ACTTION - IMMPACT Research Design Considerations for Randomized Clinical Trials of SCS for Pain

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ACTTION

INITIATIVE ON METHODS, MEASUREMENT, AND PAIN ASSESSMENT IN CLINICAL TRIALS

Institute of Neuromodulation
International Neuromodulation Society

Research Design Considerations for Randomized Clinical Trials of Spinal Cord Stimulation for Pain

Thursday, November 15, 2018
8:05 a.m. to 5:29 p.m.

Westin Georgetown
Washington, DC

C O N T E N T S

Moderators: Salim Hayek, MD
Nathaniel Katz, MD
Systematic Review of Methodologic Characteristics and Outcomes in RCTs of SCS for Pain
Ewan McNicol, PharmD 214
Inclusion/Exclusion Criteria (e.g., Diagnoses, Pain Severity, Pain Duration Psychosocial Vulnerabilities, Treatment History, Concomitant Analgesics)
John Markman, MD 241
Primary and Secondary Outcomes (e.g., Pain, Function, Opioid Sparing, Duration of Follow-Up)
Ali Rezai, MD 282
Adverse Events: Assessment and Reporting
Salim Hayek, MD 324
Group Discussion: Inclusion/Exclusion Criteria, Outcomes, and Safety 339
Moderators: Nathaniel Katz, MD
Richard North, MD
Adjournment 418

P R O C E E D I N G S

(8:05 a.m.)

Welcome and Introductions

DR. TURK: Good morning. Thank you all for coming. My name is Dennis Turk, and I'm from the University of Washington, and I'm delighted to have all of you here for what I think is going to be not only important but a very interesting and productive meeting. And I'm looking forward to learning a lot from you.

I'm going to be introducing the conveners of the meeting first before we actually start the formal presentations. There are a few housekeeping details that we need to put up so you'll be aware of those. Please put that slide up.

When you registered, there's a sign-in desk. Please make sure you sign in and out. And I think you have to do that both days, if I'm correct.

MS. THOMPSON: Just sign in.

DR. TURK: Just sign in?

MS. THOMPSON: Yes.

DR. TURK: Okay. And silence your cell

Page 5

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

Page 6

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

Page 7

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

Page 8

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

Page 9

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

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

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

Bob, is that still correct?

(Dr. Dworkin gestures yes.)

DR. TURK: Okay.

What IMMPACT is not. In case you're

Page 10

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

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

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

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

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

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

Page 11

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

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

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

Page 12

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

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

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

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

Page 13

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

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

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

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

Page 14

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

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

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

Page 15

international group. When we've had people from the EMA, especially, we've tried to make sure we could involve them to the extent it's possible. For those that are not familiar with the EMA, it's run quite different from the FDA, so it's a little bit more complex in how to deal with them.

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

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

There have also been consumer advocacy

Page 16

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

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

(Dr. Dworkin gestures no.)

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

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

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

Page 17

publications that come out of those. We also have on the IMMPACT website, if you're interested in any past meetings, who attended, the background presentations, the slides. We ask for permission, and if we get permission from these speakers, we've put those up there. They're available.

Later meetings have been audiotaped, so those transcripts are available should you be interested in listening to us talk for two days. And to my knowledge, no one has ever requested or use those, but if you want one, or someone in your office wants to hear the details, they can read all that.

These are just some more meetings. The last one that we had was on clinical trials for opioid sparing in patients with acute and chronic Pain, and the one before that was on pelvic pain and irritable bowel. So that's the most recent ones.

We have another one that will be coming up in June, which we'll be looking at central sensitization syndromes and seeing how you would do -- remember, we're not looking at these from the

Page 18

standpoint of treatment and product. It's how would you do a study. If you wanted to study pelvic pain, for example, what would be the outcomes that you would use? How would you design the study? How would you analyze the data? How would you interpret the data? So that's what we're trying to do with these meetings. And you've already heard what this meeting is about.

What else do we do? Well, in addition to the meetings, we also have commission papers. The commission paper that's going to be developed from this meeting specifically will be looking at meta-analysis. That will be coming out that you all will see. We conduct scientific studies. We develop some different measures.

We support educational initiatives. The North American Pain -- Society. The North American Pain something meeting that goes on in Montreal brings in 50 young investigators from different areas and tries to educate them about doing research, so we support that. We also develop diagnostic criteria. I think you've got that on

Page 19

your table there.

So we've done a lot of different things, and if you want to know more about, obviously you can go to the website. We've had over 7,600 different citations, and we've been cited in the papers in over 600 different journals ranging anywhere from addiction medicine, to women's health, to my favorite, veterinary medicine, which I would never have thought that anybody would find an interest. But I guess when you're talking about clinical trials, and data analysis, and how to interpret things, that would make some sense.

So there's the website that you can go to. And you could see along the bottom, the publications, the background papers, the presentations, that's all available to you.

What are the objectives of this meeting? And you're going to hear more about this. To discuss important considerations and provide suggestions regarding the design of clinical trials of spinal cord stimulators. That's what this is going to be all about; to disseminate these

Page 20

considerations, observations, suggestions, and peer-reviewed articles.

The meeting is scheduled to end tomorrow at 3:00, I believe, but if we don't have enough information for Dr. Nate Katz to develop the manuscript with the recommendations on that, then we could stay longer. We'd be more than happy to stay for forever if you want to keep talking. But an incentive to you will be that we will be pushing you to try to get to the point where we can do that.

In order to do this, we've got to herd the cats. And you may note that we've learned this from trying to herd cats with IMMPACT members. Participants don't like to be herded. In fact, you can rarely herd participants, but that doesn't stop us from keeping to try to do this.

Participants prefer to herd themselves, and they're not very good at it. Participants understand that they sometimes need to be herded, however, that doesn't make them any easier to be herded. Harsh herding usually has negative

Page 21

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

Page 22

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

Page 23

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

Page 24

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

Page 25

DR. NORTH: Increasingly, I find I'm asked to address that topic, but I think it's a nice opportunity. Here are my disclosures. You can see, they go back to 1974. And my previous employers, the nonprofit that I now head, have benefited from support from all of the important players in the field.

My history with this goes back, I dare say farther than almost anybody else I see in the room, and I plan to take advantage of that perspective. Were I to cover the history of mechanisms, efficacy, and safety in detail, I would preempt a lot of what I know my colleagues are going to say.

So I'm going to try to bring this perspective to my remarks, and I'm going to begin with mechanisms and talk about mechanisms as a rationale for what we do. "Mechanism-based medicine" is a fashionable term, and it's certainly an important idea. This is one of many statements, this one specific to our field, about how important it is to develop an understanding of what's behind what we do.

Page 26

This is wordier statement of the problem. I don't intend to e-read it, but rather that you step back and consider that the literature upon which rely is not always right. And if you consider that and then consider the fragility of any mechanism-based rationale, you end up here. And you could look at this dynamic as you honor this squared or cubed. So important as mechanisms are, I think it's important to keep an open mind because serendipity remains important.

That said, spinal cord stimulation is a prime example of a therapy based on a theoretical mechanism. Back in 1965, Melzack and Wall published there seminal paper in science, hypothesizing that there was a central gating mechanism in the cord and that it determined whether neuroactivity signaling pain would be transmitted to the brain.

It was hypothesized to be open by an excess of small fiber activity and closed by an excess of large fiber activity. And conveniently enough, large fibers can be selectively depolarized by an

Page 27

externally-applied electrical field. And at just the right amplitude, they can close the gate.

Within a couple of years, Pat Wall, one of the co-authors of the gate theory, and Bill Sweet, a neurosurgeon at Harvard, tried this with percutaneous electrodes on peripheral nerves and found that, indeed, they were able to abolish pain, temporarily.

Most peripheral nerves of course are mixed. They have sensory and motor fibers. Jay Law among others has pointed out that the thresholds for motor and sensory side effects are very close together, so it's easy to have uncomfortable motor effects occur at amplitudes near sensory threshold.

The spinal cord, however, is organized in such a way as to encourage us to stimulate it because their primary efferents conveniently segregate it from motor fibers, and the dorsal columns in particular have collateral processes into the dorsal horn that can give access to the gate.

This is a slide, one of a number in my

Page 28

presentation, that Bengt Linderoth was kind enough to provide. And this little cartoon shows that rostral electrodes will produce action potentials that are propagated and antidromically and then via collaterals into the dorsal horn. There are also propagated all the way out under the periphery. And furthermore, they are propagated centrally. Hence, the feeling of parasthesia.

So it wasn't too long after Wall and Sweet reported peripheral nerve stimulation that Norm Shealy, then working in Cleveland as a neurosurgeon, reported the first spinal cord stimulator, and it's been 51 years now.

Tom Mortimer, his collaborator, was a biomedical engineering doctoral student, and this was a successful project. However, the gate control theory came under criticism rather promptly, and that criticism has continued. However, some 25 years out, Anthony Dickenson published this editorial in the British Journal of Anesthesia to the effect that the gate control theory stands the test of time. You continue to

Page 29

hear it invoked routinely as the explanation for why spinal cord stimulation works, although it's more complicated than that, as I will try to explain in the available time.

"Dorsal column stimulation" was the original term for spinal cord stimulation, which is now preferred. It is certainly topographically accurate, and it's been confirmed physiologically that dorsal column fibers are recruited. But it's simplistic as other structures are affected, too.

Back when Bengt Linderoth published his PhD thesis in the early '90s, dorsal column stimulation was still preferred terminology. Bengt was working in Bjorn Meyerson's lab, and they developed little electrodes scaled to the animal model, and figured out how to scale stimulation parameters. They worked with a chronic pain model, which then was in its early stages looking at sciatic nerve ligature.

They were able to show in one of their first projects that hyperactive flexion withdrawal reflex, as a model for allodynia, were attenuated my spinal cord stimulation. They have gone on to

Page 30

make a number of important findings, among them the neurochemistry underlying the effects, or at least some of the effects, of spinal cord stimulation.

This slide shows percent changes from basal and levels of GABA and of glutamate, and here, spinal cord stimulation is administered. And as you can see, there's an increase in GABA and a corresponding decrease in glutamate. It occurs only in the animals that respond in the model, suggesting that this is a responsible mechanism.

If the GABA-B receptor is blocked, then the glutamate effect goes away. That led, speaking again of mechanism-based medicine, to a new therapy, albeit a cumbersome one; that is putting in a pump along with a stimulator to administer intrathecal baclofen. And this showed, over a more than 5-year follow-up, that patients who were not responding well to spinal cord stimulation could be considerably improved by intrathecal baclofen.

The neurochemistry is much more complicated than time permits me to explain, and it includes not only segmental spinal cord mechanisms, but

Page 31

rostral mechanisms. Recall, I showed the action potential propagation upward to the brain and the brain stem. So there are mechanisms in the rostral ventral medulla. 5-HT is implicated as an important transmitter there. And the locus coeruleus, which seems to be involved in everything, has been implicated, too.

I put this up as a reminder that we're antidromically stimulating peripheral afferents. So when the patient reports parasthesias extending out into a limb, you can record activity in the limb. This was just a report of an unusual case, but it reminds me of something that I read back in '74, when I was getting started in the field, about afferent nerve impulses originating from neuroma, one of many neuropathic pain conditions, and at electrical stimulation propagates out into the periphery. That's not much talked about in our mechanisms literature, but we're still just getting started on explaining the underlying mechanisms.

Let's back away for a moment and ask what we mean by the word "stimulation." So just thinking

Page 32

in terms of so-called conventional spinal cord stimulation at pulse rates on the order of 100 per second, we're talking about action potential propagation, which is achieved more easily in a cathode than in an anode. You can generate an action potential if you use an anode, turn the amplitude up high enough for a long time, and then shut it off, the so-called anodal break.

This is one of many basic mechanisms. This goes back to 1975. James Ranck is still often quoted 10 days ago at a Cleveland meeting, which was more basic mechanisms oriented. Many of the engineers continued to quote him. We've moved on from these traditional stimulation parameters to play some new tunes through the spinal cord, and that requires that we rethink some of our premises.

J. Law back in the '80s did a good job of articulating the technical requirements for spinal cord stimulation. It was understood from the mid '70s, Hosobuchi, among others, Nascholt [ph], said that it was necessary that stimulation parasthesia overlap an area of pain if we were to expect pain

Page 33

relief. And Law defined the amplitude range within which that needed to occur, founded below of course by perceptual threshold and above by discomfort or motor threshold, which can be synonymous.

But now we have paresthesia-free stimulation. And so we've moved down into the range below perceptual threshold. And at some of the stimulation parameters that we're using, perception is followed rather promptly by discomfort. So we need to rethink what we're talking about here, and we need to consider some other factors. One is that we're stimulating a moving target, so when a patient lies down supine, the spinal cord moves close to the dorsal epidural space where our electrode is, and then when they sit or stand or assume a prone position, it moves away.

This is from a paper that we published back in '98 showing a 25 percent average difference in thresholds. This is from some still unpublished work where we looked at voltage versus current sources and found that the postural effect is more than double for current sources.

Page 34

Current sources are becoming more fashionable despite this disadvantage. It's what you would expect from a model; that is the spinal cord is higher impedance or electrical resistance than the CSF that surrounds it. So when the cord moves closer to the electrodes, the impedance or resistance that the pulse generator sees goes up. So a voltage generator will respond by doing nothing, but a current generator will jack the voltage up to maintain the current, which is quite the opposite of what we might want to do.

Fortunately, there are automated ways of adjusting amplitude compensate for that.

Another mechanistic approach to all of this has been to model the structures in the electrical fields in a finite element fashion. So this goes back to Barry Coburn in the '80s, and Holsheimer and his various collaborators have modeled this. I refer to the variable conductivity.

White matter actually has different impedance sideways than it does longitudinally, and all of that needs to be considered in the model.

Page 35

Here is the segmentation that we're talking about, and here are some of the model predictions that shows isopotential lines going through the spinal cord, and this shows the same thing. Note the intense fields in the CSF.

So the models predict a number of things. Recruitment threshold will vary as the spinal cord moves closer to the dura and the electrodes. If you want to minimize lateral recruitment, that is dorsal root stimulation, which can be uncomfortable, optimal longitudinal contact spacing can be defined in the model. There are other predictions, such as dual electrodes side by side will be inferior to a midline position, and there might be advantages for three columns, adding lateral anodes to shield the roots from recruitment. That's been called a transverse tripole configuration.

Clinical corroboration of those modeling predictions has come out. Our group did a trial comparing dual with single electrodes and found disadvantages for the dual electrodes. Konstantin

Page 36

Slavin and Kim Burchiel and the group at Oregon studied the transverse tripole and found that although they could steer using the lateral anodes, that this was not the answer to chronic low back pain.

Getting back to the alternative waveforms, let's look at burst stimulation. Bursts resemble normal neuronal activity. Single-unit recordings from the nervous system in general and the pain system in particular do show bursting activity. Back when I started working with Fred Lenz who records from the thalamus, we had a computer controlled system, and we talked about playing back his neuronal recordings through the system, but we never got around to doing that.

Dirk De Ridder deserves a lot of credit for pursuing this as he has. He's demonstrated by source localized EEG that bursts activates dorsal anterior cingulate and prefontal cortex, which are involved in emotion more than tonic SCS, and has inferred that bursts might modulate attention to pain. He's further hypothesized that burst has a

Page 37

differential effect on a medial pathway, which you can see here projects to DAC and can in turn affect a pain modulating pathways.

This is from the animal literature, and this is one of the several slides that Bengt Linderoth provided. This shows that nucleus gracilis neurons, which are the first relay station from the dorsal columns, are not affected by bursts. This next slide shows, from a series of animal experiments, that serum GABA concentrations -- Bengt has these delightful built up slides -- burst effect not dependent on GABA receptor activation. And then in other experiments, that blocking the GABA-B receptor did not abolish the burst effect. So that's not the mechanism.

Turning our attention to high frequency, specifically 10 kilo hertz stimulation, here is another cartoon showing the way this works. We're no longer propagating action potentials into the gate. We're stimulating the segments of the core, the same segments, by the way, that are targeted by

Page 38

conventional SCS indirectly. And this is where hyperactive wide dynamic range cells are located.

This is a demonstration by Song et al. that there is no block or activation of dorsal column neurons by HF10. Here is 50 hertz stimulation, which will evoke parasthesia and is recruiting the dorsal columns. When you go to 10 kilo hertz, however, and 50 percent of motor threshold is pretty high, there's no recruitment of the dorsal columns. The same is seen even when this particular model is tested with application of a 5-gram weigh.

This is from Johns Hopkins where a Yun Guan's lab has generated a lot of important work. Here we are, 40 percent of motor threshold, which is supposed to be parasthesia free or below sensory threshold. And we're looking at the effects of SCS at a variety of frequencies starting at 50 hertz and going all the way up to 10 kilo hertz. And as you can see here, there are effects of SCS at all the frequencies studied, and they do not differ significantly.

Page 39

At 20 percent of the motor threshold, no differences are observed. When you go up to 80 percent of motor threshold, which is higher than anyone would use clinically, the biggest differences were seen for a 1 kilo hertz, not for 10. So this doesn't seem clinically relevant to high frequency.

Here is another model. This is Song et al., and they are looking at the behavior of a rat in a dark environment, which is when exploration and grooming behavior begins. So at 40 percent -- sorry; motor responses are here at point 0.5, so it's a different scale. Behavior arrest and motor response delimit the clinically relevant range, so a sub-perceptive region of amplitude is chosen. And here's another study showing similar effects for all frequencies from 50 hertz up to 10 kilohertz.

What is 10 kilo hertz stimulation doing differently from conventional stimulation? Steve McMahon at King's College in London had a poster at NANS early this year. Here he's recording from

Page 40

superficial dorsal horn neurons. He is a patient fellow because you can see here, he waits 90 minutes to see an effect by comparison with 45 minutes.

This is 10 kilo hertz sham. This is 10 kilo hertz at 20 percent of motor threshold. So we see a distinct effect of 10 kilohertz that does not occur at the lower frequencies. And here he's looking at wind-up and lamina 1 projection neurons, and this is sham. The next slide, 20 percent of motor threshold, and you can see that at these different time points, wind-up is attenuated to a significant degree.

Sham-treated dorsal horn neurons show significantly increased fiber activity in their model with 10 kilohertz stimulation by comparison with sham. This is attenuated. McMahon went on to look at 1 kilohertz to see that this particular effect, although it was statistically significant, was nowhere near as pronounced as with 10 kilohertz.

This might or might not be relevant to the

Page 41

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

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

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

Page 42

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

Harkening back to the 1960's, we knew back then that just turning the volume up all the way --

(Laughter.)

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

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

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

Page 43

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

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

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

Page 44

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

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

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

Page 45

persistence after it's turned off. That was important we thought to the design of a device. We were designing a rechargeable stimulator and actually implanted two prototypes in '79, but it wasn't until 2004 that the same group finally developed a commercially reasonable device.

Of course we looked at drug usage. We didn't report this much detail in the scientific literature, but I think we would nowadays because there's increasing focus on this as an outcome measure. And indeed, the last IMMPACT meeting was devoted to opioid-sparing effects.

We didn't have the tester instruments that we now have to look at indirect measures of pain relief, so we developed a grading scale for ability to perform various activities, and we asked patients to rate their degree of difficulty. And we ended up with this data. This is in our '77 report in black and white. But in color, it lends itself to this stacked bar graph presentation.

This is from our SCS versus repeat back surgery RCT in 2005. So we continued using this.

Page 46

There are other test measures that have been developed you'll be hearing about from other speakers, but this shows how many patients improve on these scales by comparison with how many in fact say they've been made worse.

We published a short version of this in a dedicated issue in volume 1 of Neurosurgery. I've gone on, as all of you may know, to make a career out of reporting spinal cord stimulation clinical results and designing and developing new devices. The point of this is to show that as of 1991, the entire clinical literature in spinal cord stimulation would fit in one table on one page, but as of 2006, the last time we did this, Jane Shipley and I put together a table. And this was just the new literature since the last table.

This was a cumbersome addition to a textbook, and that inspired WikiStim, which is a free online database. Many of you have signed up. I would urge the rest of you to do so. It's an extremely handy resource when one wants to look up any of the many references on clinical efficacy,

Page 47

which now number over a thousand.

Moving on to safety and harkening back to our 1977 paper, Salim Hayek is going to talk about safety and complications as a dedicated lecture, so I'm going to skip over a lot of things. But I thought it would be interesting to him and to you to say that back in 1977, when percutaneous electrodes were brand new, electrode displacement or migration was a very common problem. That's since been substantially solved.

I've remained active in the field of reporting complications and guidelines to try to minimize them and have made limited contributions. One is anchoring techniques for migration. This is another one that is in progress. There's one person in the audience who knows where this is from.

It's from an RCT, and I might say that this is RCT evidence of an effect of trial duration on the rate of infection. What this shows is 10 times the incidence of infection in patients whose SCS trials go on for more than 10 days. But if you

Page 48

listen carefully to what I said, this is evidence from an RCT, but it was not among the study hypotheses. It was observed serendipitously. So I hasten to point out that this is a great example of confirmation bias.

We happen to see something that was in accord with the long-held belief, and although it supports that belief, there were people who saw through this centuries ago, and all of us should continue to see through it.

This is a poster that the SUNBURST group put up at the last NANS meeting. I put this up under the topic of safety in a deliberate attempt to be a little provocative. If you do a number-needed-to-treat analysis of spinal cord stimulation, like other surgical procedures, the NNT is very low. And if you look specifically at number needed to harm, it's very high indeed.

Now, one might look at this and say, well, yeah, but SCS is invasive, and these drugs are not. But as a clinician, I've never seen a patient die from a stimulator procedure, but it's well

Page 49

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

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

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

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

Page 50

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

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

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

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

Page 51

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

(Applause.)

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

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

So thank you very much indeed, Rod.

Presentation - Rod Taylor

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

Page 52

introduction. Thank you.

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

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

Just in terms of housekeeping, my conflicts of interest, I haven't put them on a slide, but I think everybody's conflicts are already documented, so people have got them if they want to see them. The other thing I'm also going to say in terms of introduction is that I'm going to really try and

Page 53

respond to Bob's challenges for me for this morning because clearly there's a lot of stuff that we need to cover over the next 36 hours.

My particular things I've been asked to talk about are, first of all, the issue of superiority and noninferiority, which I've called hypothesis testing; reflect a little bit on study designs in this area; and then last but not least talk about comparators. I think, like Rick, there's going to be a lot of overlap. And I think not just overlap but also perhaps a difference in perspective and even a difference in views, which I think is really healthy and great.

Now, I'm not going to try to steal the thunder of Ewan.

Where are you, Ewan? You're here. Hi, Ewan. We haven't met I think taskingly [indiscernible] before. So I've had the benefit of having access to your database, Ewan, but I'm not going to steal your thunder.

(Laughter.)

Ewan and his group have done a huge amount

Page 54

of work, by the looks of it, in terms of doing a systematic review of the randomized controlled trials in the spinal cord stim space.

But with your permission, Ewan, I'm going to use your database just to make a couple of reflections on these questions. But as I say, I'll really try not to steal your thunder for later, if that's all right.

So hypothesis testing, I suspect much of this is familiar with you, but I think an important part of this morning is setting the scene. So for those of you who are trialists, again, just say to say, I'm not a clinician. I'm not an implanter. I'm just a humble statistician who's kind of bumbled into the pain space, but actually, as Simon was intimating, I do a lot of trials in the cardiovascular space. And I think pain is probably one of the more challenging areas. When I do my cardiovascular trials in pain, actually, I'm often scratching my head more in this space than I am in that space.

So why is that? Well, certainly I think one

Page 55

of the commonalities of most trials that we do is that most of them are really about trying to show things are better. And of course we're all slaves to the p-value, not just statisticians, but as an interventionist, statistically better than the reference treatment.

The invention of the randomized control trial and the superiority trial, the best thing since sliced bread. But of course one of the limitations of a superiority design is if you don't show a difference between the two groups, it doesn't mean the two therapies are equivalent. And for that reason, we need to think about other questions in the space.

Clearly, if you like, the polarized opposite of superiority is equivalence. And in superiority, a null hypothesis says that the groups are the same, but actually in equivalence, the null hypothesis says the groups are different, and we're trying to test against that. What we're really trying to show is that a new intervention is the same as the reference.

Page 56

But actually, again, if you look at the trial, not just an in our space but in other areas of medicine, equivalence trials are pretty uncommon, certainly in the phase 3/phase 4 side of things. One of the main reasons for that, at least in my perception, is that, actually -- I'll go on and talk about it in a minute -- is we're often interested in noninferiority. And actually, equivalence is something that tends to be more actually in the pharmacokinetic space. So in other words, we might want to know whether there's a difference in either direction from the reference of importance.

In my brief, I was asked to talk about noninferiority. So again, just to be clear, what is non inferiority? This is a situation where we seek to show that the new intervention is not worse than the reference. You might say to me, "Well look, Rod. In Washington, can we not be more ambitious than saying not worse than?" But I would put it to you that that's actually an important question. Many of the trials that I design are in

Page 57

the payer space, so we may be interested in equivalence of clinical effect, but what we might be interested in is the new intervention has some other advantages.

Rick's already given some indication that one of the things I think we should be particularly interested in, in this space, is adverse effects and harm. One of the big things in my area of heart failure is actually a lot of our therapies are evidence based, but none of them are actually available to patients. So are some therapies more applicable if they're in a home-based setting than a hospital-based setting? Although they're equivalent clinically, patients may be able to access them better, so availability.

I'm a closet health economist for my sins, so I often think about the economic impacts of treatments. And maybe the two are equivalent clinically, but economically, one offers benefits over the other. Clearly, we've heard about invasiveness again this morning and obviously, as I said, fewer adverse effects.

Page 58

Sometimes I think those of us who work with industry are maybe a little bit tough on those guys and say, "Well, you know what guys? Doing noninferiority studies, are you being a little bit under-ambitious?" But I will put it to you that it is an important trial design in our tool bag, and we have to think about it, but clearly, something quite different to superiority. And I want to maybe walk you through why we need to think about that methodological difference between superiority and noninferiority.

Here's a classic picture. This actually comes from the CONSORT guidelines for noninferiority trials. And if I may walk you through this, basically the X-axis is we're comparing our new treatment to the reference. Zero here would be no difference between treatments. Clearly, this result, result A, is I think a pretty undisputable one. Here we can see that the reference treatment is doing better than the control. Here is the mean where A is, and the 95 percent confidence interval does not cross 1, so

Page 59

we've got evidence statistically that this is superior.

Similarly, let's go down to H, and I'll come back and talk about this. But let's just say the delta might be a level of difference that might matter to patients. And you can see in this situation, this is the opposite. So the intervention is clearly doing worse than the reference treatment. And it's not just statistically significant, but it seems to be a level of effect where it may be inferior as a clinically important level.

I guess the point I want to make to you is can you see that we have a lot of stuff going on in the middle where often we will have our trial results. Just to go back, what is this delta? This delta is an important concept as far as noninferiority trials, which is called the noninferiority margin. In other words, it's the level of difference we'd be prepared to accept between intervention and the control that may not matter.

Page 60

Let's just perhaps go through some alternatives. Let's imagine our trial result was B. Now you can see with B, the intervention is doing better than control, but can you see that it's not statistically significant? But more importantly, it excludes the noninferiority margin.

In this case, again, we've got a result where we are noninferior. Here, we've got a bit of a conundrum. Actually, the intervention is noninferior because the constant doesn't cross the noninferiority margin. But can you see we've got an issue that it is actually clinically less effective but still not inferior, if that makes sense? So the level of noninferiority isn't clinically important; you could perhaps paraphrase.

Here, we've just got a very small sample size, haven't we? Very, very wide confidence intervals. But importantly, it's an inconclusive result in terms of noninferiority because the confidence interval crosses the noninferiority margin, and similar, these other two alternatives would be inconclusive as well.

Page 61

So I guess the point I'm making to you is when we do noninferiority studies, it allows us to rule out what may be a clinically important difference between the two treatments and our inference.

So as I say, there is much published in the whole area of noninferiority, and if you want some bedtime reading this definitely will get you off to sleep. It's as good as melatonin.

(Laughter.)

DR. TAYLOR: I tried it last night. But it's a great publication, and a couple of things I just want to draw with that.

The first one is one of the things when we do noninferiority is the thing that we're comparing to; so our reference treatment. This is going to be a theme for me that I'm going to try and set up for today, which is that when we're looking at a reference treatment, we should have evidence that that reference treatment is effective.

I think one of the themes of previous IMMPACT meetings I think has been assay

Page 62

sensitivity. In other words, we could set up a noninferiority study where we choose a reference that is quite convenient for us; in other words, a reference that has perhaps shown not necessarily to what before. And if show we are noninferior to that, that's not terribly helpful, is it?

So what this guideline says is that when we're doing these noninferiority studies, it's tremendously important that the reference that we choose has itself been proven to be effective. And that might seem a very obvious thing to say, but I think it's an important one. And I will give you at least one example where I think we may not be in that situation in SCS; so clearly, superiority of the reference treatment.

What's also interesting -- and this is a quote. This is not my words, "relative to placebo." And again, I'll come back to this idea, but what should be the right comparator in this space, and clearly that's a difficult one because as Rick has very eloquently told us, the history of SCS has been a parasthesia based therapy. So how

Page 63

does one give a placebo when the patient can perceive the treatment?

That's a real conundrum in this space. And clearly, with other alternative stimulation frequencies that are parasthesia free, we now have more of an opportunity to try and get at that. But if we take that this is our gold standard, you can see it's quite difficult for us in the neuromodulation space to achieve that gold standard with noninferiority studies because of the challenge of placebo studies.

Sorry. I should have just said that from the beginning, but that was the point of that slide.

We are in Washington DC. I eventually got in last night. By the way, I was going through customs, and they obviously saw this stodgy Scottish guy. So I had the pleasure of an extra 2 hours with U.S. customs. And gee, they don't really have a strong sense of humor, those guys don't.

(Laughter.)

Page 64

DR. TAYLOR: I was trying to celebrate jokes, and I was realizing as I was doing it, I think I was actually -- they were putting me farther down on the waiting list. So I thought, no, no, I'll just not tell any more jokes. And then eventually, I was able to text Sam that they released me.

Anyway, that's a long way to say that I am a European, so as well as the FDA -- the FDA have published guidelines on noninferiority. And actually, the FDA and the EMA guidelines are very similar, as you might expect. This is from the EMEA guidelines, our European. And again, they make the same point, that when we're looking at a drug or any technology in a European space, we need to know that the thing we're comparing it to has actually been compared to placebo.

But what I want to now get into is a little bit of a technicality, which I think is another challenge for you, or arise in this space, is how do we go about working out what is this noninferiority margin? Remember, we had that

Page 65

delta? And of course, Simon was sitting there going, "Well, that's all very well, Rod, theoretically, but how do we get to that?"

Well, here's a rule of thumb. This is taken from this document. Basically they say a noninferiority margin should be 0.5, preferably even less, maybe even down to 0.3, of the mean control effect of the reference treatment against placebo. So do you want to just imagine that?

You know what the effect is of the reference against placebo. The noninferiority margin should be about half of that or about a third, and that's the kind of rule of thumb. And it's important to say that this is a rule of thumb. This is a value-based judgment. It's not a statistical hard fact. Different trials may have different noninferiority margins. But I think one of the questions I'm going to put to you is what might be a noninferiority margin in our space and what might be the implications of that?

So just peeling back, this is back to Ewan now. If we were to say all the -- I think, Ewan,

Page 66

you identified 32 included randomized controlled trials and their database. I just did a head count of what proportion of them fell into these various questions. Perhaps not surprisingly, superiority is in the dominance; 4 noninferiority trials. Many of the people in this audience will know them and indeed have been involved in the trials directly, so the Senza trials, Sunburst, 10 [indiscernible] Deer DRG versus conventional SCSc. So SCSc with a small C here is conventional, and then Schu comparing Burst versus conventional.

They were all formally designed as noninferiority trials. Simon's PROCOS trial, in the paper you actually say equivalence. I think it may be noninferiority, Simon, but anyway, it was one or the other. But interestingly, 11 of the randomized control trials, what was the hypothesis? Well, didn't he tell you?

Let's sort of maybe continue along with this thing. Here's an example of one trial, which was a superiority trial. I had the pleasure of being involved in this study. This was a Medtronic

Page 67

funded trial, but run by effectively an independent scientific group led by the late Kris Kumar but had many individuals in this audience involved.

Here's the primary result here. Well actually, this isn't the primary result. The primary result was 50 percent pain relief or naught. This was the secondary outcome in terms of a continuous pain measure. I think you would all agree with me that that result is pretty clear that in this case, adding spinal cord stim to conventional medical management alone appears to give a benefit in terms of leg pain, and the mean result on a 0 to 100 scale and the confidence interval supports that.

So yes, we've got a statistically significant result. But again I would put it to you, that that's not enough. And what we need to think about is, okay, maybe statistically significant, Rod, but does it matter to patients? And this gets into another concept, which is the whole issue of clinical meaningfulness. And of course the IMMPACT group, you've talked about this

Page 68

area.

Just to go back again, one of the recommendations from this guideline is that a minimally important difference should be between 10 to 20 percent on a 0 to 10 NRS scale. In other Words, just quickly do your sums; about a difference of 20 on a 0 to 100 scale.

If we were to look at the process result -- and I'm going to ask you the question -- here's the result from the process trial. It's statistically significant, but is the result clinically meaningful? What would be your take on that?

(No response.)

DR. TAYLOR: And you're all like me. You probably need a bit more coffee, so I'll help you along. And I would say probably it is because we can't rule out that it's not clinically meaningful because the bottom confidence interval crosses that number. But the mean's above the minimal important difference. So I would put it that probably, by and large, we've got evidence from process that not

Page 69

only is the result statistically significant, but it's also clinically important as well. And the MCID, or the minimal clinically important difference, is an important metric we can use to determine whether treatments aren't just statistically important but also clinically important.

Noninferiority, let's move on to this. Here's an example of a non inferiority trial. Again, this is not the primary result in the Senza trial. They used 50 percent pain relief for more. This is the secondary outcome. And I've slightly reanalyzed the data for the purpose of this presentation. But as I say, the Senza trial was a noninferiority trial. For those of you who don't know it, it was a comparison effectively between two devices; one that delivers high frequency stimulation and one that delivers low frequency or conventional spinal cord stim.

As I say, if you can see it, if you're in the cheap seats at the back, that's a statement about how they got their noninferiority margin.

Page 70

And if you can't read it says, "Using an binomial test for noninferiority with a 10 percent noninferiority margin." So their primary outcome here is a 50 percent pain relief or naught. So the difference in those proportions by 10 or more they were arguing as being noninferior. And then the usual statements, 80 percent power, et cetera, et cetera.

So over to you, a straightforward one. It's a statistically significant result. The question I guess we need to go back to is they've set this up as a noninferiority study. Now, I've treated a bit here, so actually, because the primary outcome was set on a noninferiority margin of 10 percent, what I've done here is to take a previously published noninferiority margin on the continuous scale of 8. And you might say, well where does that come from? That with the Sunburst trial that set up its noninferiority margin of being 8. And I guess the point putting this to you is that although the Senza trial was set up as being noninferiority. You can see that the final result clearly excludes

Page 71

noninferiority, doesn't it?

Yes. And indeed, one of the benefits of doing a noninferiority study is if you show that the active is better than the reference, you can automatically go on and then test superiority without statistical penalty. That's quite an accepted approach. So that's another benefit of noninferiority. If you think that the two treatments may be similar. But also, once you prove that, you want to go on and demonstrate the superiority exists, then one can.

So I'm with the author so far. I think when the Senza trial was done, we didn't know if HF10 would be better than conventional, so let's set up a noninferiority study to test that. But remember, what was our gold standard for the reference here? The reference is conventional spinal cord stim. And the answer to that is that spinal cord stim conventional should have been proven against placebo. So clearly that did not exist in this setting.

So you may say that the CONSORT, police if

Page 72

you like, get hold of this trial, they're going to have a wee bit of problems with that. But the trial did report, and I think clearly the result demonstrates noninferiority. But the question I would put to you now is can the authors here claim superiority based on this result?

They do say so in this paper substantially, certainly superior statistically, but there's the MCID. Now, I'm seeing a few head shakes at the back. So maybe actually this trial doesn't prove superiority. Yes? Because we've got an effect where actually the upper confidence interval overlaps.

Anyway, I'm just putting it to you that I think these hypothesis definitions are important, and they're tremendously important and the way in which we interpret the trial. I'm kind of beating neuromodulation up here a bit, but actually I could beat up other areas of chronic pain as well, probably.

(Laughter.)

DR. TAYLOR: But I'm just trying to make the

Page 73

point that I think it's terribly important we get these hypothetical frameworks right and we interpret trials genuinely in those senses, because I think otherwise we get a lot of confusion in the system.

Now, the other bit about noninferiority -- and you'll be glad to know I'm going to move on just a sec -- is the impact it might have on actually just the logistics of doing a trial. This is an example of a trial that Sam and I are actually cooking up at the moment. I won't tell you what the comparisons are. That's intellectual property to Sam. But we could either set up as a superiority design, and if we did -- I'm giving away the population we're going to do this in. This will be in failed back surgery syndrome -- we could use the IMMPACT MCID.

We know that the standard deviation for the VAS NRS pain scale is typically about 2.5. Run the sums, also accounting, by the way, for 30 percent attrition. We need 48 patients per group. So the magic number I always have in my head is that a

Page 74

trial should be at least 100 patients if we're trying to demonstrate superiority in the pain space. Eric and I were just saying last night, how many trials does he get to see as an editor. There are at least as big as 100, and actually probably not as many as he would like.

However, let's just imagine for a minute we set up as a noninferiority design. Now, you can see the impact is huge, isn't it, on the sample size. What I've done here is I've taken a noninferiority margin -- and it's difficult because remember, we don't have the placebo versus control effect here, and I would take half of that. But if we said that the surrogate effect size was the MCID, if we took half of that, that's 1. But you can see it has a tremendous impact on the sample size.

So in this case, if we are going to run the randomized-controlled trial, we don't need 100 patients, but we would actually need over 300 patients assuming everything else being constant, 90 percent power, 5 percent alpha, 30 percent

Page 75

attrition, and understand the deviation being the same.

So I think I'm just putting out there that I think noninferiority studies are important, but they do come at a cost, and of course that's one of the issues maybe where we see them less.

So time to move on. I've talked about inferiority/ noninferiority. What I want to move on now is to talk about different sorts of trial design. This is a real area of personal interest because a lot of the trials I do in the cardiovascular space are what are called complex interventions. They're not drugs, they're behavioral therapies. So I'm very interested in exercise-based rehabilitation. There the therapy is a complex one itself and multidimensional. It's delivered by more than one individual, and it can be delivered in different settings.

Therefore, I think we need to be more innovative in our trial design. But again, using Ewan's database, if we look, classically the majority of trials in the SCS space are 2-groups,

Page 76

sometimes 3-group parallel randomized controlled trials; a lot of crossover studies in that space. And actually, a lot of them are quite a more recent.

But interestingly for me, no cluster randomized controlled trials are in that space at all. Just to be clear, normally when we randomize, we randomize individual patients. Cluster, we randomize at the level of an organization. So in my setting, we might randomize one general practice of a particular way of delivering cardiovascular therapy versus another general practice, or in your case we could randomize you. We could randomize patients to either get one implant or another.

And I would put it to you -- this is our paper that goes back to the BMJ -- this is a really neat way of thinking about things, and this is what they called expert T-based randomized controlled trials. Because I put it to you that a lot of you, the effects of an intervention in your space isn't just the technology, but it's the interaction between the implanter, the setting, the team, and

Page 77

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

Page 78

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

Page 79

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

Page 80

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

Page 81

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

Page 82

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

Page 83

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

Page 84

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

Page 85

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

Page 86

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

Page 87

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

Page 88

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

Page 89

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

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

Here are a few selected causes of these kind

Page 90

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

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

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

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

Page 91

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

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

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

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

Page 92

don't necessarily have to.

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

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

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

Page 93

are different. That's high placebo effect. I'll talk a little bit more, but not a lot.

Rescue medication and concomitant medication, I draw a difference between these two. I don't know how important it is. Concomitant medication, I think of something that the patient has been taking every day for a while. They're going to continue to take it during your clinical trial. Rescue medication is things that you take when you need them. That's how I use this vocabulary.

It's been shown, the more concomitant medications and the more concomitant treatments of any kind you allow patients in your clinical trial to take, the better everybody's going to do. And again, that squeezes down the difference between the two groups and creates a bias towards the null result. Your treatment might work; you're not going to see it in that trial.

Obviously, this is more of a problem in drug trials, I think. You tell me, and maybe I'm wrong. But if people aren't using the treatments, it

Page 94

biases the study to the null. It's as if you're not studying anything, so that's a source of bias to the null.

There are a million different other kinds of measurement error, and I'll refer to one or two of them. One thing that I'll talk about in particular is extremes of variability of reporting of the primary endpoint. Let's say that we're doing pain studies and we're talking about a daily pain diary, for example. Obviously, it's not the only way to measure outcome in a pain study, but it's a common way.

People with very high variability or people with extremely low variability, that population will not distinguish between two different treatments that are in fact different. We can have a long discourse in that today, but the short version of that story is that they just don't report their symptoms accurately.

So it's as if you're measuring something where your measurement instrument is broken. It's no different than if you're doing a blood pressure

Page 95

study, and your blood pressure cuffs are not calibrated. It's the same problem, and that biases studies to the null because in pain studies, whether we like it or not, the patient is the measurement instrument. If patients can't report their symptom intensity accurately, sorry, you can't do your clinical trial and distinguished effective treatments. That could be a whole hour talk by itself.

So that's vocabulary. Positive bias exaggerates the effect, negative bias minimizes true effects, and there are different causes of each one.

Now I'm just going to show a few illustrations selected from a large amount of research on the impact of these various sorts of biases on treatment effects. This is a study that probably many of you are familiar with. This is a study in acute migraine done by a buddy of mine called Ted Kaptchuk, who's a world renowned expert on the placebo response, who heads the Center for Placebo Research at Harvard Medical School in

Page 96

Boston. So yes, there is a center of research on everything if you weren't aware of that before.

I'm not going to go through the whole thing because it's complicated, but this is a study of acute migraine where patients with a migraine came in 7 times into the research center for 7 discrete migraine attacks.

What happened to them during those 7 times? They either got no treatment, which are these black dots, so you had to sit there with your migraine and watch it get worse over time -- yes, patients did this -- or in these blue dots, you got a single pill that was placebo; or in these red dots, you got a single pill that was a real migraine medication called Maxalt.

So why did you come in 3 times for placebo and why did you come in 3 times from Maxalt? Because there were actually other differences between these two. In the 3 times that you came in for placebo, every time you came in, you got a word written on a card, and the researcher handed you that card, and you read that one word. This is a

Page 97

one-word study. So if you came in for placebo, the card might say, guess what? "This is a placebo pill."

I'm going to just digress on that. Ted Kaptchuk, this same guy, is very interested in conscious versus unconscious placebo effects. He believes that it doesn't really matter whether -- or it doesn't completely matter. You can't abolish the placebo effect by telling people that they are getting placebo because a lot of these mechanisms are unconscious.

In fact, that's demonstrated in this study where you can see that in this group, they got a placebo, and they were told that they were getting a placebo. "Here's your placebo. Good luck with your migraine." And lo and behold, it was quite effective, the open-label placebo, as they called it.

This is just to give you a sense of how powerful these effects are. I don't believe that's a sugar pill; that's going to work. Well, guess what? It works any way, whether you like it or

Page 98

not; or you could be told that you were getting the Maxalt. So in this group, the patients were lied to; they were deceived. They were really getting a sugar pill, but the card said Maxalt. And you can see that the effectiveness of the placebo was more or less doubled by that one word on that index card.

Then you can guess the rest of the story. Here's the Maxalt. If you were told that the Maxalt was Maxalt, it had a very good effect. If you were told that the Maxalt was placebo, then the effect was more or less cut in half. So a word is as powerful as a drug when it comes to pain or subjective symptoms, et al.

What about the rest of it? That's just one word. What about everything else that happens in the research center? So imagine how powerful all that stuff is, so think about that in context of spinal cord stimulator trials, and just let that sink into your mind for a minute.

What about other sources of information or expectations that patients have? This is like the

Page 99

grandfather of all studies on deliberate manipulation of expectation in randomized-controlled trials of drugs. I believe this is the largest trial ever done of this type. It's a 2-by-2 design where you're randomized to drug versus placebo. This is Singulair and asthma. It's on the market. People use it.

You're randomized to drug or placebo, and then you're re-randomized to what you might call a high expectation condition or a low expectation condition. And it's only in that kind of a study that you can look at the impact of different kinds of manipulations on the difference that's observed between drug and placebo.

There's a lot that one can say about this trial. In this particular trial, one group, they got the high expectation where they got a glossy print advertisement and looked beautiful. It was put together by the marketing people from Merck. It had colors. It was shiny. It had nice words on it. They had access to the actual television advertisement in the United States for Singulair,

Page 100

which has butterflies and people dancing through meadows. I'm making that part up, but you get the idea.

There was a fancy doctor with gray hair wearing a white coat in the room. And in the other treatment arm, the drug and placebo was the same, but you had a schleppy, young research assistant wearing jeans, and you got black and white, and you didn't see the TV ad, so it was a very neutral presentation.

There are a lot of things to learn from this trial, but I'm going to just show you one thing, which is what was the impact of those different expectation conditions on the response to the placebo inhaler? You can see here, this is a self-report asthma scale.

Here you can see that in the neutral expectation group where you had the schleppy research assistant on the ugly ad, you had a very low placebo response, whereas in the high expectation group where you had the TV advertisement and the old doctor, you more than

Page 101

doubled the response to placebo, such that in that group, Singulair could not be demonstrated to be more efficacious than placebo.

Imagine now you're doing a trial on spinal cord stimulation. Does it matter what materials the patients see? Does it matter what advertisements they're able to see? Does it matter what's in your informed consent form? And if those things operate asymmetrically between the two groups, then you have this.

Let's say I was doing just a fake spinal cord stimulator, I wasn't even putting in a real spinal cord stimulator to anybody, just fake spinal cord stimulator versus fake spinal cord stimulator. Imagine a study designed like that, but in one arm, they got this kind of messaging, and the other arm, they got this kind of messaging. The difference would be statistically significant between the two groups.

So what's my conclusion? That fake spinal cord stimulation works better than fake spinal cord stimulation? No, it's because of these asymmetric

Page 102

biases that operate in these kinds of clinical trials.

That's what I meant by what I said at the beginning, which is that, sure, you can claim superior. It's superior. There is no doubt that it's superior, but it has nothing to do with the treatment that you're studying. It's just because of these extraneous effects that are operating asymmetrically between groups. Make sense? Yes.

There are a number of studies on this. This is about investigator expectation. I'm the investigator. I go up to you. I know what treatment that you're getting. You don't know. I don't say a word about it to you. You can video me. You can follow me home. I don't say a word to the patient about what treatment that they're on. My expectation for that patient is transmitted unconsciously and non-verbally to that patient, so that can bias the outcome as strongly as any of the other influences I just showed you.

This is just one study from Rick Gracely in Michigan. This was a dental pain study. These are

Page 103

two different groups. All these patients got placebo. It was a more complicated study, but these are just the placebo arms from that clinical trial; placebo on placebo.

What's the difference between these two groups of placebo patients? In this group, the investigators were told that the patient was either going to get placebo or naloxone, which of course doesn't relieve pain. In this group, the investigators were told something else. You could get placebo, or naloxone, or fentanyl, which is a high potency opioid analgesic.

Just that investigator knowledge that you might be randomized to fentanyl, this group did much better than that group from a pain intensity perspective. Nothing was said to the patients about this in this clinical trial, and there's literature showing the same thing going back to the 1950s. Jerome Frank from Hopkins showed this in psychiatry research. So the expectation bias is transmitted down the chain.

One obvious conclusion from this set of data

Page 104

is that single blind equals no blind in clinical research. You told me that you did a single blind study; I tell you did an unblinded study.

There are lots of body language and other interpersonal factors that also impact outcome in studies where subjective endpoints are being measured. There's a lot of research on warmth and empathy. This is a study of acupuncture for irritable bowel syndrome.

Patients were randomized into either wait lists -- you just sat around and gotten nothing -- or a limited group where the acupuncturists were trained to be very neutral, like bank tellers, "Hello, how are you, let's see your acupuncture, see you later," that kind of an approach; whereas in the augmented group, the acupuncturists were trained to be warm and empathetic, "Hello, how are you, how are your kids, so nice to see you, let me rub your back, I think you're going to do great from this treatment," all the things that we're trained to do as healthcare providers that help us in that setting but that

Page 105

make us terrible clinical researchers if we act that way.

So you can see that the response to -- actually, sorry. This was placebo acupuncture. I forgot to -- that might not actually make a difference, but if that matters to you, it's placebo acupuncture. And you can see that the outcome measures, which are primarily focused on pain, and this irritable bowel syndrome group were statistically significantly better in the nice acupuncturists than the bank teller type acupuncturists.

So you can imagine and think about your spinal cord stimulator trial. Again, if people in one arm get the really nice people, and people on the other arm get the really boring people, then that's enough to produce statistical superiority, and I venture to say clinically significant superiority between groups, even if the two types of spinal cord stimulation are not different.

This is a summary slide. In summary, expectation bias can influence studies in all

Page 106

different directions. It comes from a lot of different places. It's leaky expectation bias. It comes through the air. It's very difficult. Even if you expend effort, it's difficult to control. Of course, if you don't expend effort or if your study is designed in a way that kind of admits it by necessity, then you can't claim that difference between groups is due to the treatment.

The directionality of the impact of expectation bias can go in two different ways. If everybody thinks they're going to do great, it actually can bias your study to the null result. So you actually fail to show differences when there truly are differences. Or if the expectation bias is asymmetric, it operates differently in the two groups. It can create an impression of a difference between two groups that's not actually there.

I'm just going to say a word; I actually mentioned concomitant rescue treatments. I review a lot of clinical trials, including a lot of failed clinical trials. You'd be amazed how often in

Page 107

clinical trials, even of drugs, people don't even bother to track what medications patients are taking while they're on a trial. And then you get, "Gee, this person took some amount of ibuprofen; I don't really know." The concomitant medication log says this person was taking Vicodin on a PRN basis, but nobody quantified how much. You can't do a pain study like that and expect to learn anything from it.

I'm going to just make a comment on this extreme variability issue. We've been doing some research on this issue for quite a long time. This is patients with pain due to osteoarthritis of the knee. We created an experimental paradigm where we measured how accurately patients reported experimental pain.

To make a long story short, it turns out that about a third of patients don't report experimental pain accurately. If you translate that into the clinic, this predict whether they will discriminate drug from placebo in clinical trials. There are lots of reasons to believe that

Page 108

patients differ one from the other in terms of how accurately they can report their clinical pain. It's not just about listening to the patient. Some patients are better than others at conveying the reality of their experience using these strange scales that we give them.

I can tell you if I'm at a social gathering and I tell people that I'm a pain researcher, I could just shut my mouth for the next hour and listen to people telling me story after story after story about how they fabricated their 0 to 10 pain scale when they were sitting in the emergency room because they wanted to move up in the queue, and how nobody can tell the difference between a 5 and 6, and what does zero really mean anyway?

You don't have to be a pain researcher to just flitter around your social circles and realize that it's very difficult to use these scales we give people to convey their pain intensity. And like all other human skills that have ever been studied, the level of skill differs between one person or another. So there's no reason to think

Page 109

it wouldn't be the same with the scale of reporting you're paying accurately, and in fact it isn't.

This is data that's not been published yet. I pulled this from a trial -- we do a lot of statistical surveillance of ongoing clinical trials where we monitor all sorts of things during ongoing studies to identify problems with data quality. So I pulled this data from a recent large clinical trial of osteoarthritis of the knee. This is a drug study.

This study's been completed, so normally of course we monitor only blinded data during the course of this study, but this study is complete, so we have the unblinded data. What we did is we segmented people into 4 groups based on how variable their daily pain intensity scores were.

Bob, I put this here because I knew you were going to love it when I showed it. There's a lot of data out there in the literature already, and many of you probably know about it because it's been discussed at many IMMPACT meetings that patients with very high at least baseline pain

Page 110

reporting variability, don't separate drug from placebo.

That's this quartile here. These are the patients with the highest quartile of pain reporting variability. In this particular clinical trial, blue is the drug results; yellow is the placebo results. You can see there's no difference between drug and placebo in patients with very high variability. That's been shown many times before; nothing new here. And I think it's because these patients don't know how to report their pain accurately, and there's plenty of data to indicate that that's true.

What hasn't been shown before, but what I was dying to do, is the patients with very low pain are reporting variability. These are the people who every day their pain is a 6, or a 2, or a 10, or whatever it was. And I can tell you from my experience with chronic pain patients looking at daily pain scores, there is no chronic pain patient whose pain is really exactly the same every day for weeks and months on end. I don't know what that

Page 111

is, but it's not pain intensity reporting.

(Laughter.)

DR. KATZ: And you can see here -- this is I think for the first time -- that those patients also don't separate drug from placebo. Why? Whatever it is that they're doing, they're not reporting pain intensity in your clinical trial. And it's only these two groups in the middle of variability that actually will reveal a difference between a truly efficacious drug and placebo because they're the ones who were actually reporting their pain intensity.

So imagine now, let's say you're doing -- what was it, Rod, a 48-patient per arm clinical trial? So imagine that in your 48 patients in one arm, 20 of them aren't reporting their pain accurately, and in a different arm, 5 of them are not reporting their pain accurately. So how can you possibly expect to have an accurate estimate of treatment effect? You can't.

Rod gave a very eloquent discussion, in much more detail than I'm planning to, about

Page 112

noninferiority studies. I'm just going to add one quick comment on it. If you do a noninferiority study between treatment A and treatment B -- a lot of you can anticipate what's coming up on the slide -- what's the interpretation if you just have two active arms?

Well, if you had put a sham treatment in your trial, the interpretation might have been that both of your active treatments are efficacious. If this was the result of your sham, then your interpretation will be totally different. Neither treatment was efficacious.

So the simple point I want to make is that an active controlled study, one active treatment versus another active treatment, if both treatments produce a similar effect and you don't have an internal demonstration of assay sensitivity, then that study cannot be used to make any inferences whatsoever about the efficacy of the treatment. Why did you do that study?

Another point about noninferiority studies -- and Rod alluded to this earlier -- is

Page 113

that measurement error is the friend of the person trying to make mischief for the noninferiority study. What do I mean by that?

If you're trying to show that your fancy new spinal cord stimulation is just as good or not worse than some established type of spinal cord stimulation, and you design a noninferiority study to prove that point, the more measurement error you have in your study, the more likely there is to be a finding of noninferiority, and the wider your confidence intervals, and the more likely they will fall into those ranges that Rod showed.

So crappy research methods is the way to be successful on your noninferiority study, which, again, the only way to defend against that is with an internal demonstration of assay sensitivity. So without that -- is it ethical to do such studies like that? That's an interesting question.

Anyway, I was assigned to talk not only about sources of measurement error and be the bad guy, but to present some possible approaches to preventing or mitigating such sources of

Page 114

measurement error. Again, we could spend a whole meeting just making a huge table of all the different kinds of measurement error and what the type of mitigation could be, but I just wanted to suggest a few general approaches that I think we should consider in this project that we're involved with over the next day or two.

To state the obvious, double blinding and sham controls, for all sorts of reasons that I hope are obvious now, this is really a key point, which is that there are nonspecific influences and outcome. I outlined some of them during this presentation. I did not outline all of them.

The study should be designed such that those nonspecific influences can be expected to be similar between groups. So in your methods section of your paper and in your methods section of the protocol, a laundry list of what are all the nonspecific influences that I could imagine.

The programmer or the person who's going to be supporting the patient when they come for their visits, are they getting psychological therapy,

Page 115

physical therapy? How often are they being seen? What is the nature of their experience in the context of the visits in their research center?

Those things not only should be designed to be similar between groups, but they should be documented. What rescue medication did they take? What concomitant medications? What kind of ancillary staff interactions? How long did they take? How frequently did they occur? What information did the patients get access to? What websites did they see? What's in the consent form?

This all needs to be specified, otherwise you might have statistical superiority, but you won't be able to claim that that superiority has anything to do with your treatment unless you can credibly state that these nonspecific influences were symmetric because you counted it up as you did your trial.

You might count how long the patients were in the clinic. How do you really know that the patients had a similar expectation of benefit if they're in one arm versus another? Because you

Page 116

counted how many minutes they spent with their rep? I mean, that's kind of an indirect measure. So another option to consider would be to actually ask the patients, do you think you're in the good treatment or the bad treatment? How likely do you think you are to benefit from this treatment?

There are a variety of different expectation type questionnaires that are available. However you try to design your studies so these nonspecific influences are symmetric and the patient really does perceive that the perceptions are equally distributed across groups, you don't know until you measure it.

This is going to be a bit of an annoying a comment. You are all familiar with these hierarchies of levels of evidence, right? We all worship them. It's like a form of idolatry, like the p-value less than 0.05, these hierarchical levels of evidence. And here they are, 1 through 3; there are a million of them. This is one particular established one.

The highest level of evidence is the

Page 117

randomized-controlled trial. People get up there at meetings and they say because they did a randomized-controlled trial, therefore I've made it to the promised land, and everything about my randomized-controlled trial can be believed.

Well, what I just spent a half an hour telling you is that that's wrong, and that even though you do a randomized-controlled trial, these biases have plenty of opportunity to creep in and can undermine the credibility and interpretability of a randomized-controlled trial.

So this is not the highest form of evidence. I'm sorry. This is the higher form of evidence, which in fact I think should be our basic standard, and it's not even mentioned in any of these evidence hierarchies, which is a randomized, double-blind, placebo- or sham-controlled trial, if that's appropriate for the treatment context, with measures implemented to minimize bias and maximize assay sensitivity; and that those factors are measured and documented. That's actually what we need in order to believe the results of

Page 118

randomized-controlled trials

So, sorry, level 0 is the new level 1 --

(Laughter.)

DR. KATZ: -- or something like that.

In conclusion -- well I think I just gave you my conclusion. Of course, I do want to make one comment, which is that this is a lot easier said than done. It's easier to stand up here and be critical, but when you actually get to designing and doing these trials, it's actually not easy, complicated, and probably not fully achievable, to be perfectly honest.

So what I'm advocating for is an effort to at least be aware of what sorts of biases you are controlling and what sorts of biases you're not controlling. At least make an effort to quantify the extent that those biases are operating in your clinical trial. And if we can just do that, I think we will have taken a step forward in our clinical research methodology. And that's it. Thank you very much for your attention.

(Applause.)

Page 119

DR. THOMSON: Absolutely perfect timing. Well done to all of our speakers who've actually made up for each other. I think we were entertained and very informed by what was going on. And I think that sets the scene for later for our discussion.

So now we're going to break for tea; no, coffee and comfort, and then we are going to come back here at 10:45 and we're going to hear from regulatory agencies, and then we'll go into our discussion after that. So thanks very much, everybody.

(Whereupon, at 10:16 a.m., a recess was taken.)

DR. THOMSON: We're going to go on to our second session of the morning. I think one of the unique things about this group that we formed is that we're not just talking to ourselves, and we now are going to have two talks from regulatory agencies, both sides of the Atlantic. One will be Carlos Pena -- I probably pronounced that badly -- who is what I used to call the FDA, but I

Page 120

think it's the Center for Devices and Radiological Health of the Food and Drug Administration. He is the director of the Division of Neurological and Physical Medicine Devices, Office of Device Evaluation. So he seems to be just the right person.

Then we have Rahul Singh from the MHRA. He'll explain, but we approached the EMEA. They don't really have a big device portfolio, so they look to their friends at the UK MHRA as well. So we'll get a European perspective as well on device regulation.

Carlos, are you in the room? Good. I've introduced you. So Carlos, please, thank you very much indeed.

Presentation - Carlos Pena

DR. PENA: Good morning. Welcome to DC, in the snow. I feel your pain. The Food and Drug Administration, we are involved in medical devices, too, not just drugs. So today, I'm going to be taking you a little bit on a overview of the Center for Devices and Radiological Health and telling you

Page 121

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

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

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

Page 122

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

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

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

Across these three classes, we use what's

Page 123

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

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

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

Page 124

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

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

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

Page 125

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

Page 126

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

Page 127

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

Page 128

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

Page 129

devices that can be categorized with not typical medical terms, but more of like relaxation and other soft clinical terms that are low-risk products.

So there are a number of pathways to get to market. The question here is how can you get to the marketplace with more of the higher risk devices, which is spinal cord stimulation.

A few points to consider. One is, in the device world, we're different from drugs, but the bars are the same. We require safety and effectiveness data, especially for PMA, class 3, high-risk devices. The differences come by the data sets we are able to look at.

In drug world, you can typically anticipate the potential for two well-controlled randomized studies from any drug product approvals, typically. In the device world, by law, we are supposed to look at all types of valid scientific evidence, which come from no control studies, to historically-controlled studies, to placebo-controlled studies, all the way down to the

Page 130

randomized, blinded sham-controlled study.

I'd like to think that at devices, we have a lot of different tools we can bring to bear to the process. Nevertheless, the randomized, blinded sham-controlled study is the best way, in some circles, to identify the impact of the medical device in a clinical setting. We have the least amount of uncertainty when we typically can use a randomized-controlled study. We have a lot of uncertainty when we're looking at a study that compares itself to a historical control.

By law, we have to look at all of these. That's why the best way to figure out how we can move together towards getting a product to market is the presubmission pathway, when we set our expectations on making sure that you know the types of questions that we might have for any given trial design.

Another couple of points to consider, I mentioned that trials are different from drug studies, but the standards are the same. Devices can be difficult to blind. In our Division of

Page 131

Neurological and Physical Medicine Devices, we also have prosthetics. It's very hard to make a randomized-controlled double blind study with a prosthetic arm.

We have different tools that we can use to bring to bear to our products. For spinal cord stimulators, where you've heard in prior sessions, placebo effect is an issue. Blinding is an issue. The assessment tools are an issue. The trial design of superiority versus inferiority trial designs are an issue.

A couple of things, endpoints can be highly diverse between studies. Typically, a single pivotal trial follows feasibility stages, but devices are designed to support a reasonable assurance of safety and effectiveness.

Many times when I go to a conference, it's like parting the Red Sea, like no one wants to talk to me. But sometimes people will come to me and say, "Hey, I have this device. Can you approve it?" And I'm like, I look at that less and I'm like, well, you need to tell us about the device,

Page 132

the indications for use, the intended patient population, the prior studies, and any kind of precedent decisions.

There are a lot of different details that fold in to a given submission to the FDA. There are many times where we can generalize about a different a device area, device class, like spinal cord stimulation, but we have to quickly delve down into the details of what was studied, was there a comparison group, and what was the outcomes, and can we have certainty in the outcomes.

Let me move a little quicker. A couple other points to consider, many times we want to be very specific with the patient population, but we like to have it generalizable. These are smaller studies than the drug studies, so we do have to make some type of decisions with an imperfect data set. Time frame should be defined in pain studies, acute versus chronic, and we look for more than one safety and effectiveness endpoint, and we look very closely at the safety endpoints.

The last couple of slides are about the

Page 133

organization. One is we are the Division of Neurological and Physical Medicine Devices. I'm accompanied here by Ms. Pamela Scott. She's the new branch chief of our neurostimulation psychiatry branch, which includes pain.

Our division is one of several in the Office of Device Evaluation. We're thinking about combining these offices into a super office where when we work with folks, like sponsors, they can work with one office on both the premarket and the postmarket surveillance. That should be coming up, and I hope to share with you more updates about the organizational changes that are happening at FDA in the coming weeks, actually.

But now, the Division of Neurological and Physical Medicine Devices, it's five branches. The neurostimulation devices psychiatry branch deals with a lot of the pain products, the spinal cord stimulation products. As I mentioned at the start of the talk, the best way to engage with FDA is the presubmissions. There are a variety of different settings. They could be from informational to

Page 134

introduce your product to the agency, all the way to a specific question: is my trial design the trial design that is most likely to reach a positive outcome when under FDA review? So there are a variety of questions you ask, and it's free; it's free, and it's free. Use it.

A couple of closing remarks. One is that when a device can make it to market, it depends upon a lot of different things. It depends upon the data set that device was studied under, and in our case, under an IDE. But it also depends upon prior studies; the history that we have with the product; the intended use; the patient population. It depends upon the details.

Two, if you think it's too early to contact the agency, that's the best time to contact us, through the presubmission process, and I mentioned it's free. We want to make sure that our expectations are matched with your expectations about the outcomes, about the trial design, about the endpoints, because it would be a very bad situation for us to not talk until you have a nice

Page 135

polished data set before the agency.

Three, I showed you some of the timelines that we're interested in pursuing, standing up IDE studies typically for class 3 devices. They're aggressive. We cannot do it on our own. We need your help to work together to stand up those studies, so patients can get into those studies as quickly as possible. I you'll be surprised with the contact that you have with the agency. Thank you.

(Applause.)

DR. THOMSON: Carlos, are you going to be able to stay for the discussion today?

(Dr. Pena gestures yes.)

DR. THOMSON: Great.

Rahul Singh, I'd like to hear from you. The whole setup of regulation is different in Europe, and I suspect Rahul will explain that to us. There's obviously a little transatlantic competition.

Presentation - Rahul Singh

DR. SINGH: Good morning, everybody. My

Page 136

name is Rahul, and I work as a clinical advisor for MHRA and also work as an orthopedic surgeon. I'm going to give you a top-level review of what our regulatory roles are within the UK and Europe, and hopefully to give you a pragmatic view if you are intending to make a device and bring it all the way towards CE marketing.

Just a show of hands, how many of you guys have heard of MHRA?

(Show of hands.)

DR. SINGH: Excellent, so there's some good knowledge here.

I'm going to show you three slides and three objectives. The first one is the journey of a medical device. You have a research and development area within your manufacturing company or your research university and that goes to device development. Within MHRA, we've got an innovation office where you can start inquiries, Q&As, and if you decide to submit any clinical investigations for a medical device.

When you submit documents to MHRA and it's

Page 137

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

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

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

Page 138

management and their roles within the EU directive.

This slide is very complicated, so I'll briefly touch upon it, and it touches slightly about Brexit, and it's the new medical device regulation. It came into play in 2017. It's got a three-year transition period for general medical devices and active implantable, i.e., spinal cord stimulators. There's a five-year transition period for in vitro diagnostic medical devices.

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

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

Page 139

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

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

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

Page 140

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

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

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

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

Page 141

manufacturers are required to achieve those. There's a clear move towards expectations of the new medical device regulations, which are being implemented in the transition period.

These are the stages of the clinical evaluation. We've got five general steps. Number one is to plan your clinical investigation, evaluation; identify what personal data you require; and appraise the individual data set specific for your medical device. So not all one package will fit for one for one medical device. You need to show the analyzed data and conclude appropriately for that medical device. And obviously, the last step is final conclusion of the clinical evaluation report.

The pertinent data is data generated by the manufacturer for all preclinical investigations. And as you can read there, it's relevant for that medical device. The data retrieved from the literature is relevant to the device under evaluation. Again, each medical device is different depending on its active implantable or in

Page 142

vitro device.

There's another standard I mentioned, which is ISO. I'm going to go over a couple of them. The main one that we use as clinicians is ISO 14155, and it addresses the group's clinical practice and requirements, the design, conduct, recording, and reporting of clinical investigations. It looks at demonstration conformity with the relevant and general safety performance requirements, and evaluation of the pros and cons of the device with the risk-benefit ratio. You need to justify what level of clinical evidence you will use for your device, and it's not all the same for all devices.

This is another example of a different ISO standard. It's ISO 10993. Don't worry too much about the numbers. It's for biological evaluation, to make sure that the materials, substances that are contained within the medical device are safe for patients' safety. And this is a big area where a lot of manufacturers actually fail upon; and hence, why we actually object to the clinical

Page 143

trial.

This is a framework for the biological safety and assessment from this ISO. Essentially, we look at different things, so if you've got a bone graft substitute, for example, which is permanent, we'll expect you to investigate those different aspects of toxicology and biocompatibility.

What's the MHRA review process? The validation takes about five days to take in terms of validating all the documents that you have submitted, and there's an online criteria which you need to fulfill. We've got 60 days to make a final verdict. If we don't give you a verdict within 60 days, you are free to carry out your clinical investigations, but it's not advisable to do that because the notified bodies will pick up on this, obviously.

Within the 60-day period, we'll ask many questions from different sections of the MHRA. They include internal clinical assessors and external clinical assessors; a technical team;

Page 144

biocompatibility person; and someone from the pharmaceuticals medicine aspect if the medical device has ancillary medicine in there; and sterilization and statistics experts.

Again, with the 60-day period, questions and responses are carried out, and then we come up with a decision at the end of the day. The decision isn't always completely yes. It may be yes with conditions that need to be adhered to and be implemented.

What are the common reasons for objection? Ninety percent of all clinical investigations that we receive, we usually approve, and we do implement some conditions on those. The usual ones are a lack of relevant clinical endpoints for that particular device.

Statistical issues. A lot of manufacturers will try to claim that you will need any amount of patients such as 20 or 30 for safety, but the actual fact, they want to prove efficacy, which is not possible essentially. And this inadequate preclinical testing, one of the main areas is

Page 145

sterilization or toxicology biological assessment and inadequate electrical software testing. There's been a lot of influx over the last couple of years with artificial intelligence being used as medical devices and medical apps.

If MHRA approved it, good news. During the clinical investigation, we are still involved. We'll approve any study amendments; review adverse events on a regular basis, minimum every three months; review protocol deviations; and review the final study endpoints. During this period, if anything goes wrong or if there's an issue, for whatever reason, we can suspend and terminate the clinical investigation.

The second part of what I said that MHRA does is being the designated authority, which we also review the notified body for CE marking. Once the manufacturer has completed the clinical investigations, they submit their data to a notified body and they carry out a conformity assessment. It's basically a strict protocol which assesses all the performance of the device from

Page 146

idea conception to reviewing all of the data at the final endpoint of the clinical investigation, and postmarket surveillance notified bodies carry those out as well.

What is postmarket surveillance? It's a system to monitor the clinical performance and the safety of device once it hits the market after CE. It needs to be appropriate for the device intended use, and data must be evaluated for risk versus benefit ratio.

This all falls into postmarket surveillance. There are different aspects to it. There's reactive, which is adverse events. So if you're lucky and you don't have any adverse events, you don't have to tell us about it. Postmarket clinical follow-up is proactive and you do need to inform us how well you're doing with the device, and implant registry. For example, in the UK, we've got national joint registry, and that actively seeks information on how well the device is doing. National joint registry is for orthopedic implants, hips and knees for example.

Page 147

A bit more about postmarket clinical follow-up. Again, it's part of MEDDEV 2.12, and it's for following a proper premarket clinical evaluation, and it must be based on the identification of possible residual risks and unclarity on long-term clinical performance based on risk and benefit ratio.

Different methods you can use for postmarket clinical follow-ups depending on the device and the number of patients that you require. Notified body review; notified bodies, all class III and class IIb devices need to be reviewed by an in-house clinician. Sampling of IIa's and IIb's is also carried and done by notified bodies and not routinely monitored by MHRA unless the device is slightly a high risk or not much history, historical data, is present there.

Again, this is a quick slide of the summary, original objective. This is the journey of a medical device. Hopefully, it's been informative and you guys know about it more. The regulatory roles of a competent authority, i.e., MHRA and

Page 148

notified bodies in getting your product/medical device onto the market. And again, this is a simplified version of the new medical device regulations, which will be coming into effect in 2020 for general medical devices and 2022 for in vitro diagnostic medical devices. Thank you.

(Applause.)

Group Discussion

DR. KATZ: We're going to have a 45-minute discussion now. I'd appreciate it if everyone who spoke this morning can join me up here on the panel. I'll be co-moderating this session with Salim, so if he feels like we've wandered off the reservation, he'll jump in.

Salim, if you could come up and all the other speakers; Dr. Singh; Dr. Pena, and other regulatory colleagues, feel free to join us up here. It's a special opportunity to have the regulators with us, especially ones that flew across the ocean. So we want to take advantage of you.

If you look at your agenda, the main purpose

Page 149

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

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

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

DR. THOMSON: Simon Thomson from the UK.

DR. KATZ: Nicely done.

(Laughter.)

DR. THOMSON: Thank you.

DR. KATZ: You're a role model for all of

Page 150

us.

DR. THOMSON: I listen to you, Nate.

The interesting thing, actually, Rahul brought it up, and I suspect the FDA have got a view on it. I think everybody can contribute to this. One of the things with spinal cord stimulation is that we've got the target, which is stimulating the spinal cord. We've got a variety of different diseases that we treat.

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

In the past, as clinicians, we had this loose regulatory thing of treatment of the back of limbs, and nobody really look used to look -- it was more of an argument we had, if you like, with the people who reimbursed us as to whether this was a valid treatment.

Is there a change in regulatory climate such

Page 151

that now an approach to the regulatory people have to be made when we're starting to treat different conditions?

DR. KATZ: You can just speak, and it will pick up.

DR. SCOTT: Again, my name is Pamela Scott, and I am the branch chief of the neurostimulation psychiatry branch within our Center for Devices and Radiological Health.

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

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

Page 152

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

Dr. Pena, do you have anything else to add to that?

DR. PENA: To build upon what Pamela has described, for specific indications, I think we continue to ask questions about what specific patient populations are going to be improved with any given device. So there could be unilateral or bilateral issues. It could be pain in specific areas or generalized pain.

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

Page 153

benefiting population.
So I don't think things have changed from how you've asked your question. We may be asking some more questions about who's really benefiting.
DR. KATZ: Rod, do you want to focus on that, before we go to Rahul, from your perspective?
DR. TAYLOR: And indeed, I'll bring you in, Rahul, as well, if that's okay.
I wonder if I can ask a specific question to our regulator friends.
DR. MARKMAN: You can.
(Laughter.)
DR. TAYLOR: Thank you. I'm being very careful about any questions to the U.S. government at the moment because I've had problems entering the country.
No. But seriously, there's an example -- I think what Simon is saying is that in the past, spinal cord stim has -- there's been a lot of 510(k) stuff; so in other words, grandfathering. So we've had this technology out there. We know it broadly works and it's safe. Regulators, you're

Page 154

relaxed.
What's been interesting is that one of the new therapies that's entered into your air space and our air space is high frequency stim. So I'm going to give us very specific examples.
Do you know the device, Senza?
DR. KATZ: We do.
DR. TAYLOR: Okay. Good, Nate.
I was intrigued that the FDA's recommendation when Senza entered the market I think palpably different to what had happened with previous devices. And in fact, I think the noninferiority study that I presented in my earlier slides actually came from yourselves.
I know you don't often like talking about specific companies or devices, but I think it's a useful vehicle here to maybe just try and winkle out a little bit about what might be your change in thinking, because as you've heard from people like Rick, this is a fast-moving area. We're getting many more devices that are spinal cord stim, but with a twist; thus changing stimulation frequency

Page 155

or not.
I think it intrigues me -- as a payer, I'm very pleased that you're doing this, actually, because then I'm getting the evidence further up. But I'm intrigued with your change in behavior at least with Senza and whether you'd be willing to talk a little bit about that specific example to help us think through the future.
DR. PENA: I don't like to talk about specific companies, but I think probably you're referring to the trial design of a noninferiority trial design sort of approach. And like I had discussed during my talk, we look at submissions for them to stand on their own, and we look at the data that's been submitted to us, hopefully with our input during the development of that study.
The other thing to keep in mind is that many times we're given a study that has some uncertainty that may not be the most optimal trial design, but we're asked to make a cut on whether the data collected from that study, whether it was a RCT or superiority study, or noninferior study like the

Page 156

Senza, and ask ourselves is there a benefit potentially to patients here with the data that was submitted, understanding that there could be limitations. And we make that on a case-by-case basis.
Is it comparable to other spinal cord stimulation class 3 devices? They're class 3 devices. I don't think it's 510(k), except --
DR. SCOTT: The ones with the external.
DR. PENA: Yes. But typically, we look at these studies with the data that's been generated and try to make the best cut. There are a variety of trial designs that come at play here.
So I'm not sure if there's been a shift much more so as we try to make the best decision with the data that's been provided.
Did you want to add anything?
DR. SCOTT: And I can just add, the spinal cord stimulators that have an implanted pulse generator are class 3. Those that have an external pulse generator that's not implanted our class 2. So they are regulated by two different regulatory

Page 157

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

Page 158

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

Page 159

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

Page 160

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

Page 161

There are a lot of details here that would need to be worked out. There are a lot of staff at the agency that we work with -- clinicians, statisticians, engineers, and in some cases epidemiologists -- that all come together to evaluate the particular question before the agency.

So it's hard for me to answer your question about a particular trial design or a particular output without having all the other pieces that I presented on the slide, that we would need to have before us to give an informed decision, which would take a review of certain amount of days for us to come to a conclusion.

I'm not trying to be elusive. I'm trying to be honest.

DR. FIELDS: You're doing a very good job of it.

(Laughter.)

DR. PENA: Who was that? Did someone speak?

DR. FIELDS: That was me.

DR. PENA: You're asking questions where I don't have the information -- Pamela doesn't have

Page 162

the information -- before us.

DR. TAYLOR: But I think to get you out of a hole, if I may, what you're not seeing is no. So I think back to Nate's point, we've got some worries about noninferiority studies, quite fundamental scientifically about assay sensitivity and all the rest. But what you're actually saying, which is quite reassuring, is that even in the face of that uncertainty, as a regulator, you would still, in the totality of consideration, be prepared to accept noninferiority evidence, I think, if I may paraphrase you.

DR. KATZ: That's a nice summary.

DR. SCOTT: I think the other thing to keep in mind is when we do these reviews, like Dr. Pena pointed out, we have an actual review team that will often consist of, like he said, engineers; clinicians; epidemiologists; if necessary, statisticians, who are all looking at that data.

Oftentimes, when we have questions, sometimes we have some of the same types of questions that we've heard raised in this

Page 163

discussion this morning, and we will ask the sponsor to provide us with information, with data, to answer those questions to the best of their ability based on the data set that they have and based on other information that is in the literature.

So oftentimes, we're going back to the sponsor also ourselves to gather as much information, as much data, to help us make that determination of safety and effectiveness. And again, we're looking at the benefits and the risk of the device, and then what's the level of uncertainty that we are faced with based on the data set and the other maybe historical information that we do have.

DR. PENA: Just one last point. If a study comes to us that does not demonstrate or has a high degree of uncertainty, and we're very concerned about what the device or what the company's purported to say about that product, we will communicate our concerns.

I don't think we are not communicating the

Page 164

concerns or the questions we may have with any particular product or trial design. We have very difficult discussions. We're not elusive when we have all the details before us.

DR. KATZ: So let's go to Rahul, finally.

DR. SINGH: All those kind of questions.

So start off with off-label and label use as a regulator and also as a practicing clinician. Off-label use is not recommended by MHRA because it's not intended -- it's for instructions for use, not intended use, for that medical device based on the manufacturer's claims.

So if the clinician does use a device out of scope from the intended use, IFU, we don't control what the clinician can do. That's a different regulatory body. That would be the hospitals, and that would be the General Medical Council in the UK. The clinician obviously has to make their risk-benefit ratio themselves on a granular level, where that device can be used and beneficial for that patient, i.e., the spinal cord stimulator for migraines, for example.

Page 165

Another comment would be, we don't comment on the trial design based on the instructions for use for that device. We don't advise manufactures or applicants what you should do. We advise on what you have submitted and what we believe is a negative or positive. So it's based on those.

If we're seen as advising, you should do X, Y, zed, and that's out of our agreement. All of these things, as Carlos mentioned, we've got a whole entire team, clinicians, statisticians, engineers, et cetera, blah, blah blah, so it would be unfair to ask for the highest level of evidence for a manufacturer when it may not be necessary to do that and subject patients to a device, a hundred patients in each treatment arm when you can achieve the same thing with a less number of patients using a different trial design.

That was it. Was there anything else? And I agree with Carlos' comment regarding Richard's question as well, that you asked. That's about it, I think.

DR. KATZ: Great. So let's go to the floor.

Page 166

I have Howard and Greg and Sam, and then we'll come back to the panel.

Howard?

DR. FIELDS: Howard Fields, University of California, San Francisco, a background of seeing a lot of patients with chronic pain, including neuropathic pain, low back pain. I also have done a lot of electrophysiology on pain modulation and spinal cord wiring.

In all my years of taking care of patients, I never recommended a patient get spinal cord stimulation. And the reason was I wasn't sure how it worked, even though there was a model out there. And the other one is I could never decide which patients would benefit from it.

So I wanted to ask Dr. North, who's had the most experience with spinal cord stimulation, not how it works because he talked about that, but I'm sure over the years, you developed a feeling for which kind of patient would actually benefit, because obviously some don't. So what's your advice on that?

Page 167

DR. NORTH: Well, that's quite right. It goes beyond spinal cord stimulation. In clinical practice, practice of medicine in general, I dare say, a neurosurgical practice focusing on pain patients, it's clear to me with some patients, even without seeing them, just based on the referral information, that I'm not going to be able to help them, and one learns to recognize those patients.

As to whether it is essential that I think I understand the mechanism of effect to offer a patient an operation or a treatment, I certainly would like to know the mechanism or to think I know the mechanism, but I don't regard that as an essential ingredient. I think there remains a place in medicine for empiricism and serendipity.

DR. FIELDS: Which patients benefit? In your experience, what would it be about a patient that would make you think this spinal cord stimulation was appropriate?

DR. NORTH: That it would --

DR. FIELDS: Was appropriate for that patient? What patient characteristics?

Page 168

DR. NORTH: Oh, okay. Well, so-called failed back surgery syndrome is the most common indication. But as one who does back surgery, I routinely insisted on all of the patient's prior records before I would see them as a candidate for a stimulator. That's the only time you really have a chance of getting those records, when the patient is motivated to provide them.

It was often apparent from those records that the patient never needed back surgery at all. So it was not really a failure of surgery as much as selection in the first place. Patients often are encumbered by issues of secondary gain. If is inappropriate utilization of medical resources, if there's heavy legal overtone, those are all reasons that I would hesitate to recommend any surgical procedure, including a stimulator for such a patient.

DR. FIELDS: Okay. Thank you.

DR. THOMSON: Can I just sort of add something here? Is that okay? Dr. Simon Thomson from the UK.

Page 169

What I think is that we're very good at talking about what we won't do and why we wouldn't recommend spinal cord stimulation, but we're not very good at signposting what I think you're asking: what's the ideal patient for spinal cord stimulation?

DR. FIELDS: Exactly. Think of yourself as an investor, and you're starting a clinical trial, and you want to do your best to guarantee that you're going to have a robust effect of the intervention.

DR. THOMSON: Yes. And actually in Europe, in fact, next month, we've got a working group where we're going to be doing sort of a modified delphi exercise, RAND/UCLA methodology, where what we're trying to do is define the gut. So everybody who does stim, we know the kind of patients that this is going to be helpful for.

But let me just say a few specific things. One is we're treating neuropathic pain. So if you can see somebody with physical manifestations, and it makes sense, that the examination fits with the

Page 170

history; that they've tried reasonable therapies in order to adjust, to help them, and some of them have often helped temporarily; or the side effects have dominated and they've not been able to continue, that's the physical, some kind of neuropathy. Then we talk about the psychology, and it's like patients who've maintained a role have within the family and within work. They've got supporters who help look after them.

So there are actually positive things that we look for as to whether they'll do well with a device. And it certainly seems to clinically bear out. In my unit, we have a dynamic multidisciplinary assessment of patients: psychology, nurse. And the point is our trial to implant ratio is 92 percent compared to in the U.S. where it may be 65 percent, and our explant rate is 6 percent at 4-5 years as opposed to 30 percent at 5 years.

The difference in the U.S. is most SCS is done in private practice I think, that they don't necessarily -- there are differences, and the

Page 171

generalizability of the psychologist is a bit of a tick box and doesn't necessarily alter whether they progress on to SCS and so on. So I think we can be quite clear as to the positive type of patients.

DR. NORTH: If I can supplement what you're saying, continuing the failed back surgery patient archetype, if a patient has a clear history and supporting imaging studies showing that before their operation, which failed, they had a big refragment disk, say at L5 accompanied by a foot drop, and they still have a sensory abnormality when I examine them, and they have pain in the distribution of that nerve, to me that is neuropathic pain in the literal sense that I can say -- surgeons tend to be concrete; that there is something wrong with a nerve.

That's what neuropathic means. Right? It's not just a buzzword you add so as to get reimbursement. So there are candidates that are ideal for clinical practice and study subjects.

DR. FIELDS: I think that this is an incredibly important point in terms of trial design

Page 172

because if you look back over treatments for neuropathic pain, when there's been a clearcut diagnosis, such as diabetic neuropathy or post-herpetic neuralgia, it's been possible to show robust effects, for example, gabapentin and duloxetine. But probably it's the case that most patients who receive spinal cord stimulation, at least in the states, don't have a clearcut neuropathic component to their pain.

DR. KATZ: Greg, you were next, and then Sam. Go ahead. Introduce yourself, please, if you remember your question.

DR. FIORE: And who I am. Greg Fiore from INS and also primarily a drug developer, my background -- ION, apologies.

My question is, building on all that's been said, really, related to the regulatory aspect of evaluating applications, I always enjoy presentations like yours, Nate, and conversations with Bob about all the myriad factors that can impair our ability to demonstrate treatment effect even for treatments that we really know are

Page 173

effective.
Appreciating the health authorities have to wade through all the data that they have, how do you actually become informed, in a specific application, about all the things that might have happened to decrease the likelihood of demonstration of effect? Because it seems like those things keep drug developers and device developers up at night worrying about how to control, but the risk is really borne by the patients because these factors impede drugs and devices from getting onto the market when they really are effective.
DR. TAYLOR: I think I was careful in my presentation because I think what you're saying is are we going to raise the bar so far. So we've got statistical and clinical trial perfection, but no one can do the studies, and the patients don't get the technology. That's the kind of causality link of where we could end up. I think we need to be pragmatic. I do think we need to be pragmatic, but I think the value of this group going forward is

Page 174

being explicit about what the issues are.
Nate and I were talking over coffee that some of these issues are not as explicit with trial design as they could be; so I think at least having consideration of them when people go forward. I'm going to kind of take the FDA rule here that it's a maybe. Well, that's an important issue, but do we have to deal with that in this setting? We'll at least think about it, but do we have to definitely implement that? Well, maybe not.
I think part of this is just a general move towards trying to improve quality rather than acting as a barrier. And I am speaking as a scientist and I'm also speaking as a chief investigator because I design trials as well, and I want these guys on both my right and left-hand side to say yes to those trials. But I don't think anything we're saying here is going to raise the bar so far that we prevent completely. But I think it is a risk that you're saying.
If I may say one last thing, Nate. For instance, one of the things that has come up in

Page 175

your presentation is that we might want to be very canny with what we tell patients before a trial about what they're going to take part in. So going to an ethics committee where we basically don't tell them what the trial is about is a real problem for ethics committees.
Okay. We may help to minimize the placebo effect, Nate, but we may have an ethics committee that will say no, that patient information sheet is not explicit enough for that patient to enter the trial with clear understanding of what the relative tradeoffs between harms and benefits are. So that's a dilemma, but it's a dilemma we need to collectively solve.
DR. KATZ: Rahul?
DR. SINGH: So we are raising the bar. In Europe, the new medical device directive has come into play, and it's focusing on three main areas. Number one, postmarket surveillance -- number one would be premarket clinical evidence relevant for that medical device; and number two, postmarket surveillance. This came to effect because of

Page 176

numerous stakeholders coming into play, the European Union in Brussels, major manufacturers, and competent authorities and designated authorities, which are notified bodies.
As an example, anyone heard of metal-on-metal hips, for example? They were amazing about 10-15 years ago, but it's a shamble. The premarket clinical data was amazing. Postmarket clinical follow-up was a shamble. Things came into play. The medical device alert started coming into play in 2010. All these legal litigation and appeals are happening in Europe and in America.
So we are raising the bar. There's more scrutiny and more stringent work that is being implemented. Obviously due to Brexit, things may be a bit different depending on which member of state gets a better deal, i.e., if UK gets a good deal or not.
Secondly of all, trying to mitigate your risks as a manufacturer and as a clinician, it depends on your outcome measures for your clinical

Page 177

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

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

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

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

Page 178

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

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

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

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

Page 179

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

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

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

DR. SCOTT: Not at this point.

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

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

Page 180

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

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

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

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

Page 181

I see from the trials that we've done and the trials that we're doing at the moment that the way Simon does things is quite different to the way I do them, to the way Barani [ph] does them. Yet no study has taken account of that potential for clustering of effect.

If there is one, what impact would it have on the outcomes of these studies?

DR. TAYLOR: So it's a great question, Sam. We can take clustering into effect I think in a couple of ways. One is the way that I suggested, which is we actually design it into the study at the outset. In other words, we may allocate patients to receive the therapy, not on an individual basis, but by people like you, by implanter, or by hospital. And as I said, we just don't see those in this space.

Without being too simplistic, they would help us very much with the question that you've said. So in other words, the success of the therapy is the interaction between the therapy, the clinician, and the setting therein. That's

Page 182

effectively I think what you're saying, and I think I would agree with that.

Cluster designs will help us look at that in terms of allocation, but we don't ignore clustering, even in individual designs. There's at least one trial that Rick and I are currently involved in where we have multiple sites, and there was heterogeneity treatment effect across those sites.

As a statistical advisor in that trial, one of the things that we have done is to adjust the analysis for site; for instance in sensitivity analysis. I'm seeing Howard nodding his head. Our statistical things we can do and probably should be doing more, Sam, to take account of that.

So if we have a multicenter trial of SCS, I think we should be almost defaulting in our protocol design to, A, think about stratifying by site, which we would normally do; and then B, predefining that we would maybe use a random effects model to take account of that potential clustering just to check that we're not being

Page 183

underly conservative in our statistical estimates. So that's helpful.

DR. ELDABE: Thank you.

DR. KATZ: Yes? Please introduce yourself, Eric.

DR. BUCHSER: I'm Eric Buchser from Morges, Switzerland. I'm a pain clinician there. I have a question about the efficacy considering from the standpoint of the FDA and the MHRA.

How important is the efficacy of a new device system in getting the CE labeling?

DR. SINGH: Your question is --

DR. BUCHSER: My understanding is that FDA is not concerned about efficacy; basically, concerned about safety, right? Now in Europe, as far as I understand, efficacy is getting a big issue as well. So if I have a new device, do I have to prove that it's more efficacious than the other one or at least equally effective? How important is efficacy in your evaluation?

DR. SINGH: Efficacy is important, but our main concern, motto, is patient safety. So if

Page 184

you're bringing a new device in that you want to trial on humans, it's needs to be based on risk-benefit ratio. If it's a new device, truly novel, and if it is high risk -- for example, spinal cord stimulator -- we will probably ask that you have low numbers in your study to be recruited. If that's satisfactory in terms of low numbers of serious adverse events or major adverse events, then you can progress to stage 2 or stage 3 and recruiting more patients.

So the question is, is efficacy important? From the MHRA point of view, no. It's patient safety.

DR. BUCHSER: CE labeling.

DR. SINGH: For CE, it's patient safety, essentially. Your product doesn't have to be more efficacious, more superior compared to other similar marked CE devices. If your device is very similar or if it's not novel, if you just want to get into the market to commercialize, you can go through another route, through equivalence.

So you may not even need to do trials in

Page 185

human beings if all the standards which are required for equivalence are met, all those standards based on statistics, historical data, sterilization, toxicology, biocompatibility, and clinical trials, et cetera. So summary, efficacy is not first; it's patient's safety.

DR. SCOTT: From an FDA perspective, yes, efficacy is very important in our decision-making process. In terms of the overall answer to your question, yes. From a purely regulatory perspective, we usually use the term "safety and effectiveness," but that is a key point of our decision-making.

I think the thing to keep in mind, though, in terms of level of evidence for spinal cord stimulator, is it a new device? Is it a new device area? Are you using it for a new indication? Are you modifying the device? Those are some of the things that we would take into consideration as we interact with the sponsor in terms of level of evidence necessary for demonstrating the efficacy of that particular device, for a particular

Page 186

indication.

DR. KATZ: Rick?

DR. NORTH: I have a question about enrichment of study populations, something we haven't talked about yet. Once we get past patient selection and have identified the clinically appropriate group to subject to a study, there are additional things that we can do.

Precision medicine is a buzzword nowadays. I'm just waiting to hear of a genotype being identified to predict which patients are good stimulator candidates. And I assume that will be straightforward from the labeling standpoint once that happens.

(Laughter.)

DR. NORTH: But there's something we're doing now to enrich study populations, and that is we do a stimulation trial first. The study I referred to earlier, patients had a trial of conventional stimulation, and only those who passed it and were implanted were then randomized to conventional versus stim du jour. And I wonder to

Page 187

what extent there might be regulatory skepticism about enriching the study population with a trial of the therapy.

DR. SCOTT: I think, again, we rely on the sponsor to provide us what their protocol is going to be. I don't know if it's safe to say we have seen that study design before. But again, we rely on the sponsor to provide their justification for their particular trial design that they are seeking at them. And then from that point, we will, again, point out to them what the concerns may be and what the limitations may be of that particular design.

Anything else you want to add, Carlos?

DR. PENA: I think that's good. There may also be labeling considerations that we need about the product.

DR. KATZ: Salim?

DR. HAYEK: So it seems that we have progressed gradually from anecdotal reports to parasthesia-based studies, and now we have the opportunity of having parasthesia-free devices. But the elephant in the room is, is it time to have

Page 188

a level of zero study similar to what Nate discussed? Can we prove that spinal cord stimulation works for any indication, neuropathic, nociceptive? And if so, when can we do such a study, and does the FDA and the MHRA require such a study for efficacy?

DR. PENA: We would not require that. That is a decision we would look to many other stakeholders to identify if a zero study needs to be done for a given product or a class of products. We would not mandate something like that. That's just not our role. We would contribute to asking the questions about how that study, maybe if it comes to us, could be designed or points to consider, but I don't think we would mandate something.

DR. NORTH: Would even it even need to come to you? That is something that clinicians and payers and all of us want to know.

DR. HAYEK: But for us as a scientific body, do we need to make that recommendation?

DR. PENA: If you're doing a study on label,

Page 189

it begs the question of whether a study is needed. If it's on label for already an approved use -- if it's for a new use, then we may have some questions. But if it's for an approved use, you could use the presubmission process to get some free advice about the trial design, but it would not necessarily be an IDE study for an approved use on label.

DR. THOMSON: Can I just say something there? I think, Salim, really what you're saying is what will it take for how it feels to refer a patient for spinal cord stimulation. Essentially, that's really why he's there, what he's saying, is that I don't recognize the patients that you're treating, and I'm not completely convinced by the clinical evidence to date. That's quite different from the regulator, is something safe and efficacious?

DR. PENA: One additional point, this may not necessarily be an FDA question but more of a CMS question, at least in the U.S., is this procedure necessary and reasonable? That could be

Page 190

a question for CMS, or maybe even our NIH colleagues would have some play in this. But I'm not sure it's a regulatory question if it's for approved uses.

DR. KATZ: Since we're on the topic of who is interested in what kind of evidence, I know that, Rod, you are immersed in the payer community, and Brian sitting in the back will be giving a talk specifically on this issue.

Do either of you want to make a quick comment right now about the payer perspective, whether this level zero type study that we're talking about is of any interest to that constituency?

DR. KOPELL: Hi. Brian Kopell. I think the way you have asked the question sort of answers itself. The payers more and more are beginning to push back, despite the fact that they are achieving FDA approval in the United States. The bottom line is that they don't see how these new technologies are essentially a cost benefit additive to the healthcare system. They are simply not going to

Page 191

pay for it. And you could see this across not just the pain stimulation but in various forms of neurostimulation devices that have basically faced this.

So the answer is, at some point, if companies do not actually include this in their pivotal trial design, they're not going to get it paid for, and we're going to end up in a situation where the payers are going to say we want that zero study, basically.

DR. KATZ: Rod, did you want to add anything?

DR. SINGH: Just so I don't give the wrong answer, when you say zero level of evidence, what do you mean? I'm discussing it with Rod as well.

DR. KATZ: That term seemed to have been invented this morning during my presentation.

(Laughter.)

DR. SINGH: Maybe it was an American --

DR. KATZ: I don't want to say it's a standard term, or at least it's only been standard for about 45 minutes if it is a standard. We were

Page 192

just talking about how randomized-controlled trials are not enough because there can be all sorts of biases that can create the appearance of efficacy, where fact there is no efficacy.

So I just threw out the term "level zero" as sort of an even higher part of the evidence hierarchy, where not only is a trial randomized, but you've at least attempted to control other major sources of bias that could create a false positive clinical trial. So that's what we're talking about with that term.

DR. SINGH: That's a good level.

So it's based on what the indication for use for medical devices. If it's a high-level risk device, we require more risk assessment of the pros and cons of the device. Necessarily, if it's a high-level of risk and completely novel, we wouldn't ask for a randomized-controlled trial, and I don't think the sponsors would take the time and effort to doing an RCT. They would probably go for a simple, unblinded, 20-K series to see if it doesn't kill 10 of those patients, for example.

Page 193

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

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

DR. TAYLOR: Could I comment on this one?

Brian, hello. Thank you for comments, and I agree completely. I think the observation I would make -- and this is I think particularly a European observation, on the money where I think you are, Brian, is that often when we come to make decisions as payers, in other words -- because basically,

Page 194

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

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

(Laughter.)

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

Sorry. It's slightly contentious. I've slightly parodied that, but that is often a dilemma for us. And it doesn't happen in the drug space because drug regulators don't allow it. If you don't have two confirmatory RCTs, you're dead in the water. With medical devices, you can get away with a much lower level of regulatory evidence, and then that comes back and bites us.

Page 195

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

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

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

Page 196

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

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

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

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

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

Page 197

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

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

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

Page 198

stimulation, basically, doing designs similar to drug studies.

DR. KATZ: Rod, did you have any further comments on this little debate about whether the level of evidence for drugs is similar to devices?

DR. TAYLOR: No, but I think it is an important question, but I think Carlos hit it right on the head in his final comment, which is that there are increasing models in the U.S. but also in Europe for what we're calling joint scientific advice. In other words, where we researchers, clinicians, and industry -- we're all in this together -- meet with regulators and payers in the same room at the same time to try and design a trial that may address both those issues.

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

Page 199

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

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

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

Rahul, and then I'll go to Simon.

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

Page 200

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

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

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

Page 201

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

DR. KATZ: Simon?

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

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

Page 202

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

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

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

Page 203

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

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

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

Page 204

to gaming study designs.

Is that a good way to put it?

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

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

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

Page 205

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

Page 206

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

Page 207

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

Page 208

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

Page 209

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

Page 210

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

Page 211

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

Page 212

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

Page 213

anyone on the panel have any final comments before we break for lunch? Then you can be the bad guy that held up lunch.

DR. MARKMAN: Biasing the audience.

DR. KATZ: Yes, exactly.

Well, with that, I'd like to thank our panel for their wonderful presentations and for their participation.

(Applause.)

DR. KATZ: Bob or Dennis, are there any housekeeping announcements with respect to lunch? Where is lunch?

If you want to know where lunch is, ask Valorie right outside. See you guys after the break.

(Whereupon, at 12:32 p.m., a lunch recess was taken.)

Page 214

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

(1:37 p.m.)

DR. KATZ: Good afternoon. I'm pleased to introduce Ewan McNicol. Many of you probably know him because of all of his work in meta-analyses and systematic reviews over the years, and he'll be presenting a systematic review of methodological characteristics of spinal cord stimulation RCTs.

How was that? Close?

DR. McNICOL: Sounds good.

DR. KATZ: Okay. Thanks, Ewan.

Presentation - Ewan McNicol

DR. McNICOL: Well, thanks, Nate.

Hi, everybody. Thanks for the introduction. As you saw earlier this morning, the vast majority of the ACTTION meetings to date have been based on drug interventions. So if you were being cynical at all, you might wonder why or you might question the wisdom of Bob in asking four pharmacists to do a systematic review of spinal cord stimulation. I'm not one of those cynics. I think it allowed us to look at it with a completely unbiased eye and no

Page 215

preconceived ideas -- literally no preconceived ideas -- of what spinal cord stimulation would be.

So with that said, and just to reiterate what Nate said, our background, we're clinical pharmacists, but we also have conducted evidence-based research, systematic reviews of pharmacological interventions, but we're looking more at the results of those studies rather than this. And just to reiterate what Dennis said this morning, this is about methodology, not about the results themselves; so just to make that clear.

Really briefly, the objectives, I'll very quickly describe the review process. This is a post-prandial audience, so I'll keep it short. The meat of my talk is going to be to report on the findings of the analysis itself. And then just for the last couple of slides, I'll look at some gaps or deficiencies in reporting and methodology. And then lastly, some things that we might want to talk about on the panel discussion afterwards.

These are our inclusion criteria, not the inclusion criteria for the studies themselves, but

Page 216

what we set out to look at. It had to be a randomized-controlled trial. It could be spinal cord stimulation for pain of any nature. Example comparatives could basically be anything as long as there was a control group. We looked at any pain outcome be it primary or secondary.

I'm not actually aware of any spinal cord stimulation studies in children, but we restricted our review to adults or adolescence. And given what we talked about earlier with conventional SCS being parasthesia based, we felt that we had to include unblinded studies with no main on-study duration, and we allowed any sample size.

Now, I mentioned earlier that we did Cochrane reviews, and we continue to do Cochrane reviews. And for those reviews, we have a stipulation that each arm must have at least 10 patients in it or 10 participants. Just to keep this as broad as possible, we allowed any size of the study whatsoever.

I'm not expecting you to retain this. Just really quickly, our search strategy involved a

Page 217

number of terms for spinal cord stimulation, a number of terms for various disease states or pain, and we combined that with a filter for randomized-controlled trials. We searched four databases. We looked at Medline, Central, Embase, and WikiStim, and we also looked at the reference sections of any included studies we did have way. We came up with 1227 non-duplicate citations.

This might look like an incredible amount, but this is actually quite typical when you use a sensitive search strategy, to have about 95 percent citations that are completely useless or not valid.

From these 1227, we've pulled 108 full text just to delve farther into whether the studies actually met our inclusion criteria or not. From these 119, we had 32 articles, as Rod spoke about earlier, that actually met our criteria; 64 of them were excluded. Then if you look over to the side here, we have some additional ones here with 23 others, with 16 angina studies that we'll come back to, and 7 extension studies. And I'll talk about both of these towards the end of the talk.

Page 218

This just basically shows you the same thing in tabular form. But then on the bottom here, you'll see the reason why we excluded some of the studies. Abstract protocols only, there's just not enough data for us to extract. Known RCTs, cost effectiveness only. Rod will be looking into that, and Brian as well. We'll be talking about that later. So unless it was part of a larger clinical study, we left those out. No pain outcome.

Duplicate manuscripts. This is kind of naughty. You're not supposed to do this anymore. But this was stuff where they presented exactly the same results but in a different journal or slightly differently, but we knew it was the same population. So that was 12 we got rid of.

I'm not going to go into these in detail because I will get into them in detail when I show you the findings. But we were looking at 5 or 6 basic features. We're looking at the study features themselves, the inclusion criteria of the studies, and what sort of patients they looked at. We spent a lot of time in study design. We looked

Page 219

at the statistical analysis, and then how they reported results. So again, not the results themselves but how did they present them.

We set up a form with Jennifer's help. This is the first time we've done a methodological review rather than a results review. We had about 60 questions in there with about 110 possible answer options. And what we found compared to when we do Cochrane reviews, the system was the same. We do every extraction and duplicate independently. So two people will look at the same manuscript, and then you compare your results just to look for mistakes, or disagreements, or whatever. For a Cochrane review, we usually have about two or three disagreements. For our data extraction for this, we averaged 18 disagreements per study. And there was actually one study with 36 disagreements between the two reviewers.

We're not exactly sure what the reasons for this were. It could just be the nature of the review. When you're doing a methodological review and you're asking more questions, there's more

Page 220

opportunity for things to go wrong, I guess. It could be deficiencies in our coding manual. We trialed our coding manual and our extraction form on about half a dozen studies, but even with that, we were still finding disagreements 20 or 25 studies into our extraction series.

Lack of reviewer knowledge, definite possibility.

(Laughter.)

DR. McNICOL: We were learning as we're going along. But I think one of the major things was weaknesses in reporting. In part, it was because when you're developing a manuscript, you have a small space to actually put your findings in. So some of this stuff could be the data, but they just didn't tell us about it, or they said it in such a vague manner that we couldn't really work out what they were trying to tell us.

So common disagreements. What was the role of the sponsor? Six of the studies actually didn't even mention if there was a sponsor, and then those that did, they tended to tell us what the sponsor

Page 221

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

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

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

Page 222

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

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

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

(Laughter.)

DR. McNICOL: It has potential, but it's quite messy.

(Laughter.)

DR. McNICOL: This is the meat of my talk. This is the study findings themselves. We extracted 32 studies, and this is what we find. There's about a 50/50 split in sites. This surprised us. Only about a third of the sites were

Page 223

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

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

Page 224

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

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

Page 225

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

Page 226

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

Page 227

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

Page 228

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

Page 229

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

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

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

Page 230

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

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

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

Finally amongst design characteristics,

Page 231

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

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

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

Page 232

again, adverse events are poorly reported across studies.

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

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

Page 233

study, where they were just looking at a select number of patients.

So we really struggled with this; 41 percent of the studies really didn't define clinical significance in any way, and then there was about a 50/50 split in those that did define it. So it was either a point reduction; for example a 2-point reduction on an NRS, or it was a present change, number of patients with a 30 percent pain relief, 50 percent pain relief, et cetera.

The population analysis itself, 13 of the studies used an intention-to-treat analysis or both intention to treat and per protocol, and 18 studies only did a per-protocol analysis, so patients had to complete the study to be involved in the analysis. And of those that did use an intention-to-treat analysis, only 5 of those specified how they accounted for missing data. So if patients dropped out of the study, did they use last observation carried forward, baseline observation carried forward, et cetera.

Moving on to the results, participant

Page 234

demographics, a mean number of 50 participants in the primary analysis, so about 25 per arm; mean age of 55; 40 percent were female, and around 60 percent had no information stated about similarity between groups or it was unclear.

This is somewhat skewed. This is, again, a question that we might set up differently if we did it again, and this question didn't account for crossover studies. And in crossover studies, almost by definition, the patients match up perfectly unless their condition changes over time. So really, actually, it was probably somewhat better than this amongst the parallel studies. I think more often than not, they either stated the groups were similar at baseline, or we were able to look at table 1, and we were able to ascertain that the groups were similar.

We haven't really gotten to how the primary and secondary outcomes were reported yet. This has gotten to a really messy part of the analysis. Just to boil it down, it was a really mixed bag. It was number of responders; mean change within

Page 235

groups; mean difference within patients. It could be anyone. There were a number of things, in part, dictated by what the outcome was itself; so to follow, but it was a mixed bag.

Again, this is a somewhat busy slide, but what it really just illustrates is the fact that amongst all the reported adverse events, very few of them were actually specified in the methods section. They reported the results, but they never told us that we're actually looking for them.

That was the analysis itself; again, it's somewhat preliminary. We're going to do a little bit more analysis when we look back at some of the disagreements. We'll look more closely at what the control interventions were, et cetera, but it gives you an idea of where we're at with it.

Just to speak to some of the additional stuff, extension studies, we identified 7 extensions related to randomized- controlled trials that met our inclusion criteria, and they assessed outcomes from 6 months up to 5 years. What they did is they assessed secondary outcomes that

Page 236

weren't assessed in the primary findings, or they looked at secondary endpoints of primary outcomes. So if the primary outcome had been pain intensity at 3 months, they then looked at that at 6 months, or a year, or 2 years, or whatever.

We will add these to the final analysis, but it would be good to get your thoughts on how exactly we incorporate those in. Do we just lump all into the same study, or do we call it a different study, et cetera?

I'll finish off with some observations and maybe some things that we might want to talk about when we have our panel discussion. Again, we were not familiar with spinal cord stimulation or the literature, so we might have set up our questions a little bit differently if we'd known that, but we did road test it.

I think you all know this already, but the timeline of studies, the earlier studies were spinal cord stimulation versus usual care. Early 2000s, it started looking at one method of spinal cord stimulation versus another, adjusting various

Page 237

aspects of it. And then the newer studies are looking at burst or high-frequency SCS versus conventional, or other burst or high-frequency settings.

As I mentioned earlier, there are technical versus clinical studies, and I don't know if we should really throw these altogether in that they really are different ways in which they're set up. The technical studies as well tend to have fewer patients in them.

This is something we weren't sure about. Conventional spinal cord stimulation may not be homogenous. So are the comparisons of high-frequency bursts with conventional fair comparisons, are we comparing an ultra high def TV with a high def TV or a black and white TV? We don't know about spinal cord or conventional SCS to be able to make that assumption, but you guys know better than us.

There were generally small sample sizes and short durations for chronic diseases. Andrew Murer [ph] with the Kofron [ph] collaboration, when

Page 238

we're doing drug studies, we say that a study has a high risk of bias, a high risk of study sample bias, if each arm has less than 200 participants in it. That's a really high bar. None of these studies get anywhere close to that.

Then lastly, as I mentioned, the definition of what was clinically meaningful was kind of all over the place with us, and we had a hard time with it. It was both within patient and between groups, and I don't know if this is something that should be clarified going forward.

So really quickly, just some points that we might want to talk about in panel. Should we include on angina studies? I think so, but they're a little bit different. And should we analyze them differently if we do include them? It's kind of an acute exacerbation of a chronic disease as opposed to where pain is the disease itself.

Should we include the DRG studies? We don't know enough, again, about SCS, know if we should have done that. I will say of the two studies that we included, the data of SCS arms in the

Page 239

[indiscernible], so they would have been included regardless. Should we look at location versus diagnosis? Which is more important?

We touched on this earlier. I promised I'd put this in independently. Should there be different outcomes for spinal cord stimulation studies versus pharmacotherapy studies?

What is a reasonable study sample size? Clearly not 200 per arm; that's not going to happen. So what's more pragmatic? Given the cost of a unit and the cost of the patient and undergoing surgery, is it really reasonable to expect large study samples?

What's a reasonable study duration? Is it chronic disease? Is 6 months long enough? And can these be offset by the extension studies I spoke about?

Then lastly, should it be crossover studies or parallel studies? In its most basic form, crossover studies need less patients; parallel studies need less time. Obviously, there's a whole lot more to it than that, but I just thought it was

Page 240

something that maybe we could talk about when we get to the panel.

So I think I brought that in about a minute under time. Just a couple of acknowledgements, thanks to our core reviewers who are not here today, and also thank you to Jennifer who is here today, and to Shannon, for helping us with our initial questionnaire and also with how we were setting up our slides for this talk today. So thank you all, and thanks for listening.

(Applause.)

DR. KATZ: Thanks very much, Ewan. That's a great list of questions. I may actually put it up during the discussion to help frame our discussion. You're doing my job for me.

With that, we'll do the same thing that we did this morning. We'll keep the lectures going, write down your questions, and during the discussion, we will have an opportunity to ask all of the speakers their questions.

So with that, I'd like to introduce my friend and colleague, and former co-worker, John

Page 241

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

Presentation - John Markman

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

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

Page 242

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

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

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

Page 243

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

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

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

(Video played.)

DR. MARKMAN: You had a stimulator put into your low back; is that right?

Page 244

PATIENT: Yes.

DR. MARKMAN: Why was that done?

PATIENT: I was having pain down the right side of my hip and into my foot.

DR. MARKMAN: And has it helped?

PATIENT: Yes.

DR. MARKMAN: And how long has it been in for?

PATIENT: Probably a little over a year.

DR. MARKMAN: And you had had back surgery before; is that right?

PATIENT: Multiple times.

DR. MARKMAN: How many had you had?

PATIENT: In total, I've had 5

DR. MARKMAN: Five. And how much has this stimulator reduced your pain intensity in the low back and the leg, on the right side, over the past year?

PATIENT: Probably 75 to 80 percent.

DR. MARKMAN: And what's going on now?

(Video ends.)

DR. MARKMAN: This is not a homage to Andy

Page 245

Warhol. These are three different video clips. This patient is a patient who's obviously had multiple back surgeries and has what many people can think as the classic diagnosis for neuropathic pain. He's got numbness and spontaneous pain, leg worse than back. And this might be sort of that archetypal patient, is the word that was used earlier.

He endorses relief. I have no idea whether his relief is on target or off target. I'm the person who put it in. I'm the person who's asking the question. We learned from Dr. Katz this morning that introduces a bit of bias. So who knows whether he's actually getting relief or not?

The reason I saw him on Monday is because he got re-injured at work, and in order for a patient who gets injured at work in the United States, to open a new claim and to get care in our system, you have to see the doctor again. So that's how I got to see him on Monday.

(Video played.)

PATIENT: Strained my back at work.

Page 246

DR. MARKMAN: And what happened? What were you doing?

PATIENT: Taking leg shackles off an inmate.

DR. MARKMAN: And when did that happen?

PATIENT: At work in the morning.

DR. MARKMAN: What day?

PATIENT: Friday the 9th.

DR. MARKMAN: The 9th of?

PATIENT: November.

DR. MARKMAN: November. And does your stimulator help for the new pain in your back?

PATIENT: No, it doesn't.

DR. MARKMAN: Why not?

PATIENT: I'm not sure. I just know it doesn't work. I had it on. I tried it when I got home from work, and it doesn't help it at all.

DR. MARKMAN: Does it still help for your other pain?

PATIENT: Yes.

DR. MARKMAN: And how would you describe the difference between those two pains?

PATIENT: The leg pain is more like a

Page 247

numbness and tingling type thing that stays down towards the lower part of my leg. This is more of a stabbing pain in my back and my hip.

DR. MARKMAN: And is it severe right now?

PATIENT: Yes.

DR. MARKMAN: Have you ever had this before?

PATIENT: I have.

(Video ends.)

DR. MARKMAN: So he's telling you he has two distinct paints. Right? He has this chronic pain, this is chronic pattern, anatomic pattern, which is different from what he is currently experiencing, this acute on chronic exacerbation. He's making this distinction. And he's making the observation that his pain is relieved by the stimulation system for the chronic pattern but not for this acute one, this acute thing while he was bending over putting the shackles on the prisoner. He works in a very large penal system we have in upstate New York.

So he says this is a different kind of pain, and it's not responsive. If you ever have these archetypal notions, well, this is acute,

Page 248

nociceptive low back pain. It's low back strain. It's mild fascial in origin. That has a different underlying pathophysiologic mechanism than the nerve injury pain with associated sensory deficit, reflex change, motor changes that you would expect in someone who's had 5 back surgeries who's been exposed to traction and cautery, and probably an initial insult with root compression at some level.

So he's got these two different syndromes in the same patient. This is part of life. Most patients in a pain clinic have more than one pain problem, as you know. It makes it especially complex to do clinical trials. He has these kind of very nice dichotomist syndromes, both low back pain syndromes. One's acute. One is stimulation responsive; one isn't. One's nociceptive; one's neuropathic. And this is sort of the archetypal discussion I think maybe a little bit beneath some of the dialogue you heard earlier.

(Video played.)

DR. MARKMAN: Had your pain been well controlled until this episode on the 9th?

Page 249

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

Page 250

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

Page 251

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

Page 252

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

Page 253

different conditions, which help you exclude syndromes which could look like diabetic peripheral neuropathy but aren't.

Then you'd want to use the all generic assortment of measures, which are used in all the other trials: the pain interference scores; probably some measure of anxiety; the PIGIC [ph], as we talked about earlier; sleep; quality of life; and then probably some pain quality component as well.

Again, we have to think about together whether it makes sense to include neuropathy as a large bucket: diabetic peripheral neuropathy; HIV neuropathy; small fiber neuropathy or punch biopsy; chemotherapy induced neuropathy; whether we want to lump all those folks together, introduce that heterogeneity and degrade our assay sensitivity, or do you want to go for some homogenized population with just diabetes and hope that that's on target neuropathic for what we're thinking about for the way this problem works. And that's one of the things hash out before we leave on Friday.

Page 254

So I'm going to just leave that where it is and just come back to these at the end with some general thoughts. But I'm now going to turn to focus for the next 15 minutes on the low back pain issue because I do think that this is where the heart of the challenges come in.

These are both patients. These are the imaging studies of two patients recently seen who both have axial predominant nociceptive pain at some level, but also have radicular or so-called neuropathic pain, leg worse than back, numbness, weakness, sensory deficits, spontaneous pain, which keeps them up at night.

As you can obviously see from the patient on the right, obviously this is a patient who has an unstable fusion construct who's got listhesis. And they have a lot of axial low back pain. They have a lot of nociceptive pain, not only because they've got this broken screw mostly, but really because you have all those other structures -- muscle, ligament, tendon, bone -- which are all being moved as that patient places mechanical force over that

Page 255

unstable construct.

That patient has a lot of axial low back pain, but in the process of having that, that patient's nerve root gets entrapped as it goes down their leg, and they also can have some chronic burning, numbness, tingling, reflex change in that leg as well. But that's not a patient you want in your trial. They've got these two different syndromes. They have neuropathic pain, sure, but they've got all this other mechanical, nociceptive pain from the instability of the fusion construct that you don't want to see in there.

In this patient, obviously, is a classic post-lumbar fusion patient also, but this patient has this little -- you can see this little waste right here of narrowing, which is really dramatic on other views. But it gives you a sense of what's called adjacent segment disease, and this is a patient who's going to have evoked pain with standing and walking, but no pain when they're lying flat, no pain at rest.

This is a patient with the classic adjacent

Page 256

segment story after many years of having a fusion, who has neurogenic claudication. That's an evoked pain syndrome. Unless you prespecified it, as Dr. Eldabe talked about they do in his clinic and said we're only interested in your neuropathic pain when you're upright and walking, unless you really did the careful work to do that up front, you probably wouldn't want this patient in your trial either, because it's such a different phenomenology clinically than the other patients.

So there are two major gaps in understanding as we heard. In the first talk, we heard about the second gap from Dr. North, the idea that we really still have a lot of uncertainty about the different mechanisms of how neuromodulation works, and it's only gotten more complex as we've introduced different stimulation paradigms. And then there's another question, which I'm trying to noodle around right now, which is who has neuropathic pain, and is it the right kind of neuropathic pain to respond to neuromodulation?

So we've got these two gaps. And again, Dr.

Page 257

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

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

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

Page 258

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

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

Page 259

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

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

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

Page 260

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

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

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

Page 261

it keeps you up more at night, and you can do less, then it's more likely to be neuropathic. And the worst it is, the more likely it is to be neuropathic.

As you can see, those orange bars are growing for the neuropathic pain as the pain gets worse and worse, and they did this in three different cohorts: worst pain, more neuropathic. That's basically the take-home.

Now they found almost 50 percent in some cohorts have this type of worst pain being more neuropathic. There are other investigators from Europe who put that number at 4 percent. So there's an enormous amount of professional uncertainty about who has neuropathic low back pain, 4 percent versus 50 percent; different methodologies.

Now obviously, they were laying the groundwork for a positive study of this drug in neuropathic low back pain, which never materialized. Ralph Barone's negative study in 2011, published in Pain; more recently this

Page 262

negative study in New England Journal of Medicine.

So the idea was they were going to create this playing field with this pain detect tool to identify patients with neuropathic low back pain, and we were going to have this drug which solved the problem. But unfortunately, the pain detect tool doesn't discriminate, as we're about to learn here. This is the New England Journal study showing that you couldn't see any difference on the pain detect tool as a predictor of outcome or anything else meaningful in these patients who didn't respond to pregabalin.

These tools have never really panned out, but they were supposed to be a heuristic that primary care physicians and other folks could use to decide who has neuropathic low back pain. It's just not that simple. It's a hard issue.

This is our own little tiny study. We screened 150 patients, and we looked at the tools that are commonly used to characterize the phenotypes or the clinical presentations of neuropathic pain in post-surgery, post-laminectomy

Page 263

pain syndromes. These are patients who had prior surgery, and we said we're going to take 158 of them, and we're going to winnow them down, and get the ones who we think have neuropathic pain. And then we're going to use the DN4, which is a common tool used to characterize like the pain detect. And we're going to use the LANSS, and we're going to decide whether these tools can help us pick the right patients for stimulation.

This of course was a failure. What we found was unlike other neuropathic pain syndromes, the neuropathic component of failed back surgery syndrome is less reliably identified by the LANSS and the DN4 than it turns out to be in post-herpetic neuralgia.

Nadine Attal and her group found a similar thing, and they were a little more eloquent in their conclusions, but basically said neuropathic pain is not restricted to a typical radiculopathy. So there were patients with axial syndromes who had neuropathic pain using the DN4 in this series, basically.

Page 264

So it's not so easy to pick out who has neuropathic pain in these syndromes. This is one of the challenges. So how are we going to solve this is really the question here. What I would argue for is using some of the key clinical symptom features, which you heard articulated earlier this morning in the debate during the discussion session. The reason why is because it makes enrollment efficient.

There are so many of these patients, and it does lend itself, in my mind, to some broader generalizability about post-traumatic neuropathic pain syndromes. It's also biologically plausible that the diverse sets of neuropathic syndromes might be stimulation responsive. So just because it was a traction on a nerve root in one case, and cautery in another, or the original disk causive [ph] injury to the nerve root in another case.

It doesn't so much matter. It matters a little bit more in the cases that Dr. North pointed out when the patient was operated on low back pain

Page 265

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

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

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

Page 266

just tried to tell you what some of it's about. Some of the uncertainty is about who has neuropathic pain among these patients. We just don't know. We're just not good at picking it. And what more perfect illustration than this paper?

This is a study of about 21,000 spinal cord stimulation trials across 9 years in the United States, and the trial to perm rate is 41.4 percent, which is well, well below the literature when you look at the trial to implant rate in clinical trials, which is in the 60's, 70's, as high as 93 percent.

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

Page 267

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

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

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

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

Page 268

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

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

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

Page 269

What would be the necessary cutoff for a reduction in analgesic medication than someone who's on a stable baseline dose? And what would be the tolerability issues within therapy, whether they liked parasthesias or didn't, or whether they knew how to use it, or used it a certain amount of time during the trial or didn't?

Many of us are already doing this in practice. This is the standard, right now, tonic SCS trial period, 3 to 7 days. You get a diary. You talk about how your pain was and what it was like. But many of us are really experimenting. Now that we have all these hard choices to make, it's like going to a sneaker store and having to pick about a hundred different types of running shoes.

It's hard as a doctor to pick which kind of stimulation system you're going to recommend. We have all these competing claims: burst affects your mood; high frequencies in this special G-spot for pain intensity with wide dynamic neurons in the spinal cord. Tonic stimulation is you can only get

Page 270

relief if you have parasthesia coverage. These are not mutually agreeable terms. You cannot reconcile these as someone who's making the decision for patients and say, well, I know which one of these is right. You can't, so then how do you do it?

This is what we tried to do. Listen to this patient.

(Video played.)

DR. MARKMAN: Is there any change in the amount of relief that you have between the two systems? Which one gave you more relief?

PATIENT: Yes, the first one was better.

DR. MARKMAN: The first one gave you more relief.

PATIENT: Yes, but I think -- and it's because I had more adjustability and flexibility of the unit versus the second.

DR. MARKMAN: Okay. But the amount of reduction and pain intensity in your back and legs was more dramatic with the first than the second?

PATIENT: Yes.

DR. MARKMAN: How much more? How much of a

Page 271

difference did you detect?

PATIENT: At least 10, 10-50 percent minimal.

DR. MARKMAN:

PATIENT: So it was enough difference.

DR. MARKMAN: And you said you -- I guess I'm trying to understand. Did you want to try this one out for longer because you're uncertain about whether it's giving you a relief, and you feel like if you had more time to adjust to it, you'd have a better assessment? Or no? Do you feel like you can tell which system works better for you among the two?

PATIENT: I just want the permanent one, and right away.

(Patient laughs.)

DR. MARKMAN: Because it's enough relief that it matters to you.

DR. HAYEK: It made a big difference. I was going -- from work, I'm having issues with work. Again, it's affected my work drastically now, and I'm afraid I'm going to lose too much time and/or

Page 272

lose my job.

DR. MARKMAN: What is your work?

PATIENT: I'm a construction project manager.

(Video ends.)

DR. MARKMAN: I'm not telling you which device he had. I'm just telling you one thing. He can pick. He has an opinion, and that's the most important things. Patients can choose. They can identify a preference. And that was the thing I didn't know. When I first started doing this and doing these duplex trials with sham periods and things, I didn't know whether patients could identify a preference. I didn't know if they could pick one running shoe over another. It turns out they can.

I gave you somewhat a different aspect of the penal system. This is a U.S. attorney who recently had a stimulation trial.

(Video played.)

DR. MARKMAN: Do you feel like you could make a decision today or no?

Page 273

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

Page 274

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

Page 275

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

Page 276

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

Page 277

said, to prespecify when that 5 is. There are many patients with low back pain syndromes who do not have pain until they stand up and walk, or patients who only have pain when they're sitting in a chair, or patients whose pain is moderate intensity when they're in a chair but mild when they're not.

I think that if you don't understand that this is often a mechanical syndrome with an entrapment or traction component, and you don't talk about that up front, you're just going to get a lot of patients who are in your trial that shouldn't be in there. It's going to add a lot of measurement error, as Dr. Katz talked about, and you're going to get a lot of negative results.

Pain duration of one year I think is reasonable. To me, more important than pain duration is stability of the underlying pain pattern. You want to make sure that that pain pattern is not changing. I think this is one of the hardest parts of doing a complex regional pain study population because the reality is, those patients who've all had their knee scoped and have

Page 278

neuropathic pain, or had a distal radial fracture, who look like CRPS 3 weeks after their surgery, look less like that 6 months after surgery, and look a lot less like that one year after surgery.

Some of them will get worse and will always have the syndrome, but many of them look like CRPS at month 6 but not at month 14. So I think that the challenge in CRPS is even though they might have severe neuropathic pain and you think they have CRPS by the Budapest criteria, it's not a particularly stable clinical presentation, and you run the risk of putting those patients in different arms, and that will complicate, and you'll get some asymmetry there. So I think you need one year also because patients need sufficient time to try other therapies.

In terms of psychosocial vulnerabilities, obviously these are key exclusion criteria right now, but also obviously things like competence and the ability to interact with this technology, which is not always insignificant, to charge it, to reset it, to reprogram it, and to comment on that

Page 279

reprogramming.

The reality here and the huge lost opportunity is that in the United States, in order to get this device put in you, you have to go through a pain psychology evaluation. So these patients are filling out scales and paperwork, and we just are missing it, because this could be done. And this is a requirement. You can't get a device virtually in any part of the country unless you're going to pay for it yourself without a pain psychology evaluation. So this robust information could be there in a systematic way. We just have to avail ourselves of it.

Again, I have a strong feeling that if you're going to make a claim about your device affecting the Paleo spinal thalamic tract, or the limbic pathways as they relate to pain intensity, then you've got to report on baseline anxiety levels, or baseline emotional issues, because the reality is, if you're making the claim that your active therapy works on that pathway, on the emotional part of pain or the attention part of

Page 280

pain, you've got to look at attentional deficits at baseline, or you've got to look at lability of mood at baseline.

Then lastly, treatment history. Obviously you want to make sure that these patients are refractory to less invasive treatments and that these previous treatments are robustly characterized. It can't just be as similar as things like CMM, where CMM could be anything, as a comparator or treatment history of conservative therapy. It needs to be more richly detailed.

Then we'll go back and deal later with concomitant analgesics. This is obviously hugely important. There's a parallel meaning, and we've had another IMMPACT meeting on opioid sparing as Dr. North pointed out.

The reality is that concomitant analgesics are incredibly important, I think, in looking at these studies because, A, most of these patients get multimodal treatment, which is the standard of care in many places, and B, opioid sparing and the sparing of other therapies is a major benchmark for

Page 281

treatment success for patients themselves, as well as for us, as well as one of the ways that patients I think oftentimes get incentivized to try these devices.

So I think given that dialogue often occurs around trials and why patients decide to go for this therapy, I think we really have a responsibility to try and explain to them what the results are once they get one in.

So I'll stop there, and thank you very much for your attention and your patience.

(Applause.)

DR. HAYDEK: It is my pleasure and honor to introduce Dr. Ali Rezai. Dr. Rezai is currently a professor of neurosurgery at West Virginia University, but he has been a trailblazer in neuromodulation; launched at least two companies that have become commercialized; was voted by Crain's 40 under 40, and still doing a ton of amazing stuff with deep brain stimulation and neuromodulation; and currently president of International.

Page 282

Presentation - Ali Rezai

DR. REZAI: Ongoing. No, I'm just kidding.

Thank you, Salim. 40 Under 40 was 30 years ago, man. Come on. That was a long time ago.

Thank you very much. I know it's been a long day. I'm standing between you and the break, and I'm very appreciative to be here. Thank you, Bob and the entire team, IMMPACT, INS, IoN team for this assembly of this amazing group of individuals. I'm very impressed and humbled to be here with such talent.

From my talks, I'm going to talk about just outcomes that I've seen the literature, but it's been discussed many times. I want to do an interactive if I may, so I'm going to ask you questions rather than me. I'm just going to put it up on the screens and get the input to get some connectivity.

Is that okay, Nate?

Thank you very much. First, I just want to talk a few words about the IoN here, and we look forward to working more closely with IMMPACT and

Page 283

the team, and INS, and Simon also.

IoN was established by NANS in 2016, replaced the foundation, and is an independent nonprofit modeled after the National Academy of Medicine. The goal is to facilitate research and collaboration and policy matters regarding neuromodulation, based on health sciences, medical, biological, and engineering sciences.

Our goal is to identify important issues related to neuromodulation therapy and devices and prepare in collaboration authoritative statements and reports on issues important to the public; respond to requests from NANS and other societies for reports and studies; and disseminate information to public and relevant professionals based upon the institute's studies, statements, and reports; and maintain and promote liaison and active communication with government agencies, very important; FDA, CMS, and others.

The leadership of IoN here. Rick is the secretary/treasurer; Pete Konrad, vice president; and these are the committee chairs. IoN's

Page 284

committees are the main workhorse. Every one of you are invited to participate in the committee if you're interested in IoN. We have three core committees: lead device interface committee. We have a clinical trial design committee, which is a collaboration with this group here; a basic science committee; and our membership includes experts and scientists, engineers, clinicians, and other specialists focusing on the institute's research, mission, and vision.

Just the last couple of slides, the committees, first one is the lead device interface committee, and the goal is standardization of implanted connector designs as has been done in cardiac devices. Various surveys performed shows that 90 percent plus the memberships, they want this standardization like it was done in the cardiac world. We've engaged with the FDA and have had several meetings in this regard.

This is where we are today looking at best practice standards, if you will, and recommendations for clinical trial designs for

Page 285

spinal cord stim, other neuromodulation, and focusing on cost effectiveness, regulatory and reimbursement. In particular today, we're here in collaboration regarding the work with IMMPACT and INS here and looking at spinal cord stimulation.

The last one is the standards for research proposals in the field and the roadmap for basic science and really finding, for example, biomarkers that we desperately need for pain research studies and pain clinical studies. And that involves collaboration with NIH.

Clinical trial outcomes. Again, it's been discussed by all of us today, so this is simple. I guess my talk is really the most simple. I can just outline a few things about outcomes. There's a lot of variability. We need a more objective measures. But what our outcomes -- that's a question -- for neuromodulation, spinal cord stimulation? What are the different types of outcomes? We can talk about that. How are they measured? What are some of the challenges? We'll talk about that. And specifically, outcomes that

Page 286

are there in spinal cord stim trials. Please -- I want some feedback here -- as a pre-discussion.

Okay, Nate?

All right. The outcomes are basically variables here, or data points measuring the trials, to really determine the impact of the intervention on a certain measure. Typically, a lot of studies I've been involved have been deep brain stimulation, for example, pilot studies, safety feasibility, tolerability studies, and also randomized-controlled trials. But a lot of times we want to know if there's a feasibility; does a patient accept -- especially for early pilot studies. It's important on tolerability. Those are not trivial. We've had studies like DBS for obesity, where we published that there's no feasibility. Patients did not tolerate that, so we had to stop the DBS for obesity study as part of the FDA trial. It's more for earlier onset studies.

Different audiences, we discussed that earlier. CMS looks at outcomes differently than

Page 287

Medicare, than patients, than companies, so we need to just put them all together and I think be able to provide outcomes that are needed for all the stakeholders. I think that's important for getting proper reimbursement, as field is going -- as Brian was saying earlier, I'm finding in my practice, at least, a lot of times -- despite FDA approval, we're not getting insurance coverage, and that's happening more and more and more. So we really need to be smart about the outcomes and engage with these other parties.

Different types of outcomes. Obviously, you know about this; it's just a framework; patient-centered; survival, looking at outcomes; subjective pain scores; quality of life; patient satisfaction, obviously. There are surrogate ones, the indirect ones, the biomarkers. A lot of work's being done with heart rate variability and other areas. In the cardiovascular world, cholesterol, cardiovascular mortality, for example, or 6-minute walk. These are surrogate or indirect measures of outcomes.

Page 288

Obviously, I think what's important is combination of pain score plus looking at opioid use or opioid dose reduction. I think that's an important composite outcome that we need to look at.

How are they measured? Again, patient reported, subjective. Side effects, "I feel numbness. I feel increased pain," or motor deficits or whatever it is. Pain scores, it's very standardized; numerical scores, visual scores, faces and others. Family reported, that's more relevant for patients that we deal with sometimes, those, for example, with minimally conscious state or those with Alzheimer's. We're doing trials on Alzheimer's, or patients who are compromised, or the pediatric population. So it has an objective element, but also subjective overlay. The family, it's my impression my loved one's doing better or getting better treatments. Then provider report or physical measurements, blood pressure, et cetera. This is, I guess, as objective it can be, but with subjective overlay.

Page 289

A lot of challenges for outcomes. Again, we have different audiences who disagree about the relevance and the value. Again, we mentioned payers, regulators. I'm sure among physicians, or scientists, or patients, or families, outcomes are important or different. Is pain improvement a good functional outcome for a patient who wants to go back to work or not?

Validation is important. A lot of these have been proven in the literature or are used routinely, but we need to look at validation of the selected measures in the context of everything we're looking at with pain and spinal cord stimulation. The question of placebo, sham, it's a huge question. I'm baffled by it, and it happens over and over again.

Many times we've seen -- for example, a trial we did with sphenopalatine ganglion, there was a very high incidence of sham, or now they call it low-dose therapy.

(Laughter.)

DR. REZAI: So there's now sham or low dose,

Page 290

so sub-threshold or low threshold, and some groups are calling it low dose because you're delivering some sub-perceptible threshold but it's still a dose. So is it low dose or is it none? Who knows at this point.

Then generalizing this from an individual population, 100 patients for a study; 50 patients; does it apply to the broader complex population that have physical deficits, motor sensory deficits, cognitive deficits, emotional deficits, psychosocial elements, and the generalization of your specific population in the study. A very small sample to the broader population is an important question.

We often look at pain scores. It's unidimensional measures, but we're looking at a multidimensional construct. Here's an example. And again, Bob and the team, you guys -- some experts are in the audience. You're much more experts than I am. But I like this, looking at efficacy outcomes in chronic pain that was published.

Page 291

Multidimensional, looking at pain, you have -- I like this. This can be a good framework for spinal cord stimulation, obviously. But pain, numerical rating, and then looking at multidimensional pain, physical functioning, looking at maybe pain inventory or other inventory; emotional functioning, important; participants ready, global improvements, and satisfaction, very nicely done; and symptoms with adverse effects regarding also the economics, which is important. That's another thing that I added. This study is looking at these elements, but we added economic. This is a nice framework, I think, for looking at outcomes in spinal cord stimulation. It's been there, it's published, but let's go through this exercise with all of you. Relevant outcomes of spinal cords. Can you participate?

Brian, you have a big voice here. You don't need a microphone. So let's hear something from Brian or Greg or others?

Safety. Here are a few things that I wrote looking at the literature and all about safety; can

Page 292

be procedure related; bleeding, epidural hemorrhage, subcutaneous hemorrhage; infections, of course these are implantables; wound dehiscence, neurological injury, sensory motor deficit.

Are you okay with that? Anything else you want to add there for outcomes? Safety? Anybody?

FEMALE VOICE: Migration.

DR. REZAI: Sorry?

FEMALE VOICE: Migration.

DR. REZAI: Migration. That's right, so we can put that. If you can write it down, please, I will add those later. Okay. Very good. Device related: infection, erosion, hardware failure, disconnection, neurological injuries.

Anything else?

MALE VOICE: Pain.

DR. REZAI: Pain. Very good. That's right. That can be stimulation related so you can get paint. These are three categories.

FEMALE VOICE: I'm sorry. You can also have pocket pain.

MALE VOICE: Pocket pain.

Page 293

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

Page 294

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

Page 295

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

Page 296

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

Page 297

need.
Feasibility. Is it doable? A lot of these things, they're not for larger scale spinal cord sim trials, but I'm talking broadly in the neuromodulation world. Really, the impact, the treatment of patient support systems. Many treatments, practically, they sound great initially but they're not feasible or easily done.
Any comments about that from tolerability of feasibility? Can I get comments, please? Experiences? Rick?
DR. NORTH: A feasibility point. If you're primary outcome measure is pain measure, if it's something you can collect verbally over the phone, like an NRS, then we found over many years that that will improve your follow-up rate. And it's a shame to lose patients to follow-up.
Say you're trying to collect 2-year, 5-year follow-up, you just can't get everybody back for that. So that's an important practical point and a reason to use NRS, which a lot of people refer to as VAS anyway, incorrectly.

Page 298

DR. REZAI: Good. This is the exact feedback that I'm so appreciative of because we've got to write these down, put them together, so this is good. All the minds here, please, keep on talking. This is good. You're the experts here. Nate?
(No response.)
DR. REZAI: Okay. Anything?
DR. THOMSON: Well, I was just thinking, when you're doing these studies, you do your protocol with your set visit times for data collection. But because a stim is a sort of complex treatment that sometimes involves reprogramming, patients will often defer their visit to get reprogrammed and come on the data collection pain time, and say, well, it's not really very good, and what they need is tweaking, and then they would be good.
So managing that -- and then of course the gaming in studies is that one group might be seeing their patients daily
leading up to the data collection point and the

Page 299

other group might not be, and that I think is one of the things that has happened in some of the studies.
DR. REZAI: And that's very important for the study design and the industry that's here, how you're designing it, the implementation, the compliance. I agree with you.
What I've seen many times in my world, a lot of DBS trials or Alzheimer's trials, family says they're responding more -- or depression trials -- but they're coming in every week. They're seeing people. They're getting engagement. They're getting attention versus being at home.
These are not trivial factors, so that's where placebos are always higher because they're coming in from multiple visits. If you're coming in by default, you have a higher placebo versus not coming in, in my experience at least.
Anything else? Salim?
(No response.)
DR. REZAI: Okay. Good.
Technical procedure practicalities, a very

Page 300

important part, as you were saying, in terms of stimulation and others.
Let's continue on, please. Efficacy. Who was saying VAS is the same as NRS? VAS, NRS, the faces, or looking at how this pain intensity changes; the opioid use is impacting it or the use of opioids.
Greg, questions or comments?
DR. FIORE: It's Greg Fiore. To point out about the last line, and it's come up a couple of times earlier today, is that health authorities are kind of loathe to appreciate the decreased dose of opioids or use of analgesics as important in chronic pain. I don't know if others have thoughts on if that's expected to evolve in the current environment. Bob or others may.
DR. REZAI: Anybody? Comments? Opioid use. That's a hot topic, although there's not been prescribed -- a lot of my colleagues -- let me ask you all -- they're saying that the pain specialists, they're not prescribing opioids anymore.

Page 301

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

Page 302

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

Page 303

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

Page 304

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

Page 305

So I would like to say what this group should do is come up with our very best recommendations for a scientifically valid study, and let CDRH figure out on their own what the heck they mean about evidence because I don't think we're ever going to figure that out.

MALE VOICE: Makes sense. I agree.

DR. SINGH: If I can just comment from an MHRA point of view in terms of what evidence we need --

(Laughter.)

DR. DWORKIN: I left you out.

DR. SINGH: -- it would be the same thing what the FDA would probably say. We can't state what we would recommend for you for spinal cord stimulation because we'll be acting as a consulting agent; hence, why my topic was top level generic for all medical devices, but my executive medical director to me said, "Do not give specifics for your device because you will be acting as a CRO consultant," essentially.

So what clinical evidence do you need? I

Page 306

can't give you the answer. Your clinical investigation, if you propose to us, will advise you based on what you provide.

DR. DWORKIN: But, Rahul, let me beat a dead horse.

DR. SINGH: It's very vague.

DR. DWORKIN: Well, let me beat a dead horse here. If the FDA division that approves drugs was here this morning, they would have given a pretty clear answer to this question. They would have said, in most circumstances, they require two adequate and well-controlled clinical trials that replicate each other; and that unless you have some damn good reason for not bringing them two replicated, statistically significant trials that adequately deal with missing data, blah, blah, you don't get approved.

Now, there are exceptions, orphan indications and other exceptions. But we would have gotten a much more compelling, clear answer from CDER than we got from CDRH. I don't want to continue this, but I don't think this group can

Page 307

answer the question of what CDRH is looking for, but I think we can do a very good job of describing what a scientifically valid clinical trial is.

DR. NORTH: To the question about rescue medications, one recent pivotal trial that I was involved with, the urging of FDA, as I understood it, considered rescue medication use to be automatic failure --

DR. REZAI: Is that right?

DR. NORTH: -- of the patient in the trial, no matter how good their pain measures were.

DR. REZAI: Is that practical? No.

FEMALE VOICE: It's not ethnical.

DR. NORTH: Those were the rules.

DR. REZAI: That's amazing.

Rod, you have comments?

DR. TAYLOR: I was just going to chime in back to the previous discussion between the two B's, Bob and Brian, because I'm with Bob that clearly the key conclusion we got from our FDA colleagues this morning was, maybe. I mean, it doesn't go beyond maybe, but it's free.

Page 308

(Laughter.)

DR. SINGH: So I'm with you. I think our challenge is that we have to present them what we think is the right methodology. The only caveat I would make on that, and it's not specific to neuromodulation, but I would hope that Brian would agree with me, is that we should think smart that when we design trials, okay, they may be pivotal in terms of fulfilling the regulators' requirements, but I would like to hear, would people support can we think about those trials as being also potentially fulfilling the requirements of payers? Because if we can, we're going to save ourselves a lot of pain.

MALE VOICE: That's very important.

DR. REZAI: That's exactly right.

DR. TAYLOR: And if we could just say that, clearly that's an additional challenge of how do you design a trial that takes the box of both a regulator and the payer. But if we could make some, if you like, aspirational text to that effect, I think that would be a useful signal for

Page 309

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

Page 310

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

Page 311

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

Page 312

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

Page 313

questions.
May I continue? Pain quality, are these enough from your perspective? What else would you add? I'm just putting a few that I saw in literature, but I don't know what the right answer is.
DR. THOMSON: A lot people now, because we're treating mostly neuropathic pain, they put in some kind of neuropathic pain scale.
MALE VOICE: N4.
DR. REZAI: Do we agree with that, neuropathic pain scale?
MALE VOICE: Functionality as an outcome measure for efficacy, functionality, quality of life.
DR. REZAI: Yes, that's next, quality of life, functionality. So I'm just going step by step, so talking about pain quality, but these are -- again, you can read it through.
Promise. ODI, sleep quality, and days. We should probably put walking here as well.
Anything else you would add here from this

Page 314

list or take out? Any comments?
Dr. Loeser, what do you think? You've been quiet.
DR. LOESER: Well, I've been quiet because I've been trying to figure out what's going on.
(Laughter.)
DR. LOESER: I just did want to make a comment, though, about the issue of opioid consumption as some kind of a measure. It used to be that we all thought that opioids were effective in the management of pain. There now are repeated papers that show that when you stop long-term opioids, the patient's pain doesn't get any worse. Therefore, opioids are no longer a way of assessing outcome. So to rely on opioid consumption or change in opioid consumption as some proxy for pain relief, I think those days are gone. You just can't do that.
DR. REZAI: It's not being prescribed, also.
DR. THOMSON: Mainly, because I suppose I've worked with Rod and Sam, but I'm a great fan of the Euro Quality, EQ5D, because it captures multiple

Page 315

dimensions of the experience. It does translate into corlease qualities [indiscernible]. So I personally think that treating these pain long-term conditions should be our primary outcome because I think we've got into a world of VAS wars.
DR. REZAI: Yes, that's the question. What's a primary outcome? Is it VAS --
DR. THOMSON: Yeah, exactly.
DR. REZAI: -- or NRS?
DR. THOMSON: Well, I just think it's mad what's going on, and it's so easy to game that measure. It's just every meeting we go to. It's just ridiculous. How low can it go?
DR. KOPELL: And it also neglects the multidimensional aspect of pain. Patients don't have the kind of insight that we in the field. When they look at a scale, they get focused on just the somatic aspects of it.
DR. REZAI: Let me ask, who's in here from industry? Raise your hands. Industry? Okay. What is your perspective? You're sponsoring the trials. What do you all say? You've been quiet. Please

Page 316

make some comments.
(No response.)
DR. REZAI: Maybe not. Okay.
(Laughter.)
FEMALE VOICE: NRS and VAS are ridiculous to continue to use, especially when there are differences in how you collect the data, the instructions over what time period. If it's a primary region of pain, another region and overall pain, it's absolutely ridiculous, so we do need to change that.
DR. REZAI: Do you have comments, Sam?
DR. ELDABE: I think when you speak to patients about what is it that matters to them, I always get a reply over triangulation of three factors: pain, sleep, and fatigue, and one leads to the other.
DR. REZAI: Pain, sleep, fatigue.
DR. HAYEK: One other exclusion criteria that I think should go into any study, especially with spinal cord stimulation is fibromyalgia. The general population would say 9 percent, 10 percent

Page 317

of women, but in my clinic it's 50 percent of the patients. If you're keen on examining your patients, you would discover that a high proportion of patients with chronic pain come with fibromyalgia. And I'm not sure what that means, but if we are implanting those patients, I'm not sure what outcomes we're getting either.

DR. REZAI: Great comments. Okay. Satisfaction? That's an outcome. Do we agree? Patient satisfaction, provider satisfaction.

Anything else you would add here as far as outcomes?

DR. VAN DONGEN: Psychological measurements like depression and anxiety and pain catastrophizing. We don't measure that?

DR. REZAI: It's included on some of those other measures, but yes, of course.

Yes?

MALE VOICE: Preference.

DR. REZAI: Preference for --

MALE VOICE: As an aspect of satisfaction, so preferring one intervention over another.

Page 318

DR. REZAI: Okay. Anything else you would add here? We're taking notes.

Yes?

DR. TRESCOT: Andrea. One of the things that we don't pay attention to is the family's interpretation of what's going on, because just like the person who's drunk who doesn't realize he's drunk, I've often had the family member -- the patient will say, well, I know better, and the family will turn to that patient and say, "What do you mean? You were doing this. You were doing that. You were cooking yesterday. You haven't cooked in months. You're doing better. You may still be hurting, but you're doing better."

DR. REZAI: So put family satisfaction there.

Do we all like that? Brian, you say no.

DR. KOPELL: I mean, the problem is that family dynamics are very, very complicated --

DR. REZAI: But they're living with them.

DR. KOPELL: No, no, I understand that, and I'm not saying it's invalid. I'm just saying that

Page 319

you're opening up a box that's going to be very difficult to create a trial around. That's all I'm saying.

DR. REZAI: That's super important.

DR. LOESER: I think that we lose sight of the fact that anytime you elicit a behavior from a patient, the environment in which that behavior is elicited plays a big role. So I'm uncomfortable with a whole host of the measures, which I think are going to turn out to be very dependent on who assesses, how they're assessed, when they're assessed, and what the patient thinks is the meaning of the assessment.

DR. REZAI: So that goes in the design of the trial and how you're doing it.

DR. LOESER: All behaviors are environmentally contingent.

DR. KOPELL: I have a question along that line. How many people here -- and people mentioned before the neuropsychological screen. I'm just curious. How many people here think that that's an absolutely vital part of a neuromodulation implant?

Page 320

(Hands raised.)

DR. KOPELL: Okay. That's interesting. I would have expected more. But then why is that not part of the outcome measure? It's so important to get --

DR. REZAI: That's the inclusion exclusion.

DR. KOPELL: Well, but is it?

DR. REZAI: No. Okay, fair enough.

DR. TRESCOT: Or should it be? If you've got someone who has a psychosis, that's not going to get better with a stimulator, but if you've got somebody who is depressed, that's where we've seen, all along -- people who were crazy because they were depressed, you take care of their pain and you turn them back into rational human beings.

I'll use the example of the woman in labor who is totally irrational, and you put an epidural in her, and you turn her back into a rational human being. If you listened to What she was saying in labor, in pain, you'd say that she was not competent psychologically.

DR. KATZ: So speaking of people becoming

Page 321

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

Page 322

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

Page 323

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

Page 324

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

Page 325

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

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

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

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

Page 326

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

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

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

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

Page 327

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

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

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

Page 328

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

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

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

Page 329

well as an explant.

Some people have actually estimated the loss of therapeutic efficacy up to 50 percent in spinal cord stimulation. There are other potential technical complications such as 2D placement or two superficial placements of the generator; generator flipping; irritation of a bony landmark by the generator; or a anchor discomfort or anchor or wire erosion through the skin.

The other potential leads that are places in spinal cord stimulation, beside the percutaneous leads, which are shown to the left, are the paddle leads, which are surgical leads placed through a laminotomy. They're called paddle because they look a paddle, and typically they're place in the mid-thoracic spine.

I like this study. There are a lot of studies on percutaneous and paddle leads. I chose these studies because they're representative. This recent study by Bir and colleagues from Louisiana State university is interesting. They had 141 patients evaluated, but interestingly, more

Page 330

than half the patients did not have previous back surgery and just had radiculopathy that was refractory

In this study, the revision rate was 32 percent, but revision due to lead migration only occurred in 2 percent of the patients. However, interestingly, for malfunction or non-function, you had, respectively, almost 20 percent and 8 percent.

Revision-free survival was looked at in this study and was very interesting. More than half the patients were revised by 5 years; 45 percent only had their revision-free survival at 5 years. Risk factors for revision were younger patients. Patients younger than 60 years old tended to be revised more often. Males also tended to be revised more often than females.

Obese patients, defined as BMI greater than 30 kilogram per meter squared, also were found to be more likely to be revised. However, in multivariate analysis, this remains statistically significant. Diabetics were not found to be at higher risk for revision. However, patients with

Page 331

higher pain scores defined as pain scores greater than 8 on a scale of 0 to 10, or having history of fibromyalgia were at high risk of revision.

Not significant were patients who were depressed or who had axial versus neuropathic pain. Again, looking at the multivariate analysis, obesity, which was a risk factor, [indiscernible] was not a risk factor with the multivariate analysis.

There are other people that looked at risk factors with spinal cord stimulation. De la Cruz and colleagues looked at smoking, and this was correlated with lead migration and revision due to new pain symptoms. They also had similar negative trend for patients who used opioids. However, in this Bir study that I just discussed, neither smoking or drug use were a factor.

Jean-Paul Van Buyten from Europe looked at a retrospective review of patients receiving rechargeable versus non-rechargeable stimulators and found that patients who had a non-rechargeable stimulator were more likely to be revised than

Page 332

patients who had a -- I'm sorry. Patients who had a rechargeable stimulator were more likely to be revised than patients who had a non-rechargeable device.

Reprogramming is often done to salvage a device. You can reprogram the electrodes as cathodes, or anodes, or fractionate the current. However, there is reprogramming as far as algorithmic or pattern of stimulation. The studies that looked at this are within company products. For example, high density stimulation was done to rescue conventional stimulation at the lower frequency. Burst stimulation was done to rescue conventional stimulation. There are some published data on that within the company's products.

Switching among devices may be attractive to some practitioners. However, it's not supported by evidence and is quite expensive, and is generally looked at negatively by third-party payers and insurance carriers. If one decides to use it, one should probably try, if possible, to perform a trial before undergoing or subjecting the patient

Page 333

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

Page 334

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

Page 335

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

Page 336

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

Page 337

report these adverse events, so their judgment and past experiences, as well as the biases, play an important role.

Finally, how do we analyze and interpret the data? The data typically is reviewed by a treatment event committee and adjudicated by that treatment event committee. It depends whether or not this treatment event committee has set criteria for reviewing the data or is it based a lot on the reviewer judgment, and there are usually an odd number of reviewers that have to come to an agreement as to a particular adverse event or a complication and whether it's related to the product or not.

The coordinators, when they collect the data for the analysis, have to use a coding system to put the complications under a certain code, and there are a lot of variabilities also in reporting these data, depending on the detail level, level of review, which codes are used and whether or not a due-to clause is used in reporting this data.

The role of the FDA, in general, is

Page 338

restricted to reporting the unanticipated adverse device events. However, the FDA also approves the protocol in general that is submitted by the sponsor and the specific adverse events of the sponsor will be following. They get an annual report once a year, and at this once-a-year annual report, the FDA may ask questions. They also can provide guidance on the proper adverse event evaluation and who is qualified to collect the data on the adverse events.

The FDA may conduct an audit to confirm the adverse events are being reported. However, realistically and due to time constraints, this only occurs rarely and only reviews a fraction of the records. However, the FDA requires that the sponsor maintains a monitoring plan, and anytime there are changes to the protocols, the FDA needs to be notified and review the protocol.

In conclusion, spinal cord stimulation is overall safe. There are very rare reports of serious adverse events such as paralysis or death. However, they have a high frequency of

Page 339

complications that could be up to 50 percent. They may be technical or biological, and reporting device adverse events may be subjective and may be very variable from industry to another and from an investigator to another. Thank you.

(Applause.)

Group Discussion

DR. KATZ: Let me ask all the speakers from this afternoon session to come up, so that's Ewan McNicol, and John Markman, and Ali Rezai. Is Ali here? Just please come up and have a seat at the dais.

We have some time for discussion now, and I think consistent with what we did earlier today, let's just begin the discussion with any questions or comments that people have about the presentations that this august group gave this afternoon. And maybe in case people don't anymore remember what the presentations were about --

Maybe what I'll do just to get the discussion going is ask Ewan, once he's all set with the furniture, to just maybe give us a brief,

Page 340

one-minute summary of what you think you learned from the -- since you took a deep dive into methodology of spinal cord stimulator studies, maybe just jump-start us by giving us sort of the big picture of what do you think you learned that is most relevant to this group's task, which is to make recommendations about the design and conduct of such studies.

DR. McNICOL: I wish you had coached me in that before the panel discussion.

DR. KATZ: I'm a little evil. Don't worry.

DR. McNICOL: As I mentioned, it was all brand new to us. We were using as our point of reference how different our spinal cord stimulation studies are from drug studies. The differences where there were generally smaller numbers, usually longer durations of study because it was chronic pain. If you're putting a permanent implant in a patient, you're clearly going to follow them over a longer period of time; a lot of crossover studies in there, which we don't see as often with drug studies.

Page 341

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

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

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

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

Page 342

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

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

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

DR. FIELDS: When you looked at the

Page 343

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

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

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

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

Page 344

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

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

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

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

Page 345

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

Page 346

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

Page 347

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

Page 348

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

Page 349

some recommendations about describing, if you like, the granularity of the intervention to allow you to be able to replicate the study again. And that's never a bad kind of metric.

So I would really be encouraging that it may be that we can point to some particular areas of reporting that are particularly -- and I'll use that word again. So it's particularly important for neuromodulation or ICS studies that would help us in the future; critically appraised studies just as the Tufts group, but then also understand what the studies were actually up to, which is half the problem that we have, is peer reviewers.

Anyway, herein is the sermon, that I hope that is a useful comment.

DR. KATZ: I think it's useful enough that we should, expand on it further. And maybe, Andrea, you'll forgive me if I take a moment and just expand on that.

Maybe, Rod, you could expand a little bit more on what you think those particularities are that are worth focusing attention on, those papers,

Page 350

so we're not simply replicating all the guidelines that already exist out there, but just focusing primarily on what's different here that characterize this unique intervention. What do you think those particularities are?

DR. TAYLOR: I'm going to do a review -- and, gosh, that's a hospital pass you've given me, but I'll try and respond. I think there are at least two really key -- well, actually one key thing that's going on here, which is spinal cord stimulation is a medical device that's delivered as an interventional procedure.

So it's back from me to this; what are the particular challenges of evaluating an invasive procedure? Actually, they're not specific to spinal cord stim; they're generalizable to any invasive procedure. But what we've got to do is contextualize SCS, those peculiarities in the chronic pain space.

For instance, the issue we've just talked about, the effects of the therapy as the interaction between the device itself but also the

Page 351

operator and the setting. And if we don't understand those things, then we're not really understanding how the therapy works.

So I think there are some specifics we could bring out. That's just a quick punch at responding, but I think if we're doing this in the context of reviewing a manuscript, I'm sure we could tease these out in a more sophisticated way. And I suspect others will have views on those peculiarities in the room as well.

DR. KATZ: Thanks. No, that's good.

Andrea, you were next.

DR. TRESCOT: Thank you. Andrea Trescot, Stimwave. I wanted to go back to the crossover issue because one of the very few ways that we have to convince patients to do a placebo-controlled trial is the promise that they can get the active therapy if what you've offered them didn't work. So I think there are two types of crossovers, one where there's a mandatory crossover and the other where you have a "if failure, then crossover."

So I can thoroughly understand the argument

Page 352

against the forced crossover because of the comment that the first therapy always looks better. But I think if you have a failure of one treatment, then that's really the only ethical way if you're doing a true sham or a true placebo. If what you're doing is comparing -- and it has that other advantage of having the patient as their own control because part of the problem is when I'm doing a spinal cord stimulator trial for low back pain and one patient has low back pain because of a set pathology and another has low back pain because of epidural adhesions, those patients may respond very, very differently to the same stimulation, but they have the same pathology so that it would allow you to then try different therapies for that same pathology with the patient acting as their own control. So I think in that respect, the crossover trial becomes very important.

DR. KATZ: Thank you. John?

DR. MARKMAN: On our experience, I think we're over 60 duplex trials at this point using high frequency and either tonic or burst or

Page 353

something else. And we have not seen this idea borne out that the first therapy always wins.

DR. TRESCOT: But you're also not comparing it to a placebo, correct?

DR. MARKMAN: Absolutely right. So we're not putting a placebo arm, but we just haven't noticed -- and obviously, nobody likes when you do this, when you try to different stimulation paradigms with the same set of leads. That is -- really, everyone doesn't like that in terms of the representatives.

They don't want to be compared one to another, head to head like that. And the first group always claims that, "Oh, it's the post-procedural pain, which is why our device wasn't chosen because the patient had too much discomfort from the acute nociceptive pain from the two-needle placement." And the second person says, "Well, they had so much time brainwashing them during the first period about why their stuff worked, that of course by the time they got to us, ours didn't work," because they were so conditioned

Page 354

that they needed parasthesia to get relief, or they were so conditioned that they didn't need parasthesia not to have an adverse event.

But the interesting thing is that I was deeply worried about the sequence but we have not really seen an effective --

DR. TRESCOT: That actually is a critical piece of information that needs to be in the literature, is that there is no effect in the sequence, in your experience and with your studies, that there's no difference in the sequence because that would then get rid of that concern about a crossover trial.

DR. MARKMAN: No, we don't know there's carry over. That's one of the things we also worry, obviously, between one sequence to the next, whether there's some analgesic benefit conferred in first 3 or 4 days that somehow --

DR. TRESCOT: And how long is washout? How long do you have to have a wash out before you have a loss of effect?

DR. MARKMAN: These are unknowables. I

Page 355

don't know the answer to these things.

DR. HAYEK: Perhaps Sam and Eric can comment because you guys were co-authors in Cristophe Perruchoud's study, and you found a period effect.

DR. BUCHSER: Yeah, we did, and actually the first treatment that was proposed showed the best result, irrespective whether it was placebo or the stimulation.

DR. NORTH: To the extent there's maybe a period effect, doesn't that just increase sample size requirements, to try to tease out the period effect versus the therapeutic benefit.

DR. KATZ: In theory, it doesn't --

DR. TAYLOR: Yeah, period effects are a bit of a bugger, actually, in analyzing crossover trials; a technical term, Rick.

DR. KATZ: Jen?

DR. TAYLOR: It's not just a para issue; it's a kind of confounding issue. So it's difficult to make it go away with power, the period effect.

DR. KATZ: Actually, Jen just lived the year

Page 356

dealing with crossover studies or whatever it was. Do you want to comment on that?

DR. GEWANDTER: I was just wondering, in your study, was the reason the effect was bigger in the first period because they didn't come back to baseline in the second period?

DR. BUCHSER: Say that again?

DR. GEWANDTER: Was the reason that the effect was bigger in the first period in both groups because they didn't come back to their baseline in the second period? So you weren't starting as high in second period.

DR. BUCHSER: No. Actually, both treatments get the same result, roughly the same result as it was presented first. And stimulation had a very slight advantage when presented second over sham. So they were not coming back to the same result.

DR. THOMSON: Like a lot of these things, the devil's in the detail, and we're learning how to do these crossover studies with neurostimulation. Certainly, in our protocol study, preemptively we've said that the pains would

Page 357

have to return to within 80 percent of baseline before we would then go on to the next parameter. That seems --

DR. NORTH: A crossover study begins with a parallel group study, and you can analyze that in and of itself. And the additional information from the crossover period is just that; it's additional information. I don't see any reason not to do it.

DR. McNICOL: That's what we tend to do with our Cochrane reviews, is we'll only analyze the data from the first period. And the second period, as you mentioned, is just additional stuff. But then you're looking at, as you say, larger sample sizes when you're using what's essentially a parallel study with an extension on it, really.

DR. KATZ: Turo?

DR. NURMIKKO: Turo Nurmikko, UK. Coming back to the crossover issue and the washout period, as Ewan was showing, most of the studies had no washout period whatsoever, even in each arm the patient received SCS for days or weeks. And you see it's almost impossible to think that there

Page 358

wouldn't be any long-term physiological effects that could actually confound the results. And of course, the results for many of those studies, as I said, they show surprisingly little difference between groups, and these could be, in part I think, associated with the fact that the washout period has been neglected to a certain extent.

Now, I haven't seen any justification why that would be justifiable. In other words, it will be helpful to know if somebody somewhere has actually checked this issue in some context to see whether following, say, a couple of weeks of SCS, do you actually either immediately lose the effects where somebody switches off the stimulator or whether there is a true carryover effect and how long it lasts.

DR. KATZ: John was next, John Markman.

DR. MARKMAN: Well, I just would say with the crossover issue -- I'm not going to directly answer your question, but I think it's a good question. But just with regard to Simon's point that the devil's in the details with crossovers, it

Page 359

is important to note that if you go from one to the other, there are some challenges because they have slightly different specs in terms of where the leads.

We should just put that in the manuscript because this is one of the things that we ran into, is you can't really do a Nevro trial if you're not intersecting the T9/10 interspace. And you can't really do a Nevro trial if you've only got one lead in. And the Boston folks will say that you can't really do SSR therapy if we're not at the T7 vertebral body level. And the Nevro folks will say that, "Well, if we don't get to wash into 4 of our program cycles, then you can't decide that it was a failure," because it takes 20-48 hours to wash into each program cycle.

So I think there are a lot of devil in the detail type issues with regard to technical placement of the leads, but also with the paradigm to wash in of the stimulation paradigm, it's just like saying you didn't adequately titrate the gabapentin. You only got to 600 milligrams, and

Page 360

you're calling and saying our session didn't work. We need a chance. We need to do 3 more days at 1800 milligrams and decide that this was a failed study.

So I think that we are going to need to qualify -- whatever we do in crossover, we need to address that there are system-specific requirements based on how the manufacturers believe their devices work.

DR. REZAI: That's where the standardizatioon comes in. The quality elements for the study design is very important. Like we discussed, the design, the conduct, and recording of the events, there are a lot of variations in this. So I think the more they standardize that, that would help the field. I think that's very important.

DR. NORTH: John, wouldn't it be fair to say that we could standardize lead placement in a comparative study among these various waveforms, and that there's not really any affirmative evidence that it's not necessary to do parasthesia

Page 361

mapping when you put leads in for high frequency? There's just a claim of good results in circumstances where they didn't bother doing parasthesia mapping.

DR. MARKMAN: Yeah, I think that's certainly reasonable.

DR. HAYEK: So that's a nice marketing tool to be able to say that. But in the context of a study where you anticipate using the same leads that are used for HF for conventional stimulation, then you would do the mapping, which is essential for the latter, and it could only benefit the --

DR. MARKMAN: Right. There is always some back and forth -- and again, I want to make sure I understand your question -- around the lead contact spacing for some of the different systems and whether that affects these --

DR. NORTH: Yeah, but there's really no evidence for a difference there.

DR. MARKMAN: Right. I mean, again, these are marketing claims that I think certainly affect the decision-making of implanters and certainly

Page 362

affect the way that implanters explain the device to people receiving them. And most importantly, the way that the representatives who -- we have to just acknowledge openly that a lot of the care of these patients around their devices is outsourced to representatives, and the representatives are perpetuating their messages and their explanations for treatment effects. And I think that outsourcing, which is something that's an open secret, has a profound effect on the therapeutic intervention.

DR. THOMSON: Just to say, that's a peculiarly U.S. centric thing that's going on. Okay? The way you approach your process of spinal cord stimulation with other people doing trials and then referring them on to somebody else; you put the implant in, and the trial is assessed by the representative of a company, that's not what happens -- well, certainly in my institution, where it's our team who basically take on the management of the patients.

I think certainly if we're going to have any

Page 363

recommendations for clinical trials, this is one of the big things we've got to actually recommend, is the involvement of the representative has got to be minimized and monitored.

MALE VOICE: Here Here. Absolutely.

DR. MARKMAN: I think it's essential. I think this is something that is a field. I don't think this is necessarily the only forum to address this, but this is a major issue. Many companies won't even let you use a controller to program the device anymore.

MALE VOICE: That's right.

DR. MARKMAN: We've all faced this. So you're stuck with not offering your device because you don't have access to the controller to program it. And I think I'm sure I'm not the only one that faces this.

DR. KOPELL: Can I ask a question on that? I'm sorry to put out a specific company. Has anybody here ever got access to the Nevro controller device?

DR. MARKMAN: My understanding, in the UK,

Page 364

they have done it because it's a country-specific policy. I think there was something -- there was a national level issue there But in the U.S., my understanding is there's no one.

DR. KOPELL: I mean, that just boggles my mind. You know? To be honest with you, we all call neuromodulation a digital drug. You've heard that term bandied about. So we're basically saying that doctors can't administer the drug and only the companies can do that. That's just -- for me, that rankles me beyond belief because, again, it's so backward.

DR. THOMSON: There are several sort of models; Jose De Andres' study from Spain that looked at two different companies independently funded, and attracted a lot of criticism, if you like, from the companies because, essentially, a fairly minimal treatment effect in both groups. And they put it down to the fact that it was because it was done by the hospitals staff, the programming, which I think is not altogether true.

So you can have the reps do the thing, but

Page 365

they are monitored and scripted what can be said, and the timing how long they spend programming, and all that sort of thing. That can and probably should all be done if we are going to be doing studies.

DR. REZAI: I can comment on the DBS world. SCS has been "grandfathered in some ways," just some quotation. DBS is very different. It's very much sort of an organic. We're involved in the settings and all that, so the physicians do it. I think this is more unique to the spinal cord stim companies because traditionally, in the DBS trials, we actually design the stimulation parameters, and we stick by it. But I think this is mission critical. You have to really standardize, and that will really make a difference.

DR. KATZ: Andrea?

DR. TRESCOT: I've actually had a multitude of patients say that they had told the rep that they had only gotten 30 percent relief, and the rep had then told the implanter that they had 50 or 60 percent relief, and they went on to implantation.

Page 366

And this happened not one time, but multiple, multiple times. And I've had multiple patients tell me the exact same story. So it may be one of those dirty little secrets.

DR. KATZ: So just ask the rude question. Is it feasible in the United States to not have the company representatives involved in a clinical trial?

DR. MARKMAN: Well, I think they have to be in the operating room because there's so much hand off of materials. There's a supply chain issue, which is one set of issues which you can't get away from. But there is a programming issue and a patient interaction thing, which you can completely get away from. But I think the technical support you get in the OR is a very distinct thing from the continuum of therapy that you get in the outpatient setting. And I think we could clearly dichotomize that.

DR. HAYEK: One word also about the technicalities for every different manufacturer is different, and for the physicians to learn how to

Page 367

program every device is unachievable nowadays because every company has become kind of like very specific in programming, so take a long time. So I think you have to have the involvement of the --

DR. ELDABE: Again, I think specific in programming, but is that based on science?

MALE VOICE: I missed the first part.

DR. ELDABE: Companies are specific in programming, and they all have an algorithm, but what is that based on?

DR. HAYEK: Well, also the technicalities of using the device. So to choose a programmer for company X, Y, and Z takes a significant amount of a learning curve to handle it.

DR. MARKMAN: And again, I think it's a good point. I think that for myself, personally, to learn how to program five different devices, I would have to spend 4 or 5 days full time. I could do it, but when you ask me do I manage intrathecal pumps and medications, that those have much more serious complications, we would never let the reps do that.

Page 368

DR. THOMSON: This has come back to reality. We're talking about doing research. You don't have to do 5 different devices. You could just do your research with one device.

DR. KATZ: Is it possible for a paraprofessional or physician's assistant or somebody to learn to program one of these devices?

DR. MARKMAN: Absolutely. Obviously, the downside risk is lower. If you had a clinical trial coordinator doing the programming, I think that you would just want to put them in a position where there was someone overseeing them because if someone got over-stimulated and had a car accident or fell on the way out to the car or something, from a conduct point of view of the study, you just need to make sure that their PI is someone who can meaningfully oversee what the clinical trial coordinator's doing.

DR. KATZ: So by oversight, do you mean the PI's oversight or do you mean the representative from the company's oversight?

DR. MARKMAN: I think the PI. A PI who's

Page 369

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

Page 370

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

Page 371

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

Page 372

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

Page 373

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

Page 374

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

Page 375

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

Page 376

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

Page 377

depending on what they're doing, you're not going to see that money come back to you. We've actually had people -- I see the point of the bias and try minimizing that, but also there's an economic side of it, that it's actually a service that's provided where physicians have to do less and build a trust with someone on how they deliver that therapy.

So I agree with Rod in that we should just be careful. I agree that it could be improved. I just think we need to think about it.

DR. REZAI: We're talking about the design of a study. This is not about -- I mean, that's down --

DR. HAYEK: And real life, yes.

DR. REZAI: This is more of a design, right?

DR. THOMSON: It's really important to realize there is this difference between doing a clinical science and what is basically usual care, where, frankly, with usual care, we're keen to have any involvement, and help, and placebo comments to get the best result. But when we're doing studies and looking for a treatment effect, we've got to

Page 378

give advice of how we're going to really show the treatment effect or not.

DR. MARKMAN: I think that's great. It's inconceivable that you could do a drug trial in United States where the sales representatives would be running the study visits. It's unthinkable. Frankly, it's unfathomable; it could never happen. And you'd have a sales representative who is incentivized in the sale of the drug at that particular site, running the truck. We wouldn't do it. It would like if somebody explained this to what was going on, people would be dumbfounded.

DR. REZAI: Are we using the same rigor that pharmaceuticals -- what have you learned from the pharmaceuticals? Have we applied that in this context, is my question. Do you all feel comfortable that you applied the lessons learned from the pharmaceuticals in here, in this place?

DR. FIORE: Maybe I can address that question and also add some of the industry context. For industry sponsored studies, the goals are really to identify uses of products in populations

Page 379

that will benefit to the satisfaction of the practitioners and the patients because that creates the market, the payers, because that's the reimbursement, and the health authorities.

To me, what strikes me in this conversation is that the poll for the research is coming from academics and physicians rather than being driven by industry, so the motivations may be different. I think if the health authorities have set a bar that I'd venture to say is lower for device approvals than for drugs, and physicians adopt these because they're interesting, they're cool, they're novel, and there's a promise for helping the patients, then the payers are really left out here.

So to your point, if the companies don't come and take the lead for increasing the standards, increasing the rigor, and enlisting support of the sites to do that, then I think that this problem, the circularity of it, will not be broken.

DR. MARKMAN: Well, I think that's exactly

Page 380

right. I think that the point that was made this morning was really right on, that said unless the regulatory standard is raised, that's the only way to really break that cycle. Without a higher regulatory -- the marketplace cannot decide. The clinical cannot decide. It's only because it was compulsory from a regulatory perspective that the market could sort out some of these other issues. But with too low of a bar on the regulatory side, you'll never -- that's why it is so important, this document, because unless we create a standard for the regulatory world that everyone agrees to, at least as a minimum that's somehow different from the current one, we'll never resolve these issues.

DR. KATZ: Brian, I see you are dying to make a comment. Your mouth started to open.

(Laughter.)

DR. KOPELL: Maybe I'm being too rigid, but again, I look at the application of electricity on the nervous system as something wholly in the realm of the caregiver, period, full stop. Sure. If you tell a company person you can push that button,

Page 381

that I guess I'm okay with. But to let them basically independently do anything -- and I note and it happens all the time -- it would never happen in the DBS world. And every so often you hear some weird things that it is happening, and it's like horrifying. It's just horrifying to me as a physician. This should be a very simple discussion basically, from my perspective. In a clinical trial, no company independent, period, full stop.

DR. KATZ: Sam?

DR. ELDABE: A couple of points, I'll talk to you about programming issues in trials tomorrow. What you will see from the trial reporting is this is an issue that we have neglected before we start bashing the companies. You'll see how many trials actually report on programming. Every trial reports on the surgical technique, but no trial reports on the programming or reports on the programming fully. So it's not really the company, it's us. Because we subcontract this, we're not interested.

Page 382

The second issue is about the IP. I'm sorry. I don't believe that this IP is -- I think it's a red herring. Companies are more than happy to take your staff and train them off site. We've done three RCTs where no company was involved. The company came. They trained the staff. The staff carried out the programming. That is extremely possible, and companies will not object to that as long as the staff know what they're doing.

DR. KATZ: Roshini, do you have any comments about this? Introduce yourself, please.

MS. JAIN: Yes. Roshini Jain, Boston Scientific. I just want to kind of go back to I think what Rod was saying as well. A lot of studies that we're involved with, I would work with sites that do multiple studies and multiple devices as well. To kind of what Salim was saying, it's having a small research team, a couple coordinators now be fully washed in 6 different devices that have 6 different interfaces, which makes it challenging, which is why I think being up front in the study protocol, defining who touches those

Page 383

patients, how often they touch those patients, and really limiting that scope, in my opinion, I think will kind of get us further along from a study design standpoint.

DR. KATZ: Other thoughts from manufacturers on this issue? Introduce yourself, please.

MR. HILKER: Chris Hilker from Medtronic. Yeah, I would echo that. I think it's a balance of that transparency piece. And when you look at the two arms, the consistency, -- I think you can go multiple different ways, whether it's training a subset of your site with one potential industry person there for oversight and providing additional on-site support. But I think it's the transparency of what that person's doing and the consistency across the arms so that you're not seeing that variability going from arm to arm.

DR. KATZ: Great. Yes, please?

MR. BOSLEY: Bernie Bosley from Nuvectra. I think training is an aspect here. The sales reps are trained how to use the programmers in the best way, and we need objective evidence that the users

Page 384

of these devices are trained from a regulatory perspective as well.

So if you're going to move operation of the programmers to somebody else, we need to consider that as well.

DR. MARKMAN: I think that's a great point, to have some sort of competency testing for using it. I think that is a very valid point, that you should be able to make sure that the clinical trial coordinator who's using it can demonstrate some proficiency and understanding the parameters, and what it means to have coverage if that's important, and other things like that. I think that's a perfectly valid sort of competency for a clinical trial site to have to demonstrate if they're going to participate in a trial.

DR. KATZ: Are there existing training programs that have been developed with competency tests, et cetera, for the different devices?

DR. MARKMAN: Well, certainly the reps go through that, extensively.

DR. MARKMAN: The other question is can it

Page 385

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

Page 386

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

Page 387

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

Page 388

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

Page 389

DR. NORTH: And the distinctions that are made between the different waveforms, I think are distinctions that are not important as a clinical difference, because if you have a product capable of delivering all of the waveforms, one might be statistically superior to the others, but they're all important to have on the menu.

So a study that demonstrates that one of the waveforms, one of the parasthesia-free waveforms is better than placebo brings all the rest of them along for the ride, whatever their comparative effectiveness, and that should be good for everybody.

DR. MARKMAN: Right. I think the API is more alike than it is different. Double the dose, half the dose, dosing schedule changes, I think those things are noise around the issue that it's the fact that it's the same API.

DR. THOMSON: Adverse events. We're really talking about the sorts of things -- what makes this sort of minor surgical but technological procedure, treating the same pain that many other

Page 390

pain doctors treat without spinal cord stimulation, or try and treat without spinal cord stimulation, what makes it different, the fact that we're doing this procedure?

We've touched on programming. We've touched on the technology and the different waveforms. But then I think the big thing is expertise of the site to deliver the appropriate type of spinal cord stimulation, and if you're comparing it to some other usual care and being able to do the comparator or the usual care with sufficient expertise.

I think Rod talks about the SPIRIT trial, which was a, refractory angina study done in a cardiac center. And really, they had no experience, really, of spinal cord stimulation at all. They had a completely chaotic follow-up with patients strangely coming from Scotland and being randomized to SCS or PMR, which is my percutaneous myocardial revascularization.

I think the first half -- Rod, you know this -- if you looked at the incremental cost

Page 391

effectiveness ratio, which is sort of a kind of metric of whether something's cost effective, it was like a quarter of a million pounds I think for the first half of the study and got down to about 18,000 pounds for the second half of the study, because they got better at doing it.

This kind of expertise is incredibly important. So when we're talking about these studies, we have got to be able to use expert centers. And it's not just the surgical technique, but it's also, as we talked about, the programming techniques, and the follow-up.

DR. KATZ: Is your suggestion to limit these sorts of intensive studies to centers with high expertise or to quantify the degree of expertise of the sites that do participate but allow it to be more abroad or some combination? And in either case, how does one measure expertise?

DR. THOMSON: We should be saying what we think is the ideal. And the ideal should be somebody, a center that routinely offers these therapies, and monitor their results, and have a

Page 392

track record in research, and satisfy all the conditions for being a research center. Then I think as we design these studies, there are different and more complex, if you like, comparator treatments, and are they able to offer that?

You're going to hear me say the word equipose a lot tomorrow, and I think that's just incredibly important when we're actually trying to do the science and actually trying to identify treatment effects.

DR. MARKMAN: Just to I think follow up on your question on that, too, I think there are at least two domains in my mind of expertise in a center. One surrounds this issue of patient selection and treatment matching, and the other surrounds the actual technical specs of device implant.

I think that the way you would evaluate those two domains are different because you can do a lot of stims in a lot of trials and really be technically super adept, and do a complex patient who's 96 years old with scoliotic deformity and get

Page 393

the leads perfectly midline. But that's a different place potentially from the place that is identifying patients who, as a consensus view, might be the patients who meet the clinical trial inclusion criteria for the type of baseline pain condition. And I think that those are not always overlapping.

So I think that I would just specify different domains of expertise, some of them around volume, and maybe complications and reporting, and some around other factors with regard to preclinical or preimplantation assessment and follow-up.

DR. KATZ: Are you saying, John, that you don't feel that the typical long laundry list of inclusion/exclusion criteria in a clinical trial to standardize patient selection, and one needs to go further than that in some way?

DR. MARKMAN: Not necessarily. I just think you need to have experience doing that, demonstrated experience in conducting and identifying those subjects. Obviously, as you've

Page 394

done before, we've done trials where we have an outside panel of experts reviewing the included patients, and I do think that's a powerful check on the behavior of a site in terms of making sure that the patients who enroll align with some approximation of what the designers of the trial had in mind. There are many ways to do that through DSMBs or external committees. But it's one tiny little extra area of oversight, which really I think helps nail down this patient selection quality issue.

DR. KATZ: That might be worthwhile for me to expand on for just a minute. What John is referring to is we work together on this clinical trial that Pfizer sponsored on pregabalin for post-traumatic peripheral neuropathic pain. I think it ended up being about 600 patients randomized and more than 900 [indiscernible], something like that.

There was a long list of inclusion/exclusion criteria as there typically are, but this particular syndrome is kind of a squishy diagnosis

Page 395

where there's a little bit of art involved, so we created a very detailed patient intake worksheet and had the investigators complete them. And then if the investigator thought the patient was eligible, then we had that worksheet reviewed by a team of three external neurologists to provide independent verification that the patient actually had the syndrome.

We ended up excluding almost 30 percent of the patients that the investigators wanted to enroll in that clinical trial because, for example, I have post-traumatic neuropathic pain because I slipped down the stairs 6 years ago and hurt my back, and now my hands are tingling. And that was a case of post-traumatic neuropathic pain; that was an actual case, and we had many more like that.

So it's quite amazing how when you leave investigators on their own to operate a set of inclusion/exclusion criteria, you can wander pretty far off the reservation in terms of the type of patient you're actually looking for. And an extra pair of eyes, at least in our experience, made a

Page 396

very big difference.

DR. MARKMAN: I think, again, that's a study conduct issue. The trial did not separate. So we don't really know whether that has an effect on detecting signal. As an assay sensitivity issue, I think it's an open question in my mind. But what it does tell you is that the study you thought you conducted you actually conducted in those 15 countries. So from a study conduct perspective, I think it's incredibly reassuring from a quality standpoint. I think that the jury is still out on whether that has an effect on assay sensitivity.

DR. TAYLOR: And Nate, could I make a comment on that one as well?

DR. KATZ: Please.

DR. TAYLOR: So I think, again, we're going back here to the issue of what we might define as being expertise. And I would put it to you, we need to be careful not to conflate two forms of expertise here. So it's the expertise in patient selection, and I think that's what you've just articulated in that previous drug. It's very

Page 397

important to choose the right squishy patient, and you have to be really, really careful about doing that and designing the trial to ensure that inclusion/exclusion criteria, external verification of that.

But I would put it to you that that's not a peculiarity of neuromodulation; that's true of any setting, with respect. But I think what is an important peculiarity of expertise -- peculiarity again -- in this area is the learning curve. In other words, it's the expertise and the delivery of the therapy. And there's a well articulated literature in the medical device and interventional literature that there is a learning curve.

By definition -- and I'm looking around at some of my colleagues in trials that we've been involved in -- we've just said that if a center hasn't implanted at least X patients, then we wouldn't want them to be part of this trial. An X has been a little bit sort of finger in the air, but we've been clear that centers do have to have a minimum volume of expertise in the last previous 12

Page 398

months.

I think, again being explicit about that, where I probably struggle a little bit, Nate, is saying what X should always be. But would we agree, at least if we were making a statement, that in designing trials, trials should think about the learning curve and recruit centers accordingly, and just be explicit about that, and ask them to report -- going back to Jane's point -- about what their criteria is for minimum volume.

DR. MARKMAN: And I think sponsors already do that, from our experience.

DR. TAYLOR: Oh, yeah.

DR. MARKMAN: I think that this is something that's already being done; we're just codifying it. But to go back to the first point about the squishiness of this diagnosis relative to drug trials, because this is labeled for intractable pain of the trunk and legs, it's very different than enrolling a trial where the FDA is stipulating if you want an indication for spinal cord injury pain, or an indication for post-traumatic

Page 399

neuralgia, or an indication for post-herpetic neuralgia. There is a level of rigor to that characterization as opposed to intractable pain of the trunk and legs.

So I think that the issue becomes because these devices are labeled, frankly, the way that opioids are labeled, for moderate to severe pain around the clock when nothing else doesn't work, it's such a broad label that you have a quality issue right there because nobody's getting a very high bar in terms of case definition.

DR. NORTH: To your point, Rod, about X, the minimum necessary volume, that might be necessary, but it's certainly not a sufficient criterion for selecting a study center and an implanter. Just because the local rep got a big bonus because of the case volume, that does not necessarily mean that the implanter is technically skilled, just that they do a lot of cases. That's true of surgical procedures in general.

DR. KATZ: We've been maybe unintentionally making a list of the peculiarities of spinal cord

Page 400

stimulation that need to be addressed in the context of recommending research standards and what makes this different than every other kind of intervention that we're studying in chronic pain.

We've got the learning curve. We've got the issue with the programming. We've got the issue with different devices, and probably a few more that I'm not remembering right now.

Are there any other peculiarities of this type of intervention that needs special discussion or consideration in recommending research standards beyond what IMMPACT has already done for 85 papers? Greg?

DR. FIORE: One thing that also comes to mind that um, you touched on in your presentation, which is the interaction between the staff and the subject because of the point that was raised by Brian and others today around the upfront investment by the subject to undergo the procedure in a clinical trial setting.

There needs to be more interaction with the site staff. It can't just be a hands off, here's

Page 401

an option versus a sham or something like that. There has to be some selling or some upfront discussion there that may bias the subject. So that may be something that we can make some comments about.

DR. KATZ: Sure.

DR. THOMSON: I think the other thing that's peculiar is that this is a functional device. Do you Tana Gachi [ph], this electronic device that you had to look after and feed and change diapers or whatever. Nobody knows its analogy now. It's a bit like a Tana Gachi. You've got to kind of feed it and charge it. You've got to switch it into nighttime mode, and all those different things. That's the degree of interaction the patient has to have with their therapy, from passive treatments, like a fusion or taking a tablet.

DR. KATZ: Bob?

DR. DWORKIN: Nate, I think this was implicit in presentation, but I could imagine an article, like the one you're going to draft, having a checklist of the various different possibilities

Page 402

for blinding. We don't have anything like that in any articles about drug trials because it's obvious.

You've got an active pill, and a placebo pill, and they taste, and look, and smell, et cetera, the same. But it seems to me for these trials, we really can establish a checklist of the different possible ways the trial can be either fully double-blinded -- I take the point that that's going to be rare -- or semi-blinded, blind outcome assessments; blinding the patients to the characteristics of the device and the comparator; blinding the implanter if that's possible; the study nurses; the staff from industry.

So from my perspective, I'd love to see a list of blinding parameters. And then when a study gets published, they would have to ideally refer back to that and say we were able to do 1, 4, and 6, but we couldn't do 2 and 7, and explain; instead of -- and I'm thinking here of the Senza trial.

My recollection of the Senza trial, there's one sentence saying, "Because of the nature of this

Page 403

trial, blinding was not possible." To me, that's just totally inadequate. There should be some struggle in the manuscript that reflects we've done our damnedest to blind every one possible. And maybe we couldn't do it completely, but this is what we did.

DR. KATZ: I think also what we tend to forget about, we tend to think about blinding as the goal. But blinding a means to an end, and the end is having balanced expectation of benefit across groups. Blinding is just one method for accomplishing that. And when you can't blind because it's parasthesia versus -- or whatever the issue might be, maybe you can -- I'm not saying you can't blind in those circumstances. But if there's some reason why you can't blind but instead you find some alternative method for achieving balance of expectation, which you can document, then that should be done.

DR. DWORKIN: Doing that makes you think if Dennis and I are to do a study comparing cognitive behavior therapy and health education, we don't

Page 404

tell the patients the cognitive behavior therapy is the active treatment and health education is the placebo control. And we do our damnedest, if we can, to not even tell the person doing the cognitive behavior therapy and the health educator that our hypothesis is this is going to do better than that. So I think there's a lot more that can be done.

DR. HAYEK: There are other things peculiar to spinal cord stimulation or device studies is how long are you going to follow up these patients, and when do you determine that, yes, this is a long enough duration to say it's worthwhile from a cost effective standpoint and from an efficacy standpoint.

The frequency of interventions, both positive and negative, how often do you need to reprogram? Pain is not constant. Stimulation is not constantly delivered the same way. There are different paradigms of stimulation. You cycle. You give constant stimulation. You use the different stimulation parameters. There's a ton of

Page 405

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

Page 406

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

Page 407

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

Page 408

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

Page 409

messages about this reprogramming time. Maybe we could try, in the remaining few minutes we have, achieve clarity on this issue before we break for the evening.

I heard, Simon, your suggestion that if the patient needs more programming visits, well, fine, we'll give it to them in order to optimize the therapy, but we'll track that in some sense as an adverse events. If we were in a flexible dose drug trial, if the trial allowed flexibility in dosing, we probably wouldn't handle it as an adverse event unless there really was an adverse event. We would just track how many dose changes they needed or what have you as a secondary endpoint, but I hear what you're saying.

I also heard I think from Salim that there may be a possibility of fixing the amount of reprogramming. If you need more, too bad, and if your pain is not well controlled because of that, well then, that gets reflected in your endpoint. So it all comes out in the wash that way.

I've also heard that we could give more

Page 410

reprogramming if we felt the patient needed it and count it as a secondary endpoint, how many reprogramming visits did the patient require. If in this arm they require 20 reprogramming visits and that one 10, well then, that's a reflection of the efficacy of therapy, but of course that can confound the primary endpoint of pain intensity reduction.

I feel like I've heard a few different versions, each with some overlap with the other.

DR. MARKMAN: I just think, Nate, your point about a flexible dose trial, I think that's the perfect metaphor. In a flexible dose trial, you're allowed a defined period and a defined number of dose changes, and then there's a bunch of outs for adverse events.

So if your stimulation is unpleasant, if your leg's jerking, or you can't sleep at night, whatever it is, or the stimulator pocket is too hot, whatever it might be, you get a free out for a negative event just like we do when a patient is being titrated on an opioid or gabapentin, and then

Page 411

you get a set number of dose optimization during the 3-week period. You get what you get. That's how we do it in a flexible dose trial.

DR. NORTH: The parasthesia-free paradigm, for HF10, as I understand the programming strategy, because the patient can't feel anything, they come back if they don't have adequate pain relief after a few days and try a new contact combination. And if that doesn't work, they try another. And that can be standardized, but that means patients in the sham group are going to be doing the same thing. But it's all manageable.

DR. KATZ: So I'm hearing that the recommendation would be a prespecified standard frequency of reprogramming with some limited flexibility built in. And if somebody needs to go beyond that flexibility, it's tracked in some way; either there's a treatment failure or an adverse event, and obviously all those rules would need to be prespecified so that they are applied consistently across the trial.

Something like that? Is that what I'm

Page 412

hearing?

DR. McNICOL: Nate, your comment about treatment failure, I think if we're using a metaphor between spinal cord stimulation and drugs, treatment failure with a drug trial, you stop the drug. No huge investment there. You maybe try something else or a different mode of therapy.

Treatment failure with spinal cord stimulation is a much bigger adverse event. You talk about the investment going in. What's the investment coming out? You're quantifying adverse events, but you're not comparing like with like. Treatment failure with drugs, not the end of the world. Treatment failure with spinal cord stimulation explant, another surgery --

DR. MARKMAN: That is why the temporary trials is so important. That is why the temporary trial is so critical because that is a point which you can actually -- you have reversibility.

DR. REZAI: Patients have failed medications to a certain extent, it's not like a primary treatment for them.

Page 413

DR. HAYEK: Sam has a whole talk about the trial being not very predictive and we don't have good data on that.

DR. NORTH: How many weeks on a new drug are necessary before we conclude it's failed? Whereas with an SCS trial, we go for a few days, and then we start to worry about the cumulative risk of infection. It's a very different --

DR. MARKMAN: Unless you're in Belgium. You take the --

DR. KATZ: I think, Ewan, just to address your point, and then I'll go to Rod, one could imagine a different thinking about treatment failure from an analytic perspective versus from an explant perspective.

So if somebody needs to go beyond the prespecified number of reprogrammings, for example, we could take that into account in assessing their primary endpoint either through imputation or calling them a nonresponder, whatever, but still give them the treatment that they need so that the device has the best chance for the patient staying

Page 414

in. Treatment failure, I think we can look at it in those two ways.

Rod?

DR. TAYLOR: Just going back to the reprogramming, I would just, again, implore us to be careful. I think reprogramming is a pragmatic thing that happens in trials, and we ought not to constrain it. I think the way we capture it, it carries a cost. I was just going to say Brian and I would just quantify that in terms of economic costs. So it's back to your point --

MALE VOICE: Be careful what say. He's not that far.

(Laughter.)

DR. KATZ: He just moved seats. I think he's still the same person in that other seat.

DR. TAYLOR: So we would quantify the number of reprogrammings in terms of resource utilization, and therefore attach a cost to it. I think that's all I would want to --

DR. HAYEK: That should be a limit, though. Like in sham, they may have a lot of reprogramming

Page 415

sessions.

DR. TAYLOR: I agree conceptually, I wouldn't want as a patient to think I'm going to be coming back to my battery retuned everyday for the next 10 days. As much as I like you, Rick, I probably wouldn't want that. But I think again, it's just that the perfection is the enemy of the good here, so I think just being pragmatic about reprogramming and saying that we capture as a secondary process outcome, and then we can penalize the therapy by applying a cost to it because it may not change the effectiveness, but it will certainly impact on its cost.

DR. KATZ: The issue that I think we're still left with -- and I can see Howard shaking his head; maybe I can guess Let's say for example, one group, the pain scores is 4, and the other group, the pain score is 5. Great. The pain score is lower in this group. But if this group needs twice as many reprogramming sessions as this group, then how do you interpret your primary endpoint?

DR. FIELDS: You read my mind.

Page 416

DR. KATZ: I did read your mind?

DR. TAYLOR: Well, can I answer that?

DR. KATZ: Yes, please.

DR. TAYLOR: I think what I would do is look at the efficacy delta relative to the cost delta. So it may be that you can achieve better outcomes for more reprogramming with one versus two, but that will come at an additional cost. And a cost per quality framework. -- again, I can't speak for Brian -- I'd be very comfortable about assessing it in that framework.

So for me, it's more a resource utilization issue rather than an effectiveness one per se. But I think the point we're making -- and again, not wanting to be over-prescriptive -- is that we could maybe make a recommendation that it's recognized that reprogramming is an important issue in trial design and at least needs to be quantified.

Perhaps some consideration needs to be given as to whether there are some limits that should be allowed within the trial design. But again, just be careful that we're not the hostage sort of

Page 417

action.
DR. NORTH: The resource we should be talking about is just a computer. We taught a computer 30 years ago to interact directly with the patient and run the trial. So the only resource you really need is the computer and a quiet place for the patient to sit and follow the directions. We had enough artificial intelligence, which is a buzzword nowadays, 30 years ago to do this. We certainly should be able to do it now.
DR. TAYLOR: That's tomorrow. I think still today, that reprogramming -- correct me if I'm wrong -- requires a human interaction.
DR. FIELDS: We could have sham reprogramming, and you could have both of them be randomized so that people who got better and people who got worse both had reprogramming sessions. That's the only way you can keep the two groups comparable. Once you start selecting out patients for reprogramming, the groups are no longer comparable, so the study is dead in my mind.
DR. KATZ: Jane, last comment for you.

Page 418

DR. SHIPLEY: I was just wondering if we're keeping the idea of having study results be generalizable in front of us. I was especially thinking about that when we were talking about competency of the study sites, although I'm all in favor of people only doing this if they're competent in general. But if we are real specific, if we have computers and nobody else does, are our results going to be generalizable?
I'm a big fan of the computers, Richard. I'm not trying to say we shouldn't do it.
DR. NORTH: Well, once you develop the computer, the first one costs a lot of money and the next one 10 cents because it's just a matter of loading the software.
Adjournment
DR. KATZ: All right. Well, it's time. I think we'll break now. I think it's been an extremely interesting and lively discussion. I really do appreciate everyone's interest and enthusiasm.
Dinner is in the Thomas board room. If you look at your agenda, it's 7:00. Please, if you did fill out that survey, which I hope everybody did, drop it off with Valorie on the way out, and I'll try to synthesize them tonight for tomorrow. And I look forward to seeing all of you at dinner.
(Applause.)
(Whereupon, at 5:29 p.m., the meeting was adjourned.)

Page 419

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