for
14 noninferiority trials. And if I may walk you
15 through this, basically the X-axis is we're
16 comparing our new treatment to the reference. Zero
17 here would be no difference between treatments.
18 Clearly, this result, result A, is I think a pretty
19 undisputable one. Here we can see that the
20 reference treatment is doing better than the
21 control. Here is the mean where A is, and the
22 95 percent confidence interval does not cross 1, so

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1 we've got evidence statistically that this is
2 superior.
3 Similarly, let's go down to H, and I'll come
4 back and talk about this. But let's just say the
5 delta might be a level of difference that might
6 matter to patients. And you can see in this
7 situation, this is the opposite. So the
8 intervention is clearly doing worse than the
9 reference treatment. And it's not just
10 statistically significant, but it seems to be a
11 level of effect where it may be inferior as a
12 clinically important level.
13 I guess the point I want to make to you is
14 can you see that we have a lot of stuff going on in
15 the middle where often we will have our trial
16 results. Just to go back, what is this delta?
17 This delta is an important concept as far as
18 noninferiority trials, which is called the
19 noninferiority margin. In other words, it's the
20 level of difference we'd be prepared to accept
21 between intervention and the control that may not
22 matter.

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1 Let's just perhaps go through some
2 alternatives. Let's imagine our trial result was
3 B. Now you can see with B, the intervention is
4 doing better than control, but can you see that
5 it's not statistically significant? But more
6 importantly, it excludes the noninferiority margin.
7 In this case, again, we've got a result
8 where we are noninferior. Here, we've got a bit of
9 a conundrum. Actually, the intervention is
10 noninferior because the constant doesn't cross the
11 noninferiority margin. But can you see we've got
12 an issue that it is actually clinically less
13 effective but still not inferior, if that makes
14 sense? So the level of noninferiority isn't
15 clinically important; you could perhaps paraphrase.
16 Here, we've just got a very small sample
17 size, haven't we? Very, very wide confidence
18 intervals. But importantly, it's an inconclusive
19 result in terms of noninferiority because the
20 confidence interval crosses the noninferiority
21 margin, and similar, these other two alternatives
22 would be inconclusive as well.

<p style="text-align: right;">Page 61</p> <p>1 So I guess the point I'm making to you is 2 when we do noninferiority studies, it allows us to 3 rule out what may be a clinically important 4 difference between the two treatments and our 5 inference. 6 So as I say, there is much published in the 7 whole area of noninferiority, and if you want some 8 bedtime reading this definitely will get you off to 9 sleep. It's as good as melatonin. 10 (Laughter.) 11 DR. TAYLOR: I tried it last night. But 12 it's a great publication, and a couple of things I 13 just want to draw with that. 14 The first one is one of the things when we 15 do noninferiority is the thing that we're comparing 16 to; so our reference treatment. This is going to 17 be a theme for me that I'm going to try and set up 18 for today, which is that when we're looking at a 19 reference treatment, we should have evidence that 20 that reference treatment is effective. 21 I think one of the themes of previous 22 IMMPACT meetings I think has been assay</p>	<p style="text-align: right;">Page 63</p> <p>1 does one give a placebo when the patient can 2 perceive the treatment? 3 That's a real conundrum in this space. And 4 clearly, with other alternative stimulation 5 frequencies that are parasthesia free, we now have 6 more of an opportunity to try and get at that. But 7 if we take that this is our gold standard, you can 8 see it's quite difficult for us in the 9 neuromodulation space to achieve that gold standard 10 with noninferiority studies because of the 11 challenge of placebo studies. 12 Sorry. I should have just said that from 13 the beginning, but that was the point of that 14 slide. 15 We are in Washington DC. I eventually got 16 in last night. By the way, I was going through 17 customs, and they obviously saw this stodgy 18 Scottish guy. So I had the pleasure of an extra 19 2 hours with U.S. customs. And gee, they don't 20 really have a strong sense of humor, those guys 21 don't. 22 (Laughter.)</p>
<p style="text-align: right;">Page 62</p> <p>1 sensitivity. In other words, we could set up a 2 noninferiority study where we choose a reference 3 that is quite convenient for us; in other words, a 4 reference that has perhaps shown not necessarily to 5 what before. And if show we are noninferior to 6 that, that's not terribly helpful, is it? 7 So what this guideline says is that when 8 we're doing these noninferiority studies, it's 9 tremendously important that the reference that we 10 choose has itself been proven to be effective. And 11 that might seem a very obvious thing to say, but I 12 think it's an important one. And I will give you 13 at least one example where I think we may not be in 14 that situation in SCS; so clearly, superiority of 15 the reference treatment. 16 What's also interesting -- and this is a 17 quote. This is not my words, "relative to 18 placebo." And again, I'll come back to this idea, 19 but what should be the right comparator in this 20 space, and clearly that's a difficult one because 21 as Rick has very eloquently told us, the history of 22 SCS has been a parasthesia based therapy. So how</p>	<p style="text-align: right;">Page 64</p> <p>1 DR. TAYLOR: I was trying to celebrate 2 jokes, and I was realizing as I was doing it, I 3 think I was actually -- they were putting me 4 farther down on the waiting list. So I thought, 5 no, no, I'll just not tell any more jokes. And 6 then eventually, I was able to text Sam that they 7 released me. 8 Anyway, that's a long way to say that I am a 9 European, so as well as the FDA -- the FDA have 10 published guidelines on noninferiority. And 11 actually, the FDA and the EMA guidelines are very 12 similar, as you might expect. This is from the 13 EMEA guidelines, our European. And again, they 14 make the same point, that when we're looking at a 15 drug or any technology in a European space, we need 16 to know that the thing we're comparing it to has 17 actually been compared to placebo. 18 But what I want to now get into is a little 19 bit of a technicality, which I think is another 20 challenge for you, or arise in this space, is how 21 do we go about working out what is this 22 noninferiority margin? Remember, we had that</p>

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1 delta? And of course, Simon was sitting there
 2 going, "Well, that's all very well, Rod,
 3 theoretically, but how do we get to that?"
 4 Well, here's a rule of thumb. This is taken
 5 from this document. Basically they say a
 6 noninferiority margin should be 0.5, preferably
 7 even less, maybe even down to 0.3, of the mean
 8 control effect of the reference treatment against
 9 placebo. So do you want to just imagine that?
 10 You know what the effect is of the reference
 11 against placebo. The noninferiority margin should
 12 be about half of that or about a third, and that's
 13 the kind of rule of thumb. And it's important to
 14 say that this is a rule of thumb. This is a
 15 value-based judgment. It's not a statistical hard
 16 fact. Different trials may have different
 17 noninferiority margins. But I think one of the
 18 questions I'm going to put to you is what might be
 19 a noninferiority margin in our space and what might
 20 be the implications of that?
 21 So just peeling back, this is back to Ewan
 22 now. If we were to say all the -- I think, Ewan,

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1 you identified 32 included randomized controlled
 2 trials and their database. I just did a head count
 3 of what proportion of them fell into these various
 4 questions. Perhaps not surprisingly, superiority
 5 is in the dominance; 4 noninferiority trials. Many
 6 of the people in this audience will know them and
 7 indeed have been involved in the trials directly,
 8 so the Senza trials, Sunburst, 10 [indiscernible]
 9 Deer DRG versus conventional SCS. So SCS with a
 10 small C here is conventional, and then Schu
 11 comparing Burst versus conventional.
 12 They were all formally designed as
 13 noninferiority trials. Simon's PROCOS trial, in
 14 the paper you actually say equivalence. I think it
 15 may be noninferiority, Simon, but anyway, it was
 16 one or the other. But interestingly, 11 of the
 17 randomized control trials, what was the hypothesis?
 18 Well, didn't he tell you?
 19 Let's sort of maybe continue along with this
 20 thing. Here's an example of one trial, which was a
 21 superiority trial. I had the pleasure of being
 22 involved in this study. This was a Medtronic

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1 funded trial, but run by effectively an independent
 2 scientific group led by the late Kris Kumar but had
 3 many individuals in this audience involved.
 4 Here's the primary result here. Well
 5 actually, this isn't the primary result. The
 6 primary result was 50 percent pain relief or
 7 naught. This was the secondary outcome in terms of
 8 a continuous pain measure. I think you would all
 9 agree with me that that result is pretty clear that
 10 in this case, adding spinal cord stim to
 11 conventional medical management alone appears to
 12 give a benefit in terms of leg pain, and the mean
 13 result on a 0 to 100 scale and the confidence
 14 interval supports that.
 15 So yes, we've got a statistically
 16 significant result. But again I would put it to
 17 you, that that's not enough. And what we need to
 18 think about is, okay, maybe statistically
 19 significant, Rod, but does it matter to patients?
 20 And this gets into another concept, which is the
 21 whole issue of clinical meaningfulness. And of
 22 course the IMMPACT group, you've talked about this

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1 area.
 2 Just to go back again, one of the
 3 recommendations from this guideline is that a
 4 minimally important difference should be between 10
 5 to 20 percent on a 0 to 10 NRS scale. In other
 6 Words, just quickly do your sums; about a
 7 difference of 20 on a 0 to 100 scale.
 8 If we were to look at the process
 9 result -- and I'm going to ask you the
 10 question -- here's the result from the process
 11 trial. It's statistically significant, but is the
 12 result clinically meaningful? What would be your
 13 take on that?
 14 (No response.)
 15 DR. TAYLOR: And you're all like me. You
 16 probably need a bit more coffee, so I'll help you
 17 along. And I would say probably it is because we
 18 can't rule out that it's not clinically meaningful
 19 because the bottom confidence interval crosses that
 20 number. But the mean's above the minimal important
 21 difference. So I would put it that probably, by
 22 and large, we've got evidence from process that not

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1 only is the result statistically significant, but
2 it's also clinically important as well. And the
3 MCID, or the minimal clinically important
4 difference, is an important metric we can use to
5 determine whether treatments aren't just
6 statistically important but also clinically
7 important.
8 Noninferiority, let's move on to this.
9 Here's an example of a non inferiority trial.
10 Again, this is not the primary result in the Senza
11 trial. They used 50 percent pain relief for more.
12 This is the secondary outcome. And I've slightly
13 reanalyzed the data for the purpose of this
14 presentation. But as I say, the Senza trial was a
15 noninferiority trial. For those of you who don't
16 know it, it was a comparison effectively between
17 two devices; one that delivers high frequency
18 stimulation and one that delivers low frequency or
19 conventional spinal cord stim.
20 As I say, if you can see it, if you're in
21 the cheap seats at the back, that's a statement
22 about how they got their noninferiority margin.

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1 And if you can't read it says, "Using a binomial
2 test for noninferiority with a 10 percent
3 noninferiority margin." So their primary outcome
4 here is a 50 percent pain relief or naught. So the
5 difference in those proportions by 10 or more they
6 were arguing as being noninferior. And then the
7 usual statements, 80 percent power, et cetera,
8 et cetera.
9 So over to you, a straightforward one. It's
10 a statistically significant result. The question I
11 guess we need to go back to is they've set this up
12 as a noninferiority study. Now, I've treated a bit
13 here, so actually, because the primary outcome was
14 set on a noninferiority margin of 10 percent, what
15 I've done here is to take a previously published
16 noninferiority margin on the continuous scale of 8.
17 And you might say, well where does that come from?
18 That with the Sunburst trial that set up its
19 noninferiority margin of being 8. And I guess the
20 point putting this to you is that although the
21 Senza trial was set up as being noninferiority.
22 You can see that the final result clearly excludes

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1 noninferiority, doesn't it?
2 Yes. And indeed, one of the benefits of
3 doing a noninferiority study is if you show that
4 the active is better than the reference, you can
5 automatically go on and then test superiority
6 without statistical penalty. That's quite an
7 accepted approach. So that's another benefit of
8 noninferiority. If you think that the two
9 treatments may be similar. But also, once you
10 prove that, you want to go on and demonstrate the
11 superiority exists, then one can.
12 So I'm with the author so far. I think when
13 the Senza trial was done, we didn't know if HF10
14 would be better than conventional, so let's set up
15 a noninferiority study to test that. But remember,
16 what was our gold standard for the reference here?
17 The reference is conventional spinal cord stim.
18 And the answer to that is that spinal cord stim
19 conventional should have been proven against
20 placebo. So clearly that did not exist in this
21 setting.
22 So you may say that the CONSORT, police if

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1 you like, get hold of this trial, they're going to
2 have a wee bit of problems with that. But the
3 trial did report, and I think clearly the result
4 demonstrates noninferiority. But the question I
5 would put to you now is can the authors here claim
6 superiority based on this result?
7 They do say so in this paper substantially,
8 certainly superior statistically, but there's the
9 MCID. Now, I'm seeing a few head shakes at the
10 back. So maybe actually this trial doesn't prove
11 superiority. Yes? Because we've got an effect
12 where actually the upper confidence interval
13 overlaps.
14 Anyway, I'm just putting it to you that I
15 think these hypothesis definitions are important,
16 and they're tremendously important and the way in
17 which we interpret the trial. I'm kind of beating
18 neuromodulation up here a bit, but actually I could
19 beat up other areas of chronic pain as well,
20 probably.
21 (Laughter.)
22 DR. TAYLOR: But I'm just trying to make the

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1 point that I think it's terribly important we get
 2 these hypothetical frameworks right and we
 3 interpret trials genuinely in those senses, because
 4 I think otherwise we get a lot of confusion in the
 5 system.
 6 Now, the other bit about
 7 noninferiority -- and you'll be glad to know I'm
 8 going to move on just a sec -- is the impact it
 9 might have on actually just the logistics of doing
 10 a trial. This is an example of a trial that Sam
 11 and I are actually cooking up at the moment. I
 12 won't tell you what the comparisons are. That's
 13 intellectual property to Sam. But we could either
 14 set up as a superiority design, and if we
 15 did -- I'm giving away the population we're going
 16 to do this in. This will be in failed back surgery
 17 syndrome -- we could use the IMMPACT MCID.
 18 We know that the standard deviation for the
 19 VAS NRS pain scale is typically about 2.5. Run the
 20 sums, also accounting, by the way, for 30 percent
 21 attrition. We need 48 patients per group. So the
 22 magic number I always have in my head is that a

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1 trial should be at least 100 patients if we're
 2 trying to demonstrate superiority in the pain
 3 space. Eric and I were just saying last night, how
 4 many trials does he get to see as an editor. There
 5 are at least as big as 100, and actually probably
 6 not as many as he would like.
 7 However, let's just imagine for a minute we
 8 set up as a noninferiority design. Now, you can
 9 see the impact is huge, isn't it, on the sample
 10 size. What I've done here is I've taken a
 11 noninferiority margin -- and it's difficult because
 12 remember, we don't have the placebo versus control
 13 effect here, and I would take half of that. But if
 14 we said that the surrogate effect size was the
 15 MCID, if we took half of that, that's 1. But you
 16 can see it has a tremendous impact on the sample
 17 size.
 18 So in this case, if we are going to run the
 19 randomized-controlled trial, we don't need 100
 20 patients, but we would actually need over 300
 21 patients assuming everything else being constant,
 22 90 percent power, 5 percent alpha, 30 percent

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1 attrition, and understand the deviation being the
 2 same.
 3 So I think I'm just putting out there that I
 4 think noninferiority studies are important, but
 5 they do come at a cost, and of course that's one of
 6 the issues maybe where we see them less.
 7 So time to move on. I've talked about
 8 inferiority/ noninferiority. What I want to move
 9 on now is to talk about different sorts of trial
 10 design. This is a real area of personal interest
 11 because a lot of the trials I do in the
 12 cardiovascular space are what are called complex
 13 interventions. They're not drugs, they're
 14 behavioral therapies. So I'm very interested in
 15 exercise-based rehabilitation. There the therapy
 16 is a complex one itself and multidimensional. It's
 17 delivered by more than one individual, and it can
 18 be delivered in different settings.
 19 Therefore, I think we need to be more
 20 innovative in our trial design. But again, using
 21 Ewan's database, if we look, classically the
 22 majority of trials in the SCS space are 2-groups,

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1 sometimes 3-group parallel randomized controlled
 2 trials; a lot of crossover studies in that space.
 3 And actually, a lot of them are quite a more
 4 recent.
 5 But interestingly for me, no cluster
 6 randomized controlled trials are in that space at
 7 all. Just to be clear, normally when we randomize,
 8 we randomize individual patients. Cluster, we
 9 randomize at the level of an organization. So in
 10 my setting, we might randomize one general practice
 11 of a particular way of delivering cardiovascular
 12 therapy versus another general practice, or in your
 13 case we could randomize you. We could randomize
 14 patients to either get one implant or another.
 15 And I would put it to you -- this is our
 16 paper that goes back to the BMJ -- this is a really
 17 neat way of thinking about things, and this is what
 18 they called expert T-based randomized controlled
 19 trials. Because I put it to you that a lot of you,
 20 the effects of an intervention in your space isn't
 21 just the technology, but it's the interaction
 22 between the implanter, the setting, the team, and

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1 the technology.
 2 So why not just take account of all of that
 3 and use that in our study design? But
 4 interestingly that's not really sort of pulled
 5 through. Again, cluster randomized-controlled
 6 trials are not perfect, and they come with a sample
 7 size calculation overhead. I've got my
 8 noninferiority. But I just thought that was an
 9 interesting observation just to mention the study's
 10 design space. Because I think if we see the
 11 ambition of this consensus, one of the things we
 12 might want to do is to say, well look, these might
 13 be some of the things we might want to think about
 14 in the future.
 15 So I'll finish up now by talking about the
 16 comparator. So again, excuse me, Americans, but
 17 we're back over in Europe, so this is the EMEA's
 18 guidance on the development of medicinal products
 19 for the treatment of pain. I don't know if there's
 20 an equivalent FDA document. I'm looking at Bob and
 21 Dennis and not seeing any reaction. Okay.
 22 This is, again, their statement. "Due to a

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1 high and variable placebo response in pain
 2 trials" -- and remember, we're not just talking
 3 about neuromodulation here; this is all
 4 pain -- "i.e., a systematic tendency for efficacy
 5 measures to show an improvement from baseline to
 6 endpoint of the trial irrespective of treatment
 7 allocation, placebo-controlled superiority trials
 8 are necessary."
 9 So again, here's another challenge back to
 10 the placebo-controlled trial, and again making the
 11 point, I think, in a neuromodulation space, it's
 12 challenging enough to do that in the drug space,
 13 but doing it in our space is even greater.
 14 Then the other thing that I did pick up in
 15 this document, not directly related to comparators,
 16 but again I think, Rick, you mentioned this in your
 17 presentation, is that when we do
 18 randomized-controlled trials or even non randomized
 19 trials of one area of the spinal cord stim against
 20 another, or one way frequency of stimulation versus
 21 another.
 22 Of course, patients are also receiving other

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1 concomitant treatments, analgesic treatments. And
 2 I think a big question for those of us working in
 3 this space is do we run our trials pragmatically?
 4 In other words, allow those concomitant treatments
 5 to vary. For instance, in the PROCESS trial, we
 6 were pretty permissive about letting patients
 7 decide and clinicians decide what the concomitant
 8 treatments were, but clearly that introduces
 9 confounding in terms of trying to conclude whether
 10 there's a difference between the neural modulation
 11 treatment and the control.
 12 So again, I'm using the magic database. I
 13 had a look. Nine of the randomized-controlled
 14 trials use some form of conventional medical
 15 management, so what these trials are doing is
 16 basically comparing spinal cord stim versus what
 17 would be the traditional medical therapy in that
 18 area. And these include trials, for instance, in
 19 the refractory angina space where you're
 20 randomizing people to either SCS or, for instance,
 21 coronary artery bypass grafting.
 22 Can you see that conventional medical

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1 management for refractory angina would actually be
 2 coronary artery bypass grafting? So this isn't
 3 just drug therapy. I'm seeing some shakes of
 4 heads, well, that's true, but that's the way I've
 5 classified it. Increasingly what we're now seeing
 6 in our space is these alternative I'm calling SCS
 7 device trials, and 5 trials were identified. This
 8 is the example, for instance, the Senza trial,
 9 where what we're doing are effectively head-to-head
 10 comparisons of comparing one form of spinal cord
 11 stimulation with another.
 12 What's very, very clear to me -- and
 13 actually, we're blessed with having Rick in the
 14 audience because it amazes me, Rick, that we go
 15 back to the 1980s-1990s, and you were doing
 16 randomized-controlled trials of these different
 17 ways of doing things. But of course they're
 18 becoming very en vogue. But this idea that we can
 19 do a randomized-controlled trial comparing
 20 alternative stimulation parameters, alternative
 21 techniques of surgical versus percutaneous leads,
 22 we've got a fairly good body of

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1 randomized-controlled evidence here.
 2 So the question here isn't does spinal cord
 3 stim work or not, but what's the best way of doing
 4 it? And of course that's a very important
 5 question, too.
 6 I guess the last point I want to make is
 7 that actually almost as many trials now are
 8 claiming -- and I think we'll talk about this
 9 during the meeting -- to be sham or placebo
 10 controlled; so 9 randomized-controlled trials that
 11 were categorized by Ewan and his team as being
 12 randomized controlled trials.
 13 I guess the point I'm going to finish
 14 with -- because I've really seen my presentation
 15 this morning as not necessarily filling all of my
 16 time but to really perhaps give you more food for
 17 thought and discussion. We've got to be careful
 18 about being hostages of the perfect. And I'm just
 19 going to leave you with this slide.
 20 This is one that comes from MySpace. Pachal
 21 Leever [ph] and I our old muckers. Pachal is the
 22 cardiologist; I'm the scientist. This was a

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1 randomized-controlled trial where we wanted to
 2 basically test an existing treatment for heart
 3 failure. So this is cardiac resynchronization
 4 therapy.
 5 For those of you who don't know it, this is
 6 a breakthrough treatment, so the prognosis for
 7 heart failure is grim. We introduced this
 8 pacemaker, and basically the improvements we saw in
 9 mortality and quality of life were huge. This
 10 therapy is therefore now very, very widely
 11 available. But of course, what were all of the
 12 trials? Well, they were basically comparing
 13 medical therapy plus CRT versus medical therapy
 14 alone, so non-blinded randomized trials.
 15 Now, you could say, "Well, come on, Rod.
 16 Are you're going to say that the survival benefit
 17 was placebo?" That would be a bit tough. But
 18 nevertheless, still has remained the question about
 19 how would you get all [indiscernible] if you did a
 20 placebo-controlled trial in that space?
 21 Yes, I know. This is perhaps a well-named
 22 trial. This is the MIRACLE EF trial. What they

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1 did in this trial was to basically randomize people
 2 to get CRT, so everybody had a pacemaker put in
 3 their chest, and they were randomized to be either
 4 on or off.
 5 Now you could say, "Rod, is that ethical?"
 6 But remember we still have the question of really,
 7 really, really does it work? And this was going to
 8 be for a certain space of time. Don't shoot me. I
 9 didn't design. I'm just reporting. But what
 10 happened with this trial?
 11 Well actually, the trial had to stop and it
 12 didn't stop because of anything to do with efficacy
 13 futility. It's just that nobody would participate
 14 in this trial. And you might say, "Perhaps not
 15 surprisingly, Rod." So after 13 months, only
 16 44 patients, blah, blah blah.
 17 Anyway, I guess the point is that we can
 18 talk about some of these elements of perfection or
 19 trial design, and you'll get pointy headed people
 20 like me giving you all of this advice, but of
 21 course, it needs to be implementable on the
 22 grounds [indiscernible]. So again, if I can put it

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1 to you, I think we need to keep that in mind as
 2 we're working our way through the next day and a
 3 half, but thanks for your attention.
 4 (Applause.)
 5 DR. THOMSON: Thanks very much, Rod, for
 6 that, and laying the problems open for us.
 7 For the future, I'd like to introduce Nate
 8 Katz, who I think is part of the IMMPACT group and
 9 works for Analgesic Solutions, and is very
 10 important to us in getting an output of this
 11 meeting. Thanks very much.
 12 Presentation - Nathaniel Katz
 13 DR. KATZ: Good morning, everyone. I guess
 14 there are three things that came to mind as I was
 15 sitting there listening to Rod. First is that I'm
 16 very jealous of his accent, and I wish --
 17 (Laughter.)
 18 DR. KATZ: -- I could give this
 19 presentation. It would make me probably sound a
 20 lot smarter than I actually am if I could speak in
 21 a Scottish accent. So you'll just have to be
 22 satisfied with kind of a worn-out Brooklyn, New

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1 York accent.
 2 The second is that it was brought back in my
 3 mind to one of my first recollections of my own
 4 experience in the field of spinal cord stimulation
 5 as a young implanter back in the early 1990s. One
 6 of my early memories is starting to give
 7 presentations, which were funded at that time I
 8 think by Medtronic, and sitting in the back of a
 9 huge lecture hall, sitting next to this other guy
 10 who is about to give a talk on spinal cord
 11 stimulation. And I of course had been up all night
 12 preparing my talk.
 13 That was back in the day, if you recall,
 14 where we had slide carousels, and the last slide,
 15 you had to find a place in your suitcase for it and
 16 schlep it. And you could only fit so many slides
 17 into it, so you had to make your decisions well in
 18 advance about what you were going to speak about.
 19 It's not like the morning, you can just change all
 20 your slides around.
 21 I was sitting next to this guy who was also
 22 scheduled to speak and was obviously much more

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1 experienced than I was. And he was about to go up
 2 and give his presentation, and he was literally
 3 choosing his glass slides from a big slide library
 4 and just stuffing them right before he was going to
 5 go up. And I was so jealous of the confidence that
 6 that speaker had and his obvious mastery of a topic
 7 that he could just nonchalantly do his glass slides
 8 right before the meeting. And that of course was
 9 Rick North --
 10 (Laughter.)
 11 DR. KATZ: -- who I was sitting next to.
 12 So it's been a pleasure to know you and
 13 learn from you over all these years.
 14 The third thing that occurred to me as I was
 15 listening to Rod's talk is that it occurred to me
 16 that I really have one message to present in my
 17 presentation, and you'll see a lot of detail. And
 18 actually, what I'm about to say to you isn't even
 19 written into my conclusion slides, although I wish
 20 that I had put it in there, which is that if you do
 21 a superiority study and you demonstrate statistical
 22 superiority of one treatment over another, you can

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1 confidently claim that those two groups are
 2 actually different; that the people in the group,
 3 the one that was better did better than the people
 4 in group 2.
 5 But if there are biases that affect those
 6 two groups in a different way, you can say that the
 7 two groups are different, but you can't say that
 8 the difference is because of your treatment,
 9 because the difference might be due to some other
 10 thing that operated independently on those two
 11 groups.
 12 So that really is the key message that I'd
 13 like to deliver, and all the rest of it is really
 14 just detail. So in order to confidently claim that
 15 one treatment is actually better than another, you
 16 need to demonstrate statistical superiority, and
 17 you also need to show that there weren't what you
 18 could call asymmetric biases, biases affecting one
 19 group or the other. And those are really the two
 20 conditions for a persuasive or randomized control
 21 trial.
 22 That's my whole presentation in a nutshell,

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1 so you can check your email, or go to sleep, or
 2 take care --
 3 (Laughter.)
 4 DR. KATZ: -- of whatever needs you have,
 5 and I'll just be talking in my old Brooklyn accent
 6 for the next half hour or so.
 7 I work in a small research and consulting
 8 firm. Just to frame out vocabulary so we don't
 9 have a Tower of Babel situation, we're all using
 10 different words for the same thing or the same
 11 words for different things.
 12 So imagine a perfect trial where you compare
 13 some treatment to some control, and lo and behold,
 14 there's a difference between the two. What do I
 15 mean by perfect? By perfect, I mean a trial
 16 conducted in a manner that is free of measurement
 17 error. That's what I mean by perfect. There's all
 18 different kinds of measurement error. There are a
 19 million of them. We'll talk about a few salient
 20 ones in the next few minutes.
 21 So if you could conduct, or imagine
 22 conducting a trial like that, and as Rod just

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1 pointed out, there is no such trial. But if you
 2 could imagine conducting a trial like that, then
 3 you could refer to this little red arrow as the
 4 true difference between treatments, which again
 5 doesn't exist in the world of reality because of
 6 what I just said; there's no perfect trial. But
 7 you can imagine that such a thing would be the
 8 case.

9 There are really two different categories of
 10 biases that I would like to refer to during my
 11 presentation. One is what you could call positive
 12 bias. Positive bias means that compared to the
 13 perfect trial, your imperfect trial exaggerated the
 14 difference between the two treatment arms, whether
 15 it's spinal cord stimulation versus sham, or drug
 16 versus the placebo, or on treatment versus another.
 17 It doesn't matter. The concept is the same.
 18 You're claiming a larger treatment difference and
 19 actually exists because of some form of measurement
 20 error. So let's call that positive bias in
 21 epidemiology, bias away from the null result.
 22 Here are a few selected causes of these kind

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1 of positive biases, and the rest of my
 2 presentation, I'll talk about some of these.

3 There's allocation bias, which is fixed by
 4 randomization. And since my talk is just about
 5 randomized-controlled clinical trials, I'm not
 6 going to speak about that bias anymore because in
 7 theory we've eliminated that through randomization.

8 Then there's expectation biases. If
 9 patients expect that they're going to do better in
 10 one group, in this group than in that group, for
 11 whatever reason, people might expect things. Then
 12 we know from the research on the placebo response
 13 and all sorts of other research that you get what
 14 you expect, as the saying goes, and you'll do
 15 better just by virtue of expectation, not by virtue
 16 of the fact that the treatment has a true
 17 difference. That's expectation bias.

18 Observer bias is a related phenomenon where
 19 if I know what treatment you're on, I might
 20 evaluate you in a different way and measure your
 21 outcome in a different way; influence how you
 22 measure your own outcome in a different way, and

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1 that can also cause an artificial inflation of this
 2 treatment difference.

3 Then there may be nonspecific factors like
 4 maybe you can make the mood of one arm better than
 5 another arm. Maybe you can be nicer to people in
 6 one arm than another arm. Maybe people in one arm
 7 have different access to rescue treatments or
 8 supportive treatments than another arm, or they
 9 live closer to the research center, or whatever it
 10 is.

11 If there's some other nonspecific
 12 factor -- what do I mean by nonspecific? It's not
 13 the treatment that you're studying. If there's
 14 some nonspecific factor that can influence outcome
 15 that operates asymmetrically between the two
 16 groups -- those are basically the three
 17 conditions -- then you can produce this kind of
 18 positive bias. So this is a table of contents for
 19 the part of my presentation that will be focused on
 20 positive bias.

21 By the way, these slides will be made
 22 available, so if feel like writing things down, you

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1 don't necessarily have to.

2 Negative bias is the opposite where there
 3 really is a true difference between these two
 4 groups, but there's something wrong with my study.
 5 There's some form of measurement error that shrinks
 6 the difference between these two, so that it's
 7 smaller or maybe that it even disappears entirely.

8 So this little red arrow is little compared
 9 to the so-called true treatment difference. You
 10 can say that's biasing towards the null result or
 11 towards failure to demonstrate differences. And
 12 there are all sorts of things -- there's a whole
 13 laundry list of things that cause that. I've
 14 selected a few of them because I thought they were
 15 mostly relevant to spinal cord stimulation.

16 A high placebo effect will actually bias a
 17 study to the null. So everybody in this study
 18 thinks that they're going to do better, and
 19 everybody kind of does get better. It's squeezes
 20 down the difference between two groups to a point
 21 where you may not even be able to demonstrate that
 22 two groups are different even though they really

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1 are different. That's high placebo effect. I'll
 2 talk a little bit more, but not a lot.
 3 Rescue medication and concomitant
 4 medication, I draw a difference between these two.
 5 I don't know how important it is. Concomitant
 6 medication, I think of something that the patient
 7 has been taking every day for a while. They're
 8 going to continue to take it during your clinical
 9 trial. Rescue medication is things that you take
 10 when you need them. That's how I use this
 11 vocabulary.
 12 It's been shown, the more concomitant
 13 medications and the more concomitant treatments of
 14 any kind you allow patients in your clinical trial
 15 to take, the better everybody's going to do. And
 16 again, that squeezes down the difference between
 17 the two groups and creates a bias towards the null
 18 result. Your treatment might work; you're not
 19 going to see it in that trial.
 20 Obviously, this is more of a problem in drug
 21 trials, I think. You tell me, and maybe I'm wrong.
 22 But if people aren't using the treatments, it

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1 biases the study to the null. It's as if you're
 2 not studying anything, so that's a source of bias
 3 to the null.
 4 There are a million different other kinds of
 5 measurement error, and I'll refer to one or two of
 6 them. One thing that I'll talk about in particular
 7 is extremes of variability of reporting of the
 8 primary endpoint. Let's say that we're doing pain
 9 studies and we're talking about a daily pain diary,
 10 for example. Obviously, it's not the only way to
 11 measure outcome in a pain study, but it's a common
 12 way.
 13 People with very high variability or people
 14 with extremely low variability, that population
 15 will not distinguish between two different
 16 treatments that are in fact different. We can have
 17 a long discourse in that today, but the short
 18 version of that story is that they just don't
 19 report their symptoms accurately.
 20 So it's as if you're measuring something
 21 where your measurement instrument is broken. It's
 22 no different than if you're doing a blood pressure

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1 study, and your blood pressure cuffs are not
 2 calibrated. It's the same problem, and that biases
 3 studies to the null because in pain studies,
 4 whether we like it or not, the patient is the
 5 measurement instrument. If patients can't report
 6 their symptom intensity accurately, sorry, you
 7 can't do your clinical trial and distinguished
 8 effective treatments. That could be a whole hour
 9 talk by itself.
 10 So that's vocabulary. Positive bias
 11 exaggerates the effect, negative bias minimizes
 12 true effects, and there are different causes of
 13 each one.
 14 Now I'm just going to show a few
 15 illustrations selected from a large amount of
 16 research on the impact of these various sorts of
 17 biases on treatment effects. This is a study that
 18 probably many of you are familiar with. This is a
 19 study in acute migraine done by a buddy of mine
 20 called Ted Kaptchuk, who's a world renowned expert
 21 on the placebo response, who heads the Center for
 22 Placebo Research at Harvard Medical School in

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1 Boston. So yes, there is a center of research on
 2 everything if you weren't aware of that before.
 3 I'm not going to go through the whole thing
 4 because it's complicated, but this is a study of
 5 acute migraine where patients with a migraine came
 6 in 7 times into the research center for 7 discrete
 7 migraine attacks.
 8 What happened to them during those 7 times?
 9 They either got no treatment, which are these black
 10 dots, so you had to sit there with your migraine
 11 and watch it get worse over time -- yes, patients
 12 did this -- or in these blue dots, you got a single
 13 pill that was placebo; or in these red dots, you
 14 got a single pill that was a real migraine
 15 medication called Maxalt.
 16 So why did you come in 3 times for placebo
 17 and why did you come in 3 times from Maxalt?
 18 Because there were actually other differences
 19 between these two. In the 3 times that you came in
 20 for placebo, every time you came in, you got a word
 21 written on a card, and the researcher handed you
 22 that card, and you read that one word. This is a

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1 one-word study. So if you came in for placebo, the
 2 card might say, guess what? "This is a placebo
 3 pill."
 4 I'm going to just digress on that. Ted
 5 Kaptchuk, this same guy, is very interested in
 6 conscious versus unconscious placebo effects. He
 7 believes that it doesn't really matter
 8 whether -- or it doesn't completely matter. You
 9 can't abolish the placebo effect by telling people
 10 that they are getting placebo because a lot of
 11 these mechanisms are unconscious.
 12 In fact, that's demonstrated in this study
 13 where you can see that in this group, they got a
 14 placebo, and they were told that they were getting
 15 a placebo. "Here's your placebo. Good luck with
 16 your migraine." And lo and behold, it was quite
 17 effective, the open-label placebo, as they called
 18 it.
 19 This is just to give you a sense of how
 20 powerful these effects are. I don't believe that's
 21 a sugar pill; that's going to work. Well, guess
 22 what? It works any way, whether you like it or

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1 not; or you could be told that you were getting the
 2 Maxalt. So in this group, the patients were lied
 3 to; they were deceived. They were really getting a
 4 sugar pill, but the card said Maxalt. And you can
 5 see that the effectiveness of the placebo was more
 6 or less doubled by that one word on that index
 7 card.
 8 Then you can guess the rest of the story.
 9 Here's the Maxalt. If you were told that the
 10 Maxalt was Maxalt, it had a very good effect. If
 11 you were told that the Maxalt was placebo, then the
 12 effect was more or less cut in half. So a word is
 13 as powerful as a drug when it comes to pain or
 14 subjective symptoms, et al.
 15 What about the rest of it? That's just one
 16 word. What about everything else that happens in
 17 the research center? So imagine how powerful all
 18 that stuff is, so think about that in context of
 19 spinal cord stimulator trials, and just let that
 20 sink into your mind for a minute.
 21 What about other sources of information or
 22 expectations that patients have? This is like the

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1 grandfather of all studies on deliberate
 2 manipulation of expectation in
 3 randomized-controlled trials of drugs. I believe
 4 this is the largest trial ever done of this type.
 5 It's a 2-by-2 design where you're randomized to
 6 drug versus placebo. This is Singulair and asthma.
 7 It's on the market. People use it.
 8 You're randomized to drug or placebo, and
 9 then you're re-randomized to what you might call a
 10 high expectation condition or a low expectation
 11 condition. And it's only in that kind of a study
 12 that you can look at the impact of different kinds
 13 of manipulations on the difference that's observed
 14 between drug and placebo.
 15 There's a lot that one can say about this
 16 trial. In this particular trial, one group, they
 17 got the high expectation where they got a glossy
 18 print advertisement and looked beautiful. It was
 19 put together by the marketing people from Merck.
 20 It had colors. It was shiny. It had nice words on
 21 it. They had access to the actual television
 22 advertisement in the United States for Singulair,

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1 which has butterflies and people dancing through
 2 meadows. I'm making that part up, but you get the
 3 idea.
 4 There was a fancy doctor with gray hair
 5 wearing a white coat in the room. And in the other
 6 treatment arm, the drug and placebo was the same,
 7 but you had a schleppy, young research assistant
 8 wearing jeans, and you got black and white, and you
 9 didn't see the TV ad, so it was a very neutral
 10 presentation.
 11 There are a lot of things to learn from this
 12 trial, but I'm going to just show you one thing,
 13 which is what was the impact of those different
 14 expectation conditions on the response to the
 15 placebo inhaler? You can see here, this is a
 16 self-report asthma scale.
 17 Here you can see that in the neutral
 18 expectation group where you had the schleppy
 19 research assistant on the ugly ad, you had a very
 20 low placebo response, whereas in the high
 21 expectation group where you had the TV
 22 advertisement and the old doctor, you more than

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1 doubled the response to placebo, such that in that
 2 group, Singulair could not be demonstrated to be
 3 more efficacious than placebo.
 4 Imagine now you're doing a trial on spinal
 5 cord stimulation. Does it matter what materials
 6 the patients see? Does it matter what
 7 advertisements they're able to see? Does it matter
 8 what's in your informed consent form? And if those
 9 things operate asymmetrically between the two
 10 groups, then you have this.
 11 Let's say I was doing just a fake spinal
 12 cord stimulator, I wasn't even putting in a real
 13 spinal cord stimulator to anybody, just fake spinal
 14 cord stimulator versus fake spinal cord stimulator.
 15 Imagine a study designed like that, but in one arm,
 16 they got this kind of messaging, and the other arm,
 17 they got this kind of messaging. The difference
 18 would be statistically significant between the two
 19 groups.
 20 So what's my conclusion? That fake spinal
 21 cord stimulation works better than fake spinal cord
 22 stimulation? No, it's because of these asymmetric

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1 biases that operate in these kinds of clinical
 2 trials.
 3 That's what I meant by what I said at the
 4 beginning, which is that, sure, you can claim
 5 superior. It's superior. There is no doubt that
 6 it's superior, but it has nothing to do with the
 7 treatment that you're studying. It's just because
 8 of these extraneous effects that are operating
 9 asymmetrically between groups. Make sense? Yes.
 10 There are a number of studies on this. This
 11 is about investigator expectation. I'm the
 12 investigator. I go up to you. I know what
 13 treatment that you're getting. You don't know. I
 14 don't say a word about it to you. You can video
 15 me. You can follow me home. I don't say a word to
 16 the patient about what treatment that they're on.
 17 My expectation for that patient is transmitted
 18 unconsciously and non-verbally to that patient, so
 19 that can bias the outcome as strongly as any of the
 20 other influences I just showed you.
 21 This is just one study from Rick Gracely in
 22 Michigan. This was a dental pain study. These are

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1 two different groups. All these patients got
 2 placebo. It was a more complicated study, but
 3 these are just the placebo arms from that clinical
 4 trial; placebo on placebo.
 5 What's the difference between these two
 6 groups of placebo patients? In this group, the
 7 investigators were told that the patient was either
 8 going to get placebo or naloxone, which of course
 9 doesn't relieve pain. In this group, the
 10 investigators were told something else. You could
 11 get placebo, or naloxone, or fentanyl, which is a
 12 high potency opioid analgesic.
 13 Just that investigator knowledge that you
 14 might be randomized to fentanyl, this group did
 15 much better than that group from a pain intensity
 16 perspective. Nothing was said to the patients
 17 about this in this clinical trial, and there's
 18 literature showing the same thing going back to the
 19 1950s. Jerome Frank from Hopkins showed this in
 20 psychiatry research. So the expectation bias is
 21 transmitted down the chain.
 22 One obvious conclusion from this set of data

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1 is that single blind equals no blind in clinical
 2 research. You told me that you did a single blind
 3 study; I tell you did an unblinded study.
 4 There are lots of body language and other
 5 interpersonal factors that also impact outcome in
 6 studies where subjective endpoints are being
 7 measured. There's a lot of research on warmth and
 8 empathy. This is a study of acupuncture for
 9 irritable bowel syndrome.
 10 Patients were randomized into either wait
 11 lists -- you just sat around and gotten
 12 nothing -- or a limited group where the
 13 acupuncturists were trained to be very neutral,
 14 like bank tellers, "Hello, how are you, let's see
 15 your acupuncture, see you later," that kind of an
 16 approach; whereas in the augmented group, the
 17 acupuncturists were trained to be warm and
 18 empathetic, "Hello, how are you, how are your kids,
 19 so nice to see you, let me rub your back, I think
 20 you're going to do great from this treatment," all
 21 the things that we're trained to do as healthcare
 22 providers that help us in that setting but that

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1 make us terrible clinical researchers if we act
 2 that way.
 3 So you can see that the response
 4 to -- actually, sorry. This was placebo
 5 acupuncture. I forgot to -- that might not
 6 actually make a difference, but if that matters to
 7 you, it's placebo acupuncture. And you can see
 8 that the outcome measures, which are primarily
 9 focused on pain, and this irritable bowel syndrome
 10 group were statistically significantly better in
 11 the nice acupuncturists than the bank teller type
 12 acupuncturists.
 13 So you can imagine and think about your
 14 spinal cord stimulator trial. Again, if people in
 15 one arm get the really nice people, and people on
 16 the other arm get the really boring people, then
 17 that's enough to produce statistical superiority,
 18 and I venture to say clinically significant
 19 superiority between groups, even if the two types
 20 of spinal cord stimulation are not different.
 21 This is a summary slide. In summary,
 22 expectation bias can influence studies in all

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1 different directions. It comes from a lot of
 2 different places. It's leaky expectation bias. It
 3 comes through the air. It's very difficult. Even
 4 if you expend effort, it's difficult to control.
 5 Of course, if you don't expend effort or if your
 6 study is designed in a way that kind of admits it
 7 by necessity, then you can't claim that difference
 8 between groups is due to the treatment.
 9 The directionality of the impact of
 10 expectation bias can go in two different ways. If
 11 everybody thinks they're going to do great, it
 12 actually can bias your study to the null result.
 13 So you actually fail to show differences when there
 14 truly are differences. Or if the expectation bias
 15 is asymmetric, it operates differently in the two
 16 groups. It can create an impression of a
 17 difference between two groups that's not actually
 18 there.
 19 I'm just going to say a word; I actually
 20 mentioned concomitant rescue treatments. I review
 21 a lot of clinical trials, including a lot of failed
 22 clinical trials. You'd be amazed how often in

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1 clinical trials, even of drugs, people don't even
 2 bother to track what medications patients are
 3 taking while they're on a trial. And then you get,
 4 "Gee, this person took some amount of ibuprofen; I
 5 don't really know." The concomitant medication log
 6 says this person was taking Vicodin on a PRN basis,
 7 but nobody quantified how much. You can't do a
 8 pain study like that and expect to learn anything
 9 from it.
 10 I'm going to just make a comment on this
 11 extreme variability issue. We've been doing some
 12 research on this issue for quite a long time. This
 13 is patients with pain due to osteoarthritis of the
 14 knee. We created an experimental paradigm where we
 15 measured how accurately patients reported
 16 experimental pain.
 17 To make a long story short, it turns out
 18 that about a third of patients don't report
 19 experimental pain accurately. If you translate
 20 that into the clinic, this predict whether they
 21 will discriminate drug from placebo in clinical
 22 trials. There are lots of reasons to believe that

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1 patients differ one from the other in terms of how
 2 accurately they can report their clinical pain.
 3 It's not just about listening to the patient. Some
 4 patients are better than others at conveying the
 5 reality of their experience using these strange
 6 scales that we give them.
 7 I can tell you if I'm at a social gathering
 8 and I tell people that I'm a pain researcher, I
 9 could just shut my mouth for the next hour and
 10 listen to people telling me story after story after
 11 story about how they fabricated their 0 to 10 pain
 12 scale when they were sitting in the emergency room
 13 because they wanted to move up in the queue, and
 14 how nobody can tell the difference between a 5 and
 15 6, and what does zero really mean anyway?
 16 You don't have to be a pain researcher to
 17 just flitter around your social circles and realize
 18 that it's very difficult to use these scales we
 19 give people to convey their pain intensity. And
 20 like all other human skills that have ever been
 21 studied, the level of skill differs between one
 22 person or another. So there's no reason to think

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1 it wouldn't be the same with the scale of reporting
 2 you're paying accurately, and in fact it isn't.
 3 This is data that's not been published yet.
 4 I pulled this from a trial -- we do a lot of
 5 statistical surveillance of ongoing clinical trials
 6 where we monitor all sorts of things during ongoing
 7 studies to identify problems with data quality. So
 8 I pulled this data from a recent large clinical
 9 trial of osteoarthritis of the knee. This is a
 10 drug study.
 11 This study's been completed, so normally of
 12 course we monitor only blinded data during the
 13 course of this study, but this study is complete,
 14 so we have the unblinded data. What we did is we
 15 segmented people into 4 groups based on how
 16 variable their daily pain intensity scores were.
 17 Bob, I put this here because I knew you were
 18 going to love it when I showed it. There's a lot
 19 of data out there in the literature already, and
 20 many of you probably know about it because it's
 21 been discussed at many IMMPACT meetings that
 22 patients with very high at least baseline pain

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1 reporting variability, don't separate drug from
 2 placebo.
 3 That's this quartile here. These are the
 4 patients with the highest quartile of pain
 5 reporting variability. In this particular clinical
 6 trial, blue is the drug results; yellow is the
 7 placebo results. You can see there's no difference
 8 between drug and placebo in patients with very high
 9 variability. That's been shown many times before;
 10 nothing new here. And I think it's because these
 11 patients don't know how to report their pain
 12 accurately, and there's plenty of data to indicate
 13 that that's true.
 14 What hasn't been shown before, but what I
 15 was dying to do, is the patients with very low pain
 16 are reporting variability. These are the people
 17 who every day their pain is a 6, or a 2, or a 10,
 18 or whatever it was. And I can tell you from my
 19 experience with chronic pain patients looking at
 20 daily pain scores, there is no chronic pain patient
 21 whose pain is really exactly the same every day for
 22 weeks and months on end. I don't know what that

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1 is, but it's not pain intensity reporting.
 2 (Laughter.)
 3 DR. KATZ: And you can see here -- this is I
 4 think for the first time -- that those patients
 5 also don't separate drug from placebo. Why?
 6 Whatever it is that they're doing, they're not
 7 reporting pain intensity in your clinical trial.
 8 And it's only these two groups in the middle of
 9 variability that actually will reveal a difference
 10 between a truly efficacious drug and placebo
 11 because they're the ones who were actually
 12 reporting their pain intensity.
 13 So imagine now, let's say you're
 14 doing -- what was it, Rod, a 48-patient per arm
 15 clinical trial? So imagine that in your 48
 16 patients in one arm, 20 of them aren't reporting
 17 their pain accurately, and in a different arm, 5 of
 18 them are not reporting their pain accurately. So
 19 how can you possibly expect to have an accurate
 20 estimate of treatment effect? You can't.
 21 Rod gave a very eloquent discussion, in much
 22 more detail than I'm planning to, about

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1 noninferiority studies. I'm just going to add one
 2 quick comment on it. If you do a noninferiority
 3 study between treatment A and treatment B -- a lot
 4 of you can anticipate what's coming up on the
 5 slide -- what's the interpretation if you just have
 6 two active arms?
 7 Well, if you had put a sham treatment in
 8 your trial, the interpretation might have been that
 9 both of your active treatments are efficacious. If
 10 this was the result of your sham, then your
 11 interpretation will be totally different. Neither
 12 treatment was efficacious.
 13 So the simple point I want to make is that
 14 an active controlled study, one active treatment
 15 versus another active treatment, if both treatments
 16 produce a similar effect and you don't have an
 17 internal demonstration of assay sensitivity, then
 18 that study cannot be used to make any inferences
 19 whatsoever about the efficacy of the treatment.
 20 Why did you do that study?
 21 Another point about noninferiority
 22 studies -- and Rod alluded to this earlier -- is

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1 that measurement error is the friend of the person
 2 trying to make mischief for the noninferiority
 3 study. What do I mean by that?
 4 If you're trying to show that your fancy new
 5 spinal cord stimulation is just as good or not
 6 worse than some established type of spinal cord
 7 stimulation, and you design a noninferiority study
 8 to prove that point, the more measurement error you
 9 have in your study, the more likely there is to be
 10 a finding of noninferiority, and the wider your
 11 confidence intervals, and the more likely they will
 12 fall into those ranges that Rod showed.
 13 So crappy research methods is the way to be
 14 successful on your noninferiority study, which,
 15 again, the only way to defend against that is with
 16 an internal demonstration of assay sensitivity. So
 17 without that -- is it ethical to do such studies
 18 like that? That's an interesting question.
 19 Anyway, I was assigned to talk not only
 20 about sources of measurement error and be the bad
 21 guy, but to present some possible approaches to
 22 preventing or mitigating such sources of

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1 measurement error. Again, we could spend a whole
 2 meeting just making a huge table of all the
 3 different kinds of measurement error and what the
 4 type of mitigation could be, but I just wanted to
 5 suggest a few general approaches that I think we
 6 should consider in this project that we're involved
 7 with over the next day or two.
 8 To state the obvious, double blinding and
 9 sham controls, for all sorts of reasons that I hope
 10 are obvious now, this is really a key point, which
 11 is that there are nonspecific influences and
 12 outcome. I outlined some of them during this
 13 presentation. I did not outline all of them.
 14 The study should be designed such that those
 15 nonspecific influences can be expected to be
 16 similar between groups. So in your methods section
 17 of your paper and in your methods section of the
 18 protocol, a laundry list of what are all the
 19 nonspecific influences that I could imagine.
 20 The programmer or the person who's going to
 21 be supporting the patient when they come for their
 22 visits, are they getting psychological therapy,

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1 physical therapy? How often are they being seen?
 2 What is the nature of their experience in the
 3 context of the visits in their research center?
 4 Those things not only should be designed to
 5 be similar between groups, but they should be
 6 documented. What rescue medication did they take?
 7 What concomitant medications? What kind of
 8 ancillary staff interactions? How long did they
 9 take? How frequently did they occur? What
 10 information did the patients get access to? What
 11 websites did they see? What's in the consent form?
 12 This all needs to be specified, otherwise
 13 you might have statistical superiority, but you
 14 won't be able to claim that that superiority has
 15 anything to do with your treatment unless you can
 16 credibly state that these nonspecific influences
 17 were symmetric because you counted it up as you did
 18 your trial.
 19 You might count how long the patients were
 20 in the clinic. How do you really know that the
 21 patients had a similar expectation of benefit if
 22 they're in one arm versus another? Because you

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1 counted how many minutes they spent with their rep?
 2 I mean, that's kind of an indirect measure. So
 3 another option to consider would be to actually ask
 4 the patients, do you think you're in the good
 5 treatment or the bad treatment? How likely do you
 6 think you are to benefit from this treatment?
 7 There are a variety of different expectation
 8 type questionnaires that are available. However you
 9 try to design your studies so these nonspecific
 10 influences are symmetric and the patient really
 11 does perceive that the perceptions are equally
 12 distributed across groups, you don't know until you
 13 measure it.
 14 This is going to be a bit of an annoying a
 15 comment. You are all familiar with these
 16 hierarchies of levels of evidence, right? We all
 17 worship them. It's like a form of idolatry, like
 18 the p-value less than 0.05, these hierarchical
 19 levels of evidence. And here they are, 1 through
 20 3; there are a million of them. This is one
 21 particular established one.
 22 The highest level of evidence is the

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1 randomized-controlled trial. People get up there
 2 at meetings and they say because they did a
 3 randomized-controlled trial, therefore I've made it
 4 to the promised land, and everything about my
 5 randomized-controlled trial can be believed.
 6 Well, what I just spent a half an hour
 7 telling you is that that's wrong, and that even
 8 though you do a randomized-controlled trial, these
 9 biases have plenty of opportunity to creep in and
 10 can undermine the credibility and interpretability
 11 of a randomized-controlled trial.
 12 So this is not the highest form of evidence.
 13 I'm sorry. This is the higher form of evidence,
 14 which in fact I think should be our basic standard,
 15 and it's not even mentioned in any of these
 16 evidence hierarchies, which is a randomized,
 17 double-blind, placebo- or sham-controlled trial, if
 18 that's appropriate for the treatment context, with
 19 measures implemented to minimize bias and maximize
 20 assay sensitivity; and that those factors are
 21 measured and documented. That's actually what we
 22 need in order to believe the results of

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1 randomized-controlled trials
 2 So, sorry, level 0 is the new level 1 --
 3 (Laughter.)
 4 DR. KATZ: -- or something like that.
 5 In conclusion -- well I think I just gave
 6 you my conclusion. Of course, I do want to make
 7 one comment, which is that this is a lot easier
 8 said than done. It's easier to stand up here and
 9 be critical, but when you actually get to designing
 10 and doing these trials, it's actually not easy,
 11 complicated, and probably not fully achievable, to
 12 be perfectly honest.
 13 So what I'm advocating for is an effort to
 14 at least be aware of what sorts of biases you are
 15 controlling and what sorts of biases you're not
 16 controlling. At least make an effort to quantify
 17 the extent that those biases are operating in your
 18 clinical trial. And if we can just do that, I
 19 think we will have taken a step forward in our
 20 clinical research methodology. And that's it.
 21 Thank you very much for your attention.
 22 (Applause.)

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1 DR. THOMSON: Absolutely perfect timing.
 2 Well done to all of our speakers who've actually
 3 made up for each other. I think we were
 4 entertained and very informed by what was going on.
 5 And I think that sets the scene for later for our
 6 discussion.
 7 So now we're going to break for tea; no,
 8 coffee and comfort, and then we are going to come
 9 back here at 10:45 and we're going to hear from
 10 regulatory agencies, and then we'll go into our
 11 discussion after that. So thanks very much,
 12 everybody.
 13 (Whereupon, at 10:16 a.m., a recess was
 14 taken.)
 15 DR. THOMSON: We're going to go on to our
 16 second session of the morning. I think one of the
 17 unique things about this group that we formed is
 18 that we're not just talking to ourselves, and we
 19 now are going to have two talks from regulatory
 20 agencies, both sides of the Atlantic. One will be
 21 Carlos Pena -- I probably pronounced that
 22 badly -- who is what I used to call the FDA, but I

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1 think it's the Center for Devices and Radiological
 2 Health of the Food and Drug Administration. He is
 3 the director of the Division of Neurological and
 4 Physical Medicine Devices, Office of Device
 5 Evaluation. So he seems to be just the right
 6 person.
 7 Then we have Rahul Singh from the MHRA.
 8 He'll explain, but we approached the EMEA. They
 9 don't really have a big device portfolio, so they
 10 look to their friends at the UK MHRA as well. So
 11 we'll get a European perspective as well on device
 12 regulation.
 13 Carlos, are you in the room? Good. I've
 14 introduced you. So Carlos, please, thank you very
 15 much indeed.
 16 Presentation - Carlos Pena
 17 DR. PENA: Good morning. Welcome to DC, in
 18 the snow. I feel your pain. The Food and Drug
 19 Administration, we are involved in medical devices,
 20 too, not just drugs. So today, I'm going to be
 21 taking you a little bit on an overview of the Center
 22 for Devices and Radiological Health and telling you

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1 a little bit about regulatory pathways. Then I'll
2 be diving a little bit deeper into points to
3 consider for neurological devices, including spinal
4 cord stimulation. Then third, I'll be talking
5 about best practices and giving some closing
6 remarks. And my apologies for not being able to
7 stay the entire meeting, but I hope to show you how
8 busy we are in a couple of slides, and you'll
9 understand why I can't stay the entire meeting.

10 Our vision is that patients in the U.S. have
11 access to high-quality safe and effective medical
12 devices first in the world. We take this vision
13 very seriously. I'm going to show you some data
14 about how quickly we would like to stand up studies
15 in the U.S. That success depends upon obtaining
16 invitations to forums like these, where I don't
17 know many of you, which is a good thing, so that we
18 can actually work together in getting products to
19 the marketplace, in the U.S. marketplace.

20 Our medical device definition statement is
21 defined as an instrument, apparatus, implement,
22 contrivance -- it goes on and on and on. It

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1 diagnosis, treats, or prevents disease in humans,
2 and it affects the structure or function of the
3 body of humans, not through any chemical action,
4 than it may be a medical device. I'm going to talk
5 a little bit more about that definition.

6 We take a risk-based approach to medical
7 device regulation here in the United States, where
8 we have three classes, class 1, 2, and 3, with
9 regulatory control increasing from class 1 to class
10 3. The device classification drives the
11 requirements that we look for in those products.

12 For example, most class 1 devices are exempt
13 from submitting an application to FDA. Most class
14 2 devices, which we call premarket notification or
15 510(k)s, we receive several thousand applications.
16 Those are class 2. Most class 3 devices, called
17 premarket approval applications -- and I'll talk a
18 little bit more in detail about what these
19 pathways -- we receive several dozen PMA
20 applications, class 3 devices, and spinal cord
21 stimulation is currently in that classification.

22 Across these three classes, we use what's

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1 known as general and special controls for which we
2 help to communicate to sponsors what they need to
3 do to meet the regulatory requirements for any
4 given product. There are four types of studies
5 that typically one could look at a medical device,
6 most of the time class 3. It's what's called under
7 an IDE, an investigational device exemption.

8 There are early feasibility studies. These
9 are small numbers of subjects early in development.
10 Sometimes the device technologies even change
11 during the study. Then we have traditional
12 feasibility studies. These give us early safety
13 and effectiveness data. Preliminary safety data is
14 what we're focused on in these traditional
15 feasibility studies.

16 Then we move to sponsor investigator
17 studies, not necessarily for a marketing
18 application, but we typically have a couple of
19 questions on what they tend to do with the data.
20 And then pivotal studies, which is the basis for
21 collecting data in a marketing submission. They
22 are typically definitively trying to provide the

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1 evidence that we seek for safety and effectiveness
2 in a statistically justified number of subjects.

3 When is clinical data needed? For premarket
4 approval, the PMA, class 3, typically it's needed.
5 For de novos, these are low to moderate risk
6 devices. Nothing's out there on the market yet, so
7 that's why it's called de novo; typically needed
8 but may not always be needed. And then for
9 510(k)'s, these are the "like-me" device
10 applications, kind of like ANDA applications,
11 generic applications. Typically clinical data is
12 not needed.

13 So you're saying, "Carlos, there are a lot
14 of provisos, addendums; when is clinical data
15 needed for my device?" My response is you can
16 request feedback on any of the protocols that could
17 be used in these regulatory pathways through a
18 Q-sub, preferably before you start the study. We
19 hate to get data sets where we're given a very nice
20 polished data set and say, hey, here it is. It's
21 perfect. It's ready for approval. But we haven't
22 even looked at the design or we haven't worked with

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1 you about the outcome measures.
 2 That Q-sub process, to make sure you and we
 3 and us understand the expectations, it's free. The
 4 Q-sub process is a free submission process. It
 5 doesn't cost anything. It could be done by phone,
 6 letter, and in person. So the days of being FDA,
 7 like I don't know the FDA's black box, use the
 8 Q-sub process. I think you'll be surprised about
 9 the interaction you have with us in recent days.
 10 Here's a slide that I wanted to get to.
 11 This is a slide that shows our IDE, how quickly we
 12 stand up studies. So in FY11, fiscal year '11, it
 13 took approximately 400-plus days to get to full
 14 approval of an IDE investigation. That's the study
 15 where you collect the data for safety and
 16 effectiveness for a marketing application. In '13
 17 and '14, we've improved those timelines. Then in
 18 '15, we've gotten them down to 30 days, the median
 19 time. It's a median time, but it's pretty good
 20 results. I like to think of these results as
 21 research, nature, science, New England Journal of
 22 Medicine quality research activity.

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1 These have not been easy data sets to come
 2 by. We typically do not halt a study for
 3 effectiveness issues, but we do halt them for
 4 safety. The reason we can get to 30 days is
 5 because sponsor investigators like yourselves know
 6 what our expectations are with regard to protecting
 7 the patient and possibly trial design
 8 considerations.
 9 When our expectations are matched, we can
 10 sort of stand up that study pretty quick, but it
 11 takes interactions. And we're making phone calls.
 12 Once we receive your IDE, we're making phone calls
 13 within the first 5 to 10 days. A lot of times
 14 people will get on the phone, like who's that?
 15 FDA? Who are you? But we hope to stand up these
 16 studies as quickly as we can. The faster we stand
 17 up the studies, the faster we collect the data.
 18 The faster we collect the data, the faster we can
 19 make a determination on whether that's good enough
 20 to get it to the marketplace.
 21 We're hoping to make that sustainable, too.
 22 We have very limited resources. That's why coming

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1 to forums like this, we're very grateful for the
 2 invitations that we get to these forums because we
 3 can help you contact us to make sure that our
 4 expectations are matched with yours.
 5 So we have experience in moving products to
 6 the marketplace. Here's a nice panel that I'd like
 7 to show, and I sort of change it up every now and
 8 then. But on the left, you have a clot retriever;
 9 you have ablation therapy going from left to right;
 10 cognitive assessment; a device; a prosthetic; a
 11 medical device for migraine; and catheters.
 12 The purpose is not to sort of dive into the
 13 details about what data was used for each of these
 14 products, but share with you that each of these
 15 products got to the marketplace through a tailored
 16 regulatory pathway. In the first one on the left,
 17 clot retriever, there were a couple hundred
 18 patients. That was the basis for the decision.
 19 All the way to the right, which was
 20 microcatheters for the neurovasculature, it was
 21 based upon bench testing. It went through the
 22 510(k) program, based upon prior studies where we

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1 had clinical data for those newer products, so as
 2 to share with you there are a number of pathways to
 3 get to market.
 4 I'm a big believer of this, and I'm not sure
 5 if you're going to believe this. But many times,
 6 the questions about getting to the marketplace are
 7 not regulatory at all; they're scientific or
 8 clinical issues. And we need help sometimes with
 9 that. That's why we have panel meetings. That's
 10 why we public forums. That's why we send out
 11 sometimes homework assignments to folks that are
 12 experts in the field. These are not regulatory
 13 hurdles that we confront. We deal with scientific
 14 and clinical hurdles: the placebo effect, the
 15 blinding, what a device does.
 16 There are a couple of pathways. I mentioned
 17 the de novo pathway, the premarket notification
 18 pathway, and premarket approval. There's also
 19 humanitarian device exemption. They still have to
 20 show safety, but it's also probable benefit, not
 21 full effectiveness, and that's for humanitarian
 22 uses. There's also a general wellness pathway for

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1 devices that can be categorized with not typical
 2 medical terms, but more of like relaxation and
 3 other soft clinical terms that are low-risk
 4 products.
 5 So there are a number of pathways to get to
 6 market. The question here is how can you get to
 7 the marketplace with more of the higher risk
 8 devices, which is spinal cord stimulation.
 9 A few points to consider. One is, in the
 10 device world, we're different from drugs, but the
 11 bars are the same. We require safety and
 12 effectiveness data, especially for PMA, class 3,
 13 high-risk devices. The differences come by the
 14 data sets we are able to look at.
 15 In drug world, you can typically anticipate
 16 the potential for two well-controlled randomized
 17 studies from any drug product approvals, typically.
 18 In the device world, by law, we are supposed to
 19 look at all types of valid scientific evidence,
 20 which come from no control studies, to
 21 historically-controlled studies, to
 22 placebo-controlled studies, all the way down to the

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1 randomized, blinded sham-controlled study.
 2 I'd like to think that at devices, we have a
 3 lot of different tools we can bring to bear to the
 4 process. Nevertheless, the randomized, blinded
 5 sham-controlled study is the best way, in some
 6 circles, to identify the impact of the medical
 7 device in a clinical setting. We have the least
 8 amount of uncertainty when we typically can use a
 9 randomized-controlled study. We have a lot of
 10 uncertainty when we're looking at a study that
 11 compares itself to a historical control.
 12 By law, we have to look at all of these.
 13 That's why the best way to figure out how we can
 14 move together towards getting a product to market
 15 is the presubmission pathway, when we set our
 16 expectations on making sure that you know the types
 17 of questions that we might have for any given trial
 18 design.
 19 Another couple of points to consider, I
 20 mentioned that trials are different from drug
 21 studies, but the standards are the same. Devices
 22 can be difficult to blind. In our Division of

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1 Neurological and Physical Medicine Devices, we also
 2 have prosthetics. It's very hard to make a
 3 randomized-controlled double blind study with a
 4 prosthetic arm.
 5 We have different tools that we can use to
 6 bring to bear to our products. For spinal cord
 7 stimulators, where you've heard in prior sessions,
 8 placebo effect is an issue. Blinding is an issue.
 9 The assessment tools are an issue. The trial
 10 design of superiority versus inferiority trial
 11 designs are an issue.
 12 A couple of things, endpoints can be highly
 13 diverse between studies. Typically, a single
 14 pivotal trial follows feasibility stages, but
 15 devices are designed to support a reasonable
 16 assurance of safety and effectiveness.
 17 Many times when I go to a conference, it's
 18 like parting the Red Sea, like no one wants to talk
 19 to me. But sometimes people will come to me and
 20 say, "Hey, I have this device. Can you approve
 21 it?" And I'm like, I look at that less and I'm
 22 like, well, you need to tell us about the device,

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1 the indications for use, the intended patient
 2 population, the prior studies, and any kind of
 3 precedent decisions.
 4 There are a lot of different details that
 5 fold in to a given submission to the FDA. There
 6 are many times where we can generalize about a
 7 different a device area, device class, like spinal
 8 cord stimulation, but we have to quickly delve down
 9 into the details of what was studied, was there a
 10 comparison group, and what was the outcomes, and
 11 can we have certainty in the outcomes.
 12 Let me move a little quicker. A couple
 13 other points to consider, many times we want to be
 14 very specific with the patient population, but we
 15 like to have it generalizable. These are smaller
 16 studies than the drug studies, so we do have to
 17 make some type of decisions with an imperfect data
 18 set. Time frame should be defined in pain studies,
 19 acute versus chronic, and we look for more than one
 20 safety and effectiveness endpoint, and we look very
 21 closely at the safety endpoints.
 22 The last couple of slides are about the

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1 organization. One is we are the Division of
 2 Neurological and Physical Medicine Devices. I'm
 3 accompanied here by Ms. Pamela Scott. She's the
 4 new branch chief of our neurostimulation psychiatry
 5 branch, which includes pain.
 6 Our division is one of several in the Office
 7 of Device Evaluation. We're thinking about
 8 combining these offices into a super office where
 9 when we work with folks, like sponsors, they can
 10 work with one office on both the premarket and the
 11 postmarket surveillance. That should be coming up,
 12 and I hope to share with you more updates about the
 13 organizational changes that are happening at FDA in
 14 the coming weeks, actually.
 15 But now, the Division of Neurological and
 16 Physical Medicine Devices, it's five branches. The
 17 neurostimulation devices psychiatry branch deals
 18 with a lot of the pain products, the spinal cord
 19 stimulation products. As I mentioned at the start
 20 of the talk, the best way to engage with FDA is the
 21 presubmissions. There are a variety of different
 22 settings. They could be from informational to

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1 introduce your product to the agency, all the way
 2 to a specific question: is my trial design the
 3 trial design that is most likely to reach a
 4 positive outcome when under FDA review? So there
 5 are a variety of questions you ask, and it's free;
 6 it's free, and it's free. Use it.
 7 A couple of closing remarks. One is that
 8 when a device can make it to market, it depends
 9 upon a lot of different things. It depends upon
 10 the data set that device was studied under, and in
 11 our case, under an IDE. But it also depends upon
 12 prior studies; the history that we have with the
 13 product; the intended use; the patient population.
 14 It depends upon the details.
 15 Two, if you think it's too early to contact
 16 the agency, that's the best time to contact us,
 17 through the presubmission process, and I mentioned
 18 it's free. We want to make sure that our
 19 expectations are matched with your expectations
 20 about the outcomes, about the trial design, about
 21 the endpoints, because it would be a very bad
 22 situation for us to not talk until you have a nice

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1 polished data set before the agency.
 2 Three, I showed you some of the timelines
 3 that we're interested in pursuing, standing up IDE
 4 studies typically for class 3 devices. They're
 5 aggressive. We cannot do it on our own. We need
 6 your help to work together to stand up those
 7 studies, so patients can get into those studies as
 8 quickly as possible. I you'll be surprised with
 9 the contact that you have with the agency. Thank
 10 you.
 11 (Applause.)
 12 DR. THOMSON: Carlos, are you going to be
 13 able to stay for the discussion today?
 14 (Dr. Pena gestures yes.)
 15 DR. THOMSON: Great.
 16 Rahul Singh, I'd like to hear from you. The
 17 whole setup of regulation is different in Europe,
 18 and I suspect Rahul will explain that to us.
 19 There's obviously a little transatlantic
 20 competition.
 21 Presentation - Rahul Singh
 22 DR. SINGH: Good morning, everybody. My

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1 name is Rahul, and I work as a clinical advisor for
 2 MHRA and also work as an orthopedic surgeon. I'm
 3 going to give you a top-level review of what our
 4 regulatory roles are within the UK and Europe, and
 5 hopefully to give you a pragmatic view if you are
 6 intending to make a device and bring it all the way
 7 towards CE marketing.
 8 Just a show of hands, how many of you guys
 9 have heard of MHRA?
 10 (Show of hands.)
 11 DR. SINGH: Excellent, so there's some good
 12 knowledge here.
 13 I'm going to show you three slides and three
 14 objectives. The first one is the journey of a
 15 medical device. You have a research and
 16 development area within your manufacturing company
 17 or your research university and that goes to device
 18 development. Within MHRA, we've got an innovation
 19 office where you can start inquiries, Q&As, and if
 20 you decide to submit any clinical investigations
 21 for a medical device.
 22 When you submit documents to MHRA and it's

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1 for a clinical evaluation and CI, we normally plan
2 to review it and give you an answer within 60 days.
3 During that 60 day process, they'll be a lot of
4 back and forth regarding questions, which I'll
5 follow on for the slides.

6 MHRA also has a second role as being a
7 competent authority, and that is a designated
8 authority. We also overlook all of the notified
9 bodies within the UK. At present, there are four
10 of them. These notified bodies give the CE mark,
11 which will grant you the rights to distribution,
12 sales, and commercialization of your a medical
13 device. And fourthly, MHRA is also involved
14 aggressively in the vigilance and the postmarket
15 surveillance of the medical device once it has been
16 CE marked and compliance of the regulations
17 following CE marking.

18 This is a bit more of a complicated slide,
19 our second regulatory role. It's a pictorial
20 review of what we do as a competent authority and
21 how we're linked with notified bodies. Again, we
22 review and audit notified bodies to see their

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1 management and their roles within the EU directive.
2 This slide is very complicated, so I'll
3 briefly touch upon it, and it touches slightly
4 about Brexit, and it's the new medical device
5 regulation. It came into play in 2017. It's got a
6 three-year transition period for general medical
7 devices and active implantable, i.e., spinal cord
8 stimulators. There's a five-year transition period
9 for in vitro diagnostic medical devices.

10 So why has it been a big change? It's
11 because there needs to be more emphasis on the
12 clinical evidence required to bring a medical
13 device to CE marking. There needs to be more
14 stringent levels of care required from postmarket
15 surveillance. And also there's more input from
16 notified bodies of how to regulate these devices.
17 No manufacturer is exempt from these regulations.
18 So if you've already got a CE mark, if you want to
19 pursue it in Europe or in the UK, you have to
20 conform with these new regulations.

21 A bit about the terminology that I'll be
22 discussing, a regulation is a legal binding force.

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1 It's immediately applicable within a set time frame
2 for all members of state in the EU. A directive is
3 an act that sets out for all EU countries, and it
4 must be achieved, but you can adapt it and
5 implement it for your own purposes. But
6 essentially, it needs to correspond to the
7 regulation.

8 MEDDEV, what we will be talking about, is a
9 common approach, a harmonized approach, for all
10 manufacturers to hopefully adhere to, and also for
11 the notified body. There's also an ISO standard,
12 which creates documents, and again harmonized
13 standards that we need to adhere to for medical
14 devices.

15 What's a medical device? My colleague
16 Carlos touched upon this. It's essentially
17 anything that you use that is an apparatus,
18 appliance, software, material, or any other article
19 that has a medical claim, and it doesn't achieve
20 most of its action through pharmacological,
21 immunological, or metabolic actions. The three
22 different medical device directives: one, firstly,

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1 active implantable for spinal cord stimulators,
2 general medical devices, and in vitro diagnostics.

3 When do you guys need to inform MHRA? At
4 the earliest convenience, especially. If you're
5 trying to do a trial in human for a non-CE marked
6 device or if you want to do a trial or a single-arm
7 study for a CE marked device but for a different
8 indication for use.

9 What are we expecting? In the medical
10 device directives, the aims are quite simple. The
11 clinical investigations are to verify, under normal
12 circumstances, the use of a device performance
13 conforms to those referred to Annex 1, which I
14 won't go into too much detail, and also to
15 determine the undesirable side effects, adverse
16 events, under normal conditions when you are using
17 the medical device.

18 The clinical data that we use to assess the
19 clinical investigation, approaches have been taken
20 for MEDDEV 2.71. As a stepping stone, it was
21 published in 2016 and addresses some of the
22 concerns about clinical evidence and what

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1 manufacturers are required to achieve those.
2 There's a clear move towards expectations of the
3 new medical device regulations, which are being
4 implemented in the transition period.
5 These are the stages of the clinical
6 evaluation. We've got five general steps. Number
7 one is to plan your clinical investigation,
8 evaluation; identify what personal data you
9 require; and appraise the individual data set
10 specific for your medical device. So not all one
11 package will fit for one for one medical device.
12 You need to show the analyzed data and conclude
13 appropriately for that medical device. And
14 obviously, the last step is final conclusion of the
15 clinical evaluation report.
16 The pertinent data is data generated by the
17 manufacturer for all preclinical investigations.
18 And as you can read there, it's relevant for that
19 medical device. The data retrieved from the
20 literature is relevant to the device under
21 evaluation. Again, each medical device is
22 different depending on its active implantable or in

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1 vitro device.
2 There's another standard I mentioned, which
3 is ISO. I'm going to go over a couple of them.
4 The main one that we use as clinicians is
5 ISO 14155, and it addresses the group's clinical
6 practice and requirements, the design, conduct,
7 recording, and reporting of clinical
8 investigations. It looks at demonstration
9 conformity with the relevant and general safety
10 performance requirements, and evaluation of the
11 pros and cons of the device with the risk-benefit
12 ratio. You need to justify what level of clinical
13 evidence you will use for your device, and it's not
14 all the same for all devices.
15 This is another example of a different ISO
16 standard. It's ISO 10993. Don't worry too much
17 about the numbers. It's for biological evaluation,
18 to make sure that the materials, substances that
19 are contained within the medical device are safe
20 for patients' safety. And this is a big area where
21 a lot of manufacturers actually fail upon; and
22 hence, why we actually object to the clinical

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1 trial.
2 This is a framework for the biological
3 safety and assessment from this ISO. Essentially,
4 we look at different things, so if you've got a
5 bone graft substitute, for example, which is
6 permanent, we'll expect you to investigate those
7 different aspects of toxicology and
8 biocompatibility.
9 What's the MHRA review process? The
10 validation takes about five days to take in terms
11 of validating all the documents that you have
12 submitted, and there's an online criteria which you
13 need to fulfill. We've got 60 days to make a final
14 verdict. If we don't give you a verdict within 60
15 days, you are free to carry out your clinical
16 investigations, but it's not advisable to do that
17 because the notified bodies will pick up on this,
18 obviously.
19 Within the 60-day period, we'll ask many
20 questions from different sections of the MHRA.
21 They include internal clinical assessors and
22 external clinical assessors; a technical team;

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1 biocompatibility person; and someone from the
2 pharmaceuticals medicine aspect if the medical
3 device has ancillary medicine in there; and
4 sterilization and statistics experts.
5 Again, with the 60-day period, questions and
6 responses are carried out, and then we come up with
7 a decision at the end of the day. The decision
8 isn't always completely yes. It may be yes with
9 conditions that need to be adhered to and be
10 implemented.
11 What are the common reasons for objection?
12 Ninety percent of all clinical investigations that
13 we receive, we usually approve, and we do implement
14 some conditions on those. The usual ones are a
15 lack of relevant clinical endpoints for that
16 particular device.
17 Statistical issues. A lot of manufacturers
18 will try to claim that you will need any amount of
19 patients such as 20 or 30 for safety, but the
20 actual fact, they want to prove efficacy, which is
21 not possible essentially. And this inadequate
22 preclinical testing, one of the main areas is

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1 sterilization or toxicology biological assessment
 2 and inadequate electrical software testing.
 3 There's been a lot of influx over the last couple
 4 of years with artificial intelligence being used as
 5 medical devices and medical apps.
 6 If MHRA approved it, good news. During the
 7 clinical investigation, we are still involved.
 8 We'll approve any study amendments; review adverse
 9 events on a regular basis, minimum every three
 10 months; review protocol deviations; and review the
 11 final study endpoints. During this period, if
 12 anything goes wrong or if there's an issue, for
 13 whatever reason, we can suspend and terminate the
 14 clinical investigation.
 15 The second part of what I said that MHRA
 16 does is being the designated authority, which we
 17 also review the notified body for CE marking. Once
 18 the manufacturer has completed the clinical
 19 investigations, they submit their data to a
 20 notified body and they carry out a conformity
 21 assessment. It's basically a strict protocol which
 22 assesses all the performance of the device from

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1 idea conception to reviewing all of the data at the
 2 final endpoint of the clinical investigation, and
 3 postmarket surveillance notified bodies carry those
 4 out as well.
 5 What is postmarket surveillance? It's a
 6 system to monitor the clinical performance and the
 7 safety of device once it hits the market after CE.
 8 It needs to be appropriate for the device intended
 9 use, and data must be evaluated for risk versus
 10 benefit ratio.
 11 This all falls into postmarket surveillance.
 12 There are different aspects to it. There's
 13 reactive, which is adverse events. So if you're
 14 lucky and you don't have any adverse events, you
 15 don't have to tell us about it. Postmarket
 16 clinical follow-up is proactive and you do need to
 17 inform us how well you're doing with the device,
 18 and implant registry. For example, in the UK,
 19 we've got national joint registry, and that
 20 actively seeks information on how well the device
 21 is doing. National joint registry is for
 22 orthopedic implants, hips and knees for example.

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1 A bit more about postmarket clinical
 2 follow-up. Again, it's part of MEDDEV 2.12, and
 3 it's for following a proper premarket clinical
 4 evaluation, and it must be based on the
 5 identification of possible residual risks and
 6 unclarity on long-term clinical performance based
 7 on risk and benefit ratio.
 8 Different methods you can use for postmarket
 9 clinical follow-ups depending on the device and the
 10 number of patients that you require. Notified body
 11 review; notified bodies, all class III and
 12 class IIb devices need to be reviewed by an
 13 in-house clinician. Sampling of IIa's and IIb's is
 14 also carried and done by notified bodies and not
 15 routinely monitored by MHRA unless the device is
 16 slightly a high risk or not much history,
 17 historical data, is present there.
 18 Again, this is a quick slide of the summary,
 19 original objective. This is the journey of a
 20 medical device. Hopefully, it's been informative
 21 and you guys know about it more. The regulatory
 22 roles of a competent authority, i.e., MHRA and

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1 notified bodies in getting your product/medical
 2 device onto the market. And again, this is a
 3 simplified version of the new medical device
 4 regulations, which will be coming into effect in
 5 2020 for general medical devices and 2022 for in
 6 vitro diagnostic medical devices. Thank you.
 7 (Applause.)
 8 Group Discussion
 9 DR. KATZ: We're going to have a 45-minute
 10 discussion now. I'd appreciate it if everyone who
 11 spoke this morning can join me up here on the
 12 panel. I'll be co-moderating this session with
 13 Salim, so if he feels like we've wandered off the
 14 reservation, he'll jump in.
 15 Salim, if you could come up and all the
 16 other speakers; Dr. Singh; Dr. Pena, and other
 17 regulatory colleagues, feel free to join us up
 18 here. It's a special opportunity to have the
 19 regulators with us, especially ones that flew
 20 across the ocean. So we want to take advantage of
 21 you.
 22 If you look at your agenda, the main purpose

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1 of this discussion session is to try to begin to
 2 frame out what our paper will look like with
 3 respect to study objectives, study designs that can
 4 or can't achieve those objectives, and how these
 5 issues of bias might be handled. I feel like we
 6 don't need to jump right into those nitty-gritty
 7 details right now, so why don't we just open it up
 8 for any questions for any of our panelists for now.
 9 And towards the end of this discussion, I may bring
 10 it back towards the issue of objectives and
 11 designs.

12 A quick housekeeping note, Dennis reminded
 13 me to remind you that when you do speak, please
 14 reintroduce yourselves to us. Mention your name
 15 and where you're from.

16 Any questions for anybody on the panel?
 17 Yes, Simon?

18 DR. THOMSON: Simon Thomson from the UK.
 19 DR. KATZ: Nicely done.
 20 (Laughter.)
 21 DR. THOMSON: Thank you.
 22 DR. KATZ: You're a role model for all of

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1 us.

2 DR. THOMSON: I listen to you, Nate.
 3 The interesting thing, actually, Rahul
 4 brought it up, and I suspect the FDA have got a
 5 view on it. I think everybody can contribute to
 6 this. One of the things with spinal cord
 7 stimulation is that we've got the target, which is
 8 stimulating the spinal cord. We've got a variety
 9 of different diseases that we treat.

10 I know this is about pain, but there is pain
 11 of ischemia and pain of this, that, and the other.
 12 And we've also got this issue where the same device
 13 can be used outside the spinal cord for off-label
 14 indications such as the treatment of migraine, the
 15 treatment of back pain with devices under the skin.

16 In the past, as clinicians, we had this
 17 loose regulatory thing of treatment of the back of
 18 limbs, and nobody really look used to look -- it
 19 was more of an argument we had, if you like, with
 20 the people who reimbursed us as to whether this was
 21 a valid treatment.
 22 Is there a change in regulatory climate such

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1 that now an approach to the regulatory people have
 2 to be made when we're starting to treat different
 3 conditions?
 4 DR. KATZ: You can just speak, and it will
 5 pick up.
 6 DR. SCOTT: Again, my name is Pamela Scott,
 7 and I am the branch chief of the neurostimulation
 8 psychiatry branch within our Center for Devices and
 9 Radiological Health.

10 In terms of from a clinician's pure
 11 perspective in terms of using a device on label or
 12 off label, off-label use is considered -- from a
 13 clinician's perspective, you can engage in practice
 14 of medicine. So we don't formally regulate the
 15 practice of medicine. When we really become
 16 engaged is when a manufacturer wants to promote a
 17 particular device for a specific indication and
 18 wants to label it for a specific indication, and
 19 that's when we really get involved.

20 I will say if we do become aware of
 21 postmarket issues related to a specific use or
 22 indication, we will often issues safety

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1 communications to the clinical community to make
 2 you aware of various safety concerns with either
 3 on-label or off-label use as we become aware of
 4 them.

5 Dr. Pena, do you have anything else to add
 6 to that?
 7 DR. PENA: To build upon what Pamela has
 8 described, for specific indications, I think we
 9 continue to ask questions about what specific
 10 patient populations are going to be improved with
 11 any given device. So there could be unilateral or
 12 bilateral issues. It could be pain in specific
 13 areas or generalized pain.

14 I think we have not changed in that we would
 15 like as much specificity as possible in the
 16 clinical trials for a given indication, making sure
 17 that we have enough numbers and is statistically
 18 justified. But at the same time, we're also going
 19 to look at that data set, which is probably going
 20 to be smaller than drug studies, to make -- we're
 21 going to ask the question, how can we generalize
 22 that information, as well, to the broadest

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1 benefiting population.

2 So I don't think things have changed from

3 how you've asked your question. We may be asking

4 some more questions about who's really benefiting.

5 DR. KATZ: Rod, do you want to focus on

6 that, before we go to Rahul, from your perspective?

7 DR. TAYLOR: And indeed, I'll bring you in,

8 Rahul, as well, if that's okay.

9 I wonder if I can ask a specific question to

10 our regulator friends.

11 DR. MARKMAN: You can.

12 (Laughter.)

13 DR. TAYLOR: Thank you. I'm being very

14 careful about any questions to the U.S. government

15 at the moment because I've had problems entering

16 the country.

17 No. But seriously, there's an example -- I

18 think what Simon is saying is that in the past,

19 spinal cord stim has -- there's been a lot of

20 510(k) stuff; so in other words, grandfathering.

21 So we've had this technology out there. We know it

22 broadly works and it's safe. Regulators, you're

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1 relaxed.

2 What's been interesting is that one of the

3 new therapies that's entered into your air space

4 and our air space is high frequency stim. So I'm

5 going to give us very specific examples.

6 Do you know the device, Senza?

7 DR. KATZ: We do.

8 DR. TAYLOR: Okay. Good, Nate.

9 I was intrigued that the FDA's

10 recommendation when Senza entered the market I

11 think palpably different to what had happened with

12 previous devices. And in fact, I think the

13 noninferiority study that I presented in my earlier

14 slides actually came from yourselves.

15 I know you don't often like talking about

16 specific companies or devices, but I think it's a

17 useful vehicle here to maybe just try and winkle

18 out a little bit about what might be your change in

19 thinking, because as you've heard from people like

20 Rick, this is a fast-moving area. We're getting

21 many more devices that are spinal cord stim, but

22 with a twist; thus changing stimulation frequency

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1 or not.

2 I think it intrigues me -- as a payer, I'm

3 very pleased that you're doing this, actually,

4 because then I'm getting the evidence further up.

5 But I'm intrigued with your change in behavior at

6 least with Senza and whether you'd be willing to

7 talk a little bit about that specific example to

8 help us think through the future.

9 DR. PENA: I don't like to talk about

10 specific companies, but I think probably you're

11 referring to the trial design of a noninferiority

12 trial design sort of approach. And like I had

13 discussed during my talk, we look at submissions

14 for them to stand on their own, and we look at the

15 data that's been submitted to us, hopefully with

16 our input during the development of that study.

17 The other thing to keep in mind is that many

18 times we're given a study that has some uncertainty

19 that may not be the most optimal trial design, but

20 we're asked to make a cut on whether the data

21 collected from that study, whether it was a RCT or

22 superiority study, or noninferior study like the

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1 Senza, and ask ourselves is there a benefit

2 potentially to patients here with the data that was

3 submitted, understanding that there could be

4 limitations. And we make that on a case-by-case

5 basis.

6 Is it comparable to other spinal cord

7 stimulation class 3 devices? They're class 3

8 devices. I don't think it's 510(k), except --

9 DR. SCOTT: The ones with the external.

10 DR. PENA: Yes. But typically, we look at

11 these studies with the data that's been generated

12 and try to make the best cut. There are a variety

13 of trial designs that come at play here.

14 So I'm not sure if there's been a shift much

15 more so as we try to make the best decision with

16 the data that's been provided.

17 Did you want to add anything?

18 DR. SCOTT: And I can just add, the spinal

19 cord stimulators that have an implanted pulse

20 generator are class 3. Those that have an external

21 pulse generator that's not implanted our class 2.

22 So they are regulated by two different regulatory

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1 pathways, which Dr. Pena described in his talk.
2 DR. NORTH: Can I pose a variation on this
3 question? Another widely publicized comparative
4 efficacy trial between two different modes of
5 stimulation, this involved one device, was also a
6 noninferiority trial. It happened to show
7 superiority of a new waveform over the standard
8 tonic waveform. But from my perspective as a
9 clinician, I don't need to see that at all. I
10 would be very happy to see, and I would hope the
11 FDA would approve of a new waveform available
12 through an approved device that helped some
13 patients that were not helped by the standard
14 therapy.
15 Would FDA be receptive to a trial designed
16 in that fashion? That would be -- to translate
17 this into what I think Rod would say, it would be a
18 superiority trial for the new waveform in the
19 patients who have not responded to the standard
20 one.
21 DR. PENA: So a couple comments. One is we
22 are not -- we provide options to sponsors for them

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1 to study their product. We're not entirely
2 prescriptive about how their design should be. We
3 raise the concerns that we have with regard to
4 limitations or the uncertainty that could be raised
5 in a particular study, but we don't specify the
6 trial design per se.
7 In addition, many times we may raise
8 concerns about a study under IDE, and those are
9 communicated to sponsor as study considerations,
10 because at the end of the day, there may be some
11 outcome that FDA -- we don't have a council of
12 elders in the basement. There may be an outcome
13 that we haven't identified. So we don't stop
14 studies for effectiveness or trial design issues,
15 but we raise the concerns that we may have and the
16 question that would need to be answered for any
17 given question that a sponsor is trying to ask.
18 So it's hard for me to say, if you ask FDA
19 for a particular study, trial design, we're not in
20 that place. We respond to the studies that are
21 provided to us and raise the limitations and the
22 benefits when those studies come to us. But it

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1 could be very possible if there is a collaboration
2 that you think would be worth pursuing, one
3 approach could be getting that study, bringing FDA
4 to the table, bringing the sponsor to the table,
5 and bringing an academic forum like this to bear.
6 DR. NORTH: No, I know it's hard to respond
7 to a hypothetical, and you do have very nice
8 mechanisms for pre-meetings of course for a trial.
9 But it just seems obvious that we can't expect each
10 new waveform to be superior to all that have come
11 before. Rather, there will be new ones that will
12 have some incremental benefit in a subset of
13 patients, and that should be enough. It would be
14 to me as a clinician.
15 DR. PENA: I would agree with that. To go
16 back to your question about the trial design
17 inferiority versus other types, we can comment on
18 those studies. I don't think we've shifted to any
19 particular trial design, though.
20 DR. KATZ: So I'm going to actually push
21 this conversation one more step, and then I'm going
22 to go to Rahul to give the European perspective on

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1 these six or seven different issues that have just
2 arisen; I hope you've been keeping track, and then
3 I have two questions from the floor. So why don't
4 we go in that order.
5 I'm just going to take a shot at a very
6 specific question for our colleagues from FDA.
7 And, Rahul, if you can add this to your list, that
8 would be great, too.
9 Given the limitations that have already been
10 discussed today about what conclusions can be drawn
11 from noninferiority designs, do you feel that
12 noninferiority designs can be used to demonstrate
13 effectiveness of a spinal cord stimulator?
14 DR. PENA: One word, and that's maybe.
15 (Laughter.)
16 DR. KATZ: I tried.
17 DR. PENA: We would need to know a lot about
18 what was the device; what were their prior studies;
19 what is the indication of use; what is the patient
20 population? These are sort of the questions that I
21 get at a conference, where, "Hey, can you approve
22 this device?" And it's like, "Maybe."

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1 There are a lot of details here that would
2 need to be worked out. There are a lot of staff at
3 the agency that we work with -- clinicians,
4 statisticians, engineers, and in some cases
5 epidemiologists -- that all come together to
6 evaluate the particular question before the agency.
7 So it's hard for me to answer your question
8 about a particular trial design or a particular
9 output without having all the other pieces that I
10 presented on the slide, that we would need to have
11 before us to give an informed decision, which would
12 take a review of certain amount of days for us to
13 come to a conclusion.
14 I'm not trying to be elusive. I'm trying to
15 be honest.
16 DR. FIELDS: You're doing a very good job of
17 it.
18 (Laughter.)
19 DR. PENA: Who was that? Did someone speak?
20 DR. FIELDS: That was me.
21 DR. PENA: You're asking questions where I
22 don't have the information -- Pamela doesn't have

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1 the information -- before us.
2 DR. TAYLOR: But I think to get you out of a
3 hole, if I may, what you're not seeing is no. So I
4 think back to Nate's point, we've got some worries
5 about noninferiority studies, quite fundamental
6 scientifically about assay sensitivity and all the
7 rest. But what you're actually saying, which is
8 quite reassuring, is that even in the face of that
9 uncertainty, as a regulator, you would still, in
10 the totality of consideration, be prepared to
11 accept noninferiority evidence, I think, if I may
12 paraphrase you.
13 DR. KATZ: That's a nice summary.
14 DR. SCOTT: I think the other thing to keep
15 in mind is when we do these reviews, like Dr. Pena
16 pointed out, we have an actual review team that
17 will often consist of, like he said, engineers;
18 clinicians; epidemiologists; if necessary,
19 statisticians, who are all looking at that data.
20 Oftentimes, when we have questions,
21 sometimes we have some of the same types of
22 questions that we've heard raised in this

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1 discussion this morning, and we will ask the
2 sponsor to provide us with information, with data,
3 to answer those questions to the best of their
4 ability based on the data set that they have and
5 based on other information that is in the
6 literature.
7 So oftentimes, we're going back to the
8 sponsor also ourselves to gather as much
9 information, as much data, to help us make that
10 determination of safety and effectiveness. And
11 again, we're looking at the benefits and the risk
12 of the device, and then what's the level of
13 uncertainty that we are faced with based on the
14 data set and the other maybe historical information
15 that we do have.
16 DR. PENA: Just one last point. If a study
17 comes to us that does not demonstrate or has a high
18 degree of uncertainty, and we're very concerned
19 about what the device or what the company's
20 purported to say about that product, we will
21 communicate our concerns.
22 I don't think we are not communicating the

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1 concerns or the questions we may have with any
2 particular product or trial design. We have very
3 difficult discussions. We're not elusive when we
4 have all the details before us.
5 DR. KATZ: So let's go to Rahul, finally.
6 DR. SINGH: All those kind of questions.
7 So start off with off-label and label use as
8 a regulator and also as a practicing clinician.
9 Off-label use is not recommended by MHRA because
10 it's not intended -- it's for instructions for use,
11 not intended use, for that medical device based on
12 the manufacturer's claims.
13 So if the clinician does use a device out of
14 scope from the intended use, IFU, we don't control
15 what the clinician can do. That's a different
16 regulatory body. That would be the hospitals, and
17 that would be the General Medical Council in the
18 UK. The clinician obviously has to make their
19 risk-benefit ratio themselves on a granular level,
20 where that device can be used and beneficial for
21 that patient, i.e., the spinal cord stimulator for
22 migraines, for example.

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1 Another comment would be, we don't comment
2 on the trial design based on the instructions for
3 use for that device. We don't advise manufactures
4 or applicants what you should do. We advise on
5 what you have submitted and what we believe is a
6 negative or positive. So it's based on those.
7 If we're seen as advising, you should do X,
8 Y, zed, and that's out of our agreement. All of
9 these things, as Carlos mentioned, we've got a
10 whole entire team, clinicians, statisticians,
11 engineers, et cetera, blah, blah blah, so it would
12 be unfair to ask for the highest level of evidence
13 for a manufacturer when it may not be necessary to
14 do that and subject patients to a device, a hundred
15 patients in each treatment arm when you can achieve
16 the same thing with a less number of patients using
17 a different trial design.
18 That was it. Was there anything else? And
19 I agree with Carlos' comment regarding Richard's
20 question as well, that you asked. That's about it,
21 I think.
22 DR. KATZ: Great. So let's go to the floor.

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1 I have Howard and Greg and Sam, and then we'll come
2 back to the panel.
3 Howard?
4 DR. FIELDS: Howard Fields, University of
5 California, San Francisco, a background of seeing a
6 lot of patients with chronic pain, including
7 neuropathic pain, low back pain. I also have done
8 a lot of electrophysiology on pain modulation and
9 spinal cord wiring.
10 In all my years of taking care of patients,
11 I never recommended a patient get spinal cord
12 stimulation. And the reason was I wasn't sure how
13 it worked, even though there was a model out there.
14 And the other one is I could never decide which
15 patients would benefit from it.
16 So I wanted to ask Dr. North, who's had the
17 most experience with spinal cord stimulation, not
18 how it works because he talked about that, but I'm
19 sure over the years, you developed a feeling for
20 which kind of patient would actually benefit,
21 because obviously some don't. So what's your
22 advice on that?

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1 DR. NORTH: Well, that's quite right. It
2 goes beyond spinal cord stimulation. In clinical
3 practice, practice of medicine in general, I dare
4 say, a neurosurgical practice focusing on pain
5 patients, it's clear to me with some patients, even
6 without seeing them, just based on the referral
7 information, that I'm not going to be able to help
8 them, and one learns to recognize those patients.
9 As to whether it is essential that I think I
10 understand the mechanism of effect to offer a
11 patient an operation or a treatment, I certainly
12 would like to know the mechanism or to think I know
13 the mechanism, but I don't regard that as an
14 essential ingredient. I think there remains a
15 place in medicine for empiricism and serendipity.
16 DR. FIELDS: Which patients benefit? In
17 your experience, what would it be about a patient
18 that would make you think this spinal cord
19 stimulation was appropriate?
20 DR. NORTH: That it would --
21 DR. FIELDS: Was appropriate for that
22 patient? What patient characteristics?

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1 DR. NORTH: Oh, okay. Well, so-called
2 failed back surgery syndrome is the most common
3 indication. But as one who does back surgery, I
4 routinely insisted on all of the patient's prior
5 records before I would see them as a candidate for
6 a stimulator. That's the only time you really have
7 a chance of getting those records, when the patient
8 is motivated to provide them.
9 It was often apparent from those records
10 that the patient never needed back surgery at all.
11 So it was not really a failure of surgery as much
12 as selection in the first place. Patients often
13 are encumbered by issues of secondary gain. If is
14 inappropriate utilization of medical resources, if
15 there's heavy legal overtone, those are all reasons
16 that I would hesitate to recommend any surgical
17 procedure, including a stimulator for such a
18 patient.
19 DR. FIELDS: Okay. Thank you.
20 DR. THOMSON: Can I just sort of add
21 something here? Is that okay? Dr. Simon Thomson
22 from the UK.

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1 What I think is that we're very good at
2 talking about what we won't do and why we wouldn't
3 recommend spinal cord stimulation, but we're not
4 very good at signposting what I think you're
5 asking: what's the ideal patient for spinal cord
6 stimulation?
7 DR. FIELDS: Exactly. Think of yourself as
8 an investor, and you're starting a clinical trial,
9 and you want to do your best to guarantee that
10 you're going to have a robust effect of the
11 intervention.
12 DR. THOMSON: Yes. And actually in Europe,
13 in fact, next month, we've got a working group
14 where we're going to be doing sort of a modified
15 delphi exercise, RAND/UCLA methodology, where what
16 we're trying to do is define the gut. So everybody
17 who does stim, we know the kind of patients that
18 this is going to be helpful for.
19 But let me just say a few specific things.
20 One is we're treating neuropathic pain. So if you
21 can see somebody with physical manifestations, and
22 it makes sense, that the examination fits with the

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1 history; that they've tried reasonable therapies in
2 order to adjust, to help them, and some of them
3 have often helped temporarily; or the side effects
4 have dominated and they've not been able to
5 continue, that's the physical, some kind of
6 neuropathy. Then we talk about the psychology, and
7 it's like patients who've maintained a role have
8 within the family and within work. They've got
9 supporters who help look after them.
10 So there are actually positive things that
11 we look for as to whether they'll do well with a
12 device. And it certainly seems to clinically bear
13 out. In my unit, we have a dynamic
14 multidisciplinary assessment of patients:
15 psychology, nurse. And the point is our trial to
16 implant ratio is 92 percent compared to in the U.S.
17 where it may be 65 percent, and our explant rate
18 is 6 percent at 4-5 years as opposed to 30 percent
19 at 5 years.
20 The difference in the U.S. is most SCS is
21 done in private practice I think, that they don't
22 necessarily -- there are differences, and the

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1 generalizability of the psychologist is a bit of a
2 tick box and doesn't necessarily alter whether they
3 progress on to SCS and so on. So I think we can be
4 quite clear as to the positive type of patients.
5 DR. NORTH: If I can supplement what you're
6 saying, continuing the failed back surgery patient
7 archetype, if a patient has a clear history and
8 supporting imaging studies showing that before
9 their operation, which failed, they had a big
10 refragment disk, say at L5 accompanied by a foot
11 drop, and they still have a sensory abnormality
12 when I examine them, and they have pain in the
13 distribution of that nerve, to me that is
14 neuropathic pain in the literal sense that I can
15 say -- surgeons tend to be concrete; that there is
16 something wrong with a nerve.
17 That's what neuropathic means. Right? It's
18 not just a buzzword you add so as to get
19 reimbursement. So there are candidates that are
20 ideal for clinical practice and study subjects.
21 DR. FIELDS: I think that this is an
22 incredibly important point in terms of trial design

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1 because if you look back over treatments for
2 neuropathic pain, when there's been a clearcut
3 diagnosis, such as diabetic neuropathy or
4 post-herpetic neuralgia, it's been possible to show
5 robust effects, for example, gabapentin and
6 duloxetine. But probably it's the case that most
7 patients who receive spinal cord stimulation, at
8 least in the states, don't have a clearcut
9 neuropathic component to their pain.
10 DR. KATZ: Greg, you were next, and then
11 Sam. Go ahead. Introduce yourself, please, if you
12 remember your question.
13 DR. FIORE: And who I am. Greg Fiore from
14 INS and also primarily a drug developer, my
15 background -- ION, apologies.
16 My question is, building on all that's been
17 said, really, related to the regulatory aspect of
18 evaluating applications, I always enjoy
19 presentations like yours, Nate, and conversations
20 with Bob about all the myriad factors that can
21 impair our ability to demonstrate treatment effect
22 even for treatments that we really know are

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1 effective.

2 Appreciating the health authorities have to

3 wade through all the data that they have, how do

4 you actually become informed, in a specific

5 application, about all the things that might have

6 happened to decrease the likelihood of

7 demonstration of effect? Because it seems like

8 those things keep drug developers and device

9 developers up at night worrying about how to

10 control, but the risk is really borne by the

11 patients because these factors impede drugs and

12 devices from getting onto the market when they

13 really are effective.

14 DR. TAYLOR: I think I was careful in my

15 presentation because I think what you're saying is

16 are we going to raise the bar so far. So we've got

17 statistical and clinical trial perfection, but no

18 one can do the studies, and the patients don't get

19 the technology. That's the kind of causality link

20 of where we could end up. I think we need to be

21 pragmatic. I do think we need to be pragmatic, but

22 I think the value of this group going forward is

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1 being explicit about what the issues are.

2 Nate and I were talking over coffee that

3 some of these issues are not as explicit with trial

4 design as they could be; so I think at least having

5 consideration of them when people go forward. I'm

6 going to kind of take the FDA rule here that it's a

7 maybe. Well, that's an important issue, but do we

8 have to deal with that in this setting? We'll at

9 least think about it, but do we have to definitely

10 implement that? Well, maybe not.

11 I think part of this is just a general move

12 towards trying to improve quality rather than

13 acting as a barrier. And I am speaking as a

14 scientist and I'm also speaking as a chief

15 investigator because I design trials as well, and I

16 want these guys on both my right and left-hand side

17 to say yes to those trials. But I don't think

18 anything we're saying here is going to raise the

19 bar so far that we prevent completely. But I think

20 it is a risk that you're saying.

21 If I may say one last thing, Nate. For

22 instance, one of the things that has come up in

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1 your presentation is that we might want to be very

2 canny with what we tell patients before a trial

3 about what they're going to take part in. So going

4 to an ethics committee where we basically don't

5 tell them what the trial is about is a real problem

6 for ethics committees.

7 Okay. We may help to minimize the placebo

8 effect, Nate, but we may have an ethics committee

9 that will say no, that patient information sheet is

10 not explicit enough for that patient to enter the

11 trial with clear understanding of what the relative

12 tradeoffs between harms and benefits are. So

13 that's a dilemma, but it's a dilemma we need to

14 collectively solve.

15 DR. KATZ: Rahul?

16 DR. SINGH: So we are raising the bar. In

17 Europe, the new medical device directive has come

18 into play, and it's focusing on three main areas.

19 Number one, postmarket surveillance -- number one

20 would be premarket clinical evidence relevant for

21 that medical device; and number two, postmarket

22 surveillance. This came to effect because of

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1 numerous stakeholders coming into play, the

2 European Union in Brussels, major manufacturers,

3 and competent authorities and designated

4 authorities, which are notified bodies.

5 As an example, anyone heard of

6 metal-on-metal hips, for example? They were

7 amazing about 10-15 years ago, but it's a shamble.

8 The premarket clinical data was amazing.

9 Postmarket clinical follow-up was a shamble.

10 Things came into play. The medical device alert

11 started coming into play in 2010. All these legal

12 litigation and appeals are happening in Europe and

13 in America.

14 So we are raising the bar. There's more

15 scrutiny and more stringent work that is being

16 implemented. Obviously due to Brexit, things may

17 be a bit different depending on which member of

18 state gets a better deal, i.e., if UK gets a good

19 deal or not.

20 Secondly of all, trying to mitigate your

21 risks as a manufacturer and as a clinician, it

22 depends on your outcome measures for your clinical

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1 investigation. If it's a novel, innovative medical
2 device and your primary outcome is assessing
3 safety, you don't need a randomized control trial.
4 We won't ask you to do that. We would just need
5 you to do a prospective single linear cohort of 20
6 patients closely monitored within set time frames,
7 that's got good outcomes, measurable outcomes,
8 based on historical data, new data, or similar
9 devices, and that's what we would ask for.

10 If your data comes good from these outcomes,
11 you can progress to a larger study requiring more
12 numbers, 50, 100, 200, and that would be relevant
13 for getting CE marking for a notified body.

14 DR. KATZ: Carlos or Pamela, anything to
15 add?

16 DR. PENA: Sure, a couple comments. I agree
17 with my colleagues at the MHRA. Just FYI, we do
18 have conversations with MHRA as well as other
19 regulatory agencies, Health Canada, across a number
20 of product areas, which I think is encouraging to
21 hear from the public vantage point. But to
22 increase the success of studies and reduce the use

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1 of Ambien by sponsors and by investigators, one
2 thing is to have a good protocol.

3 I took a couple of notes here: good
4 assessment intervals, good outcome tools, a good
5 informed consent. The way that FDA works on these
6 issues is through the presubmission process. It's
7 a free process. If we have our expectations
8 aligned, sponsors know what's required. We know
9 what's expected. There is full transparency and
10 less uncertainty.

11 Two, I think digital health is really going
12 to be helping us in many different areas, including
13 pain, especially when you can track patients'
14 activities. You can track patients very
15 objectively during the course of study. So I would
16 encourage folks to, in this forum, can digital
17 health be helpful here. And if it can be, making
18 sure that we know how to be helpful in monitoring
19 patient activity and outcomes.

20 Third, we are looking at, more so than usual
21 these days, patient-reported outcomes. That is
22 being very focused on by the agency, especially by

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1 Center for Devices. I've tried to make a little
2 bit about trial design but also about outcome
3 measures, including patient-reported outcomes. We
4 are interested in all types of outcome measures.
5 They should be validated and well accepted in the
6 community, but patient-reported outcomes may have
7 also a place here. That would give the patient
8 voice a lot more strength so long as we both
9 understand the pros and the limitations that may be
10 associated with the patient-reported outcome.

11 But that's another way for us to improve the
12 studies, especially in the pain arena where the
13 patient voice may have a unique opportunity here to
14 help us with these studies.

15 DR. KATZ: Pamela, did you want to add
16 anything?

17 DR. SCOTT: Not at this point.

18 DR. KATZ: Sam, you are next. Introduce
19 yourself, please.

20 DR. ELDABE: Thank you. I'm Sam Eldabe.
21 I'm a pain clinician from the UK. I've got a
22 question for Rod Taylor, but before that I'd like

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1 to provide an alternative answers to Dr. Fields'
2 question about the profile of the patient who
3 benefits from spinal cord stimulation.

4 I think the honest answer to your question,
5 Dr. Fields, is we don't really know. I think the
6 majority of the studies have been carried out in
7 patients with failed back surgery. And although I
8 take Rick's point that some have what you and I
9 would say is neuropathic pain, that is diagnosable
10 as neuropathic pain, because there is a nerve
11 injury, the majority don't.

12 So the actual balance between nociceptive
13 and neuropathic pain in our patients is not very
14 clear, and that's what's making it very difficult
15 for us to answer your question clearly.

16 The question to Rod, you mentioned
17 clustering. Given the complexity of spinal cord
18 stimulation as an intervention and the fact that
19 it's dependent on surgical expertise, programming
20 expertise, the interactions, et cetera, et cetera,
21 would you expect that there would be a clustering
22 effect?

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1 I see from the trials that we've done and
 2 the trials that we're doing at the moment that the
 3 way Simon does things is quite different to the way
 4 I do them, to the way Barani [ph] does them. Yet
 5 no study has taken account of that potential for
 6 clustering of effect.
 7 If there is one, what impact would it have
 8 on the outcomes of these studies?
 9 DR. TAYLOR: So it's a great question, Sam.
 10 We can take clustering into effect I think in a
 11 couple of ways. One is the way that I suggested,
 12 which is we actually design it into the study at
 13 the outset. In other words, we may allocate
 14 patients to receive the therapy, not on an
 15 individual basis, but by people like you, by
 16 implanter, or by hospital. And as I said, we just
 17 don't see those in this space.
 18 Without being too simplistic, they would
 19 help us very much with the question that you've
 20 said. So in other words, the success of the
 21 therapy is the interaction between the therapy, the
 22 clinician, and the setting therein. That's

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1 effectively I think what you're saying, and I think
 2 I would agree with that.
 3 Cluster designs will help us look at that in
 4 terms of allocation, but we don't ignore
 5 clustering, even in individual designs. There's at
 6 least one trial that Rick and I are currently
 7 involved in where we have multiple sites, and there
 8 was heterogeneity treatment effect across those
 9 sites.
 10 As a statistical advisor in that trial, one
 11 of the things that we have done is to adjust the
 12 analysis for site; for instance in sensitivity
 13 analysis. I'm seeing Howard nodding his head. Our
 14 statistical things we can do and probably should be
 15 doing more, Sam, to take account of that.
 16 So if we have a multicenter trial of SCS, I
 17 think we should be almost defaulting in our
 18 protocol design to, A, think about stratifying by
 19 site, which we would normally do; and then B,
 20 predefining that we would maybe use a random
 21 effects model to take account of that potential
 22 clustering just to check that we're not being

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1 underly conservative in our statistical estimates.
 2 So that's helpful.
 3 DR. ELDABE: Thank you.
 4 DR. KATZ: Yes? Please introduce yourself,
 5 Eric.
 6 DR. BUCHSER: I'm Eric Buchser from Morges,
 7 Switzerland. I'm a pain clinician there. I have a
 8 question about the efficacy considering from the
 9 standpoint of the FDA and the MHRA.
 10 How important is the efficacy of a new
 11 device system in getting the CE labeling?
 12 DR. SINGH: Your question is --
 13 DR. BUCHSER: My understanding is that FDA
 14 is not concerned about efficacy; basically,
 15 concerned about safety, right? Now in Europe, as
 16 far as I understand, efficacy is getting a big
 17 issue as well. So if I have a new device, do I
 18 have to prove that it's more efficacious than the
 19 other one or at least equally effective? How
 20 important is efficacy in your evaluation?
 21 DR. SINGH: Efficacy is important, but our
 22 main concern, motto, is patient safety. So if

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1 you're bringing a new device in that you want to
 2 trial on humans, it's needs to be based on
 3 risk-benefit ratio. If it's a new device, truly
 4 novel, and if it is high risk -- for example,
 5 spinal cord stimulator -- we will probably ask that
 6 you have low numbers in your study to be recruited.
 7 If that's satisfactory in terms of low numbers of
 8 serious adverse events or major adverse events,
 9 then you can progress to stage 2 or stage 3 and
 10 recruiting more patients.
 11 So the question is, is efficacy important?
 12 From the MHRA point of view, no. It's patient
 13 safety.
 14 DR. BUCHSER: CE labeling.
 15 DR. SINGH: For CE, it's patient safety,
 16 essentially. Your product doesn't have to be more
 17 efficacious, more superior compared to other
 18 similar marked CE devices. If your device is very
 19 similar or if it's not novel, if you just want to
 20 get into the market to commercialize, you can go
 21 through another route, through equivalence.
 22 So you may not even need to do trials in

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1 human beings if all the standards which are
2 required for equivalence are met, all those
3 standards based on statistics, historical data,
4 sterilization, toxicology, biocompatibility, and
5 clinical trials, et cetera. So summary, efficacy
6 is not first; it's patient's safety.
7 DR. SCOTT: From an FDA perspective, yes,
8 efficacy is very important in our decision-making
9 process. In terms of the overall answer to your
10 question, yes. From a purely regulatory
11 perspective, we usually use the term "safety and
12 effectiveness," but that is a key point of our
13 decision-making.
14 I think the thing to keep in mind, though,
15 in terms of level of evidence for spinal cord
16 stimulator, is it a new device? Is it a new device
17 area? Are you using it for a new indication? Are
18 you modifying the device? Those are some of the
19 things that we would take into consideration as we
20 interact with the sponsor in terms of level of
21 evidence necessary for demonstrating the efficacy
22 of that particular device, for a particular

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1 indication.
2 DR. KATZ: Rick?
3 DR. NORTH: I have a question about
4 enrichment of study populations, something we
5 haven't talked about yet. Once we get past patient
6 selection and have identified the clinically
7 appropriate group to subject to a study, there are
8 additional things that we can do.
9 Precision medicine is a buzzword nowadays.
10 I'm just waiting to hear of a genotype being
11 identified to predict which patients are good
12 stimulator candidates. And I assume that will be
13 straightforward from the labeling standpoint once
14 that happens.
15 (Laughter.)
16 DR. NORTH: But there's something we're
17 doing now to enrich study populations, and that is
18 we do a stimulation trial first. The study I
19 referred to earlier, patients had a trial of
20 conventional stimulation, and only those who passed
21 it and were implanted were then randomized to
22 conventional versus stim du jour. And I wonder to

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1 what extent there might be regulatory skepticism
2 about enriching the study population with a trial
3 of the therapy.
4 DR. SCOTT: I think, again, we rely on the
5 sponsor to provide us what their protocol is going
6 to be. I don't know if it's safe to say we have
7 seen that study design before. But again, we rely
8 on the sponsor to provide their justification for
9 their particular trial design that they are seeking
10 at them. And then from that point, we will, again,
11 point out to them what the concerns may be and what
12 the limitations may be of that particular design.
13 Anything else you want to add, Carlos?
14 DR. PENA: I think that's good. There may
15 also be labeling considerations that we need about
16 the product.
17 DR. KATZ: Salim?
18 DR. HAYEK: So it seems that we have
19 progressed gradually from anecdotal reports to
20 parasthesia-based studies, and now we have the
21 opportunity of having parasthesia-free devices.
22 But the elephant in the room is, is it time to have

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1 a level of zero study similar to what Nate
2 discussed? Can we prove that spinal cord
3 stimulation works for any indication, neuropathic,
4 nociceptive? And if so, when can we do such a
5 study, and does the FDA and the MHRA require such a
6 study for efficacy?
7 DR. PENA: We would not require that. That
8 is a decision we would look to many other
9 stakeholders to identify if a zero study needs to
10 be done for a given product or a class of products.
11 We would not mandate something like that. That's
12 just not our role. We would contribute to asking
13 the questions about how that study, maybe if it
14 comes to us, could be designed or points to
15 consider, but I don't think we would mandate
16 something.
17 DR. NORTH: Would even it even need to come
18 to you? That is something that clinicians and
19 payers and all of us want to know.
20 DR. HAYEK: But for us as a scientific body,
21 do we need to make that recommendation?
22 DR. PENA: If you're doing a study on label,

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1 it begs the question of whether a study is needed.
2 If it's on label for already an approved use -- if
3 it's for a new use, then we may have some
4 questions. But if it's for an approved use, you
5 could use the presubmission process to get some
6 free advice about the trial design, but it would
7 not necessarily be an IDE study for an approved use
8 on label.
9 DR. THOMSON: Can I just say something
10 there? I think, Salim, really what you're saying
11 is what will it take for how it feels to refer a
12 patient for spinal cord stimulation. Essentially,
13 that's really why he's there, what he's saying, is
14 that I don't recognize the patients that you're
15 treating, and I'm not completely convinced by the
16 clinical evidence to date. That's quite different
17 from the regulator, is something safe and
18 efficacious?
19 DR. PENA: One additional point, this may
20 not necessarily be an FDA question but more of a
21 CMS question, at least in the U.S., is this
22 procedure necessary and reasonable? That could be

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1 a question for CMS, or maybe even our NIH
2 colleagues would have some play in this. But I'm
3 not sure it's a regulatory question if it's for
4 approved uses.
5 DR. KATZ: Since we're on the topic of who
6 is interested in what kind of evidence, I know
7 that, Rod, you are immersed in the payer community,
8 and Brian sitting in the back will be giving a talk
9 specifically on this issue.
10 Do either of you want to make a quick
11 comment right now about the payer perspective,
12 whether this level zero type study that we're
13 talking about is of any interest to that
14 constituency?
15 DR. KOPELL: Hi. Brian Kopell. I think the
16 way you have asked the question sort of answers
17 itself. The payers more and more are beginning to
18 push back, despite the fact that they are achieving
19 FDA approval in the United States. The bottom line
20 is that they don't see how these new technologies
21 are essentially a cost benefit additive to the
22 healthcare system. They are simply not going to

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1 pay for it. And you could see this across not just
2 the pain stimulation but in various forms of
3 neurostimulation devices that have basically faced
4 this.
5 So the answer is, at some point, if
6 companies do not actually include this in their
7 pivotal trial design, they're not going to get it
8 paid for, and we're going to end up in a situation
9 where the payers are going to say we want that zero
10 study, basically.
11 DR. KATZ: Rod, did you want to add
12 anything?
13 DR. SINGH: Just so I don't give the wrong
14 answer, when you say zero level of evidence, what
15 do you mean? I'm discussing it with Rod as well.
16 DR. KATZ: That term seemed to have been
17 invented this morning during my presentation.
18 (Laughter.)
19 DR. SINGH: Maybe it was an American --
20 DR. KATZ: I don't want to say it's a
21 standard term, or at least it's only been standard
22 for about 45 minutes if it is a standard. We were

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1 just talking about how randomized-controlled trials
2 are not enough because there can be all sorts of
3 biases that can create the appearance of efficacy,
4 where fact there is no efficacy.
5 So I just threw out the term "level zero" as
6 sort of an even higher part of the evidence
7 hierarchy, where not only is a trial randomized,
8 but you've at least attempted to control other
9 major sources of bias that could create a false
10 positive clinical trial. So that's what we're
11 talking about with that term.
12 DR. SINGH: That's a good level.
13 So it's based on what the indication for use
14 for medical devices. If it's a high-level risk
15 device, we require more risk assessment of the pros
16 and cons of the device. Necessarily, if it's a
17 high-level of risk and completely novel, we
18 wouldn't ask for a randomized-controlled trial, and
19 I don't think the sponsors would take the time and
20 effort to doing an RCT. They would probably go for
21 a simple, unblinded, 20-K series to see if it
22 doesn't kill 10 of those patients, for example.

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1 DR. KOPELL: I agree with you. I think that
 2 the sponsors would be crazy to do this on their
 3 own, to be honest with you, and they probably would
 4 be sued for not upholding shareholder value
 5 basically, to be honest with you. But that being
 6 said, in the U.S. we have a for-profit insurance
 7 industry that essentially controls our health care,
 8 more or less.

9 At some point, they're going to make the
 10 metric is this worth it to pay for this, and
 11 rightly so, actually; and rightly so. At some
 12 point, dollars are not infinite, even though maybe
 13 the Federal Reserve will try. But it's not
 14 infinite. So at some point, that metric is going
 15 to have to be faced.

16 DR. TAYLOR: Could I comment on this one?
 17 Brian, hello. Thank you for comments, and I
 18 agree completely. I think the observation I would
 19 make -- and this is I think particularly a European
 20 observation, on the money where I think you are,
 21 Brian, is that often when we come to make decisions
 22 as payers, in other words -- because basically,

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1 regulators want to know does the therapy work and
 2 is it safe. And you want to trade those two off.

3 Payers have got a different question. We
 4 want to know what is the added value of your
 5 technology over the pool of other things that we
 6 could offer the clinician, and then does it provide
 7 good value for the money. And the problem that
 8 Brian and they often have in the medical device
 9 space is that the level of evidence that we
 10 have -- excuse me, regulators --

11 (Laughter.)

12 DR. TAYLOR: -- because you guys have let it
 13 go through at such a low level of evidence, we've
 14 got to pick up the tab later and get the company to
 15 do the frigging randomized-controlled trial that
 16 you guys should have asked them to do at the
 17 outset.

18 Sorry. It's slightly contentious. I've
 19 slightly parodied that, but that is often a dilemma
 20 for us. And it doesn't happen in the drug space
 21 because drug regulators don't allow it. If you
 22 don't have two confirmatory RCTs, you're dead in

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1 the water. With medical devices, you can get away
 2 with a much lower level of regulatory evidence, and
 3 then that comes back and bites us.

4 DR. PENA: I disagree with that. I think
 5 there are bars of evidence that we look for to make
 6 sure that there are clinically meaningful results
 7 obtained by a device manufacturer within our
 8 medical device regulations. The questions about
 9 CMS are different questions, necessary and
 10 reasonable. Those are not our questions.

11 Was our question answered by, is it safe
 12 with a risk-benefit ratio and were there clinically
 13 meaningful results? Was there a clinically
 14 meaningful benefit to the patient? Whether that
 15 was X number of patients. I don't agree with the
 16 proposal that there are two standards of
 17 regulations at the agency because, at least in my
 18 division, safety and effectiveness are targeted.

19 DR. KOPELL: And that's not in your purview.
 20 I agree. That's why -- what's interesting in this
 21 country is that you're seeing economic law come
 22 into effect and the for-profit companies, and

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1 probably at some point, CMS is going to make the
 2 same metric. They did that with VNS. You guys
 3 approved VNS for depression, and yet CMS basically
 4 said we're not covering it. It's not good enough,
 5 basically.

6 DR. PENA: Right, for necessary and
 7 reasonable determination.

8 DR. KOPELL: Sure. At some point,
 9 though --

10 DR. PENA: The way this is solved is if FDA
 11 and CMS, which we are starting to work together on,
 12 are making sure those studies have those four
 13 points in those outcomes, which I think is a way to
 14 do that. Sometimes though, when we have
 15 conversation with sponsors, they say, you know
 16 what? I'm going to try and first take on FDA, get
 17 through the regulatory system, and then go through
 18 CMS. Other sponsors are like, yes. Let's have
 19 everybody at the table to design that study that
 20 addresses two agencies.

21 DR. KOPELL: The funny history, though, of
 22 spinal cord stimulation I think is what Rod was

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1 referring to. What was it? In '78 when the FDA
 2 went from purely a safety monitoring body to an
 3 efficacy monitoring body, DBS and spinal cord stim
 4 basically had to create a new regulatory milieu.
 5 DBS was considered too high risk to use the
 6 historical data to be approved and
 7 required -- sorry to use your term -- the
 8 zero-level evidence to become a market-approved
 9 therapy, and it took 20 years or plus before that
 10 ever happened.

11 Spinal cord stim was essentially
 12 grandfathered for whatever reason. Was that the
 13 right decision? I don't know.

14 DR. HAYEK: And to be fair to the regulatory
 15 bodies, spinal cord stimulation historically was
 16 adapted and grandfathered in as parasthesia-based
 17 stimulation. And now we have a parasthesia-free
 18 mode of stimulation, but we're still putting it all
 19 under the umbrella of spinal cord stimulation and
 20 applying the same criteria for approval of both
 21 when you could have higher marks or higher level of
 22 evidence for applying for the parasthesia-free

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1 stimulation, basically, doing designs similar to
 2 drug studies.

3 DR. KATZ: Rod, did you have any further
 4 comments on this little debate about whether the
 5 level of evidence for drugs is similar to devices?
 6 DR. TAYLOR: No, but I think it is an
 7 important question, but I think Carlos hit it right
 8 on the head in his final comment, which is that
 9 there are increasing models in the U.S. but also in
 10 Europe for what we're calling joint scientific
 11 advice. In other words, where we researchers,
 12 clinicians, and industry -- we're all in this
 13 together -- meet with regulators and payers in the
 14 same room at the same time to try and design a
 15 trial that may address both those issues.

16 I think that's possible. I think those
 17 trials are not necessarily straightforward, but I
 18 think the genuine challenge we're asking ourselves
 19 here is that the ultimate consumer is the patient.
 20 So we want to make the therapy available to the
 21 patient. And I think some companies realize that
 22 if they get CMS and FDA in the room at the outset,

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1 they can probably do that more efficiently than
 2 doing it in an a sequence way.

3 I think genuinely -- and maybe, Brian, you
 4 and I can come back to this tomorrow -- I think the
 5 overhead of having the additional evidence to, if
 6 you like, help a payer doesn't prevent us still
 7 doing the basic questions to inform the regulator.
 8 I think they can be complementary. And maybe
 9 that's a challenge that we can try and pick up
 10 again tomorrow night. But I think it's an
 11 important one because it's about societal
 12 efficiency, really; otherwise we're going to keep
 13 going around in this crazy cycle where the
 14 regulators say something, and then the payers may
 15 say something different because their motivations
 16 are different by definition.

17 DR. KATZ: I will block out some time
 18 tomorrow for discussion of that issue. It seems
 19 very important.

20 Rahul, and then I'll go to Simon.

21 DR. SINGH: On an extremely top level in
 22 Brussels, there are talks as the new medical device

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1 regulations are being implemented. So we've got
 2 stakeholders for major manufacturers, from senior
 3 clinicians, from competent authorities, from
 4 notified bodies, and statisticians, who have tried
 5 to harmonize a common language for everyone to act
 6 upon for what you're suggesting.

7 Rod, when you're starting to get the top
 8 level of evidence, number one, or this new one,
 9 zero, the manufacturer will say, "Oh, hang on; this
 10 is too expensive; why should we go and do this?"
 11 when our primary endpoint may just be for safety
 12 because it's a new drug for the medicine side or
 13 it's a new medical device, they will contract, and
 14 we, actual fact, agree with that. But if there's a
 15 device which is equivalent to another CE marked
 16 device, and it's got a lot of historical data, we
 17 will question if a manufacturer just wants to test
 18 it on 10 patients. We will ask for more patients
 19 and power calculations relative for that device,
 20 for that indication for use.

21 So in summary, I agree with what you're
 22 saying. It would be good as a clinician personally

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1 and as a regulator to have the top level of
 2 evidence available for that particular device for
 3 that indication for use, but all stakeholders have
 4 got different motives, and obviously a different
 5 amount of funds and what they can use it for,
 6 basically.

7 DR. KATZ: Simon?

8 DR. THOMSON: I find myself in agreement
 9 with Rahul here because I think the idea that a
 10 company sponsor who is trying to create market
 11 access with the regulatory body, even though these
 12 are studies under the guiding eye of the FDA, I
 13 think as we will find, these noninferiority studies
 14 are very open to study gaming.

15 So often what's happening is that these
 16 studies are, and I'm sure the devices are, as good
 17 as the comparator. But what's happened is that
 18 they've ended up being shown to be better, on that
 19 study, than the comparator. And it's only when we
 20 get into the clinical practice that we're
 21 realizing, no, they're not. They're just quite
 22 good, too.

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1 That's why I think we're maybe wasting the
 2 money at that stage doing these randomized studies
 3 at a regulatory level. I kind of like sort of the
 4 European thing. Look, it's all about let's show
 5 does it do what it says on the tin -- Rod's
 6 phrases -- and is it safe? And then there should
 7 be another body that then looks at the clinical
 8 effectiveness and the cost effectiveness, and that
 9 should be more independently funded somehow so that
 10 we can then really produce the zero data for future
 11 reimbursement. That's what I think.

12 DR. SINGH: Just one more comment. I do
 13 agree that the medicines and the drug regulatory
 14 side is a lot more advanced, but that's based on
 15 historical clinical evidence. So the medical
 16 devices landscape has been more prominent the last
 17 couple of decades, but medicine has been there for
 18 many, many decades.

19 An example would be the major shambles which
 20 occurred with thalidomide. I think it was the
 21 1950s or '60s. So that bumped up the medicines
 22 regulatory 10 notches higher. Similar to devices,

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1 metal-on-metal hips has improved a lot of standards
 2 that are required; hence, why this new medical
 3 device directive is being implemented.

4 DR. NORTH: I return to the level zero study
 5 that seems illusive. I think it's already been
 6 prototyped. Over the break, a colleague asked a
 7 question to which I responded by sending a paper
 8 about a study that involved a new parasthesia-free
 9 waveform. And a blinded randomized-controlled
 10 trial had been done comparing the parasthesia-free
 11 waveform with sham of that waveform. And then
 12 there was another arm, which becomes sort of by the
 13 way in this setting, of a conventional
 14 parasthesia-based waveform.

15 But with a small sample, they did show
 16 benefit for both active treatments over placebo.
 17 And it seems to me that an expanded version of that
 18 study following the principles you outlined, Nate,
 19 is eminently feasible. And this involves a single
 20 device that will deliver all the waveform. So you
 21 can overcome the difficulties that we've heard
 22 about and will hear about with marketing as applied

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1 to gaming study designs.

2 Is that a good way to put it?

3 DR. KATZ: Great. Other questions or
 4 comments? We have a few minutes left in this
 5 discussion session, 7 minutes to be exact. And
 6 what this discussion session was supposed to have
 7 been about is objectives for clinical trials and
 8 design issues. So maybe if no one has any further
 9 questions on the topics that have come up, maybe I
 10 can try to accelerate that part of the discussion.

11 IMMPACT met a long time ago, and I think it
 12 was actually the first IMMPACT meeting where we
 13 proposed what would be the core outcome domains for
 14 clinical trials of treatments for pain. Those
 15 were -- someone correct me if I'm wrong -- the
 16 primary would be pain. Since we're talking about
 17 pain studies, it would be some measure of pain, and
 18 then secondary domains or secondary objectives, if
 19 we want to use that terminology, would be function,
 20 mood, sleep, safety of course.

21 What was the sixth one? I think there were
 22 six.

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1 DR. DWORKIN: Withdrawals, disposition
2 withdrawals.
3 DR. KATZ: Disposition. So I wonder whether
4 we could put that up in everyone's mind's eye for
5 consideration and just ask the question, should it
6 be the same for spinal cord stimulation for pain?
7 Should it be the same 6 outcome domains? And if
8 there are any differences, if there are any
9 additional domains that are important, are some
10 that are less important, what would those be?
11 Does anybody have any thoughts about that?
12 Just thinking about writing a paper, it would be
13 nice if I could just plug and play that section in
14 there, and that would be some progress.
15 DR. HAYEK: Device survival.
16 DR. KATZ: Device survival. Thank you.
17 Any other comments about that? Rod, did you
18 have your --
19 DR. TAYLOR: I was just going to support
20 your plug and play model. I think those outcomes
21 are relevant. Why shouldn't it any as relevant to
22 neuromodulation? I think the only one that I would

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1 really encourage, and we'll talk about it again
2 tomorrow, is economic outcomes. I think that it is
3 important for any treatment, not just neuromod, but
4 the new drug therapies in the pain area are often
5 extremely expensive as well. So I'd put economics
6 in there.
7 But I think the outcome domains stay the
8 same. I think the only observation I would make is
9 that as long as those outcomes are collected, it's
10 back to what the regulators and what the payers
11 might want. I might as a payer prioritize quality
12 of life over pain, whereas a regulator may
13 prioritize pain over quality of life. But if I've
14 got the data for both, I'm a happy man.
15 DR. KATZ: The regulator doesn't care which
16 is the primary endpoint, I assume, really.
17 DR. SINGH: Sorry?
18 DR. KATZ: Does the regulator care which is
19 the primary endpoint, pain or quality of life, as
20 long as they're all represented? Sorry. Does the
21 payer care which is the primary endpoint or as long
22 as they're all measured; is that okay?

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1 DR. TAYLOR: All measured, yes, comparable
2 to what's already present in the literature for
3 devices for that indication for use.
4 DR. HAYEK: And as a subset to device
5 survival, revision-free survival, because there's a
6 lot of revisions in stimulation.
7 DR. KATZ: Bob?
8 DR. DWORKIN: Bob Dworkin. I've always
9 liked some variant or other of Rick's global
10 question at the end of the trial to the patient;
11 given everything that you've been through and
12 experience, would you do this again? And I think
13 we left that out of the original IMMPACT, the kind
14 of patient global assessment of the treatment.
15 Obviously, for prescribed medication, we
16 never ask patients this in a clinical trial. I
17 think we should, in a clinical trial of a
18 medication, say, and when the patient is blinded,
19 obviously, if this was something you could get a
20 refill for, would you want to get a refill
21 prescription for what you've had and compare active
22 versus placebo? And that's basically Rick's

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1 question. So a patient global is what I would add.
2 DR. KATZ: Actually, we had a question here
3 from Robert. Introduce yourself, please.
4 DR. VAN DONGEN: Yes. My name is Robert van
5 Dongen from the Netherlands. I wondered how do we
6 compare with the IMMPACT initiative versus the
7 ICHOM initiatives, which are also there looking at
8 outcome measures. Do we compare these or are we
9 separate from them?
10 DR. KATZ: I don't know anything about that
11 initiative. Can you describe it?
12 DR. VAN DONGEN: The ICHOM is an
13 international corporation of health outcome
14 measurements that has been designed for all kinds
15 of studies, all kinds of diseases and so on, also
16 on pain. And they have a website which shows what
17 they're doing. And it's an international
18 corporation of researchers, designers of studies,
19 and they're very active in as far as I know,
20 Europe, and there might be comparative outcome
21 measures as to what we are doing.
22 DR. KATZ: Do you know offhand what their

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1 recommendations are for studies of patients with
 2 chronic pain?
 3 DR. VAN DONGEN: They have it on the website
 4 for low back pain. Yes, I can look it up for you.
 5 It's comparable to what we do with the IMMPACT
 6 initiative. It might be some slight differences.
 7 And also patient-reported outcomes are very
 8 important with that initiative.
 9 DR. KATZ: Thank you. That's a great point.
 10 Brian?
 11 DR. KOPELL: Sorry to perseverate, but,
 12 Robert, your question about the global question --
 13 DR. KATZ: Can you pull your microphone?
 14 DR. KOPELL: Oh, sure. I'm sorry. A New
 15 Yorker; usually I'm too loud. Anyway, the global
 16 question's an interesting one, because, to be
 17 honest, it's hard to ask that question in absence
 18 of this economic cost. Now, if you're taking a
 19 pill, it's pretty easy. Right? Take a pill.
 20 That's not very hard. You say to that same person,
 21 would you refill this prescription if it cost you a
 22 thousand dollars a month, you might get a very

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1 different answer than if somebody's footing the
 2 bill.
 3 With devices, it's a little different
 4 because the cost is the pain of surgery or the pain
 5 of the implant. So there's almost a cost built
 6 into that. Those two questions are a little bit
 7 different when you're taking a pill, or an
 8 injection, or something that's surgical.
 9 So it's kind of hard to get away from this
 10 cost benefit thing when talking about this type of
 11 activity. It's hard. It's hard to extricate the
 12 two. That's all I'm just kind of pointing out.
 13 Surgery's a little bit different because you have
 14 to undergo the knife, and it's painful to undergo
 15 surgery, at the very least, so there's always that
 16 metric.
 17 DR. NORTH: That's a fair question. That's
 18 the nature of the treatment.
 19 DR. KATZ: John, introduce yourself, please.
 20 DR. MARKMAN: John Markman. Rochester, New
 21 York. I would just add also -- I think this is
 22 analogous, but just to put a finer point on it, I

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1 think use of the device needs to be in the outcome.
 2 There are a lot of zombie devices out there that
 3 have been implanted in people but haven't been
 4 recharged, or haven't been used, or used very
 5 infrequently. And I think that actually is
 6 important because you not only want to know whether
 7 patients would do it again, but you want to know
 8 that it's become a meaningful part of a multimodal
 9 regimen, not just something that they had done, and
 10 now they're on to the next thing.
 11 DR. KATZ: Sam?
 12 DR. ELDBABE: We have a habit in the UK of
 13 asking patients about which outcome measures they
 14 prefer. And if you ask patients about a question
 15 like this, or an NRS, or a VAS, they unanimously
 16 would want to answer this question. A global
 17 assessment of the score.
 18 DR. KATZ: Yes, back there? Introduce
 19 yourself, please.
 20 DR. TRESKOT: Andrea Trescot, Alaska. One
 21 of the things that we've looked at has been percent
 22 improvement because pain scores are not

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1 particularly descriptive of how the patient's
 2 doing. Somebody's pain goes from a 9 to a 7, but
 3 they describe that they're 100 percent better.
 4 Their pain goes from a 7 to a 5.
 5 We've been using those numbers as though
 6 they are true integers, but they are not. We're
 7 adding them, and subtracting them, and dividing
 8 them, and doing standard deviations for them, but
 9 they are not true numbers. They are not actual
 10 discrete integers. And instead, we need to be
 11 looking at how -- it's a little bit of the GPIC,
 12 the patient's interpretation of global improvement
 13 or change.
 14 What I found is that not only are we talking
 15 about pain scores that are not linear, they're
 16 logarithmic, and everybody's logarithmic curve is
 17 different. That change where there's a high change
 18 going from one number to another is different for
 19 every patient. So that percent improvement has
 20 been very useful in my practice.
 21 DR. KATZ: It is lunch time, so I don't want
 22 to be the guy who's going to hold up lunch. Does

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1 anyone on the panel have any final comments before
 2 we break for lunch? Then you can be the bad guy
 3 that held up lunch.
 4 DR. MARKMAN: Biasing the audience.
 5 DR. KATZ: Yes, exactly.
 6 Well, with that, I'd like to thank our panel
 7 for their wonderful presentations and for their
 8 participation.
 9 (Applause.)
 10 DR. KATZ: Bob or Dennis, are there any
 11 housekeeping announcements with respect to lunch?
 12 Where is lunch?
 13 If you want to know where lunch is, ask
 14 Valorie right outside. See you guys after the
 15 break.
 16 (Whereupon, at 12:32 p.m., a lunch recess
 17 was taken.)
 18
 19
 20
 21
 22

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1 preconceived ideas -- literally no preconceived
 2 ideas -- of what spinal cord stimulation would be.
 3 So with that said, and just to reiterate
 4 what Nate said, our background, we're clinical
 5 pharmacists, but we also have conducted
 6 evidence-based research, systematic reviews of
 7 pharmacological interventions, but we're looking
 8 more at the results of those studies rather than
 9 this. And just to reiterate what Dennis said this
 10 morning, this is about methodology, not about the
 11 results themselves; so just to make that clear.
 12 Really briefly, the objectives, I'll very
 13 quickly describe the review process. This is a
 14 post-prandial audience, so I'll keep it short. The
 15 meat of my talk is going to be to report on the
 16 findings of the analysis itself. And then just for
 17 the last couple of slides, I'll look at some gaps
 18 or deficiencies in reporting and methodology. And
 19 then lastly, some things that we might want to talk
 20 about on the panel discussion afterwards.
 21 These are our inclusion criteria, not the
 22 inclusion criteria for the studies themselves, but

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1 AFTERNOON SESSION
 2 (1:37 p.m.)
 3 DR. KATZ: Good afternoon. I'm pleased to
 4 introduce Ewan McNicol. Many of you probably know
 5 him because of all of his work in meta-analyses and
 6 systematic reviews over the years, and he'll be
 7 presenting a systematic review of methodological
 8 characteristics of spinal cord stimulation RCTs.
 9 How was that? Close?
 10 DR. McNICOL: Sounds good.
 11 DR. KATZ: Okay. Thanks, Ewan.
 12 Presentation - Ewan McNicol
 13 DR. McNICOL: Well, thanks, Nate.
 14 Hi, everybody. Thanks for the introduction.
 15 As you saw earlier this morning, the vast majority
 16 of the ACTTION meetings to date have been based on
 17 drug interventions. So if you were being cynical
 18 at all, you might wonder why or you might question
 19 the wisdom of Bob in asking four pharmacists to do
 20 a systematic review of spinal cord stimulation. I'm
 21 not one of those cynics. I think it allowed us to
 22 look at it with a completely unbiased eye and no

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1 what we set out to look at. It had to be a
 2 randomized-controlled trial. It could be spinal
 3 cord stimulation for pain of any nature. Example
 4 comparatives could basically be anything as long as
 5 there was a control group. We looked at any pain
 6 outcome be it primary or secondary.
 7 I'm not actually aware of any spinal cord
 8 stimulation studies in children, but we restricted
 9 our review to adults or adolescence. And given
 10 what we talked about earlier with conventional SCS
 11 being parasthesia based, we felt that we had to
 12 include unblinded studies with no main on-study
 13 duration, and we allowed any sample size.
 14 Now, I mentioned earlier that we did
 15 Cochrane reviews, and we continue to do Cochrane
 16 reviews. And for those reviews, we have a
 17 stipulation that each arm must have at least 10
 18 patients in it or 10 participants. Just to keep
 19 this as broad as possible, we allowed any size of
 20 the study whatsoever.
 21 I'm not expecting you to retain this. Just
 22 really quickly, our search strategy involved a

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1 number of terms for spinal cord stimulation, a
 2 number of terms for various disease states or pain,
 3 and we combined that with a filter for
 4 randomized-controlled trials. We searched four
 5 databases. We looked at Medline, Central, Embase,
 6 and WikiStim, and we also looked at the reference
 7 sections of any included studies we did have way.
 8 We came up with 1227 non-duplicate citations.
 9 This might look like an incredible amount,
 10 but this is actually quite typical when you use a
 11 sensitive search strategy, to have about 95 percent
 12 citations that are completely useless or not valid.
 13 From these 1227, we've pulled 108 full text
 14 just to delve farther into whether the studies
 15 actually met our inclusion criteria or not. From
 16 these 119, we had 32 articles, as Rod spoke about
 17 earlier, that actually met our criteria; 64 of them
 18 were excluded. Then if you look over to the side
 19 here, we have some additional ones here with 23
 20 others, with 16 angina studies that we'll come back
 21 to, and 7 extension studies. And I'll talk about
 22 both of these towards the end of the talk.

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1 This just basically shows you the same thing
 2 in tabular form. But then on the bottom here,
 3 you'll see the reason why we excluded some of the
 4 studies. Abstract protocols only, there's just not
 5 enough data for us to extract. Known RCTs, cost
 6 effectiveness only. Rod will be looking into that,
 7 and Brian as well. We'll be talking about that
 8 later. So unless it was part of a larger clinical
 9 study, we left those out. No pain outcome.
 10 Duplicate manuscripts. This is kind of
 11 naughty. You're not supposed to do this anymore.
 12 But this was stuff where they presented exactly the
 13 same results but in a different journal or slightly
 14 differently, but we knew it was the same
 15 population. So that was 12 we got rid of.
 16 I'm not going to go into these in detail
 17 because I will get into them in detail when I show
 18 you the findings. But we were looking at 5 or 6
 19 basic features. We're looking at the study
 20 features themselves, the inclusion criteria of the
 21 studies, and what sort of patients they looked at.
 22 We spent a lot of time in study design. We looked

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1 at the statistical analysis, and then how they
 2 reported results. So again, not the results
 3 themselves but how did they present them.
 4 We set up a form with Jennifer's help. This
 5 is the first time we've done a methodological
 6 review rather than a results review. We had about
 7 60 questions in there with about 110 possible
 8 answer options. And what we found compared to when
 9 we do Cochrane reviews, the system was the same.
 10 We do every extraction and duplicate independently.
 11 So two people will look at the same manuscript, and
 12 then you compare your results just to look for
 13 mistakes, or disagreements, or whatever. For a
 14 Cochrane review, we usually have about two or three
 15 disagreements. For our data extraction for this,
 16 we averaged 18 disagreements per study. And there
 17 was actually one study with 36 disagreements
 18 between the two reviewers.
 19 We're not exactly sure what the reasons for
 20 this were. It could just be the nature of the
 21 review. When you're doing a methodological review
 22 and you're asking more questions, there's more

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1 opportunity for things to go wrong, I guess. It
 2 could be deficiencies in our coding manual. We
 3 trialed our coding manual and our extraction form
 4 on about half a dozen studies, but even with that,
 5 we were still finding disagreements 20 or 25
 6 studies into our extraction series.
 7 Lack of reviewer knowledge, definite
 8 possibility.
 9 (Laughter.)
 10 DR. McNICOL: We were learning as we're
 11 going along. But I think one of the major things
 12 was weaknesses in reporting. In part, it was
 13 because when you're developing a manuscript, you
 14 have a small space to actually put your findings
 15 in. So some of this stuff could be the data, but
 16 they just didn't tell us about it, or they said it
 17 in such a vague manner that we couldn't really work
 18 out what they were trying to tell us.
 19 So common disagreements. What was the role
 20 of the sponsor? Six of the studies actually didn't
 21 even mention if there was a sponsor, and then those
 22 that did, they tended to tell us what the sponsor

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1 didn't do rather than what they did do. The type
 2 of analysis, we so relieved when we saw that Rod's
 3 interpretation of the analysis was the same as ours
 4 because we're not statisticians, so actually we got
 5 that right. But it was really difficult to tell.
 6 They didn't come right out and say this is a
 7 superiority or inferiority analysis. They would
 8 kind of hint at it based on their statistical
 9 analysis, so we have a lot of disagreements there.

10 Pain relief versus pain intensity
 11 difference, I was quite staunch about this one.
 12 Many of the studies said that an outcome was 30
 13 percent pain relief, where in fact what they were
 14 talking about was a 30 percent reduction in pain
 15 intensity. So I was insistent that it actually had
 16 to be a pain relief scale rather than a difference
 17 in pain intensity. I don't know what you guys
 18 think about that.

19 Then clinical significance was all over the
 20 place. Was it within patient? Was it between
 21 groups? Was it a part of the statistical analysis
 22 that was really a statistical thing or was it

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1 genuinely a clinical thing? So that confused this
 2 no end.

3 Then the graph down the bottom here really
 4 just demonstrates if there were more disagreements
 5 based on when the study was published. And I don't
 6 think this is particularly insightful, other than
 7 to say that the newer studies tend to just have
 8 more data that we can plug in. So the more data
 9 you have, the more opportunity there is for
 10 something to go wrong.

11 This is a picture of my daughter's bedroom,
 12 and I think this is a good metaphor for the
 13 findings of the analysis itself.

14 (Laughter.)
 15 DR. McNICOL: It has potential, but it's
 16 quite messy.
 17 (Laughter.)
 18 DR. McNICOL: This is the meat of my talk.
 19 This is the study findings themselves. We
 20 extracted 32 studies, and this is what we find.
 21 There's about a 50/50 split in sites. This
 22 surprised us. Only about a third of the sites were

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1 actually in the U.S. I think we're probably
 2 catching up now, but many of the early studies were
 3 in Europe, and less than 40 percent were registered
 4 studies. So by that we mean clinicaltrials.gov,
 5 WHO, and Netherland sites, whatever. And again,
 6 the newer studies tend to be registered and the
 7 older ones tend not to be. The funding pie chart
 8 here is fairly obvious. Most of the funding comes
 9 from industry, and given the cost of units, this is
 10 not entirely surprising.

11 This is the inclusion criteria of the
 12 studies, not our inclusion criteria. What did
 13 patients have to have before they were included in
 14 the study? If you look at the key at the top here,
 15 the orange is yes and the blue is no. What you see
 16 here is that in the majority of cases are the most
 17 common stipulations where failure of any other
 18 treatment. This is basically a lash-line [ph]
 19 treatment, which is almost setting patients up for
 20 failure in that they failed everything else;
 21 minimum duration of pain or a minimum pain
 22 intensity.

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1 If we look at the last two, the median for
 2 minimum pain intensity amongst those studies that
 3 assisted in that was a 5. So patients had at least
 4 moderate pain. Then for the minimum pain duration,
 5 the median was 6 months, which as we all know is
 6 one of the definitions of chronic pain. So nothing
 7 too surprising here. I don't think any of the
 8 findings today are going to surprise you. It's
 9 really just putting a marker down for where we're
 10 at.

11 This is the patient population pair
 12 inclusion criteria. This isn't table 1 where they
 13 break it down by exactly what people had. This is
 14 what patients had to have to get into the study.
 15 This is maybe a question that we might set up
 16 differently if we did this again. This is kind of
 17 a mish-mash of the type of pain and the location of
 18 pain. One of my questions for you at the end will
 19 be, should we have done it by diagnosis or should
 20 we have done it by location? And I'm not really
 21 sure what determines the efficacy of spinal cord
 22 stimulation. Is it position, or is it diagnosis,

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1 or mechanisms?
2 One of the problems with the way we asked
3 the question was that half of the studies here,
4 patients with leg pain, that could be an entirely
5 different diagnoses. It could be back pain with
6 radiation or radiculopathy, or it could be
7 peripheral vascular disease, limb ischemia, et
8 cetera. So this is probably not particularly
9 insightful.
10 Eight of the studies were failed back
11 surgery syndrome, one in IBS, and then various
12 other things, back pain as well, 6 in CRPS-1. And
13 note down the bottom as well that there are 16 in
14 angina, which we've not yet reviewed. So that
15 would somewhat skew the pie chart.
16 Design characteristics, I apologize; this
17 isn't very graphic, so I'll just run through it; 41
18 percent were parallel; 59 percent were crossover.
19 The washout period was really short in these
20 studies. The most, it was 2 weeks, but in most of
21 them, it was less than a day. 72 percent of the
22 studies were open labeled. Clearly, these were the

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1 earlier ones where it was conventional SCS where
2 blinding wasn't possible. Of the 9 with blinding,
3 we assessed 2 of having a high risk of bias. In
4 other words, there's a good chance that the
5 participants were able to guess which intervention
6 they'd been allotted to. Randomization was
7 performed a little bit better. 23 of the studies,
8 or 72 percent, actually a low risk of bias, and
9 this was because they used computer-generated
10 randomization.
11 We were talking about enrichment earlier,
12 how valid that is. More than half of the studies
13 at a trial are a screening phase. Then 63 percent
14 of the studies allowed for spinal cord stimulation
15 adjustments within the duration of the
16 intervention. This is the important part, I guess;
17 what were the interventions? Conventional in most
18 of the earlier studies: high frequency, high
19 frequency burst, DRG, and shuffle.
20 This pie chart's a little bit inaccurate. I
21 should say that we finished these extractions about
22 a week ago, so this is somewhat of a preliminary

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1 analysis. We've got 4 studies missing from this
2 thing. You'll note that there are more controls on
3 than there were interventions just because some of
4 the studies had multiple arms in them.
5 What's missing from here is a DRG study,
6 high frequency, and a burst study. So there's a
7 total of 36, but it kind of looks about the same as
8 what the intervention arm was, mostly conventional.
9 But in some of the earlier studies, it was usual
10 care by the clinician or usual care via some sort
11 of protocol. And there's even a placebo on/off
12 slice of the pie chart here, which would be the
13 newer studies where placebo was actually possible.
14 This really just speaks to the studies that
15 did allow for adjustments. Amplitude was the most
16 commonly adjusted aspect of patients SCS, but many
17 of the studies, 12 of them allowed for any sort of
18 combination of more than one of these.
19 This speaks to some of the things that we
20 were talking about earlier. Was co-administration
21 of other non-invasive interventions allowed, such
22 as medications, physical therapy, et cetera? Just

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1 to talk about the chart itself, the majority of
2 studies did allow this.
3 It's somewhat pragmatic. It probably
4 increases the external validity of these studies,
5 but reduces the internal validity because of what
6 we talked about earlier and not particularly. If
7 patients can do whatever they want within the
8 duration of the intervention, then the two groups
9 may be different at baseline.
10 Timing, the total duration of how long the
11 intervention was studied for was a median of 12
12 weeks and a range of zero to 208 weeks or 4 years,
13 but somewhat of a dichotomy in that, really, there
14 were two different of studies that were sort of
15 technical or proof-of-concept studies and there
16 were clinical studies.
17 The technical studies were a week or two at
18 most. The clinical studies usually averaged about
19 6 months, which is reflected in the timing of the
20 assessment of the primary outcome. A mean of 26
21 weeks is about 6 months, so this was pretty common.
22 The primary outcomes themselves were

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1 specified in 94 percent of the studies. The other
2 ones we just couldn't work out what they were
3 actually assessing as their primary. In three of
4 the studies, their primary outcome wasn't related
5 to pain. Pain was a secondary outcome. And in
6 those 3 studies, it was amputation, limb survival,
7 or battery life, which again we talked about
8 earlier.

9 A third of the studies, a little more had
10 multiple primary outcomes. The majority of studies
11 had pain intensity as either the primary outcome or
12 a component of a multiple primary outcome. This is
13 another thing that we kind of struggled with; would
14 we look at paresthesia as being an indication of
15 efficacy or was it also an adverse event, or could
16 it be both? But 73 percent of the studies
17 discussed paresthesia, and not surprisingly, those
18 were the studies that looked at conventional SCS.
19 If they reported it for burst or high frequency, it
20 was usually listed as an adverse event.

21 This is kind of similar to the primary
22 outcomes when there were single primary outcomes.

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1 But when there were multiple primary outcomes,
2 again, pain intensity was usually the most common.
3 But there's a mixture of other things here such as
4 multidimensional, quality of life, functionality,
5 et cetera.

6 The one thing I should point out is that in
7 the 11 studies that did have multiple primary
8 outcomes, only 4 of those studies specified how
9 they adjusted for multiplicity. So did they do a
10 Bonferroni adjustment? Did all the outcomes have
11 to be statistically significant for it to be a
12 positive outcome?

13 This is really messy, but this is just the
14 secondary exploratory outcomes just to let you know
15 that they looked at a whole lot of stuff. There
16 were obviously a lot more secondary outcomes than
17 there were primary. But you've got quality of
18 life. You've got functionality, sleep, depression,
19 mood, all the things that impact first suggested
20 for drug studies back in the, whatever it was,
21 early 1990s.

22 Finally amongst design characteristics,

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1 adverse events. Two studies actually assessed
2 adverse events as a primary outcome. Only 44
3 percent of the studies prespecified adverse events
4 as an outcome. Now, this isn't particular to
5 spinal cord stimulation studies. Drug studies do
6 this as well. In the results section, it will tell
7 you what adverse events the patients, or the
8 participants, but they don't mention it in the
9 methodology section. They don't tell you what they
10 looked for, and they don't tell you how they looked
11 for it.

12 Following on from that, most of the studies
13 didn't clearly specify how adverse events were
14 collected. And again, that's typical to every
15 manuscript you read, not just for spinal cord
16 stimulation.

17 Forty-four percent reported serious adverse
18 events are lack thereof. Sixty-nine percent of the
19 studies didn't clearly state the number of
20 participants who needed to have an adjustment to
21 their regimen because of adverse events. I'm
22 actually surprised it was 31 percent that did. But

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1 again, adverse events are poorly reported across
2 studies.

3 This is one of the parts we struggled with,
4 and I'm glad Rod kind of spoke to this earlier this
5 morning, the statistical analysis. We kind of came
6 up with the same numbers here, which was nice.
7 Half of the studies were superiority or we worked
8 out that that's kind of what they were looking at.
9 Eleven studies didn't specify in any sort of way,
10 and they didn't give us any sort of statistical
11 indication of what they were looking at. Four
12 studies were noninferiority and one was an
13 equivalent study.

14 Leading on from that, about half the studies
15 did a power calculation. Around half prespecified
16 an effect size that we're looking for, and this is
17 what we confused with clinical significance, was
18 the effect size that we're looking for and what
19 they designated to be clinical significance. Only
20 around half of the studies actually did a sample
21 size calculation. And most of those that didn't,
22 it was because it was a preliminary or pivotal

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1 study, where they were just looking at a select
 2 number of patients.
 3 So we really struggled with this; 41 percent
 4 of the studies really didn't define clinical
 5 significance in any way, and then there was about a
 6 50/50 split in those that did define it. So it was
 7 either a point reduction; for example a 2-point
 8 reduction on an NRS, or it was a percent change,
 9 number of patients with a 30 percent pain relief,
 10 50 percent pain relief, et cetera.
 11 The population analysis itself, 13 of the
 12 studies used an intention-to-treat analysis or both
 13 intention to treat and per protocol, and 18 studies
 14 only did a per-protocol analysis, so patients had
 15 to complete the study to be involved in the
 16 analysis. And of those that did use an
 17 intention-to-treat analysis, only 5 of those
 18 specified how they accounted for missing data. So
 19 if patients dropped out of the study, did they use
 20 last observation carried forward, baseline
 21 observation carried forward, et cetera.
 22 Moving on to the results, participant

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1 demographics, a mean number of 50 participants in
 2 the primary analysis, so about 25 per arm; mean age
 3 of 55; 40 percent were female, and around
 4 60 percent had no information stated about
 5 similarity between groups or it was unclear.
 6 This is somewhat skewed. This is, again, a
 7 question that we might set up differently if we did
 8 it again, and this question didn't account for
 9 crossover studies. And in crossover studies,
 10 almost by definition, the patients match up
 11 perfectly unless their condition changes over time.
 12 So really, actually, it was probably somewhat
 13 better than this amongst the parallel studies. I
 14 think more often than not, they either stated the
 15 groups were similar at baseline, or we were able to
 16 look at table 1, and we were able to ascertain that
 17 the groups were similar.
 18 We haven't really gotten to how the primary
 19 and secondary outcomes were reported yet. This has
 20 gotten to a really messy part of the analysis.
 21 Just to boil it down, it was a really mixed bag.
 22 It was number of responders; mean change within

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1 groups; mean difference within patients. It could
 2 be anyone. There were a number of things, in part,
 3 dictated by what the outcome was itself; so to
 4 follow, but it was a mixed bag.
 5 Again, this is a somewhat busy slide, but
 6 what it really just illustrates is the fact that
 7 amongst all the reported adverse events, very few
 8 of them were actually specified in the methods
 9 section. They reported the results, but they never
 10 told us that we're actually looking for them.
 11 That was the analysis itself; again, it's
 12 somewhat preliminary. We're going to do a little
 13 bit more analysis when we look back at some of the
 14 disagreements. We'll look more closely at what the
 15 control interventions were, et cetera, but it gives
 16 you an idea of where we're at with it.
 17 Just to speak to some of the additional
 18 stuff, extension studies, we identified 7
 19 extensions related to randomized- controlled trials
 20 that met our inclusion criteria, and they assessed
 21 outcomes from 6 months up to 5 years. What they
 22 did is they assessed secondary outcomes that

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1 weren't assessed in the primary findings, or they
 2 looked at secondary endpoints of primary outcomes.
 3 So if the primary outcome had been pain intensity
 4 at 3 months, they then looked at that at 6 months,
 5 or a year, or 2 years, or whatever.
 6 We will add these to the final analysis, but
 7 it would be good to get your thoughts on how
 8 exactly we incorporate those in. Do we just lump
 9 all into the same study, or do we call it a
 10 different study, et cetera?
 11 I'll finish off with some observations and
 12 maybe some things that we might want to talk about
 13 when we have our panel discussion. Again, we were
 14 not familiar with spinal cord stimulation or the
 15 literature, so we might have set up our questions a
 16 little bit differently if we'd known that, but we
 17 did road test it.
 18 I think you all know this already, but the
 19 timeline of studies, the earlier studies were
 20 spinal cord stimulation versus usual care. Early
 21 2000s, it started looking at one method of spinal
 22 cord stimulation versus another, adjusting various

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1 aspects of it. And then the newer studies are
 2 looking at burst or high-frequency SCS versus
 3 conventional, or other burst or high-frequency
 4 settings.
 5 As I mentioned earlier, there are technical
 6 versus clinical studies, and I don't know if we
 7 should really throw these altogether in that they
 8 really are different ways in which they're set up.
 9 The technical studies as well tend to have fewer
 10 patients in them.
 11 This is something we weren't sure about.
 12 Conventional spinal cord stimulation may not be
 13 homogenous. So are the comparisons of
 14 high-frequency bursts with conventional fair
 15 comparisons, are we comparing an ultra high def TV
 16 with a high def TV or a black and white TV? We
 17 don't know about spinal cord or conventional SCS to
 18 be able to make that assumption, but you guys know
 19 better than us.
 20 There were generally small sample sizes and
 21 short durations for chronic diseases. Andrew
 22 Murer [ph] with the Kofron [ph] collaboration, when

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1 we're doing drug studies, we say that a study has a
 2 high risk of bias, a high risk of study sample
 3 bias, if each arm has less than 200 participants in
 4 it. That's a really high bar. None of these
 5 studies get anywhere close to that.
 6 Then lastly, as I mentioned, the definition
 7 of what was clinically meaningful was kind of all
 8 over the place with us, and we had a hard time with
 9 it. It was both within patient and between groups,
 10 and I don't know if this is something that should
 11 be clarified going forward.
 12 So really quickly, just some points that we
 13 might want to talk about in panel. Should we
 14 include on angina studies? I think so, but they're
 15 a little bit different. And should we analyze them
 16 differently if we do include them? It's kind of an
 17 acute exacerbation of a chronic disease as opposed
 18 to where pain is the disease itself.
 19 Should we include the DRG studies? We don't
 20 know enough, again, about SCS, know if we should
 21 have done that. I will say of the two studies that
 22 we included, the data of SCS arms in the

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1 [indiscernible], so they would have been included
 2 regardless. Should we look at location versus
 3 diagnosis? Which is more important?
 4 We touched on this earlier. I promised I'd
 5 put this in independently. Should there be
 6 different outcomes for spinal cord stimulation
 7 studies versus pharmacotherapy studies?
 8 What is a reasonable study sample size?
 9 Clearly not 200 per arm; that's not going to
 10 happen. So what's more pragmatic? Given the cost
 11 of a unit and the cost of the patient and
 12 undergoing surgery, is it really reasonable to
 13 expect large study samples?
 14 What's a reasonable study duration? Is it
 15 chronic disease? Is 6 months long enough? And can
 16 these be offset by the extension studies I spoke
 17 about?
 18 Then lastly, should it be crossover studies
 19 or parallel studies? In its most basic form,
 20 crossover studies need less patients; parallel
 21 studies need less time. Obviously, there's a whole
 22 lot more to it than that, but I just thought it was

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1 something that maybe we could talk about when we
 2 get to the panel.
 3 So I think I brought that in about a minute
 4 under time. Just a couple of acknowledgements,
 5 thanks to our core reviewers who are not here
 6 today, and also thank you to Jennifer who is here
 7 today, and to Shannon, for helping us with our
 8 initial questionnaire and also with how we were
 9 setting up our slides for this talk today. So
 10 thank you all, and thanks for listening.
 11 (Applause.)
 12 DR. KATZ: Thanks very much, Ewan. That's a
 13 great list of questions. I may actually put it up
 14 during the discussion to help frame our discussion.
 15 You're doing my job for me.
 16 With that, we'll do the same thing that we
 17 did this morning. We'll keep the lectures going,
 18 write down your questions, and during the
 19 discussion, we will have an opportunity to ask all
 20 of the speakers their questions.
 21 So with that, I'd like to introduce my
 22 friend and colleague, and former co-worker, John

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1 Markman, who is an active implanter and
 2 interventional neurologist like myself, and also
 3 active clinical investigator, who will be talking
 4 about patient selection.

5 Presentation - John Markman
 6 DR. MARKMAN: Good afternoon, everyone.
 7 It's a real privilege to be here for many different
 8 reasons. But first and foremost, I really want to
 9 thank Dr. Thomson; Dr. North; Dr. Hayek;
 10 Dr. Eldabe; Dr. Katz; and of course, Drs. Dworkin
 11 and Turk. This meeting is so long overdue, and
 12 without the leadership of each of you, we wouldn't
 13 be here right now.

14 As someone who does this a routine basis, as
 15 you'll see, and is often plagued by a bit of
 16 uncertainty about the benefits that we're
 17 delivering to patients, and also the hardships that
 18 we're putting our own selves through in doing this,
 19 because it is demanding to provide this care, this
 20 meeting will help clarify this and give us a lot of
 21 direction. So just first and foremost, thanks for
 22 your leadership.

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1 I sat down at dinner last night, just got
 2 here, raced in -- sat down at dinner. I had a
 3 glass of wine. I had this piece of fish next to
 4 me, and Dr. van Dongen sits down next to me and he
 5 goes, "Wow. I looked at the agenda, and it looks
 6 like you've got the hardest talk." The hardest
 7 part of this is picking the patients.

8 So my talk today is about picking the
 9 patients, about selection criteria. With that, I
 10 will launch into this, if I can. Alright, great.
 11 These are some of my entanglements. None are with
 12 device companies. They're all with companies that
 13 make drugs and different federal and state
 14 administrations. I have served as an investigator
 15 in several device trials.

16 My talk really has three main parts. I'm
 17 going to talk about selection criteria with a real
 18 focus on diagnosis. Then I'm going to talk about
 19 the trial period, that period before permanent
 20 implantation, as a unique window, which I think can
 21 help us answer a lot of difficult questions. You
 22 heard some of that rat-tat-tat, of the debate

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1 between Dr. Fields and Dr. North, and Dr. Eldabe,
 2 and Dr. Thomson earlier about which patients have
 3 neuropathic pain and whether we know that or not.
 4 And I think the trial period, at least, may help us
 5 get a little closer to thinking about who may best
 6 benefit from this therapy, maybe not who has
 7 neuropathic pain.

8 Then I'm going to talk about the other
 9 inclusion/exclusion criteria such as pain severity,
 10 duration, psychosocial vulnerabilities, treatment
 11 history, and concomitant and rescue analgesics that
 12 I think Dr. McNicol did a beautiful job summarizing
 13 the literature.

14 As Dr. Pena said, it's all about the
 15 patients, so I want to start with the patient from
 16 Monday, a patient with a neuromodulation system.
 17 Let's think about how this relates to some of the
 18 conventional wisdom, which you heard today about
 19 diagnosis.

20 (Video played.)
 21 DR. MARKMAN: You had a stimulator put into
 22 your low back; is that right?

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1 PATIENT: Yes.
 2 DR. MARKMAN: Why was that done?
 3 PATIENT: I was having pain down the right
 4 side of my hip and into my foot.
 5 DR. MARKMAN: And has it helped?
 6 PATIENT: Yes.
 7 DR. MARKMAN: And how long has it been in
 8 for?
 9 PATIENT: Probably a little over a year.
 10 DR. MARKMAN: And you had had back surgery
 11 before; is that right?
 12 PATIENT: Multiple times.
 13 DR. MARKMAN: How many had you had?
 14 PATIENT: In total, I've had 5
 15 DR. MARKMAN: Five. And how much has this
 16 stimulator reduced your pain intensity in the low
 17 back and the leg, on the right side, over the past
 18 year?
 19 PATIENT: Probably 75 to 80 percent.
 20 DR. MARKMAN: And what's going on now?
 21 (Video ends.)
 22 DR. MARKMAN: This is not a homage to Andy

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1 Warhol. These are three different video clips.
2 This patient is a patient who's obviously had
3 multiple back surgeries and has what many people
4 can think as the classic diagnosis for neuropathic
5 pain. He's got numbness and spontaneous pain, leg
6 worse than back. And this might be sort of that
7 archetypal patient, is the word that was used
8 earlier.
9 He endorses relief. I have no idea whether
10 his relief is on target or off target. I'm the
11 person who put it in. I'm the person who's asking
12 the question. We learned from Dr. Katz this
13 morning that introduces a bit of bias. So who
14 knows whether he's actually getting relief or not?
15 The reason I saw him on Monday is because he
16 got re-injured at work, and in order for a patient
17 who gets injured at work in the United States, to
18 open a new claim and to get care in our system, you
19 have to see the doctor again. So that's how I got
20 to see him on Monday.
21 (Video played.)
22 PATIENT: Strained my back at work.

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1 DR. MARKMAN: And what happened? What were
2 you doing?
3 PATIENT: Taking leg shackles off an inmate.
4 DR. MARKMAN: And when did that happen?
5 PATIENT: At work in the morning.
6 DR. MARKMAN: What day?
7 PATIENT: Friday the 9th.
8 DR. MARKMAN: The 9th of?
9 PATIENT: November.
10 DR. MARKMAN: November. And does your
11 stimulator help for the new pain in your back?
12 PATIENT: No, it doesn't.
13 DR. MARKMAN: Why not?
14 PATIENT: I'm not sure. I just know it
15 doesn't work. I had it on. I tried it when I got
16 home from work, and it doesn't help it at all.
17 DR. MARKMAN: Does it still help for your
18 other pain?
19 PATIENT: Yes.
20 DR. MARKMAN: And how would you describe the
21 difference between those two pains?
22 PATIENT: The leg pain is more like a

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1 numbness and tingling type thing that stays down
2 towards the lower part of my leg. This is more of
3 a stabbing pain in my back and my hip.
4 DR. MARKMAN: And is it severe right now?
5 PATIENT: Yes.
6 DR. MARKMAN: Have you ever had this before?
7 PATIENT: I have.
8 (Video ends.)
9 DR. MARKMAN: So he's telling you he has two
10 distinct pains. Right? He has this chronic pain,
11 this is chronic pattern, anatomic pattern, which is
12 different from what he is currently experiencing,
13 this acute on chronic exacerbation. He's making
14 this distinction. And he's making the observation
15 that his pain is relieved by the stimulation system
16 for the chronic pattern but not for this acute one,
17 this acute thing while he was bending over putting
18 the shackles on the prisoner. He works in a very
19 large penal system we have in upstate New York.
20 So he says this is a different kind of pain,
21 and it's not responsive. If you ever have these
22 archetypal notions, well, this is acute,

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1 nociceptive low back pain. It's low back strain.
2 It's mild fascial in origin. That has a different
3 underlying pathophysiologic mechanism than the
4 nerve injury pain with associated sensory deficit,
5 reflex change, motor changes that you would expect
6 in someone who's had 5 back surgeries who's been
7 exposed to traction and cautery, and probably an
8 initial insult with root compression at some level.
9 So he's got these two different syndromes in
10 the same patient. This is part of life. Most
11 patients in a pain clinic have more than one pain
12 problem, as you know. It makes it especially
13 complex to do clinical trials. He has these kind
14 of very nice dichotomist syndromes, both low back
15 pain syndromes. One's acute. One is stimulation
16 responsive; one isn't. One's nociceptive; one's
17 neuropathic. And this is sort of the archetypal
18 discussion I think maybe a little bit beneath some
19 of the dialogue you heard earlier.
20 (Video played.)
21 DR. MARKMAN: Had your pain been well
22 controlled until this episode on the 9th?

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1 PATIENT: Yeah.
2 DR. MARKMAN: Were you able to work?
3 PATIENT: Yes.
4 DR. MARKMAN: Was there anything you
5 couldn't do on a regular basis?
6 PATIENT: No, there wasn't. I was able to
7 do pretty much everything.
8 DR. MARKMAN: Okay. But right now, you're
9 going to take a couple days out of work. Is that
10 right?
11 PATIENT: Yes.
12 DR. MARKMAN: Okay. Well, I hope you feel
13 better soon.
14 PATIENT: I hope so.
15 (Video ended.)
16 DR. MARKMAN: Okay. So here we are opening
17 a new chapter. I'm uncertain whether -- sorry.
18 So just with that as a backdrop, because I
19 think it really illustrates some of the issues
20 we're facing when we think about diagnosis, I'm
21 going to make it more complex now. I'm setting up
22 as a little bit of a strawman because that's a very

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1 simplified, beautiful picture which just fell into
2 my lap on Monday.
3 Here's the literature of some of the key
4 randomized-controlled trials, these 9 studies. And
5 as has been noted earlier, 65 percent of these have
6 been done in chronic low back pain syndromes,
7 almost all in failed back surgery, or
8 post-laminectomy, or neuropathic low back pain
9 syndromes, however you want to use the terms.
10 Again, I'm going to focus on that in my talk
11 because I think, as Dr. Taylor said, we don't want
12 to be the hostage of perfection. Because these are
13 the cases we see and these are the cases we're
14 doing most of these stimulation procedures for, I
15 think that's what's the focus of the talk should be
16 in terms of the diagnostic challenge.
17 But I'm just going to take a quick detour
18 into this study, because there are 35 percent of
19 those studies which are in diabetic peripheral
20 neuropathy and in complex regional pain syndrome,
21 and some of the landmark studies in the field are
22 in complex regional pain syndrome. So I think it's

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1 worth just commenting. But I do think that how we
2 think about those underlying syndrome as the study
3 populations for this technology have some different
4 implications in how we think of chronic low back
5 pain after spine surgery.
6 So again, this is Davos' [ph] study, and
7 this was a multicenter study. It was 60 patients.
8 It suffers from many of the problems, which I'm
9 Dr. Katz identified regarding I think the potential
10 for introducing bias, but it has some strengths as
11 well.
12 I think what's important is, in my opinion,
13 this gives us a little bit of a clue about how to
14 think about inclusion/exclusion criteria in
15 diabetes. They had a mean VAS score of 50
16 millimeters. They had pain for at least one year.
17 They failed all conventional pain treatments,
18 whatever that is, and that needs to be more
19 robustly characterized in the future. They had
20 certain key exclusion criteria, which is really
21 big. They had to have a distal to proximal grading
22 of sensory abnormality, which you'd expect, so they

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1 had a lot of upper extremity neuropathic pain in
2 addition to distal foot pain. They were excluded.
3 That's what you can surmise from what's written
4 here. And they had to be non-depressed and not
5 have an active history of substance abuse.
6 So I would take that, and then just say that
7 in CRPS and in diabetic peripheral neuropathy, what
8 you probably want to have is some disease-specific
9 or condition-specific criteria. You can use the
10 Budapest criteria or some combination of the
11 elements in that to reach a certain threshold for
12 complex regional pain syndrome.
13 In diabetes, obviously, for diabetic
14 peripheral neuropathy, obviously you want to have
15 diabetes. That helps, adult onset probably. You
16 want to have at least a score of 3 on the Michigan
17 neuropathy screening tool, which would be one way
18 to do my own personal cutoff. You'd want to
19 exclude mimicking syndromes. Dr. Katz and
20 Analgesic Solutions does have what I think is very
21 impressive, what's called a masquerading diagnosis
22 tool, which we use in many different trials for

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1 different conditions, which help you exclude
2 syndromes which could look like diabetic peripheral
3 neuropathy but aren't.
4 Then you'd want to use the all generic
5 assortment of measures, which are used in all the
6 other trials: the pain interference scores;
7 probably some measure of anxiety; the PIGIC [ph],
8 as we talked about earlier; sleep; quality of life;
9 and then probably some pain quality component as
10 well.
11 Again, we have to think about together
12 whether it makes sense to include neuropathy as a
13 large bucket: diabetic peripheral neuropathy; HIV
14 neuropathy; small fiber neuropathy or punch biopsy;
15 chemotherapy induced neuropathy; whether we want to
16 lump all those folks together, introduce that
17 heterogeneity and degrade our assay sensitivity, or
18 do you want to go for some homogenized population
19 with just diabetes and hope that that's on target
20 neuropathic for what we're thinking about for the
21 way this problem works. And that's one of the
22 things hash out before we leave on Friday.

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1 So I'm going to just leave that where it is
2 and just come back to these at the end with some
3 general thoughts. But I'm now going to turn to
4 focus for the next 15 minutes on the low back pain
5 issue because I do think that this is where the
6 heart of the challenges come in.
7 These are both patients. These are the
8 imaging studies of two patients recently seen who
9 both have axial predominant nociceptive pain at
10 some level, but also have radicular or so-called
11 neuropathic pain, leg worse than back, numbness,
12 weakness, sensory deficits, spontaneous pain, which
13 keeps them up at night.
14 As you can obviously see from the patient on
15 the right, obviously this is a patient who has an
16 unstable fusion construct who's got listhesis. And
17 they have a lot of axial low back pain. They have
18 a lot of nociceptive pain, not only because they've
19 got this broken screw mostly, but really because
20 you have all those other structures -- muscle,
21 ligament, tendon, bone -- which are all being moved
22 as that patient places mechanical force over that

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1 unstable construct.
2 That patient has a lot of axial low back
3 pain, but in the process of having that, that
4 patient's nerve root gets entrapped as it goes down
5 their leg, and they also can have some chronic
6 burning, numbness, tingling, reflex change in that
7 leg as well. But that's not a patient you want in
8 your trial. They've got these two different
9 syndromes. They have neuropathic pain, sure, but
10 they've got all this other mechanical, nociceptive
11 pain from the instability of the fusion construct
12 that you don't want to see in there.
13 In this patient, obviously, is a classic
14 post-lumbar fusion patient also, but this patient
15 has this little -- you can see this little waste
16 right here of narrowing, which is really dramatic
17 on other views. But it gives you a sense of what's
18 called adjacent segment disease, and this is a
19 patient who's going to have evoked pain with
20 standing and walking, but no pain when they're
21 lying flat, no pain at rest.
22 This is a patient with the classic adjacent

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1 segment story after many years of having a fusion,
2 who has neurogenic claudication. That's an evoked
3 pain syndrome. Unless you prespecified it, as Dr.
4 Eldabe talked about they do in his clinic and said
5 we're only interested in your neuropathic pain when
6 you're upright and walking, unless you really did
7 the careful work to do that up front, you probably
8 wouldn't want this patient in your trial either,
9 because it's such a different phenomenology
10 clinically than the other patients.
11 So there are two major gaps in understanding
12 as we heard. In the first talk, we heard about the
13 second gap from Dr. North, the idea that we really
14 still have a lot of uncertainty about the different
15 mechanisms of how neuromodulation works, and it's
16 only gotten more complex as we've introduced
17 different stimulation paradigms. And then there's
18 another question, which I'm trying to noodle around
19 right now, which is who has neuropathic pain, and
20 is it the right kind of neuropathic pain to respond
21 to neuromodulation?
22 So we've got these two gaps. And again, Dr.

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1 Fields brought up this point earlier, which I was
 2 super intrigued and just felt so lucky when he
 3 brought it up because I had this slide in my pocket
 4 already made, and I didn't even know he was going
 5 to be here.

6 I really believe that failed back surgery
 7 syndrome or post-laminectomy pain syndrome is
 8 really an important syndrome. It's a sterile
 9 neuralgia. It's a post-traumatic neuralgia. It's
 10 incredibly common. On an iatrogenic basis, we make
 11 these patients in the United States daily. We make
 12 100,000 of these patients a year. I don't know how
 13 you do it in Europe because you guys don't do that
 14 much spine surgeon and don't do that much fusion
 15 surgery, but here, we are making these patients
 16 every single day, and it's a common syndrome. So
 17 for us to study and get this right, there's an
 18 enormous opportunity because, sadly, there are so
 19 many patients who develop these neuropathic pain
 20 syndromes. This is why it's like PHN.

21 First of all, the reason PHN has been so
 22 successful, and many of the folks in our room here

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1 will go to a drug company, and they'll be saying we
 2 have this new candidate therapy; what should we
 3 test it in? And we always say PHH, reflexively,
 4 because there's a successful track record in PHN of
 5 things, multiple drugs separating multiple times
 6 replication. So we know something, as Dr. Katz
 7 said, about the assay. We have this sense about
 8 this study population in a neuropathic pain assay,
 9 which gives us some confidence that if your drug
 10 actually works, this is a population we're going to
 11 be able to show it in.

12 I feel there are enough similarities between
 13 PHN and post-traumatic neuralgia in this syndrome
 14 because it has a time of origin just like that rash
 15 developing. It's a relatively defined lateralized
 16 segmental syndrome in many patients. Now again,
 17 segmental, just like when you look at Henry Head's
 18 picture of segmental in post-herpetic neuralgia,
 19 there's a little patch of allodynia here, there's a
 20 little patch of hyperalgesia here, and it's not a
 21 Michelin [indiscernible] man stripe like you see in
 22 a teaching textbook.

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1 So it's patchy, just like the radicular
 2 deficits and sensory deficits on the top of
 3 someone's foot or the side of their calf are also
 4 patchy in a patient with post-laminectomy syndrome.
 5 But I do think it has a segmental plausible
 6 neuroanatomical localization.

7 The mechanism of injury is reasonably well
 8 understood in these cases. They're multiple
 9 mechanisms in a single case: cautery, traction,
 10 other forms of surgical trespass, the issue in the
 11 muscles and the skin, and other tissues
 12 notwithstanding, but there is a relatively known
 13 mechanism of injury with regard to what's going on
 14 in the surgery. Again, there could be multiple of
 15 those, but there is some sense of what that
 16 entails.

17 It's an accepted condition. Everybody
 18 believes that this condition exists. It's a
 19 post-traumatic syndrome, post-surgical syndrome.
 20 And it's highly prevalent, as I said. Zoster was
 21 the most common acquired infectious disease of the
 22 nervous system until fairly recently; that's going

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1 to change. But that's why initially it was a very
 2 powerful tool and important one to study
 3 neuropathic pain, and I think we have the same sad
 4 opportunity in this condition.

5 So I really want to make the case -- and
 6 what's great about this meeting, always, is that
 7 it's a methods meeting. You come here to argue and
 8 champion your methods. It's not like a meeting
 9 where someone asked me, "Well, which company do you
 10 use?" It doesn't matter which company you use.
 11 This is a methods meeting. I care about the
 12 methods that we're going to use. And I think we
 13 need to stick with this study population. I want
 14 to make a pitch to it because I think it's so
 15 important.

16 Now, all that being said, there's an
 17 enormous amount of uncertainty about this. This is
 18 a study by some fantastic colleagues in Germany who
 19 developed this tool called the pain detect tool,
 20 which is this handy-dandy tool to diagnose
 21 neuropathic pain, and they found what everyone else
 22 has found, which is that if your pain is worse and

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1 it keeps you up more at night, and you can do less,
 2 then it's more likely to be neuropathic. And the
 3 worst it is, the more likely it is to be
 4 neuropathic.
 5 As you can see, those orange bars are
 6 growing for the neuropathic pain as the pain gets
 7 worse and worse, and they did this in three
 8 different cohorts: worst pain, more neuropathic.
 9 That's basically the take-home.
 10 Now they found almost 50 percent in some
 11 cohorts have this type of worst pain being more
 12 neuropathic. There are other investigators from
 13 Europe who put that number at 4 percent. So
 14 there's an enormous amount of professional
 15 uncertainty about who has neuropathic low back
 16 pain, 4 percent versus 50 percent; different
 17 methodologies.
 18 Now obviously, they were laying the
 19 groundwork for a positive study of this drug in
 20 neuropathic low back pain, which never
 21 materialized. Ralph Barone's negative study in
 22 2011, published in Pain; more recently this

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1 negative study in New England Journal of Medicine.
 2 So the idea was they were going to create
 3 this playing field with this pain detect tool to
 4 identify patients with neuropathic low back pain,
 5 and we were going to have this drug which solved
 6 the problem. But unfortunately, the pain detect
 7 tool doesn't discriminate, as we're about to learn
 8 here. This is the New England Journal study
 9 showing that you couldn't see any difference on the
 10 pain detect tool as a predictor of outcome or
 11 anything else meaningful in these patients who
 12 didn't respond to pregabalin.
 13 These tools have never really panned out,
 14 but they were supposed to be a heuristic that
 15 primary care physicians and other folks could use
 16 to decide who has neuropathic low back pain. It's
 17 just not that simple. It's a hard issue.
 18 This is our own little tiny study. We
 19 screened 150 patients, and we looked at the tools
 20 that are commonly used to characterize the
 21 phenotypes or the clinical presentations of
 22 neuropathic pain in post-surgery, post-laminectomy

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1 pain syndromes. These are patients who had prior
 2 surgery, and we said we're going to take 158 of
 3 them, and we're going to winnow them down, and get
 4 the ones who we think have neuropathic pain. And
 5 then we're going to use the DN4, which is a common
 6 tool used to characterize like the pain detect.
 7 And we're going to use the LANSS, and we're going
 8 to decide whether these tools can help us pick the
 9 right patients for stimulation.
 10 This of course was a failure. What we found
 11 was unlike other neuropathic pain syndromes, the
 12 neuropathic component of failed back surgery
 13 syndrome is less reliably identified by the LANSS
 14 and the DN4 than it turns out to be in
 15 post-herpetic neuralgia.
 16 Nadine Attal and her group found a similar
 17 thing, and they were a little more eloquent in
 18 their conclusions, but basically said neuropathic
 19 pain is not restricted to a typical radiculopathy.
 20 So there were patients with axial syndromes who had
 21 neuropathic pain using the DN4 in this series,
 22 basically.

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1 So it's not so easy to pick out who has
 2 neuropathic pain in these syndromes. This is one
 3 of the challenges. So how are we going to solve
 4 this is really the question here. What I would
 5 argue for is using some of the key clinical symptom
 6 features, which you heard articulated earlier this
 7 morning in the debate during the discussion
 8 session. The reason why is because it makes
 9 enrollment efficient.
 10 There are so many of these patients, and it
 11 does lend itself, in my mind, to some broader
 12 generalizability about post-traumatic neuropathic
 13 pain syndromes. It's also biologically plausible
 14 that the diverse sets of neuropathic syndromes
 15 might be stimulation responsive. So just because
 16 it was a traction on a nerve root in one case, and
 17 cautery in another, or the original disk
 18 causive [ph] injury to the nerve root in another
 19 case.
 20 It doesn't so much matter. It matters a
 21 little bit more in the cases that Dr. North pointed
 22 out when the patient was operated on low back pain

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1 for domestic violence or because of a worker's comp
 2 claim. I think in those cases, it's not going to
 3 be particularly useful. But in many of the cases
 4 where we think there is a bona fide neurologic
 5 injury to a nerve root or the cauda equina, I do
 6 think it's possible that multiple different types
 7 of insults could all respond to the whatever the
 8 mechanism is of neuromodulation.

9 Again, another reason to do this is because
 10 this is a story, as I tried to tell you with
 11 post-herpetic neuralgia, which we recognize as a
 12 clinical syndrome. And the experts in the room and
 13 I think regulators and insurers all recognize this
 14 syndrome. So there's some sense that this pain
 15 pattern is meaningful to attack, and we just have
 16 this uncertainty. The challenge is that there is
 17 heterogeneity here, and that heterogeneity is going
 18 to reduce our assay sensitivity to detect a
 19 difference in a device that works. So I recognize
 20 that as the big drawback.

21 How to address that? There's enormous
 22 professional uncertainty in this field, and I've

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1 just tried to tell you what some of it's about.
 2 Some of the uncertainty is about who has
 3 neuropathic pain among these patients. We just
 4 don't know. We're just not good at picking it.
 5 And what more perfect illustration than this paper?
 6 This is a study of about 21,000 spinal cord
 7 stimulation trials across 9 years in the United
 8 States, and the trial to perm rate is 41.4 percent,
 9 which is well, well below the literature when you
 10 look at the trial to implant rate in clinical
 11 trials, which is in the 60's, 70's, as high as 93
 12 percent.

13 Here's how it breaks down across the
 14 country. And again, your insurance drove this, the
 15 age of the patient, but the key thing to understand
 16 is there was no neuropathic pain phenotype which
 17 drove one group to be higher or lower. And it's
 18 fairly tight across the regions. This doesn't look
 19 like a collection of red states and blue states.
 20 This is something slightly different. But they're
 21 fairly close, 36 to 43 percent, but it's all lower
 22 than one would expect.

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1 This was something for the field to wrestle
 2 with. Two experts wrote 4 commentaries for this.
 3 Dr. Thomson, "I recently reviewed a sequential case
 4 series over the last 175 cases of SCS and found the
 5 conversion rate to be 94 percent," is what he was
 6 describing this morning.

7 "It may be that high conversion rates are
 8 indicative of too many false positives and
 9 resulting in poor long-term outcomes with
 10 explanation, or it may reflect good pretrial
 11 selection criteria," as he described this morning,
 12 "using a multidisciplinary team."

13 Dr. Slavin had a completely different take
 14 on this low trial to perm rate. "Now knowing the
 15 disturbingly low nationwide trial to perm rates,
 16 one has to figure what can and should be changed;
 17 what can be done to maximize pain improvement
 18 during the trial. And perhaps most importantly, is
 19 there any way to quantify the trial's success?"

20 Well, obviously Dr. Katz has a lot of
 21 opinions on how to maximize the trial to perm rate
 22 because he gave us some great examples about how to

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1 goose expectation and increase that rate. Now
 2 again, whether those patients will be responders, I
 3 doubt it, but we all know many techniques where we
 4 could get the trial to perm rate up to 100 percent.
 5 But none of those are actually going to predict
 6 treatment response.

7 So I think the trial period does represent
 8 this incredible opportunity just like in an
 9 analgesic drug trial where enriched enrollment has
 10 been such a powerful tool to select patients who
 11 can tolerate a therapy and then go on to the
 12 double-blind phase.

13 So too, I think the trial phase here gives
 14 us some real guidance and help. And I think that
 15 one thing we could potentially do in this meeting
 16 is begin to stipulate what would a meaningful trial
 17 look like and how would that need to be designed.
 18 What would be the necessary reduction in pain
 19 intensity? The standard in the field now is 50
 20 percent. What would be the necessary improvement
 21 on function on an RMDQ, or Oswestry, or whatever
 22 tool you wanted?

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1 What would be the necessary cutoff for a
2 reduction in analgesic medication than someone
3 who's on a stable baseline dose? And what would be
4 the tolerability issues within therapy, whether
5 they liked parasthesias or didn't, or whether they
6 knew how to use it, or used it a certain amount of
7 time during the trial or didn't?
8 Many of us are already doing this in
9 practice. This is the standard, right now, tonic
10 SCS trial period, 3 to 7 days. You get a diary.
11 You talk about how your pain was and what it was
12 like. But many of us are really experimenting.
13 Now that we have all these hard choices to make,
14 it's like going to a sneaker store and having to
15 pick about a hundred different types of running
16 shoes.
17 It's hard as a doctor to pick which kind of
18 stimulation system you're going to recommend. We
19 have all these competing claims: burst affects your
20 mood; high frequencies in this special G-spot for
21 pain intensity with wide dynamic neurons in the
22 spinal cord. Tonic stimulation is you can only get

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1 relief if you have parasthesia coverage. These are
2 not mutually agreeable terms. You cannot reconcile
3 these as someone who's making the decision for
4 patients and say, well, I know which one of these
5 is right. You can't, so then how do you do it?
6 This is what we tried to do. Listen to this
7 patient.
8 (Video played.)
9 DR. MARKMAN: Is there any change in the
10 amount of relief that you have between the two
11 systems? Which one gave you more relief?
12 PATIENT: Yes, the first one was better.
13 DR. MARKMAN: The first one gave you more
14 relief.
15 PATIENT: Yes, but I think -- and it's
16 because I had more adjustability and flexibility of
17 the unit versus the second.
18 DR. MARKMAN: Okay. But the amount of
19 reduction and pain intensity in your back and legs
20 was more dramatic with the first than the second?
21 PATIENT: Yes.
22 DR. MARKMAN: How much more? How much of a

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1 difference did you detect?
2 PATIENT: At least 10, 10-50 percent
3 minimal.
4 DR. MARKMAN:
5 PATIENT: So it was enough difference.
6 DR. MARKMAN: And you said you -- I guess
7 I'm trying to understand. Did you want to try this
8 one out for longer because you're uncertain about
9 whether it's giving you a relief, and you feel like
10 if you had more time to adjust to it, you'd have a
11 better assessment? Or no? Do you feel like you
12 can tell which system works better for you among
13 the two?
14 PATIENT: I just want the permanent one, and
15 right away.
16 (Patient laughs.)
17 DR. MARKMAN: Because it's enough relief
18 that it matters to you.
19 DR. HAYEK: It made a big difference. I was
20 going -- from work, I'm having issues with work.
21 Again, it's affected my work drastically now, and
22 I'm afraid I'm going to lose too much time and/or

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1 lose my job.
2 DR. MARKMAN: What is your work?
3 PATIENT: I'm a construction project
4 manager.
5 (Video ends.)
6 DR. MARKMAN: I'm not telling you which
7 device he had. I'm just telling you one thing. He
8 can pick. He has an opinion, and that's the most
9 important things. Patients can choose. They can
10 identify a preference. And that was the thing I
11 didn't know. When I first started doing this and
12 doing these duplex trials with sham periods and
13 things, I didn't know whether patients could
14 identify a preference. I didn't know if they could
15 pick one running shoe over another. It turns out
16 they can.
17 I gave you somewhat a different aspect of
18 the penal system. This is a U.S. attorney who
19 recently had a stimulation trial.
20 (Video played.)
21 DR. MARKMAN: Do you feel like you could
22 make a decision today or no?

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1 PATIENT: No.
 2 DR. MARKMAN: Why is that?
 3 PATIENT: I think to make a good decision,
 4 it would have to be a more well-informed one.
 5 Specifically, I would need a period of time without
 6 these devices for the next couple of days to sort
 7 of compare the experience that I had with the
 8 experience of not having anything in there.
 9 DR. MARKMAN: And how much time do you think
 10 you would need to make that determination?
 11 PATIENT: It would be a matter of days
 12 because I want to put my body through its ordinary
 13 workload, you know, and rest and work cycles to see
 14 what effect it would have without it.
 15 DR. MARKMAN: And have you been keeping
 16 track with like a diary these last couple of days?
 17 PATIENT: I have.
 18 (Video ends.)
 19 DR. MARKMAN: So again, I don't claim to
 20 have refined this method. I think that
 21 Dr. Taylor's point about doing a cluster randomized
 22 trial With different centers who do this in

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1 different ways is a brilliant idea and
 2 something --
 3 (Video played.)
 4 DR. MARKMAN: Do you feel like there's any
 5 change in the amount of relief --
 6 (Video interrupted.)
 7 DR. MARKMAN: Okay. So again, this is just
 8 a simple model of what these trials look like,
 9 taking one type of stimulation and putting it after
 10 another. But the real, I think, proof in the
 11 pudding will be to have a trial phase where you do
 12 a sham phase. So you would basically have one
 13 therapy, another therapy, and then a period of
 14 inert or active placebo, if you will, period, and
 15 do all three, and really identify patients who can
 16 benefit before you make this huge commitment to put
 17 a device in them.
 18 So I think, to me, that's my zero phase
 19 trial. That's the prelude to my zero phase trial
 20 with its double-blind randomized period. This is
 21 the study, by the way, that was mentioned earlier,
 22 and this trial does try to get at this multi-period

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1 crossover. The one issue I have with this trial is
 2 these are all patients who had an existing
 3 neuromodulation system implanted already, so they
 4 have all the bias baked in. And then they were put
 5 in this 500K stimulation, versus burst paradigm,
 6 versus placebo rotation in three different periods.
 7 But I do think this is a reflection, this
 8 and the Alkasey [ph] study, about how the field is
 9 moving forward and how this group can accelerate
 10 that move forward, because it's already happening.
 11 Right? People are incorporating these placebo
 12 phases in, and we just need to be more systematic
 13 and directive about how we're going to do it, then
 14 we really can get closer to an answer about who
 15 we're helping in an on-target analgesic way and who
 16 are not.
 17 Okay. I've got two minutes left, I think.
 18 Three? Two.
 19 So I just wanted to deal with some of these
 20 issues that I was asked to deal with, and I didn't.
 21 First, just to recap on diagnosis, the question is
 22 obviously homogeneity of your study population and

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1 the implications of that for generalizability. And
 2 we can do that based on an etiologic diagnosis like
 3 diabetic peripheral neuropathy. And again, there
 4 are different ways to set the cutpoint in that
 5 tradeoff and how you want to deal with it. But we
 6 have to think about that as a group.
 7 Again, for the conditions where there's a
 8 syndrome specific like diabetes, we can do that in
 9 a more, if you will, a disease-based strategy as
 10 opposed to others where we're going to be more
 11 bound by symptoms. I think that an enrichment
 12 period or the trial period of stimulation,
 13 especially with a prespecified reduction in pain
 14 intensity, gives us an enormous opportunity to ask
 15 some questions which have not systematically asked
 16 before.
 17 With regard to pain severity, you've already
 18 heard from this baseline characteristic from
 19 Dr. McNicol, who I thought gave a beautiful summary
 20 of the field. But typically, moderate pain
 21 intensity is going to be the cutoff, typically
 22 around 5. I do think it's important, as Dr. Eldabe

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1 said, to prespecify when that 5 is. There are many
 2 patients with low back pain syndromes who do not
 3 have pain until they stand up and walk, or patients
 4 who only have pain when they're sitting in a chair,
 5 or patients whose pain is moderate intensity when
 6 they're in a chair but mild when they're not.
 7 I think that if you don't understand that
 8 this is often a mechanical syndrome with an
 9 entrapment or traction component, and you don't
 10 talk about that up front, you're just going to get
 11 a lot of patients who are in your trial that
 12 shouldn't be in there. It's going to add a lot of
 13 measurement error, as Dr. Katz talked about, and
 14 you're going to get a lot of negative results.
 15 Pain duration of one year I think is
 16 reasonable. To me, more important than pain
 17 duration is stability of the underlying pain
 18 pattern. You want to make sure that that pain
 19 pattern is not changing. I think this is one of
 20 the hardest parts of doing a complex regional pain
 21 study population because the reality is, those
 22 patients who've all had their knee scoped and have

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1 neuropathic pain, or had a distal radial fracture,
 2 who look like CRPS 3 weeks after their surgery,
 3 look less like that 6 months after surgery, and
 4 look a lot less like that one year after surgery.
 5 Some of them will get worse and will always
 6 have the syndrome, but many of them look like CRPS
 7 at month 6 but not at month 14. So I think that
 8 the challenge in CRPS is even though they might
 9 have severe neuropathic pain and you think they
 10 have CRPS by the Budapest criteria, it's not a
 11 particularly stable clinical presentation, and you
 12 run the risk of putting those patients in different
 13 arms, and that will complicate, and you'll get some
 14 asymmetry there. So I think you need one year also
 15 because patients need sufficient time to try other
 16 therapies.
 17 In terms of psychosocial vulnerabilities,
 18 obviously these are key exclusion criteria right
 19 now, but also obviously things like competence and
 20 the ability to interact with this technology, which
 21 is not always insignificant, to charge it, to reset
 22 it, to reprogram it, and to comment on that

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1 reprogramming.
 2 The reality here and the huge lost
 3 opportunity is that in the United States, in order
 4 to get this device put in you, you have to go
 5 through a pain psychology evaluation. So these
 6 patients are filling out scales and paperwork, and
 7 we just are missing it, because this could be done.
 8 And this is a requirement. You can't get a device
 9 virtually in any part of the country unless you're
 10 going to pay for it yourself without a pain
 11 psychology evaluation. So this robust information
 12 could be there in a systematic way. We just have
 13 to avail ourselves of it.
 14 Again, I have a strong feeling that if
 15 you're going to make a claim about your device
 16 affecting the Paleo spinal thalamic tract, or the
 17 limbic pathways as they relate to pain intensity,
 18 then you've got to report on baseline anxiety
 19 levels, or baseline emotional issues, because the
 20 reality is, if you're making the claim that your
 21 active therapy works on that pathway, on the
 22 emotional part of pain or the attention part of

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1 pain, you've got to look at attentional deficits at
 2 baseline, or you've got to look at lability of mood
 3 at baseline.
 4 Then lastly, treatment history. Obviously
 5 you want to make sure that these patients are
 6 refractory to less invasive treatments and that
 7 these previous treatments are robustly
 8 characterized. It can't just be as similar as
 9 things like CMM, where CMM could be anything, as a
 10 comparator or treatment history of conservative
 11 therapy. It needs to be more richly detailed.
 12 Then we'll go back and deal later with
 13 concomitant analgesics. This is obviously hugely
 14 important. There's a parallel meaning, and we've
 15 had another IMMPACT meeting on opioid sparing as
 16 Dr. North pointed out.
 17 The reality is that concomitant analgesics
 18 are incredibly important, I think, in looking at
 19 these studies because, A, most of these patients
 20 get multimodal treatment, which is the standard of
 21 care in many places, and B, opioid sparing and the
 22 sparing of other therapies is a major benchmark for

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1 treatment success for patients themselves, as well
 2 as for us, as well as one of the ways that patients
 3 I think oftentimes get incentivized to try these
 4 devices.
 5 So I think given that dialogue often occurs
 6 around trials and why patients decide to go for
 7 this therapy, I think we really have a
 8 responsibility to try and explain to them what the
 9 results are once they get one in.
 10 So I'll stop there, and thank you very much
 11 for your attention and your patience.
 12 (Applause.)
 13 DR. HAYDEK: It is my pleasure and honor to
 14 introduce Dr. Ali Rezai. Dr. Rezai is currently a
 15 professor of neurosurgery at West Virginia
 16 University, but he has been a trailblazer in
 17 neuromodulation; launched at least two companies
 18 that have become commercialized; was voted by
 19 Crain's 40 under 40, and still doing a ton of
 20 amazing stuff with deep brain stimulation and
 21 neuromodulation; and currently president of
 22 International.

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1 Presentation - Ali Rezai
 2 DR. REZAI: Ongoing. No, I'm just kidding.
 3 Thank you, Salim. 40 Under 40 was 30 years
 4 ago, man. Come on. That was a long time ago.
 5 Thank you very much. I know it's been a
 6 long day. I'm standing between you and the break,
 7 and I'm very appreciative to be here. Thank you,
 8 Bob and the entire team, IMMPACT, INS, IoN team for
 9 this assembly of this amazing group of individuals.
 10 I'm very impressed and humbled to be here with such
 11 talent.
 12 From my talks, I'm going to talk about just
 13 outcomes that I've seen the literature, but it's
 14 been discussed many times. I want to do an
 15 interactive if I may, so I'm going to ask you
 16 questions rather than me. I'm just going to put it
 17 up on the screens and get the input to get some
 18 connectivity.
 19 Is that okay, Nate?
 20 Thank you very much. First, I just want to
 21 talk a few words about the IoN here, and we look
 22 forward to working more closely with IMMPACT and

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1 the team, and INS, and Simon also.
 2 IoN was established by NANS in 2016,
 3 replaced the foundation, and is an independent
 4 nonprofit modeled after the National Academy of
 5 Medicine. The goal is to facilitate research and
 6 collaboration and policy matters regarding
 7 neuromodulation, based on health sciences, medical,
 8 biological, and engineering sciences.
 9 Our goal is to identify important issues
 10 related to neuromodulation therapy and devices and
 11 prepare in collaboration authoritative statements
 12 and reports on issues important to the public;
 13 respond to requests from NANS and other societies
 14 for reports and studies; and disseminate
 15 information to public and relevant professionals
 16 based upon the institute's studies, statements, and
 17 reports; and maintain and promote liaison and
 18 active communication with government agencies, very
 19 important; FDA, CMS, and others.
 20 The leadership of IoN here. Rick is the
 21 secretary/treasurer; Pete Konrad, vice president;
 22 and these are the committee chairs. IoN's

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1 committees are the main workhorse. Every one of
 2 you are invited to participate in the committee if
 3 you're interested in IoN. We have three core
 4 committees: lead device interface committee. We
 5 have a clinical trial design committee, which is a
 6 collaboration with this group here; a basic science
 7 committee; and our membership includes experts and
 8 scientists, engineers, clinicians, and other
 9 specialists focusing on the institute's research,
 10 mission, and vision.
 11 Just the last couple of slides, the
 12 committees, first one is the lead device interface
 13 committee, and the goal is standardization of
 14 implanted connector designs as has been done in
 15 cardiac devices. Various surveys performed shows
 16 that 90 percent plus the memberships, they want
 17 this standardization like it was done in the
 18 cardiac world. We've engaged with the FDA and have
 19 had several meetings in this regard.
 20 This is where we are today looking at best
 21 practice standards, if you will, and
 22 recommendations for clinical trial designs for

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1 spinal cord stim, other neuromodulation, and
 2 focusing on cost effectiveness, regulatory and
 3 reimbursement. In particular today, we're here in
 4 collaboration regarding the work with IMMPACT and
 5 INS here and looking at spinal cord stimulation.
 6 The last one is the standards for research
 7 proposals in the field and the roadmap for basic
 8 science and really finding, for example, biomarkers
 9 that we desperately need for pain research studies
 10 and pain clinical studies. And that involves
 11 collaboration with NIH.
 12 Clinical trial outcomes. Again, it's been
 13 discussed by all of us today, so this is simple. I
 14 guess my talk is really the most simple. I can
 15 just outline a few things about outcomes. There's
 16 a lot of variability. We need a more objective
 17 measures. But what our outcomes -- that's a
 18 question -- for neuromodulation, spinal cord
 19 stimulation? What are the different types of
 20 outcomes? We can talk about that. How are they
 21 measured? What are some of the challenges? We'll
 22 talk about that. And specifically, outcomes that

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1 are there in spinal cord stim trials. Please -- I
 2 want some feedback here -- as a pre-discussion.
 3 Okay, Nate?
 4 All right. The outcomes are basically
 5 variables here, or data points measuring the
 6 trials, to really determine the impact of the
 7 intervention on a certain measure. Typically, a
 8 lot of studies I've been involved have been deep
 9 brain stimulation, for example, pilot studies,
 10 safety feasibility, tolerability studies, and also
 11 randomized-controlled trials. But a lot of times
 12 we want to know if there's a feasibility; does a
 13 patient accept -- especially for early pilot
 14 studies. It's important on tolerability. Those
 15 are not trivial. We've had studies like DBS for
 16 obesity, where we published that there's no
 17 feasibility. Patients did not tolerate that, so we
 18 had to stop the DBS for obesity study as part of
 19 the FDA trial. It's more for earlier onset
 20 studies.
 21 Different audiences, we discussed that
 22 earlier. CMS looks at outcomes differently than

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1 Medicare, than patients, than companies, so we need
 2 to just put them all together and I think be able
 3 to provide outcomes that are needed for all the
 4 stakeholders. I think that's important for getting
 5 proper reimbursement, as field is going -- as Brian
 6 was saying earlier, I'm finding in my practice, at
 7 least, a lot of times -- despite FDA approval,
 8 we're not getting insurance coverage, and that's
 9 happening more and more and more. So we really
 10 need to be smart about the outcomes and engage with
 11 these other parties.
 12 Different types of outcomes. Obviously, you
 13 know about this; it's just a framework;
 14 patient-centered; survival, looking at outcomes;
 15 subjective pain scores; quality of life; patient
 16 satisfaction, obviously. There are surrogate ones,
 17 the indirect ones, the biomarkers. A lot of work's
 18 being done with heart rate variability and other
 19 areas. In the cardiovascular world, cholesterol,
 20 cardiovascular mortality, for example, or 6-minute
 21 walk. These are surrogate or indirect measures of
 22 outcomes.

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1 Obviously, I think what's important is
 2 combination of pain score plus looking at opioid
 3 use or opioid dose reduction. I think that's an
 4 important composite outcome that we need to look
 5 at.
 6 How are they measured? Again, patient
 7 reported, subjective. Side effects, "I feel
 8 numbness. I feel increased pain," or motor
 9 deficits or whatever it is. Pain scores, it's very
 10 standardized; numerical scores, visual scores,
 11 faces and others. Family reported, that's more
 12 relevant for patients that we deal with sometimes,
 13 those, for example, with minimally conscious state
 14 or those with Alzheimer's. We're doing trials on
 15 Alzheimer's, or patients who are compromised, or
 16 the pediatric population. So it has an objective
 17 element, but also subjective overlay. The family,
 18 it's my impression my loved one's doing better or
 19 getting better treatments. Then provider report or
 20 physical measurements, blood pressure, et cetera.
 21 This is, I guess, as objective it can be, but with
 22 subjective overlay.

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1 A lot of challenges for outcomes. Again, we
 2 have different audiences who disagree about the
 3 relevance and the value. Again, we mentioned
 4 payers, regulators. I'm sure among physicians, or
 5 scientists, or patients, or families, outcomes are
 6 important or different. Is pain improvement a good
 7 functional outcome for a patient who wants to go
 8 back to work or not?
 9 Validation is important. A lot of these
 10 have been proven in the literature or are used
 11 routinely, but we need to look at validation of the
 12 selected measures in the context of everything
 13 we're looking at with pain and spinal cord
 14 stimulation. The question of placebo, sham, it's a
 15 huge question. I'm baffled by it, and it happens
 16 over and over again.
 17 Many times we've seen -- for example, a
 18 trial we did with sphenopalatine ganglion, there
 19 was a very high incidence of sham, or now they call
 20 it low-dose therapy.
 21 (Laughter.)
 22 DR. REZAI: So there's now sham or low dose,

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1 so sub-threshold or low threshold, and some groups
 2 are calling it low dose because you're delivering
 3 some sub-perceptible threshold but it's still a
 4 dose. So is it low dose or is it none? Who knows
 5 at this point.
 6 Then generalizing this from an individual
 7 population, 100 patients for a study; 50 patients;
 8 does it apply to the broader complex population
 9 that have physical deficits, motor sensory
 10 deficits, cognitive deficits, emotional deficits,
 11 psychosocial elements, and the generalization of
 12 your specific population in the study. A very
 13 small sample to the broader population is an
 14 important question.
 15 We often look at pain scores. It's
 16 unidimensional measures, but we're looking at a
 17 multidimensional construct. Here's an example.
 18 And again, Bob and the team, you guys -- some
 19 experts are in the audience. You're much more
 20 experts than I am. But I like this, looking at
 21 efficacy outcomes in chronic pain that was
 22 published.

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1 Multidimensional, looking at pain, you
 2 have -- I like this. This can be a good framework
 3 for spinal cord stimulation, obviously. But pain,
 4 numerical rating, and then looking at
 5 multidimensional pain, physical functioning,
 6 looking at maybe pain inventory or other inventory;
 7 emotional functioning, important; participants
 8 ready, global improvements, and satisfaction, very
 9 nicely done; and symptoms with adverse effects
 10 regarding also the economics, which is important.
 11 That's another thing that I added. This study is
 12 looking at these elements, but we added economic.
 13 This is a nice framework, I think, for looking at
 14 outcomes in spinal cord stimulation. It's been
 15 there, it's published, but let's go through this
 16 exercise with all of you. Relevant
 17 outcomes of spinal cords. Can you participate?
 18 Brian, you have a big voice here. You don't
 19 need a microphone. So let's hear something from
 20 Brian or Greg or others?
 21 Safety. Here are a few things that I wrote
 22 looking at the literature and all about safety; can

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1 be procedure related; bleeding, epidural
 2 hemorrhage, subcutaneous hemorrhage; infections, of
 3 course these are implantables; wound dehiscence,
 4 neurological injury, sensory motor deficit.
 5 Are you okay with that? Anything else you
 6 want to add there for outcomes? Safety? Anybody?
 7 FEMALE VOICE: Migration.
 8 DR. REZAI: Sorry?
 9 FEMALE VOICE: Migration.
 10 DR. REZAI: Migration. That's right, so we
 11 can put that. If you can write it down, please, I
 12 will add those later. Okay. Very good. Device
 13 related: infection, erosion, hardware failure,
 14 disconnection, neurological injuries.
 15 Anything else?
 16 MALE VOICE: Pain.
 17 DR. REZAI: Pain. Very good. That's right.
 18 That can be stimulation related so you can get
 19 pain. These are three categories.
 20 FEMALE VOICE: I'm sorry. You can also have
 21 pocket pain.
 22 MALE VOICE: Pocket pain.

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1 FEMALE VOICE: IPG -- the pocket pain.
 2 DR. REZAI: Perfect, pocket pain. Do we
 3 agree on this pocket pain?
 4 DR. THOMSON: And [indiscernible].
 5 DR. REZAI: And what? Sorry, Simon.
 6 DR. THOMSON: Anchor site.
 7 DR. REZAI: Okay. Got it. Anything else?
 8 MALE VOICE: Seroma.
 9 DR. REZAI: Seroma. Very good. Okay.
 10 Good.
 11 Any new pain syndromes, worsening of pain,
 12 or poor hardware replacement, or migration.
 13 DR. KATZ: How do you recommend [off mic -
 14 inaudible].
 15 DR. REZAI: How do you recommend that these
 16 be captured as part of the protocol? Also, you
 17 have to have good monitors, compliance, and asking
 18 the patients questions; open-ended questions.
 19 DR. KATZ: Questionnaires, for the
 20 investigator, did you have a seroma? Did you have
 21 anchor site pain?
 22 DR. REZAI: Good point. I've seen it both

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1 ways. There are certain elements. For example, on
 2 the informed consent, we have all of these
 3 outlined, so we do have forms.
 4 What do you all use here? I'm just curious.
 5 What do you like?
 6 MALE VOICE: I think it's useful to have a
 7 questionnaire [inaudible - off mic].
 8 DR. REZAI: Sam is saying a questionnaire is
 9 important because if you don't have it, it
 10 underrepresents. I agree.
 11 Greg? Use the microphones, please.
 12 DR. FIORE: Yes, sure. It's Greg Fiore, an
 13 interesting point about questionnaires versus the
 14 open-ended questions because what we often do in a
 15 situation where we understand that there may be
 16 some risk that we're looking to quantify
 17 specifically, that may be where we prespecify maybe
 18 even a statistical analysis, but in least case, a
 19 questionnaire, so that we don't underrepresent, as
 20 you said.
 21 Often in safety, we take a little bit more
 22 of an epidemiologic approach, which is not leading

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1 the witness, so to speak, so that we find out what
 2 comes to the surface. So that's something that
 3 really needs to be thought through on a case by
 4 case basis.
 5 DR. REZAI: That not leading is an important
 6 point, as well.
 7 Brian, you're quiet. Anything from you?
 8 You usually have a lot of comments nonstop, but
 9 okay.
 10 DR. KOPELL: I'll wait.
 11 (Laughter.)
 12 DR. REZAI: He's going to wait. Okay, fine.
 13 All right. We'll continue on.
 14 Feasibility. Yes? Sorry, Rick?
 15 DR. NORTH: Before we leave the shopping
 16 list, if you will --
 17 DR. REZAI: Yes?
 18 DR. NORTH: -- there's a nice scheme that is
 19 in the NTAC [ph] paper, Tim Deer, lead author,
 20 starting with biological complications; technical.
 21 And I think that's worth referring to so that we
 22 don't reinvent and reorganize the spokes on the

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1 wheel.
 2 DR. REZAI: This is just for discussion, but
 3 I think if you can use as a framework -- I just
 4 went through a whole bunch of different literature
 5 from my perspective. But yes, we can put that.
 6 DR. NORTH: And that expands a bit on an old
 7 paper by
 8 Tracy Cameron, but that is a nice scheme as well.
 9 DR. REZAI: Go ahead, Simon. Sorry.
 10 DR. THOMSON: I also think that -- because
 11 often everybody gets obsessed about the
 12 investigator treatments. And I know whatever the
 13 question this particular study's trying to design
 14 may be all about that. But if you're doing against
 15 usual care or some other comparative treatment,
 16 then you need to be able to pick up adverse events
 17 in the comparator treatment, and often that that
 18 gets a bit weak often in studies.
 19 DR. REZAI: Good. Any other comments? Very
 20 good comments; excellent.
 21 (No response.)
 22 DR. REZAI: Okay. This is the feedback we

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1 need.

2 Feasibility. Is it doable? A lot of these

3 things, they're not for larger scale spinal cord

4 sim trials, but I'm talking broadly in the

5 neuromodulation world. Really, the impact, the

6 treatment of patient support systems. Many

7 treatments, practically, they sound great initially

8 but they're not feasible or easily done.

9 Any comments about that from tolerability of

10 feasibility? Can I get comments, please?

11 Experiences? Rick?

12 DR. NORTH: A feasibility point. If you're

13 primary outcome measure is pain measure, if it's

14 something you can collect verbally over the phone,

15 like an NRS, then we found over many years that

16 that will improve your follow-up rate. And it's a

17 shame to lose patients to follow-up.

18 Say you're trying to collect 2-year, 5-year

19 follow-up, you just can't get everybody back for

20 that. So that's an important practical point and a

21 reason to use NRS, which a lot of people refer to

22 as VAS anyway, incorrectly.

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1 DR. REZAI: Good. This is the exact

2 feedback that I'm so appreciative of because we've

3 got to write these down, put them together, so this

4 is good. All the minds here, please, keep on

5 talking. This is good. You're the experts here.

6 Nate?

7 (No response.)

8 DR. REZAI: Okay. Anything?

9 DR. THOMSON: Well, I was just thinking,

10 when you're doing these studies, you do your

11 protocol with your set visit times for data

12 collection. But because a stim is a sort of

13 complex treatment that sometimes involves

14 reprogramming, patients will often defer their

15 visit to get reprogrammed and come on the data

16 collection pain time, and say, well, it's not

17 really very good, and what they need is tweaking,

18 and then they would be good.

19 So managing that -- and then of course the

20 gaming in studies is that one group might be seeing

21 their patients daily

22 leading up to the data collection point and the

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1 other group might not be, and that I think is one

2 of the things that has happened in some of the

3 studies.

4 DR. REZAI: And that's very important for

5 the study design and the industry that's here, how

6 you're designing it, the implementation, the

7 compliance. I agree with you.

8 What I've seen many times in my world, a lot

9 of DBS trials or Alzheimer's trials, family says

10 they're responding more -- or depression

11 trials -- but they're coming in every week.

12 They're seeing people. They're getting engagement.

13 They're getting attention versus being at home.

14 These are not trivial factors, so that's

15 where placebos are always higher because they're

16 coming in from multiple visits. If you're coming

17 in by default, you have a higher placebo versus not

18 coming in, in my experience at least.

19 Anything else? Salim?

20 (No response.)

21 DR. REZAI: Okay. Good.

22 Technical procedure practicalities, a very

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1 important part, as you were saying, in terms of

2 stimulation and others.

3 Let's continue on, please. Efficacy. Who

4 was saying VAS is the same as NRS? VAS, NRS, the

5 faces, or looking at how this pain intensity

6 changes; the opioid use is impacting it or the use

7 of opioids.

8 Greg, questions or comments?

9 DR. FIORE: It's Greg Fiore. To point out

10 about the last line, and it's come up a couple of

11 times earlier today, is that health authorities are

12 kind of loathe to appreciate the decreased dose of

13 opioids or use of analgesics as important in

14 chronic pain. I don't know if others have thoughts

15 on if that's expected to evolve in the current

16 environment. Bob or others may.

17 DR. REZAI: Anybody? Comments? Opioid use.

18 That's a hot topic, although there's not been

19 prescribed -- a lot of my colleagues -- let me ask

20 you all -- they're saying that the pain

21 specialists, they're not prescribing opioids

22 anymore.

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1 Is that true? Yes?
2 DR. KATZ: It's down, but they're still
3 [inaudible - off mic].
4 DR. REZAI: Right. In West Virginia, but
5 it's down.
6 DR. NORTH: Greg, to your comment about
7 payers, I think they're outranked by the government
8 or at least the government thinks so, right? The
9 government is very much concerned about that.
10 DR. THOMSON: I think with opioids, it's
11 what is the purpose of the study? And if the
12 purpose of your study is to look at SCS induced
13 analgesia, then you've actually got to keep that
14 constantly opioids because otherwise it becomes a
15 confounding factor. But if your study design is to
16 look at does adding SCS reduce opioid requirement,
17 then we know that, you've got to be able to look at
18 what happens if you add SCS, where everybody's
19 getting opioid reduction planning equally, and then
20 does SCS make any impact upon that.
21 DR. REZAI: Brian?
22 DR. KOPELL: You're obviously absolutely

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1 right from a strictly scientific standpoint, but I
2 guess those of us that are absolutely advocating
3 that you really can't have a pivotal trial anymore
4 without some sort of economic assessment, the
5 lowest hanging fruit of economic benefit is to
6 reduce the drugs.
7 So I agree with you. You're right. I mean,
8 from a purely scientific basis, you don't touch the
9 drugs because you want to see what the actual
10 impact of your experiment, so to speak, is on the
11 analgesia. But when you're talking about pivotal
12 trial design in the U.S., we're talking about
13 basically allowing our patients to get a safe and
14 efficacious therapy. And if they don't get it paid
15 for, they're never getting it. I don't care what
16 you prove, they're never going to get it. And
17 that's not what we want as physicians.
18 DR. REZAI: How is that with our European
19 colleagues?
20 MALE VOICE: Exactly the same.
21 DR. REZAI: Sam?
22 DR. ELDADE: I think we're making an

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1 assumption that reducing opioids equals an increase
2 in pain. The literature does not support that.
3 Reducing opioid gradually does not lead to an
4 increase in pain, and in most cases leads to
5 reduction in pain that is nonsignificant.
6 DR. REZAI: How about the use of rescue
7 medications? That's a big question that
8 comes -- the more rescue, the more complex the
9 trial or the outcomes.
10 MALE VOICE: For ethical consideration
11 anyway.
12 DR. KOPELL: I guess today, as he said, the
13 whole purpose of this group is to create a set of
14 criteria for pivotal trials. And I think it's
15 important to keep the distinction between what a
16 pivotal trial is versus a good scientific
17 randomized-controlled trial that is trying to prove
18 a scientific point.
19 There's a certain Venn overlap of those two
20 things, but they're distinct things because
21 ultimately there's a commerce part of this sort of
22 issue.

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1 DR. REZAI: Do you agree with Brian? People
2 agree? How many agree with Brian on that?
3 DR. DWORKIN: Brian, could you say what you
4 mean by pivotal trial?
5 DR. KOPELL: So in other words, a pivotal
6 trial, what I mean by a pivotal trial in the United
7 States is a trial that allows a device to come to
8 market.
9 DR. DWORKIN: That's what I thought you
10 meant. I think our colleagues from FDA aren't
11 here, but I for one, after this morning's
12 presentation, have absolutely no idea what CDRH is
13 thinking about an adequate evidence base is. Now,
14 maybe it was because I didn't have enough
15 coffee --
16 (Laughter.)
17 DR. DWORKIN: -- but if any of you really
18 understand, after what we heard from CDRH, what
19 they consider adequate evidence for device
20 approval, label change, et cetera, I'd love to hear
21 it at the break. So I'm clueless about what
22 pivotal is.

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1 So I would like to say what this group
2 should do is come up with our very best
3 recommendations for a scientifically valid study,
4 and let CDRH figure out on their own what the heck
5 they mean about evidence because I don't think
6 we're ever going to figure that out.
7 MALE VOICE: Makes sense. I agree.
8 DR. SINGH: If I can just comment from an
9 MHRA point of view in terms of what evidence we
10 need --
11 (Laughter.)
12 DR. DWORKIN: I left you out.
13 DR. SINGH: -- it would be the same thing
14 what the FDA would probably say. We can't state
15 what we would recommend for you for spinal cord
16 stimulation because we'll be acting as a consulting
17 agent; hence, why my topic was top level generic
18 for all medical devices, but my executive medical
19 director to me said, "Do not give specifics for
20 your device because you will be acting as a CRO
21 consultant," essentially.
22 So what clinical evidence do you need? I

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1 can't give you the answer. Your clinical
2 investigation, if you propose to us, will advise
3 you based on what you provide.
4 DR. DWORKIN: But, Rahul, let me beat a dead
5 horse.
6 DR. SINGH: It's very vague.
7 DR. DWORKIN: Well, let me beat a dead horse
8 here. If the FDA division that approves drugs was
9 here this morning, they would have given a pretty
10 clear answer to this question. They would have
11 said, in most circumstances, they require two
12 adequate and well-controlled clinical trials that
13 replicate each other; and that unless you have some
14 damn good reason for not bringing them two
15 replicated, statistically significant trials that
16 adequately deal with missing data, blah, blah, you
17 don't get approved.
18 Now, there are exceptions, orphan
19 indications and other exceptions. But we would
20 have gotten a much more compelling, clear answer
21 from CDER than we got from CDRH. I don't want to
22 continue this, but I don't think this group can

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1 answer the question of what CDRH is looking for,
2 but I think we can do a very good job of describing
3 what a scientifically valid clinical trial is.
4 DR. NORTH: To the question about rescue
5 medications, one recent pivotal trial that I was
6 involved with, the urging of FDA, as I understood
7 it, considered rescue medication use to be
8 automatic failure --
9 DR. REZAI: Is that right?
10 DR. NORTH: -- of the patient in the trial,
11 no matter how good their pain measures were.
12 DR. REZAI: Is that practical? No.
13 FEMALE VOICE: It's not ethical.
14 DR. NORTH: Those were the rules.
15 DR. REZAI: That's amazing.
16 Rod, you have comments?
17 DR. TAYLOR: I was just going to chime in
18 back to the previous discussion between the two
19 B's, Bob and Brian, because I'm with Bob that
20 clearly the key conclusion we got from our FDA
21 colleagues this morning was, maybe. I mean, it
22 doesn't go beyond maybe, but it's free.

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1 (Laughter.)
2 DR. SINGH: So I'm with you. I think our
3 challenge is that we have to present them what we
4 think is the right methodology. The only caveat I
5 would make on that, and it's not specific to
6 neuromodulation, but I would hope that Brian would
7 agree with me, is that we should think smart that
8 when we design trials, okay, they may be pivotal in
9 terms of fulfilling the regulators' requirements,
10 but I would like to hear, would people support can
11 we think about those trials as being also
12 potentially fulfilling the requirements of payers?
13 Because if we can, we're going to save ourselves a
14 lot of pain.
15 MALE VOICE: That's very important.
16 DR. REZAI: That's exactly right.
17 DR. TAYLOR: And if we could just say that,
18 clearly that's an additional challenge of how do
19 you design a trial that takes the box of both a
20 regulator and the payer. But if we could make
21 some, if you like, aspirational text to that
22 effect, I think that would be a useful signal for

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1 our readership. Just a thought.
2 DR. TURK: This is going backwards, but it
3 would seem like this is an opportunity, if in fact
4 we're not sure what FDA wants and we're not sure
5 what the Europeans want, the best we can do is
6 design the best, propose the best, and then, as has
7 happened to us in the past with this meeting, they
8 will make use -- they, the regulators, will make
9 use of the information we provide, and therefore we
10 can educate them about what they should be using in
11 their trials.
12 Instead of us worrying to try to fit to what
13 they want, they don't know what they want, but if
14 we can provide them the guidance, they may tweak it
15 in different ways, but they'll use it to inform
16 their decision-making.
17 DR. REZAI: One last comment. I want to
18 show the rest of the slides.
19 DR. FIELDS: This goes back to John and
20 Andrea, the videos, the patients were very clear,
21 at least a couple of them, about the benefit of
22 stimulation, which had to do with their ability to

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1 carry out their activities of daily living, their
2 job. It's possible that that could be captured by
3 an improvement scale or a relief scale as opposed
4 to an NRS or a VAS.
5 I'm just throwing that out because that's
6 the third peak of the triangle. There's the payers
7 and there's the regulators, but then there are the
8 patients who can tell you how much better they are.
9 DR. REZAI: Great point.
10 Nate, please?
11 DR. KATZ: Just a question. Maybe somebody
12 knows. Have there been any qualitative research
13 studies published where patients are asked what
14 outcome measures are most important to them in the
15 context of being implanted with a spinal cord
16 stimulator? Does anybody know?
17 MALE VOICE: Yes.
18 MALE VOICE: Yes.
19 MALE VOICE: And the answer is walking.
20 DR. KATZ: Walking.
21 MALE VOICE: Yeah.
22 MALE VOICE: Walking.

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1 MALE VOICE: Well, that's the only thing I
2 remember just now, but the primary, what they
3 wished, was to be able to walk again normally.
4 DR. FIELDS: So that has to do with their
5 physical ability to function that's being impaired
6 by the pain, and that could be a great measure that
7 captures a lot of things in a single measure.
8 FEMALE VOICE: And it's relatively easy to
9 measure because you put them on a treadmill, and
10 you can put them on inclines, and you can see how
11 far they walk.
12 DR. REZAI: And you can wear the
13 physiological monitors. You can wear wrists or a
14 ring or a chest strap.
15 FEMALE VOICE: Like a Fitbit.
16 DR. REZAI: These are simple ways to -- it's
17 being done in Parkinson's literature and others,
18 routinely. I think that's important.
19 May I continue, Salim and Nate, just to show
20 you. I think it's just 4 seconds, 3, 2, 1. Should
21 I stop or keep going?
22 (Laughter.)

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1 DR. REZAI: How about responder analysis?
2 Okay. They ask what's your responder for your pain
3 intensity? Reach 50 percent? What is it? Any
4 thoughts? What do you consider responder in terms
5 of pain intensity?
6 MALE VOICE: Global impression of change.
7 DR. REZAI: Say it again.
8 MALE VOICE: Global impression of change, a
9 significant improvement there, because that would
10 take into account the pain at night and sleep.
11 DR. THOMSON: A responder, we either put a
12 figure on it, and it always used to be 50 percent.
13 I think the pharmaceutical pain industry moved to
14 30 percent pain relief, pain reduction
15 DR. REZAI: Yes?
16 DR. THOMSON: But then in a way, it's like
17 what's important to patients, isn't it? And it
18 might even be lower. I don't know. I mean, surely
19 the IMMPACT people have thought about this.
20 DR. REZAI: It's an opportunity for this
21 esteemed group here to provide some concepts I
22 think that can lead the field. These are great

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1 questions.

2 May I continue? Pain quality, are these

3 enough from your perspective? What else would you

4 add? I'm just putting a few that I saw in

5 literature, but I don't know what the right answer

6 is.

7 DR. THOMSON: A lot people now, because

8 we're treating mostly neuropathic pain, they put in

9 some kind of neuropathic pain scale.

10 MALE VOICE: N4.

11 DR. REZAI: Do we agree with that,

12 neuropathic pain scale?

13 MALE VOICE: Functionality as an outcome

14 measure for efficacy, functionality, quality of

15 life.

16 DR. REZAI: Yes, that's next, quality of

17 life, functionality. So I'm just going step by

18 step, so talking about pain quality, but these

19 are -- again, you can read it through.

20 Promise. ODI, sleep quality, and days. We

21 should probably put walking here as well.

22 Anything else you would add here from this

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1 list or take out? Any comments?

2 Dr. Loeser, what do you think? You've been

3 quiet.

4 DR. LOESER: Well, I've been quiet because

5 I've been trying to figure out what's going on.

6 (Laughter.)

7 DR. LOESER: I just did want to make a

8 comment, though, about the issue of opioid

9 consumption as some kind of a measure. It used to

10 be that we all thought that opioids were effective

11 in the management of pain. There now are repeated

12 papers that show that when you stop long-term

13 opioids, the patient's pain doesn't get any worse.

14 Therefore, opioids are no longer a way of assessing

15 outcome. So to rely on opioid consumption or

16 change in opioid consumption as some proxy for pain

17 relief, I think those days are gone. You just

18 can't do that.

19 DR. REZAI: It's not being prescribed, also.

20 DR. THOMSON: Mainly, because I suppose I've

21 worked with Rod and Sam, but I'm a great fan of the

22 Euro Quality, EQ5D, because it captures multiple

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1 dimensions of the experience. It does translate

2 into corlease qualities [indiscernible]. So I

3 personally think that treating these pain long-term

4 conditions should be our primary outcome because I

5 think we've got into a world of VAS wars.

6 DR. REZAI: Yes, that's the question.

7 What's a primary outcome? Is it VAS --

8 DR. THOMSON: Yeah, exactly.

9 DR. REZAI: -- or NRS?

10 DR. THOMSON: Well, I just think it's mad

11 what's going on, and it's so easy to game that

12 measure. It's just every meeting we go to. It's

13 just ridiculous. How low can it go?

14 DR. KOPELL: And it also neglects the

15 multidimensional aspect of pain. Patients don't

16 have the kind of insight that we in the field.

17 When they look at a scale, they get focused on just

18 the somatic aspects of it.

19 DR. REZAI: Let me ask, who's in here from

20 industry? Raise your hands. Industry? Okay. What

21 is your perspective? You're sponsoring the trials.

22 What do you all say? You've been quiet. Please

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1 make some comments.

2 (No response.)

3 DR. REZAI: Maybe not. Okay.

4 (Laughter.)

5 FEMALE VOICE: NRS and VAS are ridiculous to

6 continue to use, especially when there are

7 differences in how you collect the data, the

8 instructions over what time period. If it's a

9 primary region of pain, another region and overall

10 pain, it's absolutely ridiculous, so we do need to

11 change that.

12 DR. REZAI: Do you have comments, Sam?

13 DR. ELDABE: I think when you speak to

14 patients about what is it that matters to them, I

15 always get a reply over triangulation of three

16 factors: pain, sleep, and fatigue, and one leads

17 to the other.

18 DR. REZAI: Pain, sleep, fatigue.

19 DR. HAYEK: One other exclusion criteria

20 that I think should go into any study, especially

21 with spinal cord stimulation is fibromyalgia. The

22 general population would say 9 percent, 10 percent

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1 of women, but in my clinic it's 50 percent of the
2 patients. If you're keen on examining your
3 patients, you would discover that a high proportion
4 of patients with chronic pain come with
5 fibromyalgia. And I'm not sure what that means,
6 but if we are implanting those patients, I'm not
7 sure what outcomes we're getting either.
8 DR. REZAI: Great comments. Okay.
9 Satisfaction? That's an outcome. Do we agree?
10 Patient satisfaction, provider satisfaction.
11 Anything else you would add here as far as
12 outcomes?
13 DR. VAN DONGEN: Psychological measurements
14 like depression and anxiety and pain
15 catastrophizing. We don't measure that?
16 DR. REZAI: It's included on some of those
17 other measures, but yes, of course.
18 Yes?
19 MALE VOICE: Preference.
20 DR. REZAI: Preference for --
21 MALE VOICE: As an aspect of satisfaction,
22 so preferring one intervention over another.

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1 DR. REZAI: Okay. Anything else you would
2 add here? We're taking notes.
3 Yes?
4 DR. TRESKOT: Andrea. One of the things
5 that we don't pay attention to is the family's
6 interpretation of what's going on, because just
7 like the person who's drunk who doesn't realize
8 he's drunk, I've often had the family member -- the
9 patient will say, well, I know better, and the
10 family will turn to that patient and say, "What do
11 you mean? You were doing this. You were doing
12 that. You were cooking yesterday. You haven't
13 cooked in months. You're doing better. You may
14 still be hurting, but you're doing better."
15 DR. REZAI: So put family satisfaction
16 there.
17 Do we all like that? Brian, you say no.
18 DR. KOPELL: I mean, the problem is that
19 family dynamics are very, very complicated --
20 DR. REZAI: But they're living with them.
21 DR. KOPELL: No, no, I understand that, and
22 I'm not saying it's invalid. I'm just saying that

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1 you're opening up a box that's going to be very
2 difficult to create a trial around. That's all I'm
3 saying.
4 DR. REZAI: That's super important.
5 DR. LOESER: I think that we lose sight of
6 the fact that anytime you elicit a behavior from a
7 patient, the environment in which that behavior is
8 elicited plays a big role. So I'm uncomfortable
9 with a whole host of the measures, which I think
10 are going to turn out to be very dependent on who
11 assesses, how they're assessed, when they're
12 assessed, and what the patient thinks is the
13 meaning of the assessment.
14 DR. REZAI: So that goes in the design of
15 the trial and how you're doing it.
16 DR. LOESER: All behaviors are
17 environmentally contingent.
18 DR. KOPELL: I have a question along that
19 line. How many people here -- and people mentioned
20 before the neuropsychological screen. I'm just
21 curious. How many people here think that that's an
22 absolutely vital part of a neuromodulation implant?

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1 (Hands raised.)
2 DR. KOPELL: Okay. That's interesting. I
3 would have expected more. But then why is that
4 not part of the outcome measure? It's so important
5 to get --
6 DR. REZAI: That's the inclusion exclusion.
7 DR. KOPELL: Well, but is it?
8 DR. REZAI: No. Okay, fair enough.
9 DR. TRESKOT: Or should it be? If you've
10 got someone who has a psychosis, that's not going
11 to get better with a stimulator, but if you've got
12 somebody who is depressed, that's where we've seen,
13 all along -- people who were crazy because they
14 were depressed, you take care of their pain and you
15 turn them back into rational human beings.
16 I'll use the example of the woman in labor
17 who is totally irrational, and you put an epidural
18 in her, and you turn her back into a rational human
19 being. If you listened to What she was saying in
20 labor, in pain, you'd say that she was not
21 competent psychologically.
22 DR. KATZ: So speaking of people becoming

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1 irrational, I don't want the break to disappear --
 2 (Laughter.)
 3 DR. KATZ: -- because I don't want to be the
 4 recipient of that irrationality.
 5 DR. THOMSON: I'm just saying one of the
 6 outcomes is the psychosocial and the antidepressant
 7 effect of, essentially, treating their pain. But
 8 the thing is, we often screen out the people who
 9 are hugely depressed. They don't necessarily get
 10 the therapy until they've had that treated, and
 11 they tend not to be the great champagne results
 12 that you can get with those who aren't depressed at
 13 the outset.
 14 Then I think we heard earlier, if you're
 15 going to claim that your therapy mode of action is
 16 on some kind of limbic system involvement, then of
 17 course you should be measuring and assessing
 18 psychological variables.
 19 DR. KATZ: Well, let me thank Dr. Rezai for
 20 an extremely animated session. That was great.
 21 (Applause.)
 22 DR. KATZ: Let's resume at a quarter to the

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1 hour.
 2 (Whereupon, at 3:19 p.m., a recess was
 3 taken.)
 4 DR. KATZ: Hello, everyone. Why don't we
 5 buckle in for the remainder of the afternoon
 6 session? This is the hardest part of the
 7 afternoon. And everybody's cortisol is at its
 8 nadir for the day, right about now. If you feel
 9 like taking a nap, then you're in good company, but
 10 let's try to motivate and get back in place so we
 11 have ample time for our discussion.
 12 I have one quick housekeeping announcement
 13 before I yield the floor to Salim Hayek to speak
 14 about adverse events. I had a sinking feeling
 15 throughout the course of the day that we might have
 16 missed an important piece of our meeting, which is
 17 that we've been having a lot of discussions about
 18 study design, but as I recall from study design
 19 school, you kind of first have to know what
 20 scientific question you're trying to answer before
 21 you design your study. That was a little bit of a
 22 gap.

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1 So what I thought I would do -- I think we
 2 all have a general sense of what questions we're
 3 trying to answer, or at least what some key
 4 candidates would be, but what I thought I would do
 5 is actually pass around a little survey, which each
 6 of you have in front of you now, which essentially
 7 asks this question, what do you think the most
 8 important question is? Not what you think
 9 regulators think they need, but what do you think
 10 are the most important scientific questions that we
 11 should be -- what is the most important scientific
 12 question, singular, that we should try to answer in
 13 a clinical trial of spinal cord stimulation for
 14 chronic pain? And then a few very high-level
 15 comments, so please don't write a whole protocol
 16 but just maybe one or two lines about, are you
 17 talking about a parallel design or a crossover
 18 design? Just the really high-level struts of the
 19 study.
 20 There are a few minor subsidiary questions.
 21 I'll try to sift through all that this evening and
 22 present what I learned from all of you tomorrow.

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1 And my hope is that that will help us put some more
 2 definition around what kind of study we're actually
 3 trying to design to inform the discussion for
 4 tomorrow. Just please give them to Valorie on your
 5 way out before 5:30 today. She'll be expecting
 6 them from everybody.
 7 Without further ado, I'd like to introduce
 8 Salim Hayek, who I think all of you know, who will
 9 be speaking about adverse events.
 10 Presentation - Salim Hayek
 11 DR. HAYEK: True to its nature, nobody wants
 12 to talk about complications. It's always relegated
 13 to the end of the day, and I'm the only thing
 14 between you and break and dinner. What I'm going
 15 to be talking about are the complications relevant
 16 to spinal cord stimulation, and that involves
 17 mostly biologic and technical complications. And
 18 that may be different depending on the type of lead
 19 used, percutaneous versus paddle leads.
 20 For the second part of my talk, I'll talk
 21 about adverse events, data collection,
 22 interpretation analysis, and device studies. And I

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1 would like to say thank you to Angela Leitner,
 2 who's in the audience here, who had sent me a
 3 detailed email about relevant things that I will
 4 talk about here in the study.

5 All of us have been involved in placing
 6 spinal cord stimulation, and we'd like to say we
 7 placed the device, the patient went home and said
 8 goodbye, and everything went fine. However, this
 9 is the farthest from the truth. Complications
 10 happen very, very commonly with spinal cord
 11 stimulation. Up to half the patients have
 12 significant problems. And the more stimulators we
 13 implant, the higher our complication numbers.

14 In general, complications can be biologic
 15 such as having an infection, or technical such as
 16 lead migration or lead fracture. There are some
 17 other complications related to procedures such as
 18 dural puncture with CSF leak.

19 Talking about biological complications, we
 20 can see that the rate of infections of spinal cord
 21 stimulation varies depending also on the studies.
 22 In retrospective studies, which are shown in red,

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1 the incidence varies between 3.4 percent and
 2 4.5 percent. However, if you look at prospective
 3 studies, they can go up as high as 10 percent, and
 4 in systematic reviews, you could see it ranges
 5 between 4 and 6 percent.

6 In general, infections tend to occur early,
 7 and by definition, they are complications that
 8 occur up to one year from the implant. For spinal
 9 cord stimulation, the most common bug involved is
 10 the staphylococcus aureus, mostly over the IPG or
 11 internal program generator. And most often in 95
 12 percent or so of the cases, especially involving
 13 deep infection, this results in device explant.

14 It's important to differentiate spinal cord
 15 stimulation infections into two categories. One is
 16 superficial, such as skin abscess, and one is deep.
 17 Typically, when you have a deep infection with
 18 involvement of the fascia or the muscle, explant is
 19 warranted, and the deep infections by definition
 20 can go up to one year after the implant.

21 The technical complications involve mostly
 22 lead migration. Lead fracture continues to occur,

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1 but it's at a much lesser rate than what used to be
 2 historically. Tracy Cameron published a nice
 3 review in 2004 that involved about 3,000 patients.
 4 Tracy was invited to this meeting. She couldn't
 5 make it; she had a conflict. And the incidence of
 6 lead migration at the time was 15 percent and lead
 7 breakage, 9 percent.

8 The lead breakage, you can see the incidence
 9 has dropped in the PROCESS study, done by Dr. Kumar
 10 in 2007, to 1 percent or so. I should say most of
 11 Tracy's data are from studies in the
 12 '90s. We published a study in 2015 on 234 implants
 13 with percutaneous leads. These are percutaneous
 14 electrodes that were placed in 234 patients. You
 15 can see that the incidence of lead migration was
 16 still around the same number, a little less than
 17 Tracy, which was 13 percent, here at 8 and a half
 18 percent. And the lead fracture somewhere between
 19 Tracy's numbers and Kumar's numbers.

20 The most common complication, however, we
 21 saw was not lead migration or lead fracture but IPG
 22 discomfort. If you look at the previous studies,

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1 they were not as high, so I'm not sure if our
 2 patients were more complainers about the device or
 3 it had to do with where we placed the device. But
 4 I heard Simon say this is a common complication,
 5 too.

6 The timeline of complications are, again,
 7 all over the place for the technical but kind of
 8 early for the biological, such as infection or
 9 seroma. Importantly, we looked at device survival,
 10 and we saw attrition with the spinal cord
 11 stimulator retention. In the column on the right,
 12 you can see the reason for the explants. But the
 13 number one reason for explanting patients was lost
 14 of therapeutic efficacy.

15 So 23 out of 234 patients, or 10 percent,
 16 were explanted due to tolerance or loss of
 17 efficacy. But I venture to say that this is an
 18 underreported number because a lot of the patients
 19 that we would have implanted may have gone
 20 somewhere else and got their stimulator explanted
 21 somewhere else or were walking around with a shut
 22 stimulator and not using it, and could be just as

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1 well as an explant.
 2 Some people have actually estimated the loss
 3 of therapeutic efficacy up to 50 percent in spinal
 4 cord stimulation. There are other potential
 5 technical complications such as 2D placement or two
 6 superficial placements of the generator; generator
 7 flipping; irritation of a bony landmark by the
 8 generator; or a anchor discomfort or anchor or wire
 9 erosion through the skin.
 10 The other potential leads that are places in
 11 spinal cord stimulation, beside the percutaneous
 12 leads, which are shown to the left, are the paddle
 13 leads, which are surgical leads placed through a
 14 laminotomy. They're called paddle because they
 15 look a paddle, and typically they're place in the
 16 mid-thoracic spine.
 17 I like this study. There are a lot of
 18 studies on percutaneous and paddle leads. I chose
 19 these studies because they're representative. This
 20 recent study by Bir and colleagues from Louisiana
 21 State university is interesting. They had
 22 141 patients evaluated, but interestingly, more

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1 than half the patients did not have previous back
 2 surgery and just had radiculopathy that was
 3 refractory
 4 In this study, the revision rate was 32
 5 percent, but revision due to lead migration only
 6 occurred in 2 percent of the patients. However,
 7 interestingly, for malfunction or non-function, you
 8 had, respectively, almost 20 percent and 8 percent.
 9 Revision-free survival was looked at in this
 10 study and was very interesting. More than half the
 11 patients were revised by 5 years; 45 percent only
 12 had their revision-free survival at 5 years. Risk
 13 factors for revision were younger patients.
 14 Patients younger than 60 years old tended to be
 15 revised more often. Males also tended to be
 16 revised more often than females.
 17 Obese patients, defined as BMI greater than
 18 30 kilogram per meter squared, also were found to
 19 be more likely to be revised. However, in
 20 multivariate analysis, this remains statistically
 21 significant. Diabetics were not found to be at
 22 higher risk for revision. However, patients with

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1 higher pain scores defined as pain scores greater
 2 than 8 on a scale of 0 to 10, or having history of
 3 fibromyalgia were at high risk of revision.
 4 Not significant were patients who were
 5 depressed or who had axial versus neuropathic pain.
 6 Again, looking at the multivariate analysis,
 7 obesity, which was a risk factor, [indiscernible]
 8 was not a risk factor with the multivariate
 9 analysis.
 10 There are other people that looked at risk
 11 factors with spinal cord stimulation. De la Cruz
 12 and colleagues looked at smoking, and this was
 13 correlated with lead migration and revision due to
 14 new pain symptoms. They also had similar negative
 15 trend for patients who used opioids. However, in
 16 this Bir study that I just discussed, neither
 17 smoking or drug use were a factor.
 18 Jean-Paul Van Buyten from Europe looked at a
 19 retrospective review of patients receiving
 20 rechargeable versus non-rechargeable stimulators
 21 and found that patients who had a non-rechargeable
 22 stimulator were more likely to be revised than

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1 patients who had a -- I'm sorry. Patients who had
 2 a rechargeable stimulator were more likely to be
 3 revised than patients who had a non-rechargeable
 4 device.
 5 Reprogramming is often done to salvage a
 6 device. You can reprogram the electrodes as
 7 cathodes, or anodes, or fractionate the current.
 8 However, there is reprogramming as far as
 9 algorithmic or pattern of stimulation. The studies
 10 that looked at this are within company products.
 11 For example, high density stimulation was done to
 12 rescue conventional stimulation at the lower
 13 frequency. Burst stimulation was done to rescue
 14 conventional stimulation. There are some published
 15 data on that within the company's products.
 16 Switching among devices may be attractive to
 17 some practitioners. However, it's not supported by
 18 evidence and is quite expensive, and is generally
 19 looked at negatively by third-party payers and
 20 insurance carriers. If one decides to use it, one
 21 should probably try, if possible, to perform a
 22 trial before undergoing or subjecting the patient

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1 to [indiscernible] and surgery.
 2 There are guidelines on how to decrease
 3 complications by consensus committees chaired by
 4 Tim Deer called the Neurostimulation Appropriate
 5 Consensus Committee, and these looked at guidelines
 6 to place the device to decrease the risk of
 7 neurological injury, to minimize the risk of
 8 infection, and also on the appropriate use in
 9 patients who are anticoagulated.
 10 There are also guidelines on who should be
 11 doing these procedures by NANS. This was published
 12 in 2009. Rick North was one of the authors. It
 13 suggested three levels or three tracks of
 14 experience if you want. Level 1 would be somebody
 15 who understands the therapy and able to reprogram
 16 the device; level 2 would be somebody who is able
 17 to trial the patient and program the device, and
 18 level 3 would be somebody who's able to program the
 19 device, trial, and implant the patient. Rick did
 20 not include level 4, like himself, which you can
 21 also create a device.
 22 (Laughter.)

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1 DR. HAYEK: Switching gears to what are the
 2 adverse events collection mechanisms and analysis
 3 and interpretation of data and device trials,
 4 unfortunately, AE data are probably the least
 5 validated and consistent process in research
 6 because there are a lot of variability in
 7 identifying the AEs.
 8 There's a general lack of consensus on
 9 definition of what constitutes and AE, and there
 10 are various methods for collecting the data,
 11 educating the data, analyzing the data, and
 12 presenting the data.
 13 This results in inconsistent reporting of
 14 adverse events. You could have the same study
 15 looked at using different criteria and come up with
 16 different AE incidences and rates or even findings.
 17 In general, adverse events are poorly
 18 defined. In the pharmaceutical industry, they are
 19 defined as untoward medical occurrence. There are
 20 less well defined in device industry, except for
 21 unanticipated adverse device effects, which are
 22 well defined by the FDA and involve any

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1 complication that results in catastrophic events
 2 such as death or life-threatening problem requiring
 3 admission to the hospital, for example, or the
 4 intensive care.
 5 Adverse events also may not include expected
 6 procedure-related events. For example, pain after
 7 the implant is not considered an adverse event for
 8 the first few days after the implant. The FDA
 9 requires medical reporting of unanticipated adverse
 10 device-related events within 30 days of death or
 11 serious injury and within 5 days of identifying an
 12 event that requires correction to prevent
 13 unreasonable sustained harm to the patient.
 14 The collection of adverse events in the
 15 device studies is very highly variable, and it
 16 depends on manufacturers. For example, where is
 17 the site where the study is taking place? Is it an
 18 academic practice? Is it a private practice? Is
 19 it in an office-based environment? Who is
 20 collecting the data? Is the coordinator a
 21 medically trained individual? Is the coordinator a
 22 nurse? How long have they been doing this? What's

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1 their experience?
 2 Is the collection of the events passive,
 3 asking the patient open-ended questions? With
 4 active collection, will it probably result in
 5 higher number of AEs, as suggested by Sam, as
 6 opposed to passive collection, where the patient
 7 would just volunteer the information? Is the data
 8 reported in detail format versus aggregate format?
 9 How do we interpret the data is also very
 10 variable, and it depends on the criteria in the
 11 protocol and the definitions set in the protocol as
 12 to what constitutes an adverse event. But there's
 13 also always a lot of leeway for medical judgment
 14 and biases of the investigator.
 15 In addition, there are also biases
 16 introduced by coding and by the coordinators, as
 17 well as by the field clinical engineer interacting
 18 with the patients, which also can introduce
 19 influence and biases.
 20 Ultimately, the device AE interpretation
 21 falls on the shoulder of the primary investigator
 22 or principle investigator at the site who has to

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1 report these adverse events, so their judgment and
 2 past experiences, as well as the biases, play an
 3 important role.
 4 Finally, how do we analyze and interpret the
 5 data? The data typically is reviewed by a
 6 treatment event committee and adjudicated by that
 7 treatment event committee. It depends whether or
 8 not this treatment event committee has set criteria
 9 for reviewing the data or is it based a lot on the
 10 reviewer judgment, and there are usually an odd
 11 number of reviewers that have to come to an
 12 agreement as to a particular adverse event or a
 13 complication and whether it's related to the
 14 product or not.
 15 The coordinators, when they collect the data
 16 for the analysis, have to use a coding system to
 17 put the complications under a certain code, and
 18 there are a lot of variabilities also in reporting
 19 these data, depending on the detail level, level of
 20 review, which codes are used and whether or not a
 21 due-to clause is used in reporting this data.
 22 The role of the FDA, in general, is

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1 restricted to reporting the unanticipated adverse
 2 device events. However, the FDA also approves the
 3 protocol in general that is submitted by the
 4 sponsor and the specific adverse events of the
 5 sponsor will be following. They get an annual
 6 report once a year, and at this once-a-year annual
 7 report, the FDA may ask questions. They also can
 8 provide guidance on the proper adverse event
 9 evaluation and who is qualified to collect the data
 10 on the adverse events.
 11 The FDA may conduct an audit to confirm the
 12 adverse events are being reported. However,
 13 realistically and due to time constraints, this
 14 only occurs rarely and only reviews a fraction of
 15 the records. However, the FDA requires that the
 16 sponsor maintains a monitoring plan, and anytime
 17 there are changes to the protocols, the FDA needs
 18 to be notified and review the protocol.
 19 In conclusion, spinal cord stimulation is
 20 overall safe. There are very rare reports of
 21 serious adverse events such as paralysis or death.
 22 However, they have a high frequency of

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1 complications that could be up to 50 percent. They
 2 may be technical or biological, and reporting
 3 device adverse events may be subjective and may be
 4 very variable from industry to another and from an
 5 investigator to another. Thank you.
 6 (Applause.)
 7 Group Discussion
 8 DR. KATZ: Let me ask all the speakers from
 9 this afternoon session to come up, so that's Ewan
 10 McNicol, and John Markman, and Ali Rezaei. Is Ali
 11 here? Just please come up and have a seat at the
 12 dais.
 13 We have some time for discussion now, and I
 14 think consistent with what we did earlier today,
 15 let's just begin the discussion with any questions
 16 or comments that people have about the
 17 presentations that this august group gave this
 18 afternoon. And maybe in case people don't anymore
 19 remember what the presentations were about --
 20 Maybe what I'll do just to get the
 21 discussion going is ask Ewan, once he's all set
 22 with the furniture, to just maybe give us a brief,

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1 one-minute summary of what you think you learned
 2 from the -- since you took a deep dive into
 3 methodology of spinal cord stimulator studies,
 4 maybe just jump-start us by giving us sort of the
 5 big picture of what do you think you learned that
 6 is most relevant to this group's task, which is to
 7 make recommendations about the design and conduct
 8 of such studies.
 9 DR. McNICOL: I wish you had coached me in
 10 that before the panel discussion.
 11 DR. KATZ: I'm a little evil. Don't worry.
 12 DR. McNICOL: As I mentioned, it was all
 13 brand new to us. We were using as our point of
 14 reference how different our spinal cord stimulation
 15 studies are from drug studies. The differences
 16 where there were generally smaller numbers, usually
 17 longer durations of study because it was chronic
 18 pain. If you're putting a permanent implant in a
 19 patient, you're clearly going to follow them over a
 20 longer period of time; a lot of crossover studies
 21 in there, which we don't see as often with drug
 22 studies.

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1 The level of reporting -- and this is a huge
 2 generalization, but given that drugs have been
 3 marketed for 100 years plus and spinal cord
 4 stimulation is 50 years old, I feel that spinal
 5 cord stimulation has just caught up in the last few
 6 years with drug reporting as far as meeting all the
 7 criteria for what you should report in a clinical
 8 study.

9 The most recent studies are really as
 10 rigorous as drug studies at this point. But some
 11 of the earlier studies, as I mentioned, are with
 12 very few disagreements because there are hardly any
 13 data in them at all. They were almost like this is
 14 something brand new, and we're just throwing out
 15 stuff, and we're following patients for 2 weeks
 16 with 4 patients in each arm.

17 So it's been a really steep progression from
 18 the first studies to the most recent studies that
 19 we've included. That's just my overarching --

20 DR. THOMSON: Can I just also say what is
 21 your impression of the treatment effect? Because
 22 broadly, when we've been in large groups like with

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1 NICE, small trials, that we've been saved by the
 2 fact that there's been quite a large treatment
 3 effect when you compare it to pharmaceutical
 4 studies, which are big trials and small treatment
 5 effect.

6 DR. McNICOL: So what I would say -- and
 7 obviously we read the papers back to front, but we
 8 didn't really concentrate on what the results of
 9 those papers were, so I couldn't really give you a
 10 definitive answer to that other than I think maybe
 11 what you're getting at is that in spinal cord
 12 stimulation studies, you need less patients to show
 13 an effect than you do in drug studies because that
 14 clinical effect is greater.

15 So just from a sample size calculation, you
 16 don't need as many patients, which might come back
 17 to one of my earlier questions about do you
 18 actually need as many patients for a spinal cord
 19 stimulation study as you do for a drug study. But
 20 again, we didn't really concentrate on the actual
 21 results of the studies.

22 DR. FIELDS: When you looked at the

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1 crossover studies for spinal cord stimulation, how
 2 did the second run compare to the first? Was this
 3 sham versus parasthesias? Was it two different
 4 kinds? Was it no stimulation?

5 DR. McNICOL: It was everything. Obviously,
 6 the earlier studies, high frequency or burst wasn't
 7 an option, but I crossed the 35 years, or whatever
 8 we looked at, and it could be anything in the
 9 crossover. It could be a different program of the
 10 conventional SCS versus patients getting burst and
 11 getting conventional or vice versa because my
 12 understanding is that devices can be programmed to
 13 both of those things now.

14 I was talking with Turo earlier about the
 15 fact that there seemed to be a first period effect
 16 in some of the studies as well, particularly when
 17 there was a short crossover or a short washout
 18 period. So there were some aspects of that in
 19 several of the studies.

20 DR. FIELDS: There's classic literature on
 21 crossover studies and pain. Or at least, for
 22 example, you follow a placebo treatment with an

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1 active treatment, the active treatment is much less
 2 active. If you follow an active treatment with a
 3 placebo treatment, the placebo treatment's much
 4 more active. Right?

5 So I would just warn against crossover
 6 trials for analgesia if that's your measure because
 7 there's a huge learning effect that's going to
 8 diminish the group differences if it's the same
 9 group that's crossed over as opposed to
 10 re-randomized in the second half. Right?

11 DR. McNICOL: I agree. I think the original
 12 clinical impression was that crossover studies were
 13 fine for chronic pain because the patient had pain
 14 over such a long period, and it wasn't generally
 15 getting any better, that it was okay to cross
 16 patients over. I think we're starting to realize
 17 now that that's probably not as -- that's an
 18 oversimplification, and even chronic pain changes
 19 over time. And as you mentioned, period effects
 20 are really important for patients. What they get
 21 first is usually better than what they get second.

22 DR. KATZ: I have McKenzie, and then I have

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1 Jane, and then I have Andrea.
2 McKenzie, can you introduce yourself please?
3 DR. FERGUSON: Sure. Hi. McKenzie Ferguson
4 from Southern Illinois University, Edwardsville. I
5 just wanted to follow up with you in some of the
6 things that I think we kind of struggled with a
7 little bit on the review, which was even just the
8 flow of the participants from prescreening all the
9 way through the final outcome assessment and why
10 patients were maybe -- because most of our analyses
11 were per protocol. So when people didn't make it
12 all the way through, was it due to efficacy? Was
13 it due to adverse events? Inconsistency in the
14 number of patients that required modifications to
15 their spinal cord stimulation due to adverse
16 events? I think those were some things, too, that
17 we learned that maybe were inconsistent.
18 DR. KATZ: Jane?
19 DR. SHIPLEY: Jane Shipley from Baltimore.
20 One thing I thought of when Salim was talking was,
21 what we're trying to do is improve studies both in
22 the design of the study and the conduct of the

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1 study. And I think we also should think about
2 improving the reporting of the study.
3 The reason I say that is because in recent
4 studies, I have seen adverse events reported as
5 adverse events. I'm like, "Well, what were they?
6 I have no idea." And these are industry-sponsored
7 studies, and they're not specific. I have little
8 places to put how many infections there were, and I
9 can't do it because I have no idea.
10 Peer reviewers can step in at that point.
11 Peer reviewers are not going to step in at the
12 point of developing a study protocol or conducting
13 the study. But when we're reporting the data, a
14 peer reviewer could come back and say to the study
15 sponsor, "You know which adverse events they were.
16 Tell us."
17 So it's just asking peer reviewers to pay
18 attention to specific details and make sure that
19 they are actually presented, and I only use this as
20 an example because one might say it's a small
21 thing. I don't think it's a small thing. But I
22 just think that if we're thinking in terms of

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1 improving -- the whole thing, I mean, what is a
2 study without a study report, and what lives the
3 longest is a study report. So I would like very
4 much to see those improved. I'd just put that out
5 there. Thank you.
6 DR. KATZ: I'll make sure to include that in
7 that paper that summarizes this meeting, a section
8 on reporting.
9 DR. NORTH: Publishers have an obligation to
10 pay attention to peer reviewers. I'm sure you've
11 all had the experience of reviewing a paper and
12 having your suggestions blown off, I think is the
13 technical term.
14 DR. TAYLOR: Nate, could I just make a quick
15 rejoinder on that? It's Rod here. I think one of
16 the challenges you're going to have, if I may give
17 you the challenge, is thinking of what are the
18 peculiarities of neurostim in terms of trial
19 recommendations over and above chronic pain. It's
20 going to be different.
21 Some of the recommendations will be common;
22 they have to be. And indeed, we need to up our

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1 game to make sure that we're at least operating
2 alongside our pharma friends. I think we'd all
3 agree with that; not a problem. But there are some
4 peculiarities, if I can call it that, and I think
5 we need to articulate the peculiarities. But
6 anyway, that's a general comment.
7 Just to go back to Jane's point, I think
8 reporting is incredibly important. And I think one
9 of the peculiarities -- and I'll use that word
10 again -- of neurostim is that we've got much more
11 of what we would define nowadays as a complex
12 intervention. That's an intervention that depends
13 on the interaction of not just the therapy, i.e.,
14 if you give a drug, we give the dose. And as long
15 as you've described what the dose is, you've kind
16 of described intervention.
17 Here, describing intervention is a much more
18 complicated thing. And there are actually some
19 guidelines already out there to help us with that,
20 so we don't need to reinvent the wheel so people
21 will know of the TIDieR guidelines. TIDieR is,
22 again, kind of consult like group that have made

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1 some recommendations about describing, if you like,
 2 the granularity of the intervention to allow you to
 3 be able to replicate the study again. And that's
 4 never a bad kind of metric.
 5 So I would really be encouraging that it may
 6 be that we can point to some particular areas of
 7 reporting that are particularly -- and I'll use
 8 that word again. So it's particularly important
 9 for neuromodulation or ICS studies that would help
 10 us in the future; critically appraised studies just
 11 as the Tufts group, but then also understand what
 12 the studies were actually up to, which is half the
 13 problem that we have, is peer reviewers.
 14 Anyway, herein is the sermon, that I hope
 15 that is a useful comment.
 16 DR. KATZ: I think it's useful enough that
 17 we should, expand on it further. And maybe,
 18 Andrea, you'll forgive me if I take a moment and
 19 just expand on that.
 20 Maybe, Rod, you could expand a little bit
 21 more on what you think those particularities are
 22 that are worth focusing attention on, those papers,

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1 so we're not simply replicating all the guidelines
 2 that already exist out there, but just focusing
 3 primarily on what's different here that
 4 characterize this unique intervention. What do you
 5 think those particularities are?
 6 DR. TAYLOR: I'm going to do a
 7 review -- and, gosh, that's a hospital pass you've
 8 given me, but I'll try and respond. I think there
 9 are at least two really key -- well, actually one
 10 key thing that's going on here, which is spinal
 11 cord stimulation is a medical device that's
 12 delivered as an interventional procedure.
 13 So it's back from me to this; what are the
 14 particular challenges of evaluating an invasive
 15 procedure? Actually, they're not specific to
 16 spinal cord stim; they're generalizable to any
 17 invasive procedure. But what we've got to do is
 18 contextualize SCS, those peculiarities in the
 19 chronic pain space.
 20 For instance, the issue we've just talked
 21 about, the effects of the therapy as the
 22 interaction between the device itself but also the

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1 operator and the setting. And if we don't
 2 understand those things, then we're not really
 3 understanding how the therapy works.
 4 So I think there are some specifics we could
 5 bring out. That's just a quick punch at
 6 responding, but I think if we're doing this in the
 7 context of reviewing a manuscript, I'm sure we
 8 could tease these out in a more sophisticated way.
 9 And I suspect others will have views on those
 10 peculiarities in the room as well.
 11 DR. KATZ: Thanks. No, that's good.
 12 Andrea, you were next.
 13 DR. TRESKOT: Thank you. Andrea Trescot,
 14 Stimwave. I wanted to go back to the crossover
 15 issue because one of the very few ways that we have
 16 to convince patients to do a placebo-controlled
 17 trial is the promise that they can get the active
 18 therapy if what you've offered them didn't work.
 19 So I think there are two types of crossovers, one
 20 where there's a mandatory crossover and the other
 21 where you have a "if failure, then crossover."
 22 So I can thoroughly understand the argument

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1 against the forced crossover because of the comment
 2 that the first therapy always looks better. But I
 3 think if you have a failure of one treatment, then
 4 that's really the only ethical way if you're doing
 5 a true sham or a true placebo. If what you're
 6 doing is comparing -- and it has that other
 7 advantage of having the patient as their own
 8 control because part of the problem is when I'm
 9 doing a spinal cord stimulator trial for low back
 10 pain and one patient has low back pain because of a
 11 set pathology and another has low back pain because
 12 of epidural adhesions, those patients may respond
 13 very, very differently to the same stimulation, but
 14 they have the same pathology so that it would allow
 15 you to then try different therapies for that same
 16 pathology with the patient acting as their own
 17 control. So I think in that respect, the crossover
 18 trial becomes very important.
 19 DR. KATZ: Thank you. John?
 20 DR. MARKMAN: On our experience, I think
 21 we're over 60 duplex trials at this point using
 22 high frequency and either tonic or burst or

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1 something else. And we have not seen this idea
2 borne out that the first therapy always wins.
3 DR. TRESKOT: But you're also not comparing
4 it to a placebo, correct?
5 DR. MARKMAN: Absolutely right. So we're
6 not putting a placebo arm, but we just haven't
7 noticed -- and obviously, nobody likes when you do
8 this, when you try to different stimulation
9 paradigms with the same set of leads. That
10 is -- really, everyone doesn't like that in terms
11 of the representatives.
12 They don't want to be compared one to
13 another, head to head like that. And the first
14 group always claims that, "Oh, it's the
15 post-procedural pain, which is why our device
16 wasn't chosen because the patient had too much
17 discomfort from the acute nociceptive pain from the
18 two-needle placement." And the second person says,
19 "Well, they had so much time brainwashing them
20 during the first period about why their stuff
21 worked, that of course by the time they got to us,
22 ours didn't work," because they were so conditioned

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1 that they needed parasthesia to get relief, or they
2 were so conditioned that they didn't need
3 parasthesia not to have an adverse event.
4 But the interesting thing is that I was
5 deeply worried about the sequence but we have not
6 really seen an effective --
7 DR. TRESKOT: That actually is a critical
8 piece of information that needs to be in the
9 literature, is that there is no effect in the
10 sequence, in your experience and with your studies,
11 that there's no difference in the sequence because
12 that would then get rid of that concern about a
13 crossover trial.
14 DR. MARKMAN: No, we don't know there's
15 carry over. That's one of the things we also
16 worry, obviously, between one sequence to the next,
17 whether there's some analgesic benefit conferred in
18 first 3 or 4 days that somehow --
19 DR. TRESKOT: And how long is washout? How
20 long do you have to have a wash out before you have
21 a loss of effect?
22 DR. MARKMAN: These are unknowables. I

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1 don't know the answer to these things.
2 DR. HAYEK: Perhaps Sam and Eric can comment
3 because you guys were co-authors in Cristophe
4 Perruchoud's study, and you found a period effect.
5 DR. BUCHSER: Yeah, we did, and actually the
6 first treatment that was proposed showed the best
7 result, irrespective whether it was placebo or the
8 stimulation.
9 DR. NORTH: To the extent there's maybe a
10 period effect, doesn't that just increase sample
11 size requirements, to try to tease out the period
12 effect versus the therapeutic benefit.
13 DR. KATZ: In theory, it doesn't --
14 DR. TAYLOR: Yeah, period effects are a bit
15 of a bugger, actually, in analyzing crossover
16 trials; a technical term, Rick.
17 DR. KATZ: Jen?
18 DR. TAYLOR: It's not just a para issue;
19 it's a kind of confounding issue. So it's
20 difficult to make it go away with power, the period
21 effect.
22 DR. KATZ: Actually, Jen just lived the year

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1 dealing with crossover studies or whatever it was.
2 Do you want to comment on that?
3 DR. GEWANDTER: I was just wondering, in
4 your study, was the reason the effect was bigger in
5 the first period because they didn't come back to
6 baseline in the second period?
7 DR. BUCHSER: Say that again?
8 DR. GEWANDTER: Was the reason that the
9 effect was bigger in the first period in both
10 groups because they didn't come back to their
11 baseline in the second period? So you weren't
12 starting as high in second period.
13 DR. BUCHSER: No. Actually, both treatments
14 get the same result, roughly the same result as it
15 was presented first. And stimulation had a very
16 slight advantage when presented second over sham.
17 So they were not coming back to the same result.
18 DR. THOMSON: Like a lot of these things,
19 the devil's in the detail, and we're learning how
20 to do these crossover studies with
21 neurostimulation. Certainly, in our protocol
22 study, preemptively we've said that the pains would

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1 have to return to within 80 percent of baseline
2 before we would then go on to the next parameter.
3 That seems --
4 DR. NORTH: A crossover study begins with a
5 parallel group study, and you can analyze that in
6 and of itself. And the additional information from
7 the crossover period is just that; it's additional
8 information. I don't see any reason not to do it.
9 DR. McNICOL: That's what we tend to do with
10 our Cochrane reviews, is we'll only analyze the
11 data from the first period. And the second period,
12 as you mentioned, is just additional stuff. But
13 then you're looking at, as you say, larger sample
14 sizes when you're using what's essentially a
15 parallel study with an extension on it, really.
16 DR. KATZ: Turo?
17 DR. NURMIKKO: Turo Nurmikko, UK. Coming
18 back to the crossover issue and the washout period,
19 as Ewan was showing, most of the studies had no
20 washout period whatsoever, even in each arm the
21 patient received SCS for days or weeks. And you
22 see it's almost impossible to think that there

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1 wouldn't be any long-term physiological effects
2 that could actually confound the results. And of
3 course, the results for many of those studies, as I
4 said, they show surprisingly little difference
5 between groups, and these could be, in part I
6 think, associated with the fact that the washout
7 period has been neglected to a certain extent.
8 Now, I haven't seen any justification why
9 that would be justifiable. In other words, it will
10 be helpful to know if somebody somewhere has
11 actually checked this issue in some context to see
12 whether following, say, a couple of weeks of SCS,
13 do you actually either immediately lose the effects
14 where somebody switches off the stimulator or
15 whether there is a true carryover effect and how
16 long it lasts.
17 DR. KATZ: John was next, John Markman.
18 DR. MARKMAN: Well, I just would say with
19 the crossover issue -- I'm not going to directly
20 answer your question, but I think it's a good
21 question. But just with regard to Simon's point
22 that the devil's in the details with crossovers, it

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1 is important to note that if you go from one to the
2 other, there are some challenges because they have
3 slightly different specs in terms of where the
4 leads.
5 We should just put that in the manuscript
6 because this is one of the things that we ran into,
7 is you can't really do a Nevro trial if you're not
8 intersecting the T9/10 interspace. And you can't
9 really do a Nevro trial if you've only got one lead
10 in. And the Boston folks will say that you can't
11 really do SSR therapy if we're not at the T7
12 vertebral body level. And the Nevro folks will say
13 that, "Well, if we don't get to wash into 4 of our
14 program cycles, then you can't decide that it was a
15 failure," because it takes 20-48 hours to wash into
16 each program cycle.
17 So I think there are a lot of devil in the
18 detail type issues with regard to technical
19 placement of the leads, but also with the paradigm
20 to wash in of the stimulation paradigm, it's just
21 like saying you didn't adequately titrate the
22 gabapentin. You only got to 600 milligrams, and

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1 you're calling and saying our session didn't work.
2 We need a chance. We need to do 3 more days at
3 1800 milligrams and decide that this was a failed
4 study.
5 So I think that we are going to need to
6 qualify -- whatever we do in crossover, we need to
7 address that there are system-specific requirements
8 based on how the manufacturers believe their
9 devices work.
10 DR. REZAI: That's where the
11 standardization comes in. The quality elements
12 for the study design is very important. Like we
13 discussed, the design, the conduct, and recording
14 of the events, there are a lot of variations in
15 this. So I think the more they standardize that,
16 that would help the field. I think that's very
17 important.
18 DR. NORTH: John, wouldn't it be fair to say
19 that we could standardize lead placement in a
20 comparative study among these various waveforms,
21 and that there's not really any affirmative
22 evidence that it's not necessary to do parasthesia

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1 mapping when you put leads in for high frequency?
2 There's just a claim of good results in
3 circumstances where they didn't bother doing
4 parasthesia mapping.
5 DR. MARKMAN: Yeah, I think that's certainly
6 reasonable.
7 DR. HAYEK: So that's a nice marketing tool
8 to be able to say that. But in the context of a
9 study where you anticipate using the same leads
10 that are used for HF for conventional stimulation,
11 then you would do the mapping, which is essential
12 for the latter, and it could only benefit the --
13 DR. MARKMAN: Right. There is always some
14 back and forth -- and again, I want to make sure I
15 understand your question -- around the lead contact
16 spacing for some of the different systems and
17 whether that affects these --
18 DR. NORTH: Yeah, but there's really no
19 evidence for a difference there.
20 DR. MARKMAN: Right. I mean, again, these
21 are marketing claims that I think certainly affect
22 the decision-making of implanters and certainly

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1 affect the way that implanters explain the device
2 to people receiving them. And most importantly,
3 the way that the representatives who -- we have to
4 just acknowledge openly that a lot of the care of
5 these patients around their devices is outsourced
6 to representatives, and the representatives are
7 perpetuating their messages and their explanations
8 for treatment effects. And I think that
9 outsourcing, which is something that's an open
10 secret, has a profound effect on the therapeutic
11 intervention.
12 DR. THOMSON: Just to say, that's a
13 peculiarly U.S. centric thing that's going on.
14 Okay? The way you approach your process of spinal
15 cord stimulation with other people doing trials and
16 then referring them on to somebody else; you put
17 the implant in, and the trial is assessed by the
18 representative of a company, that's not what
19 happens -- well, certainly in my institution, where
20 it's our team who basically take on the management
21 of the patients.
22 I think certainly if we're going to have any

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1 recommendations for clinical trials, this is one of
2 the big things we've got to actually recommend, is
3 the involvement of the representative has got to be
4 minimized and monitored.
5 MALE VOICE: Here Here. Absolutely.
6 DR. MARKMAN: I think it's essential. I
7 think this is something that is a field. I don't
8 think this is necessarily the only forum to address
9 this, but this is a major issue. Many companies
10 won't even let you use a controller to program the
11 device anymore.
12 MALE VOICE: That's right.
13 DR. MARKMAN: We've all faced this. So
14 you're stuck with not offering your device because
15 you don't have access to the controller to program
16 it. And I think I'm sure I'm not the only one that
17 faces this.
18 DR. KOPELL: Can I ask a question on that?
19 I'm sorry to put out a specific company. Has
20 anybody here ever got access to the Nevro
21 controller device?
22 DR. MARKMAN: My understanding, in the UK,

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1 they have done it because it's a country-specific
2 policy. I think there was something -- there was a
3 national level issue there. But in the U.S., my
4 understanding is there's no one.
5 DR. KOPELL: I mean, that just boggles my
6 mind. You know? To be honest with you, we all
7 call neuromodulation a digital drug. You've heard
8 that term bandied about. So we're basically saying
9 that doctors can't administer the drug and only the
10 companies can do that. That's just -- for me, that
11 rankles me beyond belief because, again, it's so
12 backward.
13 DR. THOMSON: There are several sort of
14 models; Jose De Andres' study from Spain that
15 looked at two different companies independently
16 funded, and attracted a lot of criticism, if you
17 like, from the companies because, essentially, a
18 fairly minimal treatment effect in both groups.
19 And they put it down to the fact that it was
20 because it was done by the hospitals staff, the
21 programming, which I think is not altogether true.
22 So you can have the reps do the thing, but

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1 they are monitored and scripted what can be said,
 2 and the timing how long they spend programming, and
 3 all that sort of thing. That can and probably
 4 should all be done if we are going to be doing
 5 studies.
 6 DR. REZAI: I can comment on the DBS world.
 7 SCS has been "grandfathered in some ways," just
 8 some quotation. DBS is very different. It's very
 9 much sort of an organic. We're involved in the
 10 settings and all that, so the physicians do it. I
 11 think this is more unique to the spinal cord stim
 12 companies because traditionally, in the DBS trials,
 13 we actually design the stimulation parameters, and
 14 we stick by it. But I think this is mission
 15 critical. You have to really standardize, and that
 16 will really make a difference.
 17 DR. KATZ: Andrea?
 18 DR. TRESCOT: I've actually had a multitude
 19 of patients say that they had told the rep that
 20 they had only gotten 30 percent relief, and the rep
 21 had then told the implanter that they had 50 or 60
 22 percent relief, and they went on to implantation.

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1 And this happened not one time, but multiple,
 2 multiple times. And I've had multiple patients
 3 tell me the exact same story. So it may be one of
 4 those dirty little secrets.
 5 DR. KATZ: So just ask the rude question.
 6 Is it feasible in the United States to not have the
 7 company representatives involved in a clinical
 8 trial?
 9 DR. MARKMAN: Well, I think they have to be
 10 in the operating room because there's so much hand
 11 off of materials. There's a supply chain issue,
 12 which is one set of issues which you can't get away
 13 from. But there is a programming issue and a
 14 patient interaction thing, which you can completely
 15 get away from. But I think the technical support
 16 you get in the OR is a very distinct thing from the
 17 continuum of therapy that you get in the outpatient
 18 setting. And I think we could clearly dichotomize
 19 that.
 20 DR. HAYEK: One word also about the
 21 technicalities for every different manufacturer is
 22 different, and for the physicians to learn how to

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1 program every device is unachievable nowadays
 2 because every company has become kind of like very
 3 specific in programming, so take a long time. So I
 4 think you have to have the involvement of the --
 5 DR. ELDABE: Again, I think specific in
 6 programming, but is that based on science?
 7 MALE VOICE: I missed the first part.
 8 DR. ELDABE: Companies are specific in
 9 programming, and they all have an algorithm, but
 10 what is that based on?
 11 DR. HAYEK: Well, also the technicalities of
 12 using the device. So to choose a programmer for
 13 company X, Y, and Z takes a significant amount of a
 14 learning curve to handle it.
 15 DR. MARKMAN: And again, I think it's a good
 16 point. I think that for myself, personally, to
 17 learn how to program five different devices, I
 18 would have to spend 4 or 5 days full time. I could
 19 do it, but when you ask me do I manage intrathecal
 20 pumps and medications, that those have much more
 21 serious complications, we would never let the reps
 22 do that.

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1 DR. THOMSON: This has come back to reality.
 2 We're talking about doing research. You don't have
 3 to do 5 different devices. You could just do your
 4 research with one device.
 5 DR. KATZ: Is it possible for a
 6 paraprofessional or physician's assistant or
 7 somebody to learn to program one of these devices?
 8 DR. MARKMAN: Absolutely. Obviously, the
 9 downside risk is lower. If you had a clinical
 10 trial coordinator doing the programming, I think
 11 that you would just want to put them in a position
 12 where there was someone overseeing them because if
 13 someone got over-stimulated and had a car accident
 14 or fell on the way out to the car or something,
 15 from a conduct point of view of the study, you just
 16 need to make sure that their PI is someone who can
 17 meaningfully oversee what the clinical trial
 18 coordinator's doing.
 19 DR. KATZ: So by oversight, do you mean the
 20 PI's oversight or do you mean the representative
 21 from the company's oversight?
 22 DR. MARKMAN: I think the PI. A PI who's

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1 implanting can certainly oversee a clinical trial
2 coordinator who's programming.
3 DR. REZAI: This goes back to the rigor that
4 needs to come in from the study oversight. I think
5 that's important because I believe there's a lot of
6 vagaries and looseness to this element.
7 DR. HAYEK: I agree with your idea, but you
8 need to send that coordinator for training on
9 whichever particular device product, and that takes
10 some time.
11 DR. FIELDS: Excuse me. Can anybody up
12 there tell me what the people who are programming
13 these devices tell you that they're actually doing?
14 I mean, are they setting the stimulation
15 parameters?
16 DR. HAYEK: They have software.
17 DR. FIELDS: Are they writing code?
18 DR. HAYEK: No, no, no. They have software.
19 DR. FIELDS: Yeah, I know. I know what
20 software is.
21 DR. HAYEK: They just need to learn how to
22 use the software. That's specific to the company.

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1 DR. FIELDS: I mean, you can't turn the knob
2 and change the frequency. You have to write code
3 for that?
4 DR. HAYEK: You don't have the program on
5 your computer. They have their own computer device
6 that plugs to their equipment that you're putting
7 in surgery. So you can't just put into --
8 DR. FIELDS: But you didn't answer my
9 question. What is it that they actually program?
10 What's the program?
11 DR. HAYEK: They have algorithms that they
12 follow, like Sam said, which basically fractionate
13 the current or divide the current between cathodes
14 and anodes. They follow --
15 DR. FIELDS: So they're changing the
16 stimulus parameters.
17 DR. HAYEK: Correct.
18 DR. FIELDS: Okay. That's much simpler than
19 programming.
20 DR. MARKMAN: Some of that's interactive. I
21 think the difference is that for some companies
22 this is a very one-size-fits-all algorithm, which

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1 everyone gets kind of off the rack. It's a
2 step-wise increase or decrease in intensity or
3 whatever other parameter you want to modulate;
4 whereas for other companies, where they're sort of
5 doing parasthesia mapping in some complex way, it's
6 a very interactive process with the individual
7 patient to decide what aspect of the knee you're
8 going to cover at night versus when you're walking.
9 So again, as long as you're doing it within
10 device, it's easier. But some of these things will
11 be tricky I think to do apples-to-apples
12 comparisons with. But I think that you can
13 prespecify all of these things in the context of a
14 trial.
15 DR. NORTH: Speaking of interactive, it
16 wouldn't be all that hard. And I speak from a
17 decade or more of experience with developing a
18 patient interactive system that would automatically
19 do a study protocol.
20 DR. MARKMAN: That's right.
21 DR. NORTH: And it supported two different
22 manufacturers. We did, gosh, maybe 10 RCTs looking

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1 at technical measures of stimulator performance.
2 And it was just a matter of tweaking the code,
3 putting the patient in front of the computer, and
4 saying follow the instructions on the screen. And
5 the computer would do the randomization, set the
6 parameters, and everything.
7 So for a given manufacturer's device,
8 assuming they're willing to support this, the
9 manufacturer that plays ball with this group I
10 would think would be in a better position than the
11 others.
12 DR. KATZ: Rod, I think you had a comment.
13 DR. TAYLOR: This is a fascinating debate,
14 isn't it? I guess the metaphor I'd give it is it's
15 a Kentucky Fried Chicken phenomenon, isn't it?
16 Shall I explain that?
17 (Laughter.)
18 FEMALE VOICE: Please do.
19 DR. TAYLOR: Does that translate?
20 DR. KATZ: We don't know about Kentucky
21 Fried Chicken here. Why don't you explain it to
22 us?

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1 DR. TAYLOR: Kentucky Fried Chicken, we eat
 2 a fair bit of it in UK, I'm sorry to say.
 3 (Laughter.)
 4 DR. TAYLOR: But what I'm told about --
 5 MALE VOICE: That's a lot.
 6 DR. TAYLOR: Yeah, particularly to Scotland.
 7 Anyway, KFC, the recipe is IP; we don't know. What
 8 I'm going here or not, if I may, at least they tell
 9 us in the UK it's IP, intellectual property. They
 10 know what's in the recipe.
 11 So I think we need to be cautious here, if I
 12 may. I think what we're saying is in the context
 13 of spinal cord stim, a particular peculiarity of
 14 the therapy is the involvement of the company in
 15 the delivery of the therapy. Yeah? It's another
 16 contextual issue.
 17 I think we need to be cautious that we don't
 18 box ourselves into a corner. One comment is the
 19 company may, for intellectual property reasons,
 20 want to keep their software to themselves. And if
 21 we want to know whether the therapy works or not,
 22 we might need to respect that. I think I would

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1 just plead for transparency here in terms of trial
 2 design about the involvement of the company. And
 3 that's not because I'm a company guy, but I think
 4 we need to just be cautious; as I say, don't box
 5 ourselves into a corner.
 6 So just an anecdote, I'm involved in a study
 7 in the UK with ATNAN [ph], where we're trying to
 8 deliver a placebo from a device, and we really need
 9 the company's input to help us technically achieve
 10 that. And if we don't have them at the table,
 11 excuse my technical French, we're bugged. We
 12 can't deliver the trial. So I think we need to
 13 respect the fact that companies can have an
 14 important contribution in trial design and trial
 15 delivery, but it's a transparency I think of that
 16 process. I would just perhaps encourage us not to
 17 be too overly prescriptive here.
 18 DR. KATZ: Thank you for that, Rod.
 19 You summarized it so beautifully, Rod, that
 20 this is a peculiarity of spinal cord stimulation,
 21 that the therapy is usually delivered by the
 22 company, or at least often; there may be regional

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1 variations. And I've heard three different options
 2 for how that could be addressed in clinical trials.
 3 Option number one is that the company
 4 delivers the therapy, but how that's done is
 5 transparent and quantified to the extent possible.
 6 How many visits? When were they done? How long
 7 did they take? That sort of thing. That's one
 8 option.
 9 A second option that I heard was that we
 10 would train a member of the clinical team to
 11 provide that programming and other related support,
 12 and there would have to be some description of that
 13 training process and how it's being supervised and
 14 how that's done.
 15 The third option that Rick mentioned is that
 16 perhaps in some circumstances, it could be a
 17 computerized version where it's literally between
 18 the computer --
 19 DR. NORTH: An automated version.
 20 DR. KATZ: -- an automated version. Thank
 21 you.
 22 So those are the three options that I heard.

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1 And I heard your point, Rod, that we could lay out
 2 those three options and indicate that there are
 3 advantages and disadvantages, and feasibility
 4 considerations for each one of them with
 5 transparency and quantification of the approach
 6 being the core of requirements.
 7 Does anyone from any of the manufacturers
 8 have any comments on this issue? Since you guys
 9 are here, we may as well learn about your
 10 perspectives.
 11 DR. TAYLOR: That sounds reasonable, what
 12 we've suggested.
 13 DR. KATZ: First name?
 14 MS. LEITMAN: Angela. I think it's going to
 15 be actually a reimbursement issue that people
 16 aren't going to like the outcome of --
 17 DR. KATZ: Can you speak into your
 18 microphone and introduce yourself, please?
 19 MS. LEITMAN: I think it's going to be a
 20 reimbursement issue that physicians aren't actually
 21 going to like, because you get paid so little for a
 22 programming visit. And the time it takes,

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1 depending on what they're doing, you're not going
2 to see that money come back to you. We've actually
3 had people -- I see the point of the bias and try
4 minimizing that, but also there's an economic side
5 of it, that it's actually a service that's provided
6 where physicians have to do less and build a trust
7 with someone on how they deliver that therapy.
8 So I agree with Rod in that we should just
9 be careful. I agree that it could be improved. I
10 just think we need to think about it.
11 DR. REZAI: We're talking about the design
12 of a study. This is not about -- I mean, that's
13 down --
14 DR. HAYEK: And real life, yes.
15 DR. REZAI: This is more of a design, right?
16 DR. THOMSON: It's really important to
17 realize there is this difference between doing a
18 clinical science and what is basically usual care,
19 where, frankly, with usual care, we're keen to have
20 any involvement, and help, and placebo comments to
21 get the best result. But when we're doing studies
22 and looking for a treatment effect, we've got to

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1 give advice of how we're going to really show the
2 treatment effect or not.
3 DR. MARKMAN: I think that's great. It's
4 inconceivable that you could do a drug trial in
5 United States where the sales representatives would
6 be running the study visits. It's unthinkable.
7 Frankly, it's unfathomable; it could never happen.
8 And you'd have a sales representative who is
9 incentivized in the sale of the drug at that
10 particular site, running the truck. We wouldn't do
11 it. It would like if somebody explained this to
12 what was going on, people would be dumbfounded.
13 DR. REZAI: Are we using the same rigor that
14 pharmaceuticals -- what have you learned from the
15 pharmaceuticals? Have we applied that in this
16 context, is my question. Do you all feel
17 comfortable that you applied the lessons learned
18 from the pharmaceuticals in here, in this place?
19 DR. FIORE: Maybe I can address that
20 question and also add some of the industry context.
21 For industry sponsored studies, the goals are
22 really to identify uses of products in populations

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1 that will benefit to the satisfaction of the
2 practitioners and the patients because that creates
3 the market, the payers, because that's the
4 reimbursement, and the health authorities.
5 To me, what strikes me in this conversation
6 is that the poll for the research is coming from
7 academics and physicians rather than being driven
8 by industry, so the motivations may be different.
9 I think if the health authorities have set a bar
10 that I'd venture to say is lower for device
11 approvals than for drugs, and physicians adopt
12 these because they're interesting, they're cool,
13 they're novel, and there's a promise for helping
14 the patients, then the payers are really left out
15 here.
16 So to your point, if the companies don't
17 come and take the lead for increasing the
18 standards, increasing the rigor, and enlisting
19 support of the sites to do that, then I think that
20 this problem, the circularity of it, will not be
21 broken.
22 DR. MARKMAN: Well, I think that's exactly

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1 right. I think that the point that was made this
2 morning was really right on, that said unless the
3 regulatory standard is raised, that's the only way
4 to really break that cycle. Without a higher
5 regulatory -- the marketplace cannot decide. The
6 clinical cannot decide. It's only because it was
7 compulsory from a regulatory perspective that the
8 market could sort out some of these other issues.
9 But with too low of a bar on the regulatory side,
10 you'll never -- that's why it is so important, this
11 document, because unless we create a standard for
12 the regulatory world that everyone agrees to, at
13 least as a minimum that's somehow different from
14 the current one, we'll never resolve these issues.
15 DR. KATZ: Brian, I see you are dying to
16 make a comment. Your mouth started to open.
17 (Laughter.)
18 DR. KOPELL: Maybe I'm being too rigid, but
19 again, I look at the application of electricity on
20 the nervous system as something wholly in the realm
21 of the caregiver, period, full stop. Sure. If you
22 tell a company person you can push that button,

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1 that I guess I'm okay with. But to let them
 2 basically independently do anything -- and I note
 3 and it happens all the time -- it would never
 4 happen in the DBS world. And every so often you
 5 hear some weird things that it is happening, and
 6 it's like horrifying. It's just horrifying to me
 7 as a physician. This should be a very simple
 8 discussion basically, from my perspective. In a
 9 clinical trial, no company independent, period,
 10 full stop.
 11 DR. KATZ: Sam?
 12 DR. ELDABE: A couple of points, I'll talk
 13 to you about programming issues in trials tomorrow.
 14 What you will see from the trial reporting is this
 15 is an issue that we have neglected before we start
 16 bashing the companies. You'll see how many trials
 17 actually report on programming. Every trial
 18 reports on the surgical technique, but no trial
 19 reports on the programming or reports on the
 20 programming fully. So it's not really the company,
 21 it's us. Because we subcontract this, we're not
 22 interested.

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1 The second issue is about the IP. I'm
 2 sorry. I don't believe that this IP is -- I think
 3 it's a red herring. Companies are more than happy
 4 to take your staff and train them off site. We've
 5 done three RCTs where no company was involved. The
 6 company came. They trained the staff. The staff
 7 carried out the programming. That is extremely
 8 possible, and companies will not object to that as
 9 long as the staff know what they're doing.
 10 DR. KATZ: Roshini, do you have any comments
 11 about this? Introduce yourself, please.
 12 MS. JAIN: Yes. Roshini Jain, Boston
 13 Scientific. I just want to kind of go back to I
 14 think what Rod was saying as well. A lot of
 15 studies that we're involved with, I would work with
 16 sites that do multiple studies and multiple devices
 17 as well. To kind of what Salim was saying, it's
 18 having a small research team, a couple coordinators
 19 now be fully washed in 6 different devices that
 20 have 6 different interfaces, which makes it
 21 challenging, which is why I think being up front in
 22 the study protocol, defining who touches those

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1 patients, how often they touch those patients, and
 2 really limiting that scope, in my opinion, I think
 3 will kind of get us further along from a study
 4 design standpoint.
 5 DR. KATZ: Other thoughts from manufacturers
 6 on this issue? Introduce yourself, please.
 7 MR. HILKER: Chris Hilker from Medtronic.
 8 Yeah, I would echo that. I think it's a balance of
 9 that transparency piece. And when you look at the
 10 two arms, the consistency, -- I think you can go
 11 multiple different ways, whether it's training a
 12 subset of your site with one potential industry
 13 person there for oversight and providing additional
 14 on-site support. But I think it's the transparency
 15 of what that person's doing and the consistency
 16 across the arms so that you're not seeing that
 17 variability going from arm to arm.
 18 DR. KATZ: Great. Yes, please?
 19 MR. BOSLEY: Bernie Bosley from Nuvectra. I
 20 think training is an aspect here. The sales reps
 21 are trained how to use the programmers in the best
 22 way, and we need objective evidence that the users

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1 of these devices are trained from a regulatory
 2 perspective as well.
 3 So if you're going to move operation of the
 4 programmers to somebody else, we need to consider
 5 that as well.
 6 DR. MARKMAN: I think that's a great point,
 7 to have some sort of competency testing for using
 8 it. I think that is a very valid point, that you
 9 should be able to make sure that the clinical trial
 10 coordinator who's using it can demonstrate some
 11 proficiency and understanding the parameters, and
 12 what it means to have coverage if that's important,
 13 and other things like that. I think that's a
 14 perfectly valid sort of competency for a clinical
 15 trial site to have to demonstrate if they're going
 16 to participate in a trial.
 17 DR. KATZ: Are there existing training
 18 programs that have been developed with competency
 19 tests, et cetera, for the different devices?
 20 DR. MARKMAN: Well, certainly the reps go
 21 through that, extensively.
 22 DR. MARKMAN: The other question is can it

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1 be done remotely.
2 DR. KATZ: The programming?
3 DR. HAYEK: Yes. Maybe have a central
4 programming unit that interfaces with the patients
5 regardless of a bias introduced by the programmer.
6 MALE VOICE: That's a good idea.
7 MALE VOICE: That's what one company does
8 now.
9 DR. NORTH: Wouldn't the company who's
10 device is used, to finally do your level zero
11 trial, Nate, enjoy a competitive advantage over all
12 the others, having finally shown that their fine
13 product was the first to deliver an effect shown
14 greater than placebo? I would think that the
15 company should be competing to work with this
16 group, have us put together the functional
17 specifications for the trial, and have them adapt
18 their products to support it.
19 DR. HAYEK: So to that point, we have not
20 yet identified whether all spinal cord stimulation
21 among all six companies, among all the different
22 paradigms is the same thing or is it different

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1 things.
2 DR. NORTH: Well, they tell us it's not, of
3 course.
4 DR. HAYEK: But do we know the answer?
5 DR. NORTH: Each company's product is --
6 DR. THOMSON: We mustn't get too obsessed
7 with comparative research between one company and
8 another. We should be trying to be much more
9 generic and answering those sorts of generic
10 questions. And if we are going to advise on how to
11 do comparative research, that's another thing,
12 chapter in your write up that we're going to have
13 to say about how to do it.
14 Every research question that we're going to
15 ask doesn't always have to be device specific.
16 Does a trial period bring any value to long-term
17 outcome? It really doesn't matter what company you
18 use, does it?
19 DR. NORTH: But most of the companies have
20 devices capable of delivering all of the waveforms
21 that we've been talking about, leaving intellectual
22 property concerns aside, which should be okay, at

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1 least within a scientific study context. So I
2 think that doing a study that eliminates the
3 between-company variables by using a single device
4 in each patient to deliver all of the waveforms,
5 including sham, is the way to go.
6 DR. THOMSON: I like that for that sort of
7 question.
8 DR. MARKMAN: That's absolutely feasible at
9 the present time. The technology is there to do
10 this. It's simply a matter of the will. That
11 study could be done today.
12 DR. KATZ: How do manufacturers feel about
13 that? Is there a manufacturer in the room who
14 would offer up their device for such a clinical
15 trial to answer these questions about the relative
16 effectiveness of the different waveforms?
17 DR. THOMSON: Well, they'll always
18 argue -- because you've got to remember there's the
19 marketing. We've got burst DR, and we've got
20 microburst. You've got all those different
21 marketing phrases, and they are slightly different.
22 They are all slightly different when you look at

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1 the active recharge and passive recharge. And this
2 is what makes the competitive edge for companies,
3 but we shouldn't be involved in that, particularly.
4 DR. MARKMAN: I would just argue that the
5 zero quality study would lift all boats.
6 DR. HAYEK: Level zero.
7 DR. MARKMAN: Level zero. Excuse me.
8 (Laughter.)
9 DR. MARKMAN: All right. Early days.
10 Sorry.
11 DR. KATZ: You're going in the wrong
12 direction.
13 (Laughter.)
14 DR. HAYEK: We have a lot of those zeros.
15 DR. MARKMAN: I won't be the first person to
16 make that mistake. My feeling is obviously my own,
17 but the idea that the landmark study that Rick
18 described would help every sponsor in this field
19 tremendously. That would elevate this therapy to
20 an entirely new level of consideration in
21 everyone's mind, including not making it last line.
22 That's what we're missing.

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1 DR. NORTH: And the distinctions that are
 2 made between the different waveforms, I think are
 3 distinctions that are not important as a clinical
 4 difference, because if you have a product capable
 5 of delivering all of the waveforms, one might be
 6 statistically superior to the others, but they're
 7 all important to have on the menu.
 8 So a study that demonstrates that one of the
 9 waveforms, one of the parasthesia-free waveforms is
 10 better than placebo brings all the rest of them
 11 along for the ride, whatever their comparative
 12 effectiveness, and that should be good for
 13 everybody.
 14 DR. MARKMAN: Right. I think the API is
 15 more alike than it is different. Double the dose,
 16 half the dose, dosing schedule changes, I think
 17 those things are noise around the issue that it's
 18 the fact that it's the same API.
 19 DR. THOMSON: Adverse events. We're really
 20 talking about the sorts of things -- what makes
 21 this sort of minor surgical but technological
 22 procedure, treating the same pain that many other

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1 pain doctors treat without spinal cord stimulation,
 2 or try and treat without spinal cord stimulation,
 3 what makes it different, the fact that we're doing
 4 this procedure?
 5 We've touched on programming. We've touched
 6 on the technology and the different waveforms. But
 7 then I think the big thing is expertise of the site
 8 to deliver the appropriate type of spinal cord
 9 stimulation, and if you're comparing it to some
 10 other usual care and being able to do the
 11 comparator or the usual care with sufficient
 12 expertise.
 13 I think Rod talks about the SPIRIT trial,
 14 which was a, refractory angina study done in a
 15 cardiac center. And really, they had no
 16 experience, really, of spinal cord stimulation at
 17 all. They had a completely chaotic follow-up with
 18 patients strangely coming from Scotland and being
 19 randomized to SCS or PMR, which is my percutaneous
 20 myocardial revascularization.
 21 I think the first half -- Rod, you know
 22 this -- if you looked at the incremental cost

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1 effectiveness ratio, which is sort of a kind of
 2 metric of whether something's cost effective, it
 3 was like a quarter of a million pounds I think for
 4 the first half of the study and got down to about
 5 18,000 pounds for the second half of the study,
 6 because they got better at doing it.
 7 This kind of expertise is incredibly
 8 important. So when we're talking about these
 9 studies, we have got to be able to use expert
 10 centers. And it's not just the surgical technique,
 11 but it's also, as we talked about, the programming
 12 techniques, and the follow-up.
 13 DR. KATZ: Is your suggestion to limit these
 14 sorts of intensive studies to centers with high
 15 expertise or to quantify the degree of expertise of
 16 the sites that do participate but allow it to be
 17 more abroad or some combination? And in either
 18 case, how does one measure expertise?
 19 DR. THOMSON: We should be saying what we
 20 think is the ideal. And the ideal should be
 21 somebody, a center that routinely offers these
 22 therapies, and monitor their results, and have a

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1 track record in research, and satisfy all the
 2 conditions for being a research center. Then I
 3 think as we design these studies, there are
 4 different and more complex, if you like, comparator
 5 treatments, and are they able to offer that?
 6 You're going to hear me say the word
 7 equipose a lot tomorrow, and I think that's just
 8 incredibly important when we're actually trying to
 9 do the science and actually trying to identify
 10 treatment effects.
 11 DR. MARKMAN: Just to I think follow up on
 12 your question on that, too, I think there are at
 13 least two domains in my mind of expertise in a
 14 center. One surrounds this issue of patient
 15 selection and treatment matching, and the other
 16 surrounds the actual technical specs of device
 17 implant.
 18 I think that the way you would evaluate
 19 those two domains are different because you can do
 20 a lot of stims in a lot of trials and really be
 21 technically super adept, and do a complex patient
 22 who's 96 years old with scoliotic deformity and get

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1 the leads perfectly midline. But that's a
2 different place potentially from the place that is
3 identifying patients who, as a consensus view,
4 might be the patients who meet the clinical trial
5 inclusion criteria for the type of baseline pain
6 condition. And I think that those are not always
7 overlapping.
8 So I think that I would just specify
9 different domains of expertise, some of them around
10 volume, and maybe complications and reporting, and
11 some around other factors with regard to
12 preclinical or preimplantation assessment and
13 follow-up.
14 DR. KATZ: Are you saying, John, that you
15 don't feel that the typical long laundry list of
16 inclusion/exclusion criteria in a clinical trial to
17 standardize patient selection, and one needs to go
18 further than that in some way?
19 DR. MARKMAN: Not necessarily. I just think
20 you need to have experience doing that,
21 demonstrated experience in conducting and
22 identifying those subjects. Obviously, as you've

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1 done before, we've done trials where we have an
2 outside panel of experts reviewing the included
3 patients, and I do think that's a powerful check on
4 the behavior of a site in terms of making sure that
5 the patients who enroll align with some
6 approximation of what the designers of the trial
7 had in mind. There are many ways to do that
8 through DSMBs or external committees. But it's one
9 tiny little extra area of oversight, which really I
10 think helps nail down this patient selection
11 quality issue.
12 DR. KATZ: That might be worthwhile for me
13 to expand on for just a minute. What John is
14 referring to is we work together on this clinical
15 trial that Pfizer sponsored on pregabalin for
16 post-traumatic peripheral neuropathic pain. I
17 think it ended up being about 600 patients
18 randomized and more than 900 [indiscernible],
19 something like that.
20 There was a long list of inclusion/exclusion
21 criteria as there typically are, but this
22 particular syndrome is kind of a squishy diagnosis

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1 where there's a little bit of art involved, so we
2 created a very detailed patient intake worksheet
3 and had the investigators complete them. And then
4 if the investigator thought the patient was
5 eligible, then we had that worksheet reviewed by a
6 team of three external neurologists to provide
7 independent verification that the patient actually
8 had the syndrome.
9 We ended up excluding almost 30 percent of
10 the patients that the investigators wanted to
11 enroll in that clinical trial because, for example,
12 I have post-traumatic neuropathic pain because I
13 slipped down the stairs 6 years ago and hurt my
14 back, and now my hands are tingling. And that was
15 a case of post-traumatic neuropathic pain; that was
16 an actual case, and we had many more like that.
17 So it's quite amazing how when you leave
18 investigators on their own to operate a set of
19 inclusion/exclusion criteria, you can wander pretty
20 far off the reservation in terms of the type of
21 patient you're actually looking for. And an extra
22 pair of eyes, at least in our experience, made a

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1 very big difference.
2 DR. MARKMAN: I think, again, that's a study
3 conduct issue. The trial did not separate. So we
4 don't really know whether that has an effect on
5 detecting signal. As an assay sensitivity issue, I
6 think it's an open question in my mind. But what
7 it does tell you is that the study you thought you
8 conducted you actually conducted in those 15
9 countries. So from a study conduct perspective, I
10 think it's incredibly reassuring from a quality
11 standpoint. I think that the jury is still out on
12 whether that has an effect on assay sensitivity.
13 DR. TAYLOR: And Nate, could I make a
14 comment on that one as well?
15 DR. KATZ: Please.
16 DR. TAYLOR: So I think, again, we're going
17 back here to the issue of what we might define as
18 being expertise. And I would put it to you, we
19 need to be careful not to conflate two forms of
20 expertise here. So it's the expertise in patient
21 selection, and I think that's what you've just
22 articulated in that previous drug. It's very

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1 important to choose the right squishy patient, and
 2 you have to be really, really careful about doing
 3 that and designing the trial to ensure that
 4 inclusion/exclusion criteria, external verification
 5 of that.
 6 But I would put it to you that that's not a
 7 peculiarity of neuromodulation; that's true of any
 8 setting, with respect. But I think what is an
 9 important peculiarity of expertise -- peculiarity
 10 again -- in this area is the learning curve. In
 11 other words, it's the expertise and the delivery of
 12 the therapy. And there's a well articulated
 13 literature in the medical device and interventional
 14 literature that there is a learning curve.
 15 By definition -- and I'm looking around at
 16 some of my colleagues in trials that we've been
 17 involved in -- we've just said that if a center
 18 hasn't implanted at least X patients, then we
 19 wouldn't want them to be part of this trial. An X
 20 has been a little bit sort of finger in the air,
 21 but we've been clear that centers do have to have a
 22 minimum volume of expertise in the last previous 12

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1 months.
 2 I think, again being explicit about that,
 3 where I probably struggle a little bit, Nate, is
 4 saying what X should always be. But would we
 5 agree, at least if we were making a statement, that
 6 in designing trials, trials should think about the
 7 learning curve and recruit centers accordingly, and
 8 just be explicit about that, and ask them to
 9 report -- going back to Jane's point -- about what
 10 their criteria is for minimum volume.
 11 DR. MARKMAN: And I think sponsors already
 12 do that, from our experience.
 13 DR. TAYLOR: Oh, yeah.
 14 DR. MARKMAN: I think that this is something
 15 that's already being done; we're just codifying it.
 16 But to go back to the first point about the
 17 squishiness of this diagnosis relative to drug
 18 trials, because this is labeled for intractable
 19 pain of the trunk and legs, it's very different
 20 than enrolling a trial where the FDA is stipulating
 21 if you want an indication for spinal cord injury
 22 pain, or an indication for post-traumatic

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1 neuralgia, or an indication for post-herpetic
 2 neuralgia. There is a level of rigor to that
 3 characterization as opposed to intractable pain of
 4 the trunk and legs.
 5 So I think that the issue becomes because
 6 these devices are labeled, frankly, the way that
 7 opioids are labeled, for moderate to severe pain
 8 around the clock when nothing else doesn't work,
 9 it's such a broad label that you have a quality
 10 issue right there because nobody's getting a very
 11 high bar in terms of case definition.
 12 DR. NORTH: To your point, Rod, about X, the
 13 minimum necessary volume, that might be necessary,
 14 but it's certainly not a sufficient criterion for
 15 selecting a study center and an implanter. Just
 16 because the local rep got a big bonus because of
 17 the case volume, that does not necessarily mean
 18 that the implanter is technically skilled, just
 19 that they do a lot of cases. That's true of
 20 surgical procedures in general.
 21 DR. KATZ: We've been maybe unintentionally
 22 making a list of the peculiarities of spinal cord

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1 stimulation that need to be addressed in the
 2 context of recommending research standards and what
 3 makes this different than every other kind of
 4 intervention that we're studying in chronic pain.
 5 We've got the learning curve. We've got the
 6 issue with the programming. We've got the issue
 7 with different devices, and probably a few more
 8 that I'm not remembering right now.
 9 Are there any other peculiarities of this
 10 type of intervention that needs special discussion
 11 or consideration in recommending research standards
 12 beyond what IMMPACT has already done for 85 papers?
 13 Greg?
 14 DR. FIORE: One thing that also comes to
 15 mind that um, you touched on in your presentation,
 16 which is the interaction between the staff and the
 17 subject because of the point that was raised by
 18 Brian and others today around the upfront
 19 investment by the subject to undergo the procedure
 20 in a clinical setting.
 21 There needs to be more interaction with the
 22 site staff. It can't just be a hands off, here's

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1 an option versus a sham or something like that.
2 There has to be some selling or some upfront
3 discussion there that may bias the subject. So
4 that may be something that we can make some
5 comments about.
6 DR. KATZ: Sure.
7 DR. THOMSON: I think the other thing that's
8 peculiar is that this is a functional device. Do
9 you Tana Gachi [ph], this electronic device that
10 you had to look after and feed and change diapers
11 or whatever. Nobody knows its analogy now. It's a
12 bit like a Tana Gachi. You've got to kind of feed
13 it and charge it. You've got to switch it into
14 nighttime mode, and all those different things.
15 That's the degree of interaction the patient has to
16 have with their therapy, from passive treatments,
17 like a fusion or taking a tablet.
18 DR. KATZ: Bob?
19 DR. DWORKIN: Nate, I think this was
20 implicit in presentation, but I could imagine an
21 article, like the one you're going to draft, having
22 a checklist of the various different possibilities

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1 for blinding. We don't have anything like that in
2 any articles about drug trials because it's
3 obvious.
4 You've got an active pill, and a placebo
5 pill, and they taste, and look, and smell, et
6 cetera, the same. But it seems to me for these
7 trials, we really can establish a checklist of the
8 different possible ways the trial can be either
9 fully double-blinded -- I take the point that
10 that's going to be rare -- or semi-blinded, blind
11 outcome assessments; blinding the patients to the
12 characteristics of the device and the comparator;
13 blinding the implanter if that's possible; the
14 study nurses; the staff from industry.
15 So from my perspective, I'd love to see a
16 list of blinding parameters. And then when a study
17 gets published, they would have to ideally refer
18 back to that and say we were able to do 1, 4, and
19 6, but we couldn't do 2 and 7, and explain; instead
20 of -- and I'm thinking here of the Senza trial.
21 My recollection of the Senza trial, there's
22 one sentence saying, "Because of the nature of this

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1 trial, blinding was not possible." To me, that's
2 just totally inadequate. There should be some
3 struggle in the manuscript that reflects we've done
4 our damndest to blind every one possible. And
5 maybe we couldn't do it completely, but this is
6 what we did.
7 DR. KATZ: I think also what we tend to
8 forget about, we tend to think about blinding as
9 the goal. But blinding a means to an end, and the
10 end is having balanced expectation of benefit
11 across groups. Blinding is just one method for
12 accomplishing that. And when you can't blind
13 because it's parasthesia versus -- or whatever the
14 issue might be, maybe you can -- I'm not saying you
15 can't blind in those circumstances. But if there's
16 some reason why you can't blind but instead you
17 find some alternative method for achieving balance
18 of expectation, which you can document, then that
19 should be done.
20 DR. DWORKIN: Doing that makes you think if
21 Dennis and I are to do a study comparing cognitive
22 behavior therapy and health education, we don't

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1 tell the patients the cognitive behavior therapy is
2 the active treatment and health education is the
3 placebo control. And we do our damndest, if we
4 can, to not even tell the person doing the
5 cognitive behavior therapy and the health educator
6 that our hypothesis is this is going to do better
7 than that. So I think there's a lot more that can
8 be done.
9 DR. HAYEK: There are other things peculiar
10 to spinal cord stimulation or device studies is how
11 long are you going to follow up these patients, and
12 when do you determine that, yes, this is a long
13 enough duration to say it's worthwhile from a cost
14 effective standpoint and from an efficacy
15 standpoint.
16 The frequency of interventions, both
17 positive and negative, how often do you need to
18 reprogram? Pain is not constant. Stimulation is
19 not constantly delivered the same way. There are
20 different paradigms of stimulation. You cycle.
21 You give constant stimulation. You use the
22 different stimulation parameters. There's a ton of

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1 details, and there are a lot of devils in the
2 details.
3 DR. KATZ: Let me actually ask a question
4 about that and then return to your question about
5 duration. Maybe someone here can educate me. The
6 amount of time spent in these interactions
7 reprogramming, can that be entirely prespecified or
8 is that also in some sense an outcome of the result
9 of therapy? For example, if patients are less
10 satisfied, do they need more reprogramming?
11 So can it be entirely prespecified or does
12 it need to be tracked as an outcome measure as
13 well?
14 DR. BUCHSER: It varies from patient to
15 patient.
16 DR. HAYEK: I think for study purposes, you
17 can't prespecify. You only get one reprogramming
18 session every 3 months, for example, or something
19 like that. Otherwise, the amount of attention paid
20 to the patient, the amount of interaction, just
21 like as suggested, could be a biasing factor.
22 DR. THOMSON: What we included in one of the

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1 studies is an adverse event. If essentially they
2 needed more than 3 reprogramming sessions within a
3 specified time, like a month say, then we regarded
4 that as an adverse event.
5 DR. MARKMAN: To that point, just one other
6 thing we try and do -- obviously, this is partial
7 relief we're talking about here. Right? Nobody's
8 getting complete relief. So the reality is that
9 when we finish the trial with patients, one thing
10 we often try and do is specify for what aspect of
11 your chronic pain experience was this helpful?
12 Some patients now can sleep at night when
13 they couldn't sleep at night before. They only use
14 it at night. And other patients feel like now they
15 can sit, whereas before they could only sit for 10
16 minutes, and now they can again work as a bus
17 driver. To me, if that patient comes back and
18 says, "Well, I really want to be able to hike
19 through the woods with my stimulator," I would say,
20 "Well, that's not really something we thought that
21 it was going to be effective for at the beginning."
22 So I do think there is some sense in which

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1 patients endorse relief during a trial or at
2 certain point for what they think this is going to
3 be helpful for, and that's the target. Otherwise,
4 I tend to see creeping expectations for what this
5 can and can't do. That's part of the interaction
6 with the patient, is to explain we thought this was
7 clinically meaningful, this difference, because
8 it's not going to solve your axial low back pain
9 from nociceptive because you have osteophytes.
10 DR. THOMSON: That can be an outcome
11 measure, which is talking to -- we do this in our
12 clinic, is we talk about realistic expectations.
13 That's what one of the psychologists and the nurse
14 will be doing, is talking to them. What is it that
15 they're hoping to get out of this after a
16 reasonably informed consent? And then you can
17 measure it against whether they've achieved that
18 expectation. So it can actually be an outcome.
19 DR. HAYEK: But that is hard to objectify,
20 though. These are all subjective patient desires.
21 DR. THOMSON: But these are patient-related
22 outcomes. This is the buzzword.

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1 DR. NORTH: As to programming time and face
2 time with the patient, let's remember that we're
3 going to be looking at parasthesia-free stimulation
4 by comparison with sham. And exactly how long does
5 it take to program either of those? Because you
6 get no immediate feedback from the patient at all.
7 It's the parasthesia based stimulation where you
8 can spend a lot of time, but that's just along for
9 the ride in this protocol.
10 DR. HAYEK: You could also add another level
11 of complexity with potential closed loop
12 stimulation or sensing stimulation, closed loop or
13 sensing.
14 DR. NORTH: Oh, yeah, you can.
15 DR. THOMSON: Either way, what's important
16 is that we think that this is something that should
17 be recorded. It should be transparent. But we do
18 have to stop the excessive amount of interaction
19 and multiple visits. Well, not stop it, but we
20 have to think of that is that actually a very good
21 therapy. It should be an adverse event.
22 DR. KATZ: I'm hearing a number of different

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1 messages about this reprogramming time. Maybe we
2 could try, in the remaining few minutes we have,
3 achieve clarity on this issue before we break for
4 the evening.
5 I heard, Simon, your suggestion that if the
6 patient needs more programming visits, well, fine,
7 we'll give it to them in order to optimize the
8 therapy, but we'll track that in some sense as an
9 adverse events. If we were in a flexible dose drug
10 trial, if the trial allowed flexibility in dosing,
11 we probably wouldn't handle it as an adverse event
12 unless there really was an adverse event. We would
13 just track how many dose changes they needed or
14 what have you as a secondary endpoint, but I hear
15 what you're saying.
16 I also heard I think from Salim that there
17 may be a possibility of fixing the amount of
18 reprogramming. If you need more, too bad, and if
19 your pain is not well controlled because of that,
20 well then, that gets reflected in your endpoint.
21 So it all comes out in the wash that way.
22 I've also heard that we could give more

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1 reprogramming if we felt the patient needed it and
2 count it as a secondary endpoint, how many
3 reprogramming visits did the patient require. If
4 in this arm they require 20 reprogramming visits
5 and that one 10, well then, that's a reflection of
6 the efficacy of therapy, but of course that can
7 confound the primary endpoint of pain intensity
8 reduction.
9 I feel like I've heard a few different
10 versions, each with some overlap with the other.
11 DR. MARKMAN: I just think, Nate, your point
12 about a flexible dose trial, I think that's the
13 perfect metaphor. In a flexible dose trial, you're
14 allowed a defined period and a defined number of
15 dose changes, and then there's a bunch of outs for
16 adverse events.
17 So if your stimulation is unpleasant, if
18 your leg's jerking, or you can't sleep at night,
19 whatever it is, or the stimulator pocket is too
20 hot, whatever it might be, you get a free out for a
21 negative event just like we do when a patient is
22 being titrated on an opioid or gabapentin, and then

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1 you get a set number of dose optimization during
2 the 3-week period. You get what you get. That's
3 how we do it in a flexible dose trial.
4 DR. NORTH: The parasthesia-free paradigm,
5 for HF10, as I understand the programming strategy,
6 because the patient can't feel anything, they come
7 back if they don't have adequate pain relief after
8 a few days and try a new contact combination. And
9 if that doesn't work, they try another. And that
10 can be standardized, but that means patients in the
11 sham group are going to be doing the same thing.
12 But it's all manageable.
13 DR. KATZ: So I'm hearing that the
14 recommendation would be a prespecified standard
15 frequency of reprogramming with some limited
16 flexibility built in. And if somebody needs to go
17 beyond that flexibility, it's tracked in some way;
18 either there's a treatment failure or an adverse
19 event, and obviously all those rules would need to
20 be prespecified so that they are applied
21 consistently across the trial.
22 Something like that? Is that what I'm

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1 hearing?
2 DR. McNICOL: Nate, your comment about
3 treatment failure, I think if we're using a
4 metaphor between spinal cord stimulation and drugs,
5 treatment failure with a drug trial, you stop the
6 drug. No huge investment there. You maybe try
7 something else or a different mode of therapy.
8 Treatment failure with spinal cord
9 stimulation is a much bigger adverse event. You
10 talk about the investment going in. What's the
11 investment coming out? You're quantifying adverse
12 events, but you're not comparing like with like.
13 Treatment failure with drugs, not the end of the
14 world. Treatment failure with spinal cord
15 stimulation explant, another surgery --
16 DR. MARKMAN: That is why the temporary
17 trials is so important. That is why the temporary
18 trial is so critical because that is a point which
19 you can actually -- you have reversibility.
20 DR. REZAI: Patients have failed medications
21 to a certain extent, it's not like a primary
22 treatment for them.

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1 DR. HAYEK: Sam has a whole talk about the
2 trial being not very predictive and we don't have
3 good data on that.
4 DR. NORTH: How many weeks on a new drug are
5 necessary before we conclude it's failed? Whereas
6 with an SCS trial, we go for a few days, and then
7 we start to worry about the cumulative risk of
8 infection. It's a very different --
9 DR. MARKMAN: Unless you're in Belgium. You
10 take the --
11 DR. KATZ: I think, Ewan, just to address
12 your point, and then I'll go to Rod, one could
13 imagine a different thinking about treatment
14 failure from an analytic perspective versus from an
15 explant perspective.
16 So if somebody needs to go beyond the
17 prespecified number of reprogrammings, for example,
18 we could take that into account in assessing their
19 primary endpoint either through imputation or
20 calling them a nonresponder, whatever, but still
21 give them the treatment that they need so that the
22 device has the best chance for the patient staying

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1 in. Treatment failure, I think we can look at it
2 in those two ways.
3 Rod?
4 DR. TAYLOR: Just going back to the
5 reprogramming, I would just, again, implore us to
6 be careful. I think reprogramming is a pragmatic
7 thing that happens in trials, and we ought not to
8 constrain it. I think the way we capture it, it
9 carries a cost. I was just going to say Brian and
10 I would just quantify that in terms of economic
11 costs. So it's back to your point --
12 MALE VOICE: Be careful what say. He's not
13 that far.
14 (Laughter.)
15 DR. KATZ: He just moved seats. I think
16 he's still the same person in that other seat.
17 DR. TAYLOR: So we would quantify the number
18 of reprogrammings in terms of resource utilization,
19 and therefore attach a cost to it. I think that's
20 all I would want to --
21 DR. HAYEK: That should be a limit, though.
22 Like in sham, they may have a lot of reprogramming

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1 sessions.
2 DR. TAYLOR: I agree conceptually, I
3 wouldn't want as a patient to think I'm going to be
4 coming back to my battery retuned everyday for the
5 next 10 days. As much as I like you, Rick, I
6 probably wouldn't want that. But I think again,
7 it's just that the perfection is the enemy of the
8 good here, so I think just being pragmatic about
9 reprogramming and saying that we capture as a
10 secondary process outcome, and then we can penalize
11 the therapy by applying a cost to it because it may
12 not change the effectiveness, but it will certainly
13 impact on its cost.
14 DR. KATZ: The issue that I think we're
15 still left with -- and I can see Howard shaking his
16 head; maybe I can guess. Let's say for example, one
17 group, the pain scores is 4, and the other group,
18 the pain score is 5. Great. The pain score is
19 lower in this group. But if this group needs twice
20 as many reprogramming sessions as this group, then
21 how do you interpret your primary endpoint?
22 DR. FIELDS: You read my mind.

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1 DR. KATZ: I did read your mind?
2 DR. TAYLOR: Well, can I answer that?
3 DR. KATZ: Yes, please.
4 DR. TAYLOR: I think what I would do is look
5 at the efficacy delta relative to the cost delta.
6 So it may be that you can achieve better outcomes
7 for more reprogramming with one versus two, but
8 that will come at an additional cost. And a cost
9 per quality framework. -- again, I can't speak for
10 Brian -- I'd be very comfortable about assessing it
11 in that framework.
12 So for me, it's more a resource utilization
13 issue rather than an effectiveness one per se. But
14 I think the point we're making -- and again, not
15 wanting to be over-prescriptive -- is that we could
16 maybe make a recommendation that it's recognized
17 that reprogramming is an important issue in trial
18 design and at least needs to be quantified.
19 Perhaps some consideration needs to be given
20 as to whether there are some limits that should be
21 allowed within the trial design. But again, just
22 be careful that we're not the hostage sort of

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1 action.

2 DR. NORTH: The resource we should be

3 talking about is just a computer. We taught a

4 computer 30 years ago to interact directly with the

5 patient and run the trial. So the only resource

6 you really need is the computer and a quiet place

7 for the patient to sit and follow the directions.

8 We had enough artificial intelligence, which is a

9 buzzword nowadays, 30 years ago to do this. We

10 certainly should be able to do it now.

11 DR. TAYLOR: That's tomorrow. I think still

12 today, that reprogramming -- correct me if I'm

13 wrong -- requires a human interaction.

14 DR. FIELDS: We could have sham

15 reprogramming, and you could have both of them be

16 randomized so that people who got better and people

17 who got worse both had reprogramming sessions.

18 That's the only way you can keep the two groups

19 comparable. Once you start selecting out patients

20 for reprogramming, the groups are no longer

21 comparable, so the study is dead in my mind.

22 DR. KATZ: Jane, last comment for you.

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1 DR. SHIPLEY: I was just wondering if we're

2 keeping the idea of having study results be

3 generalizable in front of us. I was especially

4 thinking about that when we were talking about

5 competency of the study sites, although I'm all in

6 favor of people only doing this if they're

7 competent in general. But if we are real specific,

8 if we have computers and nobody else does, are our

9 results going to be generalizable?

10 I'm a big fan of the computers, Richard.

11 I'm not trying to say we shouldn't do it.

12 DR. NORTH: Well, once you develop the

13 computer, the first one costs a lot of money and

14 the next one 10 cents because it's just a matter of

15 loading the software.

16 Adjournment

17 DR. KATZ: All right. Well, it's time. I

18 think we'll break now. I think it's been an

19 extremely interesting and lively discussion. I

20 really do appreciate everyone's interest and

21 enthusiasm.

22 Dinner is in the Thomas board room. If you

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1 look at your agenda, it's 7:00. Please, if you did

2 fill out that survey, which I hope everybody did,

3 drop it off with Valorie on the way out, and I'll

4 try to synthesize them tonight for tomorrow. And I

5 look forward to seeing all of you at dinner.

6 (Applause.)

7 (Whereupon, at 5:29 p.m., the meeting was

8 adjourned.)

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