

*IMPACT XXIII - Central Sensitization/Somatosensory
Amplification and Multiple Comorbidities*

July 26, 2019

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1 ACTTION

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5 INITIATIVE ON METHODS, MEASUREMENT, AND

6 PAIN ASSESSMENT IN CLINICAL TRIALS

7 IMPACT-XXIII

8

9 Research Design Considerations for

10 Chronic Pain Clinical Trials

11 Addressing Central Sensitization/Somatosensory

12 Amplification and Multiple Comorbidities

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16 Friday, July 26, 2019

17 8:00 a.m. to 2:53 p.m.

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20 The Westin Georgetown

21 Washington, DC

22

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3 Consensus Discussion: What Specific 167

4 Recommendations Can Be Made for

5 Chronic Pain Clinical Trials Addressing

6 Central Sensitization/Somatosensory

7 Amplification and Multiple Comorbidities?

8 Moderators - Robert Dworkin, PhD

9 Annie Kleykamp, PhD

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1 C O N T E N T S

2 AGENDA ITEM PAGE

3 Implications of Central Sensitization and

4 "Centralized Chronic Pain" for the

5 Design of Chronic Pain Clinical Trials

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7 Implications of Somatosensory

8 Amplification for the Design of Chronic

9 Pain Clinical Trials

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12 Comorbidities for the Design of Chronic

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15 Q&A and Panel Discussion 95

16 Moderator - Nathaniel Katz, MD

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

2 (8:00 a.m.)

3 DR. KATZ: Good morning, everyone. For

4 those of you that I don't know, which I think there

5 are very few of you, my name is Nathaniel Katz. I

6 have a very easy and pleasant job this morning,

7 which is to introduce some of my favorite people

8 who are speakers this morning, and I would like to

9 begin with Dr. Srinivasa Raja.

10 Where are you, Raj? There you are.

11 Everybody I think knows Raj. He's been one of the

12 most longstanding and prolific contributors to the

13 pain field, I would say, someone who I've had the

14 pleasure of learning a great deal from over the

15 years and counting as a professional friend. He'll

16 be speaking to us, introducing the first session.

17 Thank you, Raj.

18 Presentation - Srinivasa Raja

19 DR. RAJA: Good morning, everyone.

20 Yesterday, we started with an incredible journey,

21 almost a full decade journey from the start of the

22 reports of central sensitization to 2019, where we

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1 have these clinical pain syndromes and overlapping
 2 pain conditions.
 3 The task I was given was a simple task of
 4 summarizing all of this work and coming up with a
 5 design for a clinical study in the next 45 minutes.
 6 (Laughter.)
 7 DR. RAJA: When Bob or Dennis sends me an
 8 email or asks me to talk at this meeting, I usually
 9 say yes because I think of it as an exercise for my
 10 aging brain.
 11 (Laughter.)
 12 DR. KATZ: Then, as I started researching
 13 this area and figuring out what I should be saying
 14 and summarizing some of this work, I started
 15 getting a little worried because I thought I was
 16 seeing signs of the shrinking of that brain,
 17 especially in the prefrontal cortex and maybe in
 18 the hippocampal regions, because I ended up having
 19 more questions than answers.
 20 Fortunately for me, I had Helen Keller who
 21 was comforting me by telling me that it's okay to
 22 have questions. When you have these kinds of

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1 questions, then you say how do you go about talking
 2 to this erudite audience? So like Charlie, I kind
 3 of asked Lucy for some advice, and Lucy gave me
 4 this advice. "If life seems to have more questions
 5 than answers, try to be the one who asks the
 6 questions."
 7 (Laughter.)
 8 DR. RAJA: So I think in my presentations, I
 9 will provide some perspective, but I also will be
 10 asking quite a few questions, hoping that the
 11 collective expertise here will answer those
 12 questions.
 13 We heard this phrase from Clifford
 14 yesterday, "What's in the name?" And I think I have
 15 to differ from Shakespeare who said, "A rose by any
 16 other name would smell as sweet." So maybe it's
 17 true for a rose, but in researching this topic that
 18 we're discussing in the last 24 hours, what I came
 19 across is this list of names for this condition.
 20 This is not an extensive list. It's central
 21 sensitivity syndrome; centralized chronic pain;
 22 overlapping chronic pain conditions; chronic

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1 widespread; chronic primary pain;
 2 fibromyalgia-ness; nociplastic pain; and many more.
 3 Looking at Steve, I feel like we are in this
 4 field where CRPS was more than two decades ago,
 5 before things like reflex sympathetic dystrophy,
 6 causalgia, Sudeck's atrophy, et cetera, and a
 7 single name came up for that. So I think the first
 8 thing is the name does matter, and if different
 9 specialties refer to those conditions by different
 10 names, I think the field will take a lot more
 11 longer to progress.
 12 What are you talking about? Is this a
 13 condition? Is this a disease? Is it a disorder?
 14 Is this a syndrome? Each of those have special
 15 meanings. I personally think that we are dealing
 16 with a syndrome, a collection of signs or symptoms
 17 that characterize or suggest a particular disease.
 18 You also heard from Roger and several others
 19 that this central sensitization has maybe associate
 20 overlapping pain conditions. If there's one thing
 21 during my long association with Bob Dworkin, that
 22 is if you need to make an impact in a field, you

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1 have to have an appropriate acronym. And that
 2 acronym should have at least a word that has some
 3 action in it, and it has to have one or more
 4 letters that are replicated or duplicated, and it's
 5 better if you have a logo that goes with it.
 6 So here's my suggestion, CCOPSS or chronic
 7 centralized overlapping pain sensitization
 8 syndromes --
 9 (Laughter.)
 10 DR. RAJA: -- and here's the logo that goes
 11 with that.
 12 (Laughter.)
 13 DR. RAJA: So the question is why this
 14 IMMPACT meeting? What prompted Bob to say that we
 15 need to have a 2-day session to consider these
 16 conditions such as central sensitization and some
 17 somatosensory amplification? One hypothesis I had
 18 was maybe there is possibly a central common
 19 mechanism for these conditions that is different
 20 from acute or chronic thing conditions such as
 21 inflammatory on neuropathic pain states. So maybe
 22 the central sensitization that occurs in these

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1 disorders is different from the central
2 sensitization which we know occurs after
3 inflammation or after neuropathic pain. There's
4 some suggestion, based on twin studies, that they
5 may be a greater genetic influence for these
6 chronic overlapping conditions.
7 An inference of that is that treatment
8 effectiveness in central sensitization syndromes
9 may be unique and may be different from other
10 chronic pain conditions. And hence, if you want to
11 design a study, it should be appropriate for those
12 therapies.
13 I've long been interested in neuropathic
14 pain, that's been married, and the poster child for
15 the central sensitization syndrome is fibromyalgia.
16 I started by looking at are there differences in
17 terms of drugs that work for these two conditions?
18 As you've already heard, partly yesterday,
19 the FDA approved drugs for fibromyalgia,
20 duloxetine, pregabalin, and milnacipran, and they
21 are also approved for neuropathic pain states such
22 as diabetic neuropathy, chronic musculoskeletal

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1 pain; and in terms of pregabalin for diabetic
2 neuropathy, postherpetic neuralgia and spinal cord
3 injury pain. Although milnacipran, I couldn't find
4 a study that's specifically looking at neuropathic
5 pain, at least preclinical studies seem to suggest
6 it's effective in neuropathic pain states as well.
7 We also heard about other drugs or
8 treatments such as ketamine infusions, which work
9 in about 60 percent of fibromyalgia patients but is
10 also effective in neuropathic pain patients, and
11 studies to show that CBT is also effective in
12 fibromyalgia and neuropathic pain and
13 osteoarthritis. Drugs that are not effective in
14 neuropathic pain states are also not useful in
15 fibromyalgia. An example is NSAIDs, and the
16 Cochrane review suggests that NSAIDs are not
17 effective in treatment of fibromyalgia.
18 Here are the treatments that are effective
19 for neuropathic pain and are also effective for the
20 poster child condition, fibromyalgia. One can say
21 maybe the drug response or dose-response curves for
22 these two conditions may be different. Thanks to

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1 Lesley, we have this study where she looked at
2 studies of a single drug, pregabalin, post-diabetic
3 neuropathic pain, postherpetic neuralgia, and
4 fibromyalgia, and this shows the global impression
5 of change is fairly similar in PHN and fibromyalgia
6 in terms of percent responders. Also, the change
7 in sleep quality is similarly effective in both
8 neuropathic pain states and fibromyalgia.
9 One can then ask the question, is this
10 primarily an issue of assay sensitivity. The trial
11 designs are not sensitive enough to differentiate
12 central sensitization from other conditions such as
13 neuropathic pain?
14 We've talked about this amplification that
15 occurs in central sensitization and is there
16 difference between neuropathic pain and other
17 central sensitization syndromes, nearly an extent
18 of the magnitude of the amplification or the extent
19 anatomically in terms of where the amplification
20 occurs, such that in post-op pain, maybe the
21 amplifier is turned on slightly, in neuropathic
22 pain, a little bit more, and central sensitization

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1 or fibromyalgia, it is set to a maximum.
2 An ultimate explanation may be there's a
3 totally different mechanism for the central
4 sensitization that occurs in neuropathic pain
5 versus the central sensitization syndromes such as
6 chronic overlapping pain conditions.
7 In developing a clinical study, the basics
8 of it is to define the population that you're
9 interested in, which is the reference population.
10 You have an objective or a primary question that
11 you're interested in. Design the study by picking
12 a study population, including inclusion/exclusion
13 criteria, and then figure out the outcome measures
14 you'd be interested in.
15 If you have it in a tabulated format, what I
16 hope to do is to pick certain aspects of this
17 one-on-one study design, that is what should be the
18 reference population and what should be the study
19 population; how do they allocate randomly; and
20 maybe the assessment outcome measures.
21 What should be the reference population for
22 central sensitization and centralized pain? One

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1 could say that you could pick patients with central
 2 sensitization or somatosensory amplification as
 3 exemplified by an enhanced stimulus response
 4 function regardless of their clinical presentation,
 5 and regardless of whether it's musculoskeletal
 6 pain, visceral pain; or joint pain, so regardless
 7 of the primary pain state.

8 Or you could say you are interested in a
 9 population of centralized span by which some
 10 implied that this is pain which is totally
 11 independent of the peripheral afferent drive, where
 12 there's autonomous central sensitization that
 13 occurs. This will essentially be a subset of the
 14 patients with, say, fibromyalgia.

15 It's clear from some recent studies that not
 16 all patients with central sensitization have
 17 centralized pain. This is a study from Staud,
 18 where they did pressure pain thresholds, injected
 19 some local anesthetic lidocaine into a muscle, the
 20 deltoid, where they were looking at pressure pain
 21 thresholds.

22 They were comparing normal subjects with

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1 patients with fibromyalgia, and obviously they
 2 showed that the pressure pain thresholds were lower
 3 in the fibromyalgia patients. But when they
 4 injected the lidocaine and tested both the sites
 5 where it was injected or the muscle that was
 6 injected, as well as broadly across other muscle
 7 populations, they found that there was an increase
 8 both at the site as well as peripherally. So that
 9 suggests that at least in a subset of patients of
 10 fibromyalgia, the periphery seems to have played a
 11 role.

12 A study that was just published in this
 13 issue of Pain from a Danish group, looks at phantom
 14 pain and neuropathic pain states, and looked at
 15 peripheral nerve block, and showed that a
 16 significant portion of those patients, their pain
 17 was reduced significantly, complete and a good
 18 relief from a local anesthetic peripheral block,
 19 again suggesting in neuropathic pain states as well
 20 a subset of patients have an afferent drive that is
 21 plays an important role.

22 We talked about quite a bit yesterday as to

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1 whether some of you are lumpers, or some of you are
 2 splitters, and maybe some of you are sitting on the
 3 fence. The lumpers may say that central
 4 sensitization and chronic overlapping conditions
 5 share a common pathophysiology or mechanisms, that
 6 the drugs that are effective have similar efficacy
 7 across these different pain conditions.

8 The splitters may say that the patients with
 9 centralized pain may differ in their drug response
 10 compared to those where the peripheral drive has an
 11 important role. Some of those would say that the
 12 fibromyalgia phenotypes, whether it's top-down or
 13 bottom-up, may differ in the therapeutic responses.

14 So the question that you may ask and the
 15 population that you may study may vary depending on
 16 the type of questions that you're interested in.
 17 So what should be the study population, then? We
 18 said the broad clinical features were widespread
 19 pain and multisensory hypersensitivity, but other
 20 conditions such as fatigue affect, liability,
 21 changes in mood, sleep disturbances, cognitive
 22 disturbed problems; how many of these features do

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1 you need and what is the sensitivity and
 2 specificity, based on purely clinical features.

3 We also talked about certain mechanistic
 4 neurobiological correlates such as increased gain
 5 in the somatosensory system, exemplified by
 6 allodynia, hyperalgesia, temporal summation, and
 7 wind-up, and reflects nociceptive thresholds or
 8 objective markers as Vitaly talked about, such as
 9 neuroimaging.

10 In response to a question that my kids
 11 usually used to ask when we were on long drives,
 12 "Are we there yet?" the answer I heard was not yet,
 13 that these mechanistic or neurobiological
 14 correlates are not useful for diagnosis in a given
 15 patient, but maybe these may be useful as potential
 16 outcome measures for maybe subtyping or phenotyping
 17 into subgroups of patients, so we'll come to this.
 18 I'm going to talk quantitative sensory testing or
 19 imaging because my colleague Claudia will be
 20 talking much more on that in the next presentation.

21 Then we are left with some screening tools,
 22 which are rapid screening tools for fibromyalgia.

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1 Three of the tools that have been in the
 2 literature, one is a FibroDetect from the German
 3 group. Ralf Baron's group is kind of a
 4 modification of the NeuroDetect, and then Lesley's
 5 fibromyalgia diagnostic screen, I'm going to let
 6 her talk about that because I'm sure she knows more
 7 than I do, and then the fibromyalgia Rapid Screen
 8 tool.

9 The FibroDetect was started with about 14
 10 questions, and then it was pared down to about
 11 7 questions, and the total scores ranged from 0 to
 12 9. It's kind of yes/no answers. If the score was
 13 over 6, then the sensitivity and specificity for
 14 fibromyalgia was about 77 percent.

15 The FiRST, or the Fibromyalgia Rapid Screen
 16 tool is, again, a self-administered tool with
 17 6 questions; again, yes/no answers. A score of 5
 18 or more had a high sensitivity for fibromyalgia.
 19 This was compared with either the ACR-90 diagnostic
 20 tool or how clinicians diagnose these patients.
 21 And again, these tools had sensitivity of
 22 76 percent and specificity around 80 percent or so.

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1 These could be rapid screening tools for
 2 fibromyalgia, but the question is, are these tools
 3 specific to fibromyalgia or are they generic enough
 4 to detect other central sensitization conditions
 5 and/or chronic overlapping pain conditions? The
 6 answer I think is, as far as I know, they're more
 7 specific to fibromyalgia and may not be useful for
 8 other conditions.

9 Then we are left with some screening tools
 10 that are more specific for central sensitization.
 11 Obviously clinically, there is widespread
 12 unpleasant experiences that is disproportionate to
 13 any observable peripheral cause. Three of the
 14 screening tools that have been used are the Pain
 15 Sensitivity Questionnaire, the Central
 16 Sensitization Inventory, and the Sensory
 17 Hypersensitivity Scale.

18 Of these, the Central Sensitization
 19 Inventory has been studied widely and used in the
 20 literature. I am searching the NIH sites. I scan
 21 across another tool, a centralized pain index that
 22 was part of an aim for an NIH grant, and Dan may be

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1 able to tell us later because he's the PI on that
 2 grant, which is partly aimed at constructing a
 3 centralized pain index.

4 What is the Central Sensitization Inventory?
 5 It identifies key symptoms associated with central
 6 sensitization. It consists of 25 questions related
 7 to current health symptoms, and each symptom's item
 8 is measured on a 0 to 4 Likert scale, so we would
 9 have a total score of 100 at the maximum. It's
 10 been validated for fibromyalgia, chronic widespread
 11 pain, chronic low back pain, and compared with
 12 normal subjects.

13 What you see in the scale from this study by
 14 Mayer, et al. is that normal subjects, or even
 15 patients with low back pain, have a scoring of
 16 around 40 or less, and patients who are with
 17 fibromyalgia had scores of around 60 or so. That
 18 seems to be inventory that suggests, or at least
 19 goes along with, patients with more widespread
 20 pain.

21 The other hypersensitivity scale that is
 22 considered to be an index of sensory

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1 hypersensitivity looks not only at pain but also a
 2 variety of stimuli such as taste, light, touch,
 3 smell, allergies, heat and cold. What they showed
 4 is, again, it's a 25-items measure, and it's a
 5 human factorial measure of sensory
 6 hypersensitivity. It's shown to have some modest
 7 association with three quantitative sensory testing
 8 measures such as heat threshold and tolerance, as
 9 well as cold tolerance.

10 The fibromyalgia subjects scored higher than
 11 patients with low back pain, or osteoarthritis, or
 12 controlled subjects. This sensory hypersensitivity
 13 scale, unfortunately, also correlated with symptoms
 14 of depression and anxiety. Whether this is unique
 15 for the aspect of central sensitization or it shows
 16 other factors such as symptoms and depression, as
 17 well as anxiety, is unclear to me at this stage
 18 here.

19 Based on a consensus panel of sorts, Europe
 20 recommended the following criteria for diagnosis of
 21 central sensitization from muscle disorders or
 22 musculoskeletal pain; that is if the pain is

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1 disproportionate to, quote/unquote, "the pain
 2 experience," and if it has a diffuse pain
 3 distribution, then these patients have central
 4 sensitization. If they don't have both of those
 5 but yet have a score greater than 40 on the Central
 6 Sensitization Inventory, or CSI, then they still
 7 may be having central sensitization. This was by
 8 Nijs, et al.

9 Subsequently, Williams modified this a bit
 10 and says it should be a diagnosis of exclusion.
 11 You rule out neuropathic pain, you rule out
 12 nociceptive pain, and then if the pain experience
 13 is disproportionate to the nature or the extent of
 14 the injury and has a diffused distribution, and
 15 they meet criteria 1 to 3, then they have central
 16 sensitization. Or if they meet 1 and 2, that is
 17 they don't have neuropathic pain, they don't have
 18 inflammatory pain, but they have this general
 19 hypersensitivity to sensory stimuli that still
 20 could fit into this central sensitization group.

21 The pros and cons of these self-assessment
 22 tools, obviously they're practical, they are easy

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1 to administer, and they have been validated
 2 comparing other conditions to fibromyalgia.
 3 However, the cons are that they have not been
 4 tested carefully in terms of how they correlate
 5 with objective measures, such as measures of
 6 temporal summation, central pain modulations, or
 7 even neuroimaging.

8 The other question is, are these measures to
 9 specific for fibromyalgia and not generic enough
 10 for other chronic overlapping pain conditions? I
 11 think these are things that we need to discuss.

12 We talked in terms of objective biomarkers.
 13 We talked about the role of quantitative sensory
 14 testing and imaging, and those, as far as I know,
 15 are not useful as diagnostic tools. But just for
 16 completeness sake, I wanted to also indicate that
 17 studies have shown in patients with fibromyalgia,
 18 there is an increase in pain facilitating
 19 neurotransmitters such as NPY, CRS, Substance P,
 20 BDNF, and even inflammatory biomarkers such as
 21 cytokines, IL-6, IL-8, and IL-1 beta, and TNF
 22 alpha.

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1 So in patients with central sensitization of
 2 fibromyalgia, some of these biomarkers are
 3 enhanced. That is pain facilitating biomarkers or
 4 neurotransmitters, why there is a decreased
 5 production of inhibitory transmitters such as 5HT
 6 dopamine and beta endorphins, so something to
 7 consider. Again, the sensitivity and specificity
 8 of these as a diagnostic tool in a given patient is
 9 not known first.

10 I came in searching for this. I came across
 11 an article in a journal that I do normally read,
 12 the Journal of Biological Chemistry, but it tweaked
 13 my interest because it talked about a chemical
 14 fingerprint for fibromyalgia. It tweaked my
 15 interest even further because the diagnostic tool
 16 is based on a phenomena called Raman scatter, which
 17 is based on a discovery that was made by an Indian
 18 physicist who was the first Indian physicist to get
 19 the Nobel Prize in 1930, and he was knighted by the
 20 Britishers of that time.

21 This Raman scatter is actually when a
 22 indirect light hits an object, obviously the light

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1 scatters, and that is relevant as the initial
 2 light. But there are other smaller, less abundant
 3 scatters that are light, which he discovered known
 4 as the Raman scatter. In this particular study, a
 5 single dried blood spot from a finger stick was
 6 analyzed from patients with fibromyalgia, and it
 7 showed specific microspectroscopic signals, or
 8 peaks, as well as some infrared peaks. Then these
 9 peaks that were seen in patients with fibromyalgia
 10 were compared with patients with SLE, or lupus
 11 erythematosus, and with rheumatoid arthritis.

12 Using the combination of the Raman
 13 spectroscope as well as the infrared spectroscope,
 14 there were clear patterns that could be shown that
 15 could separate patients with fibromyalgia from
 16 rheumatoid arthritis, as well as SLE. And more
 17 interestingly, apart from the fact this is a single
 18 blood stick that has a metabolic fingerprint, what
 19 they showed was, in an interesting analysis, that
 20 the changes that they observed in the spectroscope
 21 correlated with self-reported disease activities,
 22 or symptoms, as determined by the FIQR score, which

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1 is a Revised Fibromyalgia Impact Questionnaire. So
 2 here is a tool that not only can diagnose this
 3 condition but also correlate symptomatically with a
 4 degree of symptoms. So maybe we'll find out
 5 whether it comes out as a tool in the future.
 6 The other question that comes to mind, we
 7 had some discussions yesterday, the question of
 8 whether we should include or exclude in a study
 9 patients with multiple comorbidities such as
 10 fatigue, mood disturbances, sleep disturbances, and
 11 cognitive changes.
 12 If you are a lump, you might say that this
 13 is part and parcel of fibromyalgia, and they may
 14 have a shared mechanism or it's secondary to a
 15 consequence of the widespread pain, and that pain
 16 relief will also result in improvement of these
 17 different factors. If you're prone to be a
 18 splitter, you might say this may confound your
 19 results, and the interpretation of the results may
 20 be difficult.
 21 In the drug study pregabalin in fibromyalgia
 22 patients, many of these patients also had

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1 osteoarthritis, and Charles Argoff did some
 2 retrospective analyses on these studies, whereas
 3 some patients with fibromyalgia also had
 4 osteoarthritis, and looked at dose-response curves,
 5 and clearly showed that regardless of all the
 6 patients with osteoarthritis or not, the pregabalin
 7 was effective in reducing the pain of fibromyalgia.
 8 But the more relevant question that was
 9 unanswered is what was the effect of the treatment
 10 of pregabalin on the osteoarthritic pain in these
 11 patients with fibromyalgia? So you don't know from
 12 the study is the drug equally a factor in treating
 13 fibromyalgia, and also a factor in treating the
 14 osteoarthritis.
 15 The other aspect is that the patients with
 16 fibromyalgia are a heterogeneous group. In this
 17 study, it looked at more than 1200 patients with
 18 fibromyalgia and classified them using cluster
 19 analysis into 5 different clusters. Cluster 1 is
 20 those who had high pain had severe mental and
 21 physical impairment. Cluster 2 had high pain but
 22 predominantly physical impairment. There were

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1 other clusters where there were more mental
 2 impairment and less pain.
 3 Then they looked at the efficacy of
 4 duloxetine in these different clusters, and the
 5 bottom line is that the mental impairment, based on
 6 the scales they used, was most attuned to
 7 comorbidity, and it influenced the outcome of the
 8 drug therapy compared to physical impairment. The
 9 better treatment effect of duloxetine they observed
 10 are those who had physical impairment and high
 11 pain, but not necessarily the high mental
 12 impairment.
 13 So the reason for bringing this study is
 14 just to say that, fibromyalgia, there are different
 15 clusters and there are different degrees of
 16 physical and mental impairment, and the efficacy of
 17 a drug may vary depending on the complexity of
 18 these different conditions.
 19 When we go into a clinical trial, we
 20 randomize patients. Sometimes we just do simple
 21 randomizations where the whole sample is then
 22 distributed into equal groups, a treatment group or

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1 a placebo group. If there are subtypes or strata,
 2 then the population may be divided into subgroups,
 3 and then the randomization occurs within each
 4 subgroup.
 5 Given the complexity of these central
 6 sensitization conditions, my suggestion is to be
 7 able to get meaningful information, that we may
 8 have to stratify these patients and use the
 9 proportional stratified random sampling tool. And
 10 the pros of such a strategy would be that it
 11 accurately will reflect and represent the
 12 population of patients that we are studying, that
 13 it will have greater position and may require a
 14 smaller sample size and may save money, and may
 15 allow us to do subgroup analysis subsequently.
 16 The cons obviously are defining the strata
 17 is critical. It requires the ability to classify
 18 our patients into subgroups a priori before we
 19 randomize those patients. Therefore, it could be
 20 more complex to organize, and the analysis may be
 21 somewhat more challenging.
 22 The more important question that we may have

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1 to decide is if we stratify, what are the relevant
2 strata? Should it be those patients who are
3 predominantly a single primary pain pathology or
4 multiple pain conditions? Are these patients who
5 have predominantly, quote/unquote, "centralized
6 pain" where the periphery contributes less to their
7 overall pain or is it a combination of both
8 peripheral and central mechanisms?
9 These patients who have comorbidities, is it
10 the degree of physical versus psychological
11 features? One would have to then appropriately
12 power these to determine differences across the
13 strata.
14 In any study, you have a primary question
15 that you are interested in answering. I can think
16 of two questions here. One, is drug A effective in
17 patients with central sensitization syndrome
18 regardless of their primary pain presentation? So
19 regardless of where they are, irritable bowel
20 syndrome, or fibromyalgia, or osteoarthritis, is
21 the drug equally effective across conditions where
22 there is central sensitization?

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1 The second question could be, drug B, does
2 it help understand the neurobiology of central
3 sensitization? That is, are the mechanisms of
4 central sensitization different from neuropathic
5 pain? Does this drug work specifically on those
6 patients who have central sensitization that is
7 different or somewhat unique in some way compared
8 to other conditions such as neuropathic pain?
9 To answer question A, you may enroll all
10 patients with central sensitization regardless of
11 their primary pain pathology and presentation and
12 study the efficacy of the drug at multiple pain
13 sites.
14 For question B, you may enroll all patients
15 with central sensitization, but stratify them based
16 on whether there is solitary or multiple pains and
17 compare these patients with a patient group of
18 neuropathic pain states so you can do a comparison
19 of whether these drugs are better or more effective
20 in central sensitization conditions compared to
21 neuropathic pain.
22 So we've talked about study designs

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1 primarily from a perspective of randomized control
2 trials. I liked the cartoon that says, "Do you
3 know about any RCTs that provide evidence that we
4 should use RCTs?" The question, in looking at
5 people who know more about clinical trial designs
6 than I do, I came across these two cohorts that
7 carefully conducted observational studies may
8 provide more evidence than poor RCTs.
9 Unfortunately, a perfect trial can only
10 exist in our imagination. Maybe RCTs may not be
11 the best or only solution, and maybe a multicenter
12 trial with large registries of patients may be also
13 a useful tool in studying the central sensitization
14 syndromes.
15 What are the outcome measures that we should
16 be studying in these patients? Obviously, a long
17 time back, the IMMPACT II suggested 6 core outcome
18 domains such as pain, physical functioning,
19 emotional functioning, global impression of change,
20 symptoms and adverse events, and participant
21 disposition.
22 These are appropriate for studies in central

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1 sensitization, as for any other pain condition.
2 The other outcome measure that's been used in
3 fibromyalgia studies, particularly -- and I know
4 Ian and Lesley had used it in some of their
5 studies -- is the Fibromyalgia Impact
6 Questionnaire, which I'll talk about in the next
7 slide. Others have talked about symptom clusters,
8 and obviously other measures could be QST measures
9 such as temporal summation and CPM, or conditioned
10 pain modulation, imaging, and other biomarkers.
11 So these could all be outcome measures. At
12 this stage, I'm going to just touch on the IMPACT
13 questionnaire. This was initially brought about in
14 the end of the last century, but then revised
15 subsequently. It consisted of 21 questions, and it
16 was shown that it could separate fibromyalgia
17 patients from rheumatoid arthritis, SLE, or healthy
18 controls.
19 Subsequently, in the revision, there were
20 four other new symptom measures that were
21 introduced such as memory, tenderness, balance, and
22 sensitivity. There are 21 items across the

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1 domains. Patients can complete in less than a
 2 minute and a half. The total score of 0 to 39 was
 3 a mild effect; greater than 39 was moderate; and
 4 greater than 60 was a severe effect, so in terms of
 5 impact of the fibromyalgia. Minimally, clinically
 6 important differences could be detected by a change
 7 in score of about 14 percent.

8 Here's just an example of a study that just
 9 came out two or three years ago, looking at an
 10 antidepressant in fibromyalgia patients. This
 11 study was done in Japan, and they did a Japanese
 12 version of the score, and again shows a reduction
 13 in their pain, the change in numerical ratings
 14 scores, and that corresponded with the change in
 15 scores in the Japanese version of the FIQ. So
 16 again, this could be an outcome measure that one
 17 could use in some of these patients.

18 People have talked about using clusters of
 19 symptoms such as the SPADE and the SPACE, and in
 20 oncology patients, the PSF. SPADE is basically
 21 sleep disturbances, pain, anxiety, depression, low
 22 energy, and fatigue. There are variations of

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1 these. The suggestion is that one should not be
 2 focusing just on pain, but should have other
 3 measures that capture the full symptom presentation
 4 of these patients with central sensitization
 5 conditions.

6 Sleep is an important measure, the study
 7 looks at what should be the appropriate sleep
 8 measured. What should be the scale? How do we
 9 detect sleep disturbances? Normally sleep diaries
 10 have been used. Others have used act, actigraphy
 11 or polysomnography. This study compared the
 12 effects of, in this case, and intervention CBT on
 13 sleep measures in fibromyalgia patients.

14 The conclusion is that although actigraphy
 15 was most sensitive in some respects, some aspects
 16 of it, sleep diaries captured the greatest
 17 improvement in all parameters. So a sleep diary
 18 seems to be sensitive enough to detect differences
 19 with the treatment.

20 A study that was just in press, and hasn't
 21 been published in European Journal of Pain, looked
 22 at the role of tapentadol and its effects on

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1 conditioned pain modulation in patients with
 2 fibromyalgia. What the studies showed in the left
 3 is that treatment with tapentadol resulted in a
 4 decrease in pain compared to the placebo group,
 5 which is in red, and that the responders were also
 6 higher in the tapentadol group in the green versus
 7 the red.

8 They also showed that there was a change in
 9 conditioned pain modulation that the tapentadol
 10 group in contrast to the placebo significantly
 11 increased the defending inhibitory pain pathway or
 12 the conditioned pain modulation. A treatment
 13 resulted in change in conditioned pain modulation.

14 The study is more relevant, or important,
 15 because they also did something, a measure using
 16 cranial confocal microscopy. They measured
 17 neurofiber length, neurofiber density, and no
 18 branching in the cornea. And if two of those three
 19 parameters were abnormal, then they would say
 20 that's an abnormal finding.

21 The interesting observation here was when
 22 they compared the drug effects on conditioned pain

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1 modulation in all patients, this conditioned pain
 2 modulation was not predictive of efficacy of the
 3 drug, but what was more predicted was the abnormal
 4 corneal fiber state. So if you had an abnormal
 5 corneal fiber, you had poor pain relief. This
 6 tells me that in fibromyalgia, there is some
 7 pathology in the peripheral nervous system that
 8 seems to predict the condition after treatment,
 9 such as tapentadol in this case. So the periphery
 10 still may have some role or maybe useful.

11 So in the design studies, we are obviously
 12 very interested in being aware of placebo analgesia
 13 and controlling for that. There was also a
 14 question that Jim Rathmell asked yesterday, that
 15 some of these trials have a different design to
 16 it -- which Sharon took the Moeller approach. I
 17 think a didn't want or took the molar approach.

18 This is a phase 3 study, two phase 3 studies
 19 of controlled release pregabalin in postherpetic
 20 neuralgia and fibromyalgia. This is the randomized
 21 withdrawal paradigm that was discussed yesterday.
 22 This includes a 6-week initial period of dose

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1 optimization, and then the patients, with a certain
 2 criteria in this case, and 50 percent or greater
 3 response are randomized, and when you have a
 4 double-blind phase of 13 weeks. The primary
 5 endpoint, then, is the time to loss of therapeutic
 6 response.

7 Between these two studies, one study in
 8 postherpetic neuralgia and the other in
 9 fibromyalgia, again, the final endpoint or the most
 10 important that they checked was the median time to
 11 loss of therapeutic response.

12 Here are the data from these two studies.
 13 Apart from Lesley, anybody want to guess which was
 14 the fibromyalgia study? Was that on the left or
 15 the right? Any guesses?

16 (No response.)

17 DR. RAJA: Okay. So here's the answer. The
 18 left was the fibromyalgia patients; the right is
 19 the postherpetic neuralgia. The difference, one
 20 thing I want to point out is that the left is from
 21 1 to 0. The scale is different from 1 to 0.5, and
 22 if you look at the difference between these two

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1 studies in terms of the treatment group, as well as
 2 the placebo group, the difference is almost the
 3 same 16.8 across the 13th week, which is the
 4 endpoint.

5 But look at the two studies and how
 6 different they are in the sense that at a 30-day
 7 period, in the PHN study, almost 85 percent of
 8 patients, when they were taking placebo, were
 9 still, quote/unquote, "not withdrawing from the
 10 drug," or still had some kind of response. In the
 11 other study, at 30 days, only 45 percent of the
 12 patients had some degree of response; so again,
 13 same drug, two studies, PHN. So one has to take
 14 into consideration the different responses across
 15 different patient populations, and then design the
 16 studies appropriately.

17 To summarize, what I want to point out is
 18 that one of the first orders of business may be to
 19 come up with a consensus on the name and the
 20 diagnostic criteria for the condition we've been
 21 talking about for the last day and a half. In
 22 defining the study population, at this stage, we

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1 are left with some self-assessment tools, maybe
 2 such as the Central Sensitization Inventory or the
 3 sensory scales, that the objective measures of
 4 central sensitization are not useful for clinical
 5 studies at this stage. The spectroscopic
 6 fingerprints may be a potential tool in the future.

7 Depending on whether you are a lumpner or a
 8 splitter, the study question of interest may be
 9 different; whether you're interested in the
 10 neurobiology of the disease and was there treatment
 11 efficacy across a heterogeneous population; that
 12 is, are we talking about efficacy versus
 13 effectiveness across a broader population?

14 The study designs should probably use some
 15 form of stratification for better understanding of
 16 where there is a shared mechanism across these
 17 different central sensitization conditions, and
 18 that outcome measures, apart from the impact
 19 measures, measures such as the Fibromyalgia
 20 Inventory Questionnaire, the revised one, or other
 21 outcome measures may be more appropriate, and we'll
 22 probably hear a little bit more of that from

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1 Claudia in the next presentation.

2 I want to thank you all for your time and
 3 allowing me to reflect on this issue, and hopefully
 4 this will help steer some discussions in the coming
 5 time period. Thank you very much.

6 (Applause.)

7 DR. KATZ: Thank you very much, Raj.

8 I think we're going to go right into the
 9 next presentation because we're running slightly
 10 behind on time, and we have lots of time for
 11 discussion both after the next few presentations,
 12 and then as well as all afternoon.

13 With that, I'd like to introduce Claudia
 14 Campbell, who's also from Johns Hopkins University
 15 for the next presentation.

16 Presentation - Claudia Campbell

17 DR. CAMPBELL: Good morning. As the last
 18 speaker today, you would think that I would
 19 summarize all of the great talks we've had so far,
 20 but I decided not to do that. Instead, I'm going
 21 to try to split some hairs and pick up some threads
 22 from previous conversations.

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1 I have to admit that I was not super
 2 familiar with the term "somatosensory
 3 amplification," which is in my title. So my first
 4 order of business was trying to figure out the
 5 distinction between central sensitization and what
 6 this somatosensory amplification really means.
 7 Then also, if I was planning a clinical trial, what
 8 kind of advice would I seek from a group like this
 9 to try to help me do a good one?

10 When we talk about somatosensory
 11 amplification and central sensitization, are we
 12 talking about this kind of overlap or more like
 13 this kind of overlap? What are we really getting
 14 at here? You don't need me to give you the
 15 definition of central sensitization; we've been
 16 talking a lot about that. It is awfully handy that
 17 the IASP has a nice taxonomy on that. It does not
 18 for somatosensory amplification.

19 I went looking at Wikipedia of course, but
 20 started to wonder, hey, is somatosensory
 21 amplification sort of like allodynia and
 22 hyperalgesia, but for non-pain; just for

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1 everything? It does appear to have central and
 2 peripheral somatosensory nervous system components.
 3 Somebody summed it up as heightened awareness of
 4 and attention to internal sensations and symptoms.
 5 So I started thinking the overlap is probably in
 6 the space of central pain-specific somatosensory
 7 amplification, and maybe that's what central
 8 sensitization is.

9 Like Rob, I went to PubMed, and I did not
 10 put "pain" in my search term, which would have been
 11 much wiser. I just looked up somatosensory
 12 amplification and came up with 200-ish different
 13 articles, and in perusing those, it does appear
 14 like this somatosensory amplification is associated
 15 with a number of physiological phenomena like EEG
 16 and different ways to get at sensitivity.

17 It's also associated with -- well, I'm going
 18 to talk a little bit more about QST in a
 19 moment -- a pain modulatory profile. It seems like
 20 this area might be where they overlap.

21 Several people have mentioned all of the
 22 different terms people use to try to understand

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1 these different phenomena. And while there were
 2 only about 200-ish for this specific somatosensory
 3 amplification, somewhere over 2,000 came in for
 4 sensory processing, sensitivity, sensory
 5 overresponsiveness, sensory alteration, and Raj and
 6 Rob both described all of the different terms we
 7 use to get at these overlapping or same constructs.

8 So I'm going to keep trying to come back to
 9 the goal of my talk is supposed to be implications
 10 for clinical trials. I keep wandering off of that
 11 specific topic. But it does seem like there have
 12 been recent studies trying to understand how
 13 somatosensory amplification and central
 14 sensitization are associated.

15 This was an interesting systematic review
 16 that came out just a couple of years ago that found
 17 this general sensitivity, whatever we're going to
 18 call it, was the strongest predictor of altered
 19 central pain modulation in chronic musculoskeletal
 20 pain conditions. So it makes one wonder like maybe
 21 this set of sensitivity precedes this more
 22 centralized pain-focused sensitivity.

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1 A number of folks have been doing different
 2 factor analyses, and profiling, and trying to get
 3 at this. I believe this is out of Dan Clauw's
 4 group, but they did a factor analysis in the MAPP
 5 study, so chronic pelvic pain. This was a large
 6 group of people, but they were trying to understand
 7 how these variables fit together. They looked at
 8 the Somatic Awareness Subscale from the Complex
 9 Medical Symptom Inventory, different sensory
 10 sensitivity measures, and sleep and depression, and
 11 found that they loaded on two distinct factors.

12 The somatosensory sensitivity loaded on the
 13 factor with a number of pain sites, while the space
 14 variables, so the psychosocial variables, were more
 15 loading on the factor with actual pain severity.

16 They summed that up by saying, look, it
 17 looks like these variables describe different
 18 constructs or at least load separately, and are
 19 probably meaningful as separate ideas. They also
 20 put forward this brief general sensitivity screen,
 21 which Dan talked about a little bit yesterday, so I
 22 won't go into. But it looks like an interesting

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1 measure that tries to get at general sensitivity as
2 opposed to central sensitivity.
3 Several groups have done profiling and tried
4 to do cluster analyses to try and get at these
5 differences. Yvonne Lee and colleagues, I believe
6 out of Dave Williams' lab, found these three
7 distinct clusters where -- oh, I should point out,
8 on the X-axis, you have these more physiological
9 variables, and on the Y-axis you have your more
10 psychosocial variables. On the X-axis more is
11 worse, and on the Y-axis, less is worse.
12 The first cluster has the lowest pain,
13 lowest swollen counts, least psych issues, while
14 the third group has the highest objective findings,
15 but more moderate psych issues, whereas the second
16 group, they have the lowest objective findings but
17 the highest widespread pain inventory and the most
18 psych issues.
19 What I thought was interesting here is that
20 they're all reporting around the same level of
21 pain. Everybody's reporting around a 3 out of 10
22 on the BPI. But they do have quite different psych

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1 variables, and how those factors are associated
2 with their clinical findings are different.
3 Almeida and colleagues did something similar
4 with pressure pain threshold testing. What I
5 thought was interesting here was that they used
6 pressure pain at a number of different potty [ph]
7 sites, so they weren't just targeting specific
8 areas where people had pain. You can see that
9 folks in this first cluster have high pain
10 sensitivity and the worst psychosocial distress.
11 Not surprisingly, those folks had the most pain and
12 the worst disability with their musculoskeletal
13 pain.
14 I added this last night because I felt like
15 we were talking a bit about OPPERA, and somebody
16 had asked about clusters that OPPERA has looked at.
17 Of course, they have an enormous data set, and it
18 probably won't surprise anybody to know those with
19 global symptoms. So they've got all this stuff.
20 Most of the TMD patients fell into this
21 group. Those healthy folks that were in this group
22 were vastly more likely to develop TMD and other

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1 symptoms as opposed to those in the adaptive
2 cluster, which were characterized more by higher
3 prevalence and healthy folks and less pain.
4 Interestingly, there is another cluster, the pain
5 sensitive cluster. They had the highest QST
6 findings, but not as high on the psychosocial and
7 physiological symptoms as I might have suspected.
8 The terms seem different. How might we
9 measure one versus the other, and do we really need
10 to measure them both? It feels obligatory to say
11 something about chicken and egg and which comes
12 first. There has been quite a bit of discussion
13 about that here. The literature seems fairly
14 convincing that psychobehavioral factors do seem to
15 contribute to the risk of developing pain and
16 likely maintaining it.
17 OPPERA and other studies, there's been well
18 over two dozen QST studies looking at postoperative
19 pain and trying to understand how those
20 physiological alterations might predict the
21 development of pain, while other studies have
22 challenged that idea and say that, well, these

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1 preexisting sensitivity issues may modify and
2 perpetuate pain, but may not actually initiate
3 them.
4 I'm interested in laboratory pain testing.
5 We talked a little bit about capsaicin yesterday.
6 We did this laboratory study in healthy folks where
7 we put capsaicin on the back of the hand.
8 Capsaicin is the active ingredient in hot chili
9 peppers. It produces this burning sensation that
10 increases over about 30 minutes.
11 If you measure pain and catastrophizing
12 repeatedly, you can do what's called a cross-lagged
13 panel analysis. While it's not a test that I would
14 say specifically addresses causality, you can try
15 to understand what proceeds and try to get a
16 temporal understanding of some variables.
17 You can look at how pain changes from early
18 to mid, and then mid to late, and how that's
19 associated with catastrophizing changes. We've
20 been talking about catastrophizing a lot. We know
21 it's a potent predictor or potentially associated with
22 pain outcomes. In this particular study, we did

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1 not find any association between how much pain
 2 increased early on to how much catastrophizing
 3 increases later. We did find a substantial
 4 association between how much catastrophizing
 5 increases early on, and then how that proceeds an
 6 increase in pain.

7 Coming back to the goal, or what the goal of
 8 my presentation is supposed to be, regardless of
 9 how things started, regardless of what caused what,
 10 it's all present. If we're going to study these
 11 folks, it's all in the soup. If you treat pain,
 12 will the other symptoms improve? We talked about
 13 that a little bit yesterday; if there's a common
 14 shared mechanism, if you treat one thing, will the
 15 rest of these global issues also improve?

16 I got into this cross-lagged panel thing and
 17 started doing that all over the place. We did that
 18 with a fibromyalgia group that we had. I'll share
 19 you the suspense. This was an exercise clinical
 20 trial, and there was no difference between the
 21 active exercise intervention and the education
 22 control condition. Everybody improved about the

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1 same, which is to say not very much. But we did
 2 find the same association where early decreases in
 3 pain did not proceed decreases later in
 4 catastrophizing, whereas a decrease in
 5 catastrophizing -- now, there was no
 6 catastrophizing intervention, but early decreases
 7 in catastrophizing for whatever reason did proceed
 8 a decrease in pain ratings.

9 I'm going to talk a little bit about a study
 10 we did with Rob Edwards -- thanks, Rob; these are
 11 all your data -- where we found that the same was
 12 true for total knee replacement. This was an
 13 observational study. We weren't trying to do
 14 anything. There was no clinical trial aspect. We
 15 weren't trying to reduce catastrophizing, but for
 16 whatever reason, there was about a 5-point drop in
 17 catastrophizing on the Pain Catastrophizing Scale,
 18 from pre- to 6-week post-surgery, and that preceded
 19 the decrease in pain that we observed from 6 weeks
 20 to 3-month post.

21 I want to talk a little bit more about this
 22 project because when I went searching through the

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1 literature for if pain changes, what else changes
 2 to, or if something else changes, does that
 3 decrease pain? I didn't see a lot of papers really
 4 focusing on what those changes are and how they
 5 look over time.

6 So a little bit about this cohort, mostly
 7 women, 65, overwhelmingly white, and these are the
 8 time points we looked at. pain just overall
 9 decreased substantially. But as many people here
 10 have mentioned, we had about 25 percent, 30 percent
 11 of people that didn't have all that much pain
 12 relief, and actually 25 percent of people had more
 13 pain at one year than they did at baseline.

14 What improves when pain improves? Well,
 15 WOMAC definitely improves, and it obscures
 16 everything else. So when you get rid of that, it
 17 looks like pain certainly improves, catastrophizing
 18 decreases substantially, and the sleep variables
 19 that we measured also improved. Nothing really
 20 happened with anxiety, depression, anger, and these
 21 other variables that I would have thought might
 22 have also improved.

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1 Then I started to wonder, well, what about
 2 this 25 percent of people that had more pain a year
 3 out? I would have bet every time that the group
 4 that had more pain a year later had higher baseline
 5 pain, would have worse function, and would have
 6 worse sleep and catastrophizing.

7 I'm going to spare you the pain of actually
 8 guessing. I would have been wrong every time
 9 because somehow those that had worse pain at a year
 10 actually had less pain at baseline, which makes me
 11 wonder, boy, how do you try to pick these people
 12 out and tease them out early because they don't
 13 have more catastrophizing, they don't have worse
 14 sleep. There's somewhere kind of in that
 15 mid-range, so I was curious about that.

16 For those that pain actually improves at a
 17 year, which is the overwhelming majority of people,
 18 their pain comes down, obviously. Catastrophizing
 19 comes down. Everything comes down except for
 20 depression. Depression just holds steady. And you
 21 could probably guess for those that had pain that
 22 continued or increased at a year, of course their

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1 pain doesn't improve. There's a spike around
 2 6 weeks in symptoms, but they just come back to
 3 their regular level, and nothing else gets better,
 4 and actually it looks like depression gets a little
 5 worse. I didn't include anxiety and anger on here.
 6 There just stayed flat.

7 How about if you treat the symptoms? If you
 8 treat pain, we don't have a lot of things that
 9 treat pain super well, unfortunately. So if you
 10 treat the symptoms, will pain improve? We talked
 11 about this a little bit yesterday as well. Coming
 12 back to catastrophizing, Karen Peterson and some of
 13 her colleagues did this interesting pain coping
 14 skills training with healthy folks, and they did
 15 find that that reduced secondary hyperalgesia to
 16 QST measures.

17 Now, that was in healthy folks, so take it
 18 how you want. Another group worked on CBT, and
 19 that lowered disability but didn't have long
 20 lasting effects. Then I was really excited a few
 21 years back when Dan Riddle came out with this
 22 experiment. Unfortunately, it was a

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1 quasi-experimental design, so he didn't have an
 2 actual control group, and these were compared to
 3 historical controls. But he found a substantial
 4 reduction in catastrophizing in WOMAC pain
 5 following 18 patients and doing 8 sessions of
 6 pain-coping skills training with them before total
 7 knee replacement.

8 These are really promising results. I was
 9 very excited. They published a really nice
 10 protocol, but then earlier this year, came out with
 11 their findings, and it was a large multisite
 12 randomized controlled trial. I'm sure you all saw
 13 this, where they had 402 patients; a really nice
 14 sample. These were selected to be high
 15 catastrophizing patients prior to undergoing total
 16 knee replacement, and their coping skills training
 17 did not reduce catastrophizing or improved function
 18 above standard of care.

19 Sleep, a lot of people have talked about
 20 sleep over the last couple of days. We know that
 21 sleep interventions are really good. Cognitive
 22 behavioral therapy for insomnia works much better

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1 than medications for improving sleep long term.
 2 Several people have looked at pain as an outcome
 3 measure but not specifically design their trial to
 4 look at pain. So the sleep folks are sort of
 5 interested in pain but not super interested.

6 Michael Smith in our group designed a trial
 7 to look at pain. He used knee osteoarthritis
 8 patients. As you can see, he substantially reduced
 9 problems with wake after sleep onset and improved
 10 that in every kind of way; so in subjective
 11 measures, self-report, actigraphy, and PSG. He
 12 improved most of the sleep measures compared to
 13 their control group but not with pain. So pain
 14 improved to the same degree regardless of
 15 intervention.

16 Emotional awareness and expression therapy
 17 is really interesting, and Mark Lumley has really
 18 popularized this, and I think it's super
 19 interesting. I didn't go into the rest of the CBT
 20 literature, but I thought I would put this out
 21 there.

22 They compared emotional awareness and

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1 expression therapy. If you're not familiar with
 2 that, you can think of the Feats of Strength in
 3 Seinfeld or Festivus, where you kind of get out
 4 your emotions with your family, anger, and it's
 5 more productive than that, but that's the idea.

6 Anyway, they did not find substantial difference in
 7 most pain outcomes compared to CBT, but they did
 8 find that emotional awareness and expression
 9 therapy improved

self-reported pain reduction and

10 very much improvement on Global Impression of
 11 Change Scale.

12 What are the implications, then, for
 13 clinical trials? Is there a way to recommend
 14 quantifying these different variables? How do we
 15 consolidate and interpret them? Do they influence
 16 treatment or influenced by treatment?

17 We've talked about many different psycho,
 18 social, and behavioral questionnaires. so I'm not
 19 going to get into those. They've been very nicely
 20 reviewed. I'd like to talk a little bit more about
 21 QST. I've come across three different ways to try
 22 to quantify or cluster QST variables, so I wanted

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1 to get into those a little bit here. Because if
 2 we're talking about doing this on a widespread
 3 scale, you can't have a battery of 20 different
 4 tests and to think about how to condense those I
 5 think would be appropriate.

6 Ezenwa and colleagues, Roger is one of them
 7 and I assume was advising them on how to do this.
 8 In sickle cell disease patients, they did thermal
 9 thresholds on three different areas, two painful,
 10 one not painful, and compared those with norms and
 11 to the reference site, and bend people into -- they
 12 have normal findings, more indicative of central
 13 sensitization, which is a good proportion of their
 14 folks, or peripheral or a mixed pain group.

15 Tangent on sickle cell disease, we've been
 16 talking a lot about fibromyalgia and how that's the
 17 poster child for central sensitization. I've been
 18 really interested in sickle cell disease. I think
 19 it's also a fascinating central sensitization,
 20 potentially condition. We knew that, as kids,
 21 patients with sickle cell disease don't really have
 22 a lot of pain. They have these crises, and there's

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1 some black box around the severity, duration,
 2 frequency of these crises, and we know by
 3 adulthood, somewhere upward of 30 percent have
 4 chronic pain. So it seems like an ideal group to
 5 try to understand central sensitization and
 6 somatosensory amplification.

7 We've been looking at sickle cell disease
 8 patients for a while, and we do a whole bunch of
 9 QST with them, and it's just a lot. Presenting
 10 those kinds of data to the uninitiated feels a
 11 little bit overwhelming. It's also overwhelming
 12 when you have variables like this, and you want to
 13 look at something. So the correlation between QST
 14 and X, Y, or Z, well, if you 20 QST variables,
 15 that's a whole lot of analyses.

16 You see differences between healthy controls
 17 in sickle cell folks on a number of tasks. We set
 18 out to try to understand those with central
 19 sensitivity or that defined by QST versus those
 20 that didn't. So just looking in the sickle cell
 21 disease cohort, we created a high CS and a low CS
 22 group based on temporal summation, both thermal and

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1 mechanical, as well as after sensations. We did
 2 not include CPM on this one because our CPM task
 3 crashed and burned in these folks.

4 Anyway, 2 of the 4 tasks had to be greater
 5 than one standard deviation above the mean of
 6 healthy folks. I wanted to delete some of the
 7 clutter from the screen so there are no demographic
 8 differences other than a body mass index. Not
 9 surprisingly, those high in CS were taking lots
 10 more short- and long-acting opioids, and you were
 11 much more likely to be in that group if you had
 12 high CS.

13 We were interested in what differentiates
 14 these groups. A high CS person from a low CS
 15 sickle cell disease person, they had a lot more
 16 pain. They had more crises, more crises related
 17 pain, more medical visits. These top data are
 18 within 3 months of our initial testing, and if you
 19 follow them out -- we followed these people for 18
 20 months, and we found that those in the high CS
 21 group had much, much more pain and were more than
 22 twice as likely to have -- well, had twice the

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1 amount of healthcare utilization as the low CS
 2 group.

3 It was also associated with psychosocial
 4 factors, so those with high CS also had higher
 5 catastrophizing, higher negative affect, lower
 6 positive affect, and just a ton of sleep variables.
 7 We've talked about sleep. You all are aware there
 8 seems to be a really high association between sleep
 9 problems and central sensitization.

10 If you Z-score all of these QST
 11 variables -- and we're not the first to do that.
 12 Roger has shown a lot of these sort of data. So
 13 Z-score them to get them all on the same scale,
 14 reverse score where needed so that they all face
 15 the same direction because for me, it's very
 16 confusing if you've got threshold going up and
 17 you've got ratings coming down, and making sense of
 18 all that. I didn't include the CS variables here,
 19 but we did average all of these non-CS, QST
 20 variables into one general sensitivity index. You
 21 can see that those with high CS had higher general
 22 sensitivity.

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1 So is there value in being able to show
 2 there isn't widespread or peripheral somatosensory
 3 amplification? Should we just be getting those CS
 4 variables when we're talking about a QST battery?
 5 If we're going to recommend that for folks, do they
 6 only need to be doing temporal summation and
 7 conditioned pain modulation?
 8 It turns out they're pretty closely related,
 9 more so in chronic pain patients than healthy
 10 controls. If you have this continuous measure of
 11 central sensitization from those CS QST variables
 12 versus general QST sensitivity, you see they are
 13 pretty highly correlated.
 14 Now, we were really interested in opioids,
 15 of course, sickle cell disease. If you split the
 16 group into those on chronic long-term opioid
 17 therapy versus not, not surprisingly, you see a lot
 18 of differences in pain, proportion of days
 19 reporting a crisis, and crisis pain. I was
 20 wondering if they are just generally sensitive;
 21 they're sensitive to everything no matter what we
 22 do and what we look at.

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1 But that wasn't the case, and I think some
 2 of the value in trying to get some of these other
 3 QST variables can go to show that kind of
 4 difference. The folks on chronic opioid therapy
 5 had a higher central sensitivity index, but not
 6 general sensitivity. They were pretty much the
 7 same on those variables with their non-chronic
 8 opioid therapy counterparts. It seems like there's
 9 something maybe special about that.
 10 I wanted to come back to this quantifying
 11 QST a little bit. This is in a different cohort.
 12 This is knee osteoarthritis folks, and this is what
 13 their QST data looked like. That's a lot of data.
 14 We ended up averaging that into those CS variables
 15 and those that were QST variables not including the
 16 CS. I like that as a way to condense these kind of
 17 data and think about them a little bit differently.
 18 The other method for doing that, we've
 19 talked a little bit. I think Rob showed a
 20 Yarnitsky's pain modulation profile and how that
 21 could be used. So I went ahead and calculated that
 22 in some of our data. Looking at taking temporal

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1 summation, if they summate, they get a 1; if they
 2 don't summate and stay the same, they get a zero;
 3 and if they habituate, they get a negative 1.
 4 Doing the same thing with CPM, if it's efficient,
 5 they get a negative 1, and you have to reverse it.
 6 I was curious to see how those measures
 7 stacked up and how they were similar. Again, in
 8 Rob's total knee replacement data, we found a
 9 higher correlation in central sensitivity index
 10 with this pain modulation profile, not
 11 surprisingly, that's what we found with general
 12 sensitivity.
 13 I was curious what mapped on closer to pain
 14 in this group, so trying to understand BPI,
 15 widespread pain inventory, symptom severity, and it
 16 seems like -- well that doesn't seem like. The
 17 only variable that was associated with those was
 18 this measure of general sensitivity. The central
 19 sensitivity did not map on as I might have thought.
 20 So it does seem like there's value in trying to
 21 understand general sensitivity as opposed to just
 22 these temporal summation and CPM variables.

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1 I'm not going to get in much to the point
 2 about samples. Raj just spoke very nicely on how
 3 we might do that. I will say just from a practical
 4 sense, it will be a whole lot easier to recruit,
 5 make things more generalizable, and probably much
 6 more meaningful to include folks that have these
 7 overlapping pain conditions instead of just our
 8 treatment of choice or our disorder of choice.
 9 Now, whether funding bodies, reviewers, and FDA are
 10 going to be on board with that, hmmm, but it does
 11 seem like stratifying those groups, as Raj was
 12 mentioning, makes a whole lot of sense.
 13 Should we subgroup or classify participants
 14 in any kind of way? We know that QST has been
 15 associated with outcomes for a lot of different
 16 medications and suggest analgesic benefit. There
 17 have been a number of reviews there. I should
 18 mention that all of these measures were not
 19 specific to central sensitization, so it wasn't
 20 just temporal summation and CPM that was used in
 21 all of these different trials.
 22 Quantifying sensory function might be

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1 interesting. We know that QST has been able to
2 help figure out or differentiate some different
3 treatment effects, so not just analgesic but in
4 multidisciplinary pain treatments, we did some work
5 with spinal cord stimulation that I won't get into;
6 topical pain treatments.

7 I had the opportunity to work with Jim
8 Campbell -- no relation -- on this clonidine
9 project that he was working on, and it was a really
10 interesting project. He had this clonidine topical
11 formulation. It was a lotion to put on painful
12 diabetic neuropathy patients feet.

13 There was no separation from baseline at the
14 12-week mark, but he had this idea that if you did
15 a capsaicin challenge prior to giving them the
16 medication -- so putting a smear of capsaicin on
17 the tibia, and just letting that soak in, and
18 getting a pain rating to that -- that those
19 patients might benefit more. Sure enough, those
20 that actually felt pain 3 or higher on capsaicin
21 did improve more with the clonidine treatment.

22 We've been talking about a whole lot of

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1 variables. There are all these QST variables,
2 psychosocial, behavioral, and physical. I get a
3 little bit confused when we talk about predictors
4 versus outcomes. It feels like they could all be
5 in all bins. We talked a little bit about the BPI
6 yesterday and stole some of my thunder. I was
7 going to mention that we don't really know what
8 people are rating when we give them a BPI. We use
9 it in our lab.

10 Is it one ring to rule them all? We ask
11 about pain, but we don't really know if people are
12 giving us pain to the specific knee osteoarthritis
13 that we're really interested in, if they're
14 averaging or summing their pain over all of their
15 different body sites, or what's actually happening
16 there?

17 As we discussed yesterday, it could make
18 people crazy if you try to get them to rate all of
19 their pain to all of the different areas that they
20 mark on one of these maps. It sounds like some
21 people have some good ideas about what can be done
22 there and are trying to consolidate and make things

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1 a little bit easier rate. But as Roger mentioned,
2 you could really get unwieldy with it; ask me about
3 the duration, the frequency of pain, what it looks
4 like, the characteristics. So certainly, coming up
5 with some kind of way to advise people on that I
6 think would be helpful.

7 Focusing on function, I happened to go to
8 this healthy women meeting last week, and one of
9 the things that came out of that meeting, or
10 several people talked about, was how we really need
11 to be focusing on function. Somebody suggested all
12 we need to know is where you are on a scale from
13 thriving to completely bedridden, or somewhere in
14 between. I don't think it's quite that simple, but
15 focus on function makes a lot of sense.

16 Turk and colleagues and others from this
17 group have a very nice recent paper on function and
18 how to measure that, the nuances and complexities
19 there. There are functional capacity tasks you can
20 do in the laboratory. There are disease-specific
21 measures you could get. There's also, I would say,
22 more real-life examples of that, so wearing a

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1 pedometer or something like that for some amount of
2 time.

3 Now, if we're talking about people with
4 somatosensory amplification, and bring it back to
5 that, we probably also need to think about how some
6 percentage of these folks are going to be really
7 sensitive to wearing a Fitbit or an actigraph, and
8 they're not going to like it.

9 In that fibromyalgia cohort I was describing
10 earlier, a good percentage of those people would
11 not wear a wearable sensor of any kind. Some
12 people took to looping it in some way on their
13 pants, or using a silk strap instead because they
14 didn't find that as bothersome, but we should be
15 aware, if we're going to do these trials, that some
16 percent of people are not going to want that, and
17 we should probably think about alternatives to
18 still be able to get real data from those folks.

19 There seems to be this constellation of
20 vulnerability, and we talked about central
21 sensitization and somatosensory amplification, or
22 general sensitivity, whatever we're going to call

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1 it, on a continuum. I've been wondering if the
 2 distribution of those factors matter, and if
 3 there's any kind of meaningful way to put it
 4 together.
 5 I was wondering if we can take a note from
 6 our cardiovascular colleagues. They've had a lot
 7 of, I don't know, I think success in getting to the
 8 lay public about what the risk factors are for
 9 cardiovascular disease. Maybe I'm just responding
 10 to the nice rainbow-ness of their information, but
 11 I was wondering about the way we present data, and
 12 we typically don't present it, I don't think, in a
 13 very user-friendly fashion.
 14 So I was wondering, well, if we have all
 15 these baseline factors, and we kind of bend them
 16 into some logical things, so clinical pain,
 17 function, laboratory markers, some kind of
 18 sensitivity, and then our space variables, is there
 19 a way to show an additive effect? So this person
 20 has 20 of these issues while this person only has
 21 3, and is there a way to make sense of that?
 22 I was just playing around with this. It

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1 might be completely outside the scope of this
 2 meeting, but it just got me thinking, well, when I
 3 read one of these papers, I usually don't know if
 4 something got a little worse for one pain area or
 5 got a little better for another, or some of those
 6 space variables improved over time.
 7 When I think about trying to see what kind
 8 of recommendations we would make or what kind of
 9 advice I would ask of you all experts, I'd be
 10 curious to know if we are at the point where we
 11 think we can reliably subgroup people and treat
 12 them differently or if we're still at the point of,
 13 well, let's phenotype everything and see what
 14 shakes out later.
 15 It feels like somewhere in between might be
 16 right. What predictors, what outcomes? Is
 17 everything both? Should we recommend using QST?
 18 QST is my bread and butter; that's what we do in
 19 the lab. I'm really interested in it, but I'm sort
 20 of an egghead like that, and I don't know if it
 21 makes sense to really be having our clinical
 22 colleagues trying to do that kind of thing,

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1 especially when we heard yesterday we're not really
 2 at N of 1 anything.
 3 How should we present data if people are
 4 going to do it? Is there a way to reduce that to
 5 make it more meaningful and compelling? Is there a
 6 better way to show what variables are impacted by
 7 others and vice versa? I want to thank all of my
 8 colleagues, collaborators, mentors, and you all for
 9 your attention. Thanks.
 10 (Applause.)
 11 DR. KATZ: Thank you very much, Claudia, for
 12 a very thoughtful and comprehensive presentation.
 13 It is time for a break, so why don't we go
 14 ahead and take that break, and we'll resume
 15 promptly at 10:00.
 16 (Whereupon, at 9:28 a.m., a recess was
 17 taken.)
 18 DR. KATZ: Hello again, everybody. Thanks
 19 so much for being here promptly at 10-ish. Our
 20 next presentation will be given by Dr. Lesley
 21 Arnold, who I've had the pleasure of collaborating
 22 with on a number of different trials in

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1 fibromyalgia and who has been, as you probably all
 2 know, one of the major contributors to clinical
 3 research in fibromyalgia for a number of years now.
 4 That will be our next presentation, then
 5 after that, we'll have time for discussion.
 6 Presentation - Lesley Arnold
 7 DR. ARNOLD: Thank you. It's been a
 8 pleasure to be here, and I've learned a lot from
 9 all of you over the last couple of days. As many
 10 of you know, I spend a lot of my time doing
 11 clinical trials in patients with chronic pain,
 12 especially fibromyalgia, so I'll be mostly speaking
 13 from my experience in working with these patients.
 14 We have made a lot of progress in identifying new
 15 treatments for patients with chronic pain, but I'm
 16 hoping that what we're learning about centralized
 17 pain will advance our studies and open up more
 18 treatment options for our patients.
 19 I thought before I got into dealing with
 20 this problem of comorbidities, I'd thought I'd
 21 share with you a typical day in the clinic with
 22 you, just to give you an idea of what we're talking

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1 about and what patients are dealing with day to
 2 day. I just want to say first, of course, these
 3 may not represent all patients with fibromyalgia
 4 because I am a specialist, so these are patients
 5 who are referred to me by primary care doctors and
 6 other physicians.

7 My day began with a 65-year-old woman. She
 8 had a relatively recent history of fibromyalgia,
 9 just 4 years, but notice all the medical
 10 comorbidities. Number one is obesity, and that's
 11 an area that we haven't discussed much. I know Dan
 12 mentioned it in his talk somewhat. But it is a
 13 very common problem in our chronic pain population,
 14 and, yes, it certainly can make pain worse, but
 15 there are some more recent information that our fat
 16 stores themselves maybe proinflammatory and may be
 17 contributing to pain sensitivity. So I think it's
 18 an important issue that we need to consider when we
 19 are looking at our patients, treating our patients,
 20 and designing clinical trials.

21 This patient also had sleep apnea. Again,
 22 this is a very common comorbid medical condition.

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1 It contributes to sleep disruption, and also as
 2 we've heard, sleep disruption contributes to pain
 3 sensitivity, so we have to look broadly at many
 4 different comorbidities, not just pain
 5 comorbidities, when we are designing trials.

6 This patient also had other pain generators,
 7 if you will: osteoarthritis, shoulder impingement,
 8 sciatica, hip pain and carpal tunnel syndrome.
 9 When we are talking about a fibromyalgia
 10 population, and people say, well, can we just focus
 11 on fibromyalgia, you're not just going to be able
 12 to do that. It's very unusual for a patient not to
 13 have other pain disorders.

14 Of course, we talked about psychiatric
 15 comorbidity yesterday, and of course not
 16 surprisingly, since I am psychiatrist, many of my
 17 patients are going to have psychiatric comorbidity.
 18 But as you saw, in general, population of patients
 19 with fibromyalgia, even in primary care settings,
 20 also have high rates of comorbid anxiety and
 21 depression.

22 My next patient was a single woman. She had

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1 a longer history of fibromyalgia, 12 years. This
 2 was a follow-up. She also had problems with
 3 obesity and spinal problems, degenerative disc
 4 disease, osteoarthritis, sciatica, and she also had
 5 one of the coexisting overlapping pain conditions
 6 that we've been talking about, migraine.

7 One of the interesting aspects of her
 8 history is that she has workman's compensation.
 9 This is also a major problem that we deal with day
 10 to day in our clinic. A substantial minority of
 11 our patients do go on disability or have disabling
 12 pain, and this becomes a problem for us when we're
 13 designing clinical trials, how to deal with that
 14 issue and whether being on disability or applying
 15 for disability would adversely affect their
 16 response to our treatment. So that's something we
 17 have to consider when we designed
 18 inclusion/exclusion criteria.

19 This patient was relatively healthy
 20 otherwise. With regard to her psychiatric
 21 comorbidity, she had attention deficit disorder,
 22 but we attributed that mostly to having chronic

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1 pain, which we know affects cognition.

2 My next patient was a new visit. This was
 3 referred by a primary care doctor. She was 48 with
 4 just a 2-year history of fibromyalgia. She also
 5 had obesity as a problem, and she had one of those
 6 chronic overlapping pain conditions, the migraine
 7 and interstitial cystitis, and she also had plantar
 8 fasciitis; so again, multiple sources of pain. She
 9 had both anxiety and depression.

10 My next patient, a 36-year-old woman, she
 11 had a 5-year history of fibromyalgia. This is a
 12 follow-up, one of my existing patients. She had
 13 migraines, endometriosis, and also osteoarthritis
 14 and depression.

15 Moving on to my next patient, a 3-year
 16 history of fibromyalgia, and she also had multiple
 17 other pain syndromes: chronic lower back pain,
 18 degenerative disc disease, cervical radiculopathy,
 19 and another medical condition of hypothyroidism.
 20 This patient had more severe psychiatric
 21 comorbidity. She had a long history of abuse
 22 growing up, and in my experience when that happens,

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1 it really affects the prognosis long term. It
 2 definitely adversely affects it.
 3 So that's something else to think about when
 4 you're thinking about including a patient in a
 5 clinical trial, how do we address that problem? Do
 6 we exclude people who have PTSD? Does it affect
 7 the prognosis? Yes, it does. So again, something
 8 to think about when we're trying to decide what
 9 patients to include in a clinical trial.
 10 My next patient is an 18-year-old woman.
 11 She had participated in one of our juvenile
 12 fibromyalgia studies. She decided to stay with me
 13 as a patient, so I've been seeing her for many
 14 years. She had migraine as a comorbid pain
 15 condition, but she also had very severe psychiatric
 16 comorbidity. Her depression led to suicidality and
 17 multiple psychiatric hospitalizations, so she has
 18 struggled some, mostly, with regard to the
 19 comorbidity of depression.
 20 Finally, my last two patients, I had a
 21 74-year-old woman and one of my existing patients.
 22 She also struggles with overweight. She has more

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1 significant medical comorbidity with regard to
 2 diabetes, neuropathic pain, and coronary artery
 3 disease. She also has osteoarthritis, so, again,
 4 multiple sources of pain and also comorbid
 5 depression.
 6 Then finally, another new patient referred
 7 by a rheumatologist, a younger woman with just a
 8 one-year history of symptoms. She also had
 9 problems with obesity and spinal disease, and then
 10 she had a couple of the chronic overlapping pain
 11 conditions, irritable bowel syndrome and TMD. She
 12 had an eating disorder as a psychiatric comorbid
 13 condition, which is a little less common in the
 14 fibromyalgia population but it does occur.
 15 I hope that gives you an idea of what we're
 16 dealing with when we're talking about comorbidity
 17 and how that can impact our clinical trials.
 18 These are some of the more common chronic
 19 overlapping pain conditions that I see in my
 20 patients: irritable bowel, chronic headache,
 21 interstitial cystitis, temporomandibular disorder,
 22 chronic pelvic pain, and low back pain. There are

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1 some other ones, but these are the most common that
 2 I see.
 3 Again, as we've been talking about, they may
 4 be linked by some common pathophysiologic problem,
 5 but as we've seen with my patients in the clinic,
 6 they have other comorbid conditions that are
 7 associated with pain: osteoarthritis, degenerative
 8 disc disorder, spinal stenosis, and is very
 9 challenging sometimes to figure out what is
 10 contributing to their pain experience and how to
 11 target our treatments.
 12 Neuropathies are very common in the
 13 population, radiculopathies, and we've heard about
 14 other rheumatologic disorders. Ehler-Danlos we
 15 heard about yesterday. That's a very common
 16 problem in my patient population. Then again, the
 17 issue with obesity, sleep disorders, especially
 18 obstructive sleep apnea, and then depression and
 19 anxiety, all of which are associated with pain.
 20 Over the years, we've worked to design
 21 clinical trials in fibromyalgia to help advance the
 22 field, and we have had success. We have three

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1 FDA-approved treatments, but we still need to do
 2 more work, and we need to expand access to
 3 treatments for all patients with these pain
 4 disorders. But there's an effort usually in a
 5 clinical trial to reduce heterogeneity if we can,
 6 and to try to focus, at least in the fibromyalgia
 7 group, on patients who have fibromyalgia as what we
 8 think is their primary pain problem.
 9 This is a typical, cut right out of one of
 10 our trials, exclusion criteria. It says, "pain due
 11 to diabetic peripheral neuropathy, postherpetic
 12 neuralgia, traumatic injury, prior surgery, complex
 13 regional syndrome, or other source of pain."
 14 By other, it's not really specified, and
 15 does not specifically exclude those other chronic
 16 overlapping pain conditions. But it's up to the
 17 investigator's judgment because it says "in the
 18 investigator's opinion, the presence of these other
 19 pain conditions would confound or interfere with
 20 the assessment of the subject's fibromyalgia pain
 21 or require excluded therapies during the
 22 participation."

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1 So my point being is that it's left to the
 2 investigator. Some of this information is not
 3 collected by the sponsor of this study, so we don't
 4 know, really, how many of our fibromyalgia
 5 patients in clinical trials to date have had these
 6 conditions. It's not tracked. My guess is that
 7 they are in the trials, that most of the patients
 8 with fibromyalgia in our clinical trial have
 9 multiple other sources of pain, other, if you will,
 10 peripheral pain generators.

11 The other exclusion is a little bit more
 12 obvious and easier. I think that patients with
 13 rheumatoid arthritis, and other kinds of infectious
 14 or inflammatory arthritis, or autoimmune diseases,
 15 are typically excluded from our fibromyalgia
 16 trials, although, again, that excludes an important
 17 patient population we have not studied, but at
 18 least in these trials, we try to exclude them.

19 But then we can't exclude osteoarthritis; we
 20 would have no patients in our trials then. So a
 21 way to get around that is to say, well, we'll
 22 exclude widespread rheumatic disease. So if they

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1 have osteoarthritis in multiple joints, they would
 2 be excluded. But again, that's very much left up
 3 to the investigator. There are patients who have
 4 pretty severe knee OA or low back pain, and they're
 5 in these trials. We just don't know the impact of
 6 these comorbid pain disorders on our outcomes.

7 As far as psychiatric illness, we heard
 8 earlier that the presence of psychiatric
 9 comorbidity can adversely affect outcomes and
 10 prognosis, so there's an effort to manage that and
 11 try to exclude certain comorbid psychiatric
 12 illnesses. Psychotic illnesses are always
 13 excluded, as is bipolar disorder.

14 We saw yesterday, when we had the review of
 15 the comorbid conditions, that bipolar disorder
 16 turns out to be more common in the patients with
 17 fibromyalgia than in the general population. We
 18 don't really know why that is, but patients with
 19 bipolar disorder do tend to have more
 20 treatment-resistant forms of mood disorder, so it
 21 makes sense that they are excluded. But again,
 22 that leaves unanswered how would these treatments

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1 work in a bipolar population, which is something I
 2 see daily in my practice.

3 As far as dealing with depression and
 4 anxiety, in the early trials, some of the programs
 5 excluded people with current depression as a way to
 6 eliminate that problem from the analysis. Other
 7 programs allowed depression in and then subgrouped
 8 the analysis at the end to see if the presence of
 9 depression affected the outcomes or not.

10 More recently, I think what's been
 11 acknowledged is that you really can't exclude
 12 people who have comorbid current depression
 13 anxiety, but you try to manage it by allowing
 14 people who have stable, mild levels of depression
 15 or anxiety, or if they're on treatment, that that
 16 treatment is on a medication that's acceptable
 17 during the trial and that the treatment is stable.

18 We typically exclude suicidality for obvious
 19 reasons and then also substance-use disorders.

20 We're faced now with a new problem of people taking
 21 cannabinoids as these become legal in many states.
 22 It's becoming a challenge of how to manage that in

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1 a clinical trial. Mostly now it's still excluded,
 2 but as we know, people, even if they say they will
 3 come off of their cannabinoid for the participation
 4 in a trial, it can take several months for that to
 5 clear out of the urine drug screen, so it is
 6 becoming a problem and a barrier.

7 There are some other exclusion criteria to
 8 try to address some these other issues of
 9 comorbidity, and the body mass index is one. We
 10 have debated with sponsors about where the
 11 appropriate cutoff would be for that, and I was
 12 saying earlier that in Cincinnati, if you cut it
 13 less than 40, I'm not going to get anybody in my
 14 trial.

15 We've negotiated somewhere between 40 and 45
 16 cutoff, but it is a real problem because the higher
 17 the BMI, you introduce more medical comorbidities,
 18 perhaps more pain sensitivity, things that we may
 19 not totally understand. So we do try to manage
 20 that, but again, it gets back to the issue, the
 21 more we exclude these people, then we leave out
 22 people who might benefit from the treatment. But

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1 again, in a clinical trial, we're trying to look
2 for a signal, so we do try to reduce the
3 variability in the population as much as we can.
4 Then generally, patients, as far as other
5 medical comorbidities, have to be reasonably
6 stable. Other medical diseases, sleep apnea, all
7 of these things, have to be treated and stable, so
8 in general, the clinical trial population is going
9 to be healthier and less severely affected.
10 Coming back to then how we view
11 comorbidities when we're looking at our outcome
12 measures, we heard a lot about this earlier today.
13 How are we assessing outcomes, and are we taking
14 all these sources of pain into account when we
15 assess pain severity?
16 Typically, in a fibromyalgia trial and other
17 chronic pain trials, pain severity is the primary
18 outcome measure. It's typically average pain
19 severity usually measured once daily, in the
20 evening or in the morning, depending on the trial.
21 It's a simple numeric rating scale, 0 to 10, no
22 pain, to 10 being worst pain, or pain as bad as you

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1 can imagine.
2 That's all we're giving patients. In some
3 cases, there is some education provided how to rate
4 that, but in most cases, not. I've had patients
5 come to me during a clinical trial and they'll say,
6 "Well, I know I'm here for fibromyalgia pain, but I
7 wasn't sure. Was I supposed to rate my headache
8 with that? I had this knee pain from my arthritis.
9 Am I supposed to rate that, too, when I'm measuring
10 my pain severity?"
11 So there's a lot of confusion out there, and
12 I suspect a great deal of variation in the pain
13 scores based upon how patients view this. So I
14 think we need to do a better job of figuring out
15 how the presence of these comorbid disorders can
16 affect pain ratings. Maybe there's a way to
17 develop some consensus around that so that when we
18 have a clinical trial, we're educating the sites on
19 how to present these scales and teach them how to
20 use the scales. We might have a better effect if
21 we do that, but I think it's an open question.
22 When we design these trials, one idea -- and

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1 this is what we're kind of trying to address -- is
2 centralized pain disorder. You think about
3 fibromyalgia as representing centralized pain that
4 is the end of the continuum, and that these other
5 chronic overlapping pain conditions might be
6 related based upon the presence of this
7 centralization.
8 I'm quoting Dan here from his slide set
9 earlier yesterday that the phenotype is quite
10 clear: multifocal pain and other CNS symptoms, and
11 in some cases, hypersensitivity to other sensory
12 stimuli. We know that, and that actually is how we
13 define fibromyalgia.
14 This was an effort to educate primary care
15 clinicians on how to diagnose fibromyalgia and how
16 to simplify it for the clinician. It really
17 emphasizes the chronic widespread pain or chronic
18 multisite pain, however you define it, and then
19 fatigue and sleep disturbance.
20 In this triad, we were trying to educate our
21 fellow clinicians that if you see this in the
22 clinic, think about fibromyalgia as a possible

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1 diagnosis. And of course, these other symptoms are
2 very important to assess, but the idea was to just
3 have them focus in on these three symptoms, and
4 that might improve the recognition of fibromyalgia
5 in the clinic.
6 Through the work at AAPT, we took that and
7 tried to create a little more simplified diagnostic
8 criteria for fibromyalgia that included multisite
9 pain, moderate or severe sleep problems, or
10 fatigue, and then symptoms present for at least
11 3 months. This is, again, an effort to try to
12 improve recognition of fibromyalgia in the clinical
13 setting, and we were able to reduce the number of
14 painful sites to 9 possible sites, and then 6 out
15 of these 9 would be a positive result.
16 This would be fibromyalgia at the end of the
17 continuum, but as we've seen, it may also be useful
18 to look at a more continuous measure. As Dan has
19 proposed and has been doing for other trials,
20 adding a sum measure of fibromyalgia, whether it be
21 syndromal or subsyndromal, might be important in
22 picking out those patients who have centralized

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1 pain, and identify those subset of people who do
 2 have -- no matter what pain disorder you're
 3 studying, it might be very important, at least
 4 maybe in a phase 2 trial, to try to get some
 5 proof-of-concept information before going forward
 6 with a larger phase 3 trial.

7 In fibromyalgia trials, I think what we can
 8 do better is to more specifically identify the
 9 other chronic pain disorders that are present in
 10 the patient population. For those of you who do
 11 clinical trials, you know that we collect medical
 12 history in what we call our source documents, and
 13 these are like our medical records. Some subset of
 14 that information gets transferred to the database,
 15 and, really, the sponsor determines what that
 16 information will be and what they plan to analyze
 17 at the end of the trial.

18 Up until now, they really haven't
 19 systematically asked the investigators to identify
 20 comorbid pain disorders and to include that on the
 21 database. I think just doing that as a first step
 22 would be really important for us to at least gather

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1 some preliminary information about responsiveness
 2 of some of these other pain disorders to the
 3 treatment.

4 It seems simple to do, but it can get
 5 complex because you have to rely on your
 6 investigator to diagnose these things, and that is
 7 variable across the sites. So we need to give some
 8 guidance to them. I know there's some work on
 9 trying to simplify that with different screening
 10 questions to help the investigators identify
 11 whether a patient has IBS, or other disorders, or
 12 TMD.

13 Also, even these other conditions like
 14 osteoarthritis and neuropathic pain, and other
 15 things that we think are getting into the trials,
 16 it might be good to know what we really are dealing
 17 with, and then we'd have a better idea of what is
 18 responding and what is not.

19 Then we have to look at our outcome measures
 20 as we've been talking about, and it gets very
 21 complex when we think about it. It's been nice in
 22 some ways to have a simple one-question primary

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1 outcome, but, really, is that capturing everything
 2 that we want to know about outcomes?

3 We heard yesterday is it important to know
 4 how widespread the pain is? Maybe that's an
 5 important outcome, or the duration, or are there
 6 other aspects of the pain experience that we need
 7 to track? Then, do we need to track specifically a
 8 regional pain question, abdominal pain with IBS,
 9 for example? Do we need to specifically ask a
 10 question about that? I would say yes, maybe at
 11 least in a phase 2 program where we're just trying
 12 to figure out how the drug is working, and then
 13 that might inform the larger trial.

14 We've talked a lot about phenotyping. I
 15 know this group has dealt a lot with phenotyping,
 16 trying to identify subpopulations of patients who
 17 might respond to a particular treatment, depending
 18 on the mechanism of that treatment. I think that
 19 is important to do. Again, we need to track our
 20 comorbidity better and maybe utilize some of these
 21 QST and imaging maybe in the proof-of-concept
 22 trials.

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1 The spectroscopy we heard about yesterday
 2 has been very effective in identifying how certain
 3 drugs might work in patients. So again, at least
 4 in the beginning here, trying to incorporate some
 5 of these measures in early-stage programs at least
 6 would give an idea of how these drugs might work,
 7 and what the mechanisms are, and what patients
 8 might respond to them.

9 Then even in other chronic pain disorders
 10 outside of the fibromyalgia realm, again, assess
 11 the degree of centralized pain using one of these
 12 scales. It doesn't matter, either including a
 13 fibromyalgia diagnostic criteria, a full syndromal
 14 fibromyalgia comorbidity, or just a continuous
 15 measure looking at the degree of centralized pain a
 16 patient may have.

17 That I think would help, again, especially
 18 early stage, to figure out what we're dealing with
 19 and what patients are then to focus on in the phase
 20 3 program. We might get more treatments that would
 21 work and beat the placebo in our clinical trial
 22 programs.

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1 There are a lot of other issues to consider.
 2 We've talked about some of these. Catastrophizing
 3 has come up a fair amount. In my clinical
 4 experience, we looked longitudinally at different
 5 factors that predicted outcome and controlled for
 6 all of these different factors: medications used;
 7 presence of opioids; whether patients were obese or
 8 not; whether they use opioids; a lot of factors.
 9 The only thing that really predicted a poor
 10 prognosis was the presence of catastrophizing at
 11 the beginning of the study. But the problem is
 12 the patients who entered our study already had
 13 pain, so I don't know when the catastrophizing
 14 started, if they had it before they developed pain,
 15 or if it developed after they developed pain.
 16 Nonetheless, it seems to be a sign of a poor
 17 prognosis, so maybe we need to identify this in a
 18 clinical trial, which we've never really done.
 19 We've never looked at this in a medication clinical
 20 trial, to my knowledge, one of the big programs for
 21 indication. Maybe we need to. Maybe we need to
 22 consider that in our inclusion/exclusion criteria.

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1 There are a lot of other factors that go
 2 into designing a trial such as lifestyle factors,
 3 stressors, disability, we discussed, and then
 4 function. I just want to bring you back to the
 5 function piece because we do assess function in our
 6 clinical trials, but it's usually one of the
 7 secondary outcomes.
 8 I think we can do a little bit better with
 9 that, maybe. We've worked on developing response
 10 indices that include function potentially as a
 11 primary outcome. Some of the trials in the past
 12 have tried to do that. I think we need to do that
 13 a little bit better, and maybe include indices that
 14 have functioned as part of it, and then also
 15 includes not just pain but maybe sleep, and
 16 fatigue, and some of these other very important
 17 symptoms so that we really get a good feel of how a
 18 drug is working on these multiple domains of
 19 fibromyalgia, because we know this condition has a
 20 profound impact on people's lives; socioeconomic
 21 consequences. We've tried to track these in some
 22 of our trials, but I think we can do better.

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1 In summary, fibromyalgia is a prototypic
 2 centralized pain state. The assessment for the
 3 presence of fibromyalgia symptoms, that is
 4 centralized pain, may be important in trials of all
 5 chronic pain disorders. Identifying these
 6 overlapping pain conditions and tracking their
 7 response to treatment may be helpful in
 8 establishing new therapies.
 9 For example, TMD, we really haven't done a
 10 lot of medication clinical trials in that
 11 condition, and maybe adding some outcomes, again,
 12 in an early-stage program, we might get some cues
 13 that a new medication might work for these other
 14 COPCs; and phenotyping, based on the presence of
 15 comorbidity, and using some of these more advanced
 16 techniques, might help to identify individuals that
 17 are more likely to respond to a particular therapy.
 18 Thank you.
 19 (Applause.)
 20 Q&A and Panel Discussion
 21 DR. KATZ: Let me invite all of our speakers
 22 from this morning's session to come up and join me

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1 up here on the panel.
 2 Friedhelm, why don't you come and join us,
 3 please, as well? We have an additional member of
 4 our panel, Friedhelm Sandbrink, who runs the pain
 5 program at the VA, who will be joining us for this
 6 discussion.
 7 We have an hour and 15 minutes. What I
 8 would like to do is see if we can discipline
 9 ourselves to start with clarifying questions about
 10 the presentations. So if anybody has any questions
 11 or comments about specifically what was presented.
 12 I'm not sure how long that will take; probably not
 13 that long. Then we can try to move into
 14 identifying what the key questions are that we need
 15 to answer at this meeting to see if we can come up
 16 with some clear answers.
 17 So I'll ask the panelists, while we're going
 18 through the initial part of this question and
 19 answer, to begin to think about what you think
 20 those key questions are and see if we can start to
 21 define some answers. I think, Dan, you had your
 22 hand up first, and then Ian, and then Lee.

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1 DR. CLAUW: Yes. This is probably more of a
 2 public service announcement than anything else. A
 3 couple of years ago, the NIH gave a contract to
 4 Bill Maixner and Dave Williams from our group to
 5 create a screener for COPCs, and that is almost
 6 done. It will be publicly available in the next
 7 couple of months. But this will make it a lot
 8 easier, in the context of a trial, to screen for
 9 all 10 of the chronic overlapping pain conditions
 10 in a very short period of time because it asks a
 11 couple of leading questions that can say, okay, is
 12 it possible the person has irritable bowel? Then
 13 it gives the actual criteria for each of the
 14 chronic overlapping pain conditions.
 15 So it will be the first time in an easy way
 16 that people, at the beginning of a trial, could say
 17 which of these 10 COPCs someone has. And I do think
 18 this would be an incredibly useful thing in phase 2
 19 of an industry trial because you might then see
 20 chronic overlapping pain conditions that you have
 21 efficacy or effectiveness, that didn't even
 22 anticipate might be something that you would be

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1 going towards with respect to an indication.
 2 I think when it's super easy to do it, like
 3 it will be, I would recommend that people start
 4 doing that.
 5 DR. KATZ: I think it's worth taking a
 6 minute and diving down that rabbit hole one step
 7 further since hopefully, we'll come up with
 8 actionable recommendations at this meeting.
 9 Dan, just made a recommendation, which is
 10 that -- I'll try to paraphrase it, Dan -- routinely
 11 in chronic pain clinical trials, we should include
 12 a screener for these chronic overlapping pain
 13 conditions so that we can -- if I can expand on
 14 what you said -- better characterize our
 15 populations at baseline and even determine whether
 16 there's an impact of therapy on these conditions
 17 that may or may not be the primary focus of the
 18 clinical trial.
 19 Is that a reasonable paraphrase?
 20 DR. CLAUW: Perfect.
 21 DR. KATZ: Okay. Who thinks that's a bad
 22 idea?

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1 (Laughter.)
 2 DR. KATZ: Lee Simon. Anybody else think
 3 it's a bad idea?
 4 John, you think it's a bad idea?
 5 DR. MARKMAN: I would want to
 6 understand -- in a lot of these clinical trials we
 7 do now, we have these tools that we incorporate to
 8 exclude mimicking disorders. So I guess some of
 9 those tools incorporate some of the questions that
 10 Dan is talking about, but they're a little more
 11 disease specific.
 12 On a peripheral neuropathy trial for
 13 idiopathic peripheral neuropathy or diabetic
 14 peripheral neuropathy trial, you have a mimicking,
 15 overlapping disease tool, which is specific for
 16 neuropathy; so osteoarthritis of the foot, peroneal
 17 nerve entrapment, blah, blah, blah, but also all of
 18 these other disorders.
 19 So I guess the only tension there would be
 20 between one which is more tailored to the indexed
 21 condition that you're studying versus one that's
 22 sort an off-the-rack solution for all trials.

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1 That's the one tension I see.
 2 DR. KATZ: Okay. Great. I think we can
 3 probably all agree that those two goals can live
 4 together, and that we'll need to do what we need to
 5 do to clarify what the actual primary diagnosis is,
 6 and make sure it's not one of these imitating
 7 disorders, and at the same time track all of these
 8 comorbid conditions.
 9 We're still just focusing on Dan's proposal.
 10 Lee, do you want to explain your objection to his
 11 proposal?
 12 DR. SIMON: It's not an objection. It would
 13 be great to have this evidence that you accrue in
 14 academic explorations of experiences to progress
 15 and further understand what populations we're
 16 looking at. But Dan went so much further to
 17 suggest that maybe using it in a phase 2 trial
 18 would be helpful.
 19 It might be helpful, or exclusion/inclusion
 20 criteria, to define your population better, but it
 21 is not an indication. And that's actually one of
 22 the issues that we have to discuss; how does one

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1 put a box around what we're looking at to determine
2 how to define a primary outcome for a disease
3 state?
4 Industry is interested in getting drugs
5 approved. I can't even imagine, based on what
6 we've heard this morning, how that would happen,
7 based on what we've heard this morning. And yet I
8 really believe in central sensitization and I think
9 it's maybe even driving the argument that chronic
10 pain is a separate chronic disease, but we have to
11 define that better. It's possible that Dan's work
12 would allow us to do that, but academic work, not
13 an industry-sponsored trial yet. That's my
14 objection.
15 DR. KATZ: Mike, go ahead. Use the mic,
16 please. Oh, and I forgot to remind everyone to say
17 their name first.
18 DR. ROWBOTHAM: Mike Rowbotham. The
19 screener that is being discussed in the whole
20 presentation yesterday on COPCs is really quite
21 different from what Lesley was saying, which has
22 been my experience recruiting for trials; patients

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1 come in, and they've got all sorts of things wrong
2 with them.
3 If you ever want to recruit a patient into
4 your trial, especially fibromyalgia patients, you
5 kind of have to downplay some of those a little
6 bit. And the patients certainly do because they
7 know what the inclusion/exclusion criteria are, and
8 they tailor what they tell you so that they're not
9 going to get kicked out right away.
10 She may want to comment further on that
11 because that's a really tough issue.
12 DR. KATZ: Lesley, you were invited to
13 comment further on that.
14 DR. ARNOLD: Yes, I agree, it's very
15 challenging. I don't think it's just the patients
16 who downplay it. I think some of the
17 investigators -- you know, sometimes we just have
18 to deal with this comorbidity, and we do the best
19 we can. But I was thinking and proposing that
20 maybe we just characterize the patients better and
21 acknowledge that these patients are in our trials,
22 and then find a way to determine, at least at

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1 early-stage programs, to see if the presence of
2 these comorbidities affect our outcomes are not.
3 They may not.
4 If these are linked by centralized pain or
5 sensitization, whatever you want to say, maybe they
6 would respond to the same treatments; I don't know.
7 But my proposal is to, well, come out of the closet
8 a little bit about it and just characterize the
9 patients better that we're putting in our trials.
10 DR. KATZ: So still focusing on the issue of
11 whether we should be tracking these comorbidities
12 in clinical trials, I have John and then Clifford,
13 and then Steven.
14 DR. FARRAR: I think there's a push and pull
15 here. There are conflicting components to this
16 that I think Lesley raised very well, which is that
17 you can't exclude everybody. You can't find the
18 one person with only centralized sensitization and
19 nothing else because it doesn't even make sense.
20 On the other hand, there are a group of patients
21 that you do want to exclude, people with
22 significant psychiatric abnormalities.

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1 So I think one of the tasks in front of us
2 with regards to this issue of coexisting problems
3 and comorbidities is trying to decide which of that
4 group need to be excluded because they will add so
5 much variability to the measurements that we do,
6 that we can't determine what actually happens
7 versus the ones we include, as Lesley was just
8 saying, and try and deal with as we go through.
9 I was struck by something that was
10 presented -- to, I think Dr. Campbell presented
11 it -- with regards to a study that she was looking
12 at where the depression and anxiety measures did
13 not change, whereas some of the pain measures and
14 other measures did change.
15 I think some of what we are going to need to
16 deal with is to get and look at some of that data
17 to understand whether we can include people with
18 depression, anxiety, or whether we need to measure
19 it. I mean, we certainly need to include them, but
20 the point is how to measure it and how to think
21 about it, and what we decide to do if both of them
22 get better versus one not [sic] getting better and

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1 one not.

2 So I think the key issue here is trying to

3 dissociate what we can include, stratify, and look

4 at versus the things that we really can't because

5 of the problems that it would impose on the study.

6 DR. KATZ: Clifford?

7 DR. WOOLF: This is a question to the panel,

8 the extent to which the presence of these comorbid

9 features are stable, do they change? When you have

10 your patients -- it looks like a very busy day you

11 had -- when they come back, is the pattern the same

12 for every patient, or for someone who has IBS, does

13 that disappear? In which case, this can make the

14 dynamic nature of that and will add some

15 complexity.

16 DR. ARNOLD: Well, I think, sadly, things

17 stay pretty much the same over time. There is

18 maybe improved coping and living with symptoms, but

19 as part of my clinic, I included the FIQR, the

20 Fibromyalgia Impact Questionnaire, and they fill it

21 out every time they come. It's disheartening

22 sometimes to see how little symptoms change over

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1 time. Maybe, again, their coping improves or their

2 adaptation to their symptoms improve. Maybe

3 there's a slight movement of these symptoms. But

4 it's really -- again, my patient population is

5 tertiary care, so you have to keep that in mind.

6 But typically, there's not much movement.

7 DR. KATZ: Although, Of course, if we don't

8 capture it, we don't really -- there could be -- if

9 there was a 40 percent improvement in something, we

10 would probably never know it. It's hard to figure

11 out if people's symptoms are improved without

12 capturing the data.

13 DR. BRUEHL: This is talking about Dan's

14 proposed overlapping pain measure, but I'll frame

15 it as a question. The measure seems to be

16 something that would be very detailed and

17 characterizing diagnostic criteria for a whole

18 variety of potential overlapping pain conditions.

19 But listening across all the presentations so far,

20 it sounds like the reason those are important

21 presumably is because they all reflect some

22 underlying mechanism; and that what we're really

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1 focused on is pain.

2 I'm wondering if we're over complexifying by

3 trying to do diagnostic criteria for a whole

4 variety of disorders rather than simply focusing on

5 number of pain sites, which would be a surrogate,

6 because if you've got IC, you've got pain in the

7 pelvis. If you've got migraine, you've got pain in

8 the head.

9 That would show up in a really simple

10 measure. And pragmatically, if you're trying to do

11 trials, would it be easier to say a cutoff out of a

12 number of pain sites at least 4 rather than saying

13 how many in which of the specific conditions you'd

14 have. And I guess I would like comments from the

15 panel as to what they would think of the value of

16 being more simple versus more detailed.

17 DR. KATZ: I think I'm hearing you ask, in

18 addition to a body map, which was a recommendation

19 that floated up yesterday, what additional

20 information is provided that aids in our

21 understanding of these patients by looking at their

22 medical comorbidities, either as a snapshot in time

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1 or even past through time?

2 Does anybody have an answer to that question

3 in terms of what additional information is added by

4 the comorbidities? Dan?

5 DR. CLAUW: Yes. So again, I was implying

6 that you would use this in addition to a body map,

7 not instead of a body map.

8 DR. KATZ: Yes.

9 DR. CLAUW: And the reason that I think it's

10 a good idea is that I think that probably half of

11 those chronic overlapping pain conditions don't

12 even currently have a single approved drug. Many

13 of them are visceral pain conditions that are part

14 of trying to get to a chronic pain indication.

15 And I do consult with a lot of people in

16 industry, Lee.

17 DR. SIMON: I know you do.

18 DR. CLAUW: And I think they have often

19 struggled in phase 2 to figure out what conditions

20 their drugs might be effective, and a lot of them

21 are looking and wondering is there a visceral pain

22 condition my centrally acting analgesic might work

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1 in or might work in this or that.
2 So all I'm saying is that in phase 2,
3 especially if you have a centrally acting compound,
4 putting that in and actually seeing the people that
5 meet criteria for irritable bowel in my study, that
6 there was a strong signal that my drug worked, I
7 think that would be a lot more helpful to the
8 average person in pharma that's trying to convince
9 their leadership that we should take the drug into
10 the great unknown, into vulvodynia, into
11 interstitial cystitis, in these conditions that
12 have not had a lot of drug development and where
13 there is a tremendous unmet need at the level of
14 the patients.
15 That's all I'm really saying, is that I
16 think it would give a little guidance to say, wow,
17 we saw a really -- if this is a fibromyalgia trial,
18 but we saw that the subset that had irritable
19 bowel, or the subset that had vulvodynia, did
20 really well with this drug, and we actually have
21 data that people met diagnostic criteria for that,
22 and not just had a site on a body map in that

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1 location, because that doesn't mean that that
2 person has that chronic overlapping pain condition.
3 So I'm just saying that in phase 2, in
4 exploring, this would be helpful in trying to get
5 maybe some signal as to which of the 10 conditions
6 your drugs might be useful in.
7 DR. KATZ: Do you want to respond
8 specifically to that, Lee? Go ahead.
9 DR. SIMON: Yes. I think that exploring
10 that kind of thing and calling it a phase 2 is what
11 my difficulty is. Usually you think about actually
12 targeting phase 2 to understand your dose duration.
13 And because of the trends that have been going on
14 in drug development, where people are trying to
15 telescope an understanding, jumping into phase 3, I
16 would ask you to think about this as being better,
17 searching for the right target, and could be done
18 with your technique. But it should be done before
19 phase 2.
20 It should be actually an early study to
21 understand who it is you're going to treat;
22 otherwise you're going to get people working in

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1 phase 2, and then they're going to come to people
2 like me and say, "Well, this is an adequate and
3 well-controlled trial. Maybe it can serve as one
4 of my pivotal trials." And it's going to be all
5 confused because of all the things that you're
6 searching for.
7 So I'm just suggesting that an understanding
8 of what you're targeting in phase 2 should already
9 have been accomplished, and looking for this kind
10 of stuff, keep it simple. That's the problem.
11 That also makes an interpretation of the evidence
12 in phase 2 that much more difficult. So search,
13 but don't do it in phase 2.
14 DR. CLAUW: Then you're developing a new
15 meaning for phase 1 or you're asking for phase 1.5.
16 And then we're just splitting hairs about -- I'm
17 just saying early in drug development, it would be
18 useful to have this information.
19 You're conflating I think people that move
20 too rapidly from phase 2 to 3 with me saying that
21 early in phase 2 -- regardless of what we call
22 that, because that's not phase 1. It's not

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1 toxicity testing anymore; that early in phase 2 --
2 DR. KATZ: Let's --
3 DR. CLAUW: -- 1B or 2A, that's fine. But
4 I'm just saying --
5 (Crosstalk.)
6 DR. KATZ: Let's leave that point there.
7 Mike, you were next.
8 DR. ROWBOTHAM: I wanted to pick up on
9 something that you said in response to Lesley's
10 comment. One thing that you've proposed is really
11 training research patients, and it's something that
12 we've always tried to do, too; it's very important.
13 So my cutoff was not so much whether or not they
14 had other conditions -- and conditions that were
15 really outside of what we've been talking about is
16 COPCs -- but whether or not they could actually
17 rate reliably the pain that it is that you're
18 supposed to be testing your treatment for.
19 I think it's great if you have a really good
20 subject who can rate the disorder that the trial is
21 aimed at, and then independently rate all their
22 other COPCs. Like they can say, "Well, my

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1 musculoskeletal pain got better, but my IBS didn't
 2 get better," or my migraines didn't get better.
 3 That would be great. I don't think it necessarily
 4 has to be at any particular phase because it's
 5 going to be a secondary measure anyway.
 6 But the key thing for picking a good subject
 7 from a not so good subject, or a subject you really
 8 don't want to have in your trials, is whether or
 9 not they can be reliable and understand what it is
 10 they're rating as opposed to just giving you this
 11 kind of global thing of, "Well, I just don't feel
 12 good, so therefore even though my FM pain is
 13 better, I'm still not happy," or I still don't feel
 14 good, and therefore they rate the drug as
 15 ineffective.
 16 DR. KATZ: I totally agree with that.
 17 Lesley, did you want to add anything to
 18 that?
 19 DR. ARNOLD: No, I totally agree with that.
 20 As I was giving an example of a patient who came
 21 back and asked me what she was supposed to be
 22 rating all this time, her headaches or not,

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1 clearly, ideally if a patient can differentiate the
 2 different pain disorder sources, that would be
 3 ideal, but it might be better to, maybe again as
 4 secondary outcomes, specifically ask about their
 5 IBS pain or their headache pain to separate it out.
 6 I think most people with fibromyalgia
 7 understand the widespread achy nature of the
 8 fibromyalgia, and they can focus on that, but it
 9 can get a little tricky there, too, because I don't
 10 know if their low back pain is related, or I don't
 11 know if their joint pain is centralized pain, or a
 12 mixture of factors.
 13 I still think the pain severity is an
 14 important primary. I think your programs, and
 15 educating patients, and teaching them how to use
 16 the scale is good in the beginning and maybe adding
 17 some more specific questions about other regional
 18 pain disorders might be helpful as secondary or
 19 exploratory.
 20 DR. KATZ: In our experience developing
 21 these training programs, it's amazing how often
 22 when you sit there with a sponsor and try to

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1 finalize a program, that reveals lack of clarity
 2 about what the sponsor is actually asking the
 3 patient and the question in the first place. So
 4 putting together these training programs is useful
 5 not only for the patients, but also to clarify what
 6 is it exactly that we're trying to elicit.
 7 Rick, you were next. Just say your name
 8 into the mic, please.
 9 DR. MALAMUT: Hi. Rick Malamut at Collegium
 10 Pharma. I have so much to talk about now --
 11 (Laughter.)
 12 DR. MALAMUT: -- just since I've raised my
 13 hand. But I'll start from the beginning, which was
 14 John's comment, that totally agree we're going to
 15 have to include comorbidities in these studies.
 16 It's going to be difficult to find that perfect
 17 patient, much less a hundred, much less more for
 18 phase 3, who meets our predefined criteria of not
 19 having too many comorbidities.
 20 I think it's doable to have them in the
 21 study. We may want to set limits as to severity.
 22 I agree that maybe severe psychiatric

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1 conditions -- we have to define that -- may not be
 2 the best study patients. Then there are validated
 3 scales for some of these; for sleep, for mood,
 4 fatigue. It's easy enough to watch those, to
 5 attract those, assuming our primary endpoint is a
 6 pain outcome. We just have to make sure that our
 7 primary endpoint is going to be reliable to make
 8 sure the patients can actually reliably tell us
 9 that their pain is due to the index condition we're
 10 studying.
 11 Then, I have to go back to Lee's comment. I
 12 agree with you that some of my colleagues in pharma
 13 do try to go too quick, and try to jump from
 14 phase 1 to phase 3 without adequate phase 2.
 15 Phase 2, as everyone knows in the room, is where
 16 studies go to fail. Phase 2 is often thought of as
 17 maybe we can use this for registration purposes,
 18 but phase 2 is where we learn.
 19 So I would suggest that phase 2 for this
 20 type of condition is the most important study we
 21 run. It's where we look at our population. We
 22 look at our outcomes. We see, okay, are these

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1 viable? We look for those subpopulations. If we
2 have a patient with fibromyalgia who also has TMD,
3 we look to see, did that patient in the
4 subpopulation analysis get better? Do they do
5 worse? And that all helps to guide us with our
6 patient population for phase 3.
7 I agree dose is important, but it's a little
8 more than that, and we can talk about biomarkers
9 later.
10 DR. KATZ: Howard, you were next.
11 DR. FIELDS: The thing that jumped out at
12 me, particularly in Lesley's talk, was how the
13 patients who were rated high in catastrophizing
14 seemed to do poorly in terms of outcome. That
15 raised to me the issue of is that a comorbidity or
16 is that a feature of the primary condition you're
17 trying to treat? If the latter is the case, you
18 might want to exclude them to have a successful
19 trial, but then it might turn out that the drug
20 isn't that effective clinically.
21 So I'm kind of glad that we have the
22 particular expertise. I was looking over at you,

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1 Roger. You seem to raise the possibility that
2 catastrophizing, whatever the neurobiological
3 mechanism is, could actually have a causal role in
4 the condition, or maybe I misunderstood what you
5 said.
6 DR. FILLINGIM: Well, I think that
7 catastrophizing, along with other psychological
8 factors, could have causal influences on
9 manifestation of the condition and potentially on
10 responses to therapy.
11 DR. FIELDS: So it's not comorbidity; it's
12 part of the disease being treated.
13 DR. FILLINGIM: Could be, yes.
14 DR. FIELDS: Okay. I just raise it because
15 it seems to me to be one of the core problems in
16 clinical trial design.
17 DR. KATZ: What's the comorbidity versus
18 what's part of the actual disease that we're
19 treating? Yes.
20 DR. FIELDS: Yes.
21 DR. KATZ: Roger, did you want to add
22 another comment? You had your hand up.

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1 DR. FILLINGIM: Yes. I had a question.
2 Mike just brought up, and I think you confirmed,
3 the importance of training participants and
4 retaining the ones who are good participants. Do
5 we have a sense that the presence of multiple
6 overlapping pain conditions, or central
7 sensitization, somatosensory amplification, or
8 catastrophizing is associated with being a bad
9 participant, and thus being at risk of being
10 excluded from trials? Because that seems relevant
11 to the discussion here.
12 MALE VOICE: What's a bad participant?
13 DR. KATZ: Roger, you asked. What's a bad
14 participant?
15 DR. FILLINGIM: Somebody who rates so poorly
16 or fails to meet whatever criterion you selected
17 for being a good participant.
18 (Laughter.)
19 MALE VOICE: I don't know what that is.
20 DR. KATZ: Okay.
21 MALE VOICE: Probably the biggest problem is
22 inconsistent.

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1 DR. KATZ: What we do know, or at least what
2 I know about that, is that we actually have looked
3 at catastrophizing as a predictor of pain reporting
4 accuracy in some of the studies that we've done.
5 We have a whole way of defining pain reporting
6 accuracy, which I won't bore you with. The
7 patients who were catastrophizers were actually not
8 bad at reporting their pain accurately, as it
9 turned out. We thought they would be, but they
10 weren't in. In one or two studies where we looked
11 at the Pain Catastrophizing Scale compared to
12 experimental pain reporting consistency, if you
13 will, it was not a bad predictor.
14 Bob?
15 DR. DWORKIN: Nat, you recently published
16 that the people who report variable pain during
17 your baseline period seemed to have less internal
18 focus, as I recall, than the people who, to use
19 Jim's phrase, are more consistent. Then my
20 question is, is there any relationship between
21 internal versus external sensory focus and
22 catastrophizing?

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1 DR. KATZ: We have not looked at that.
 2 DR. RAJA: Just a quick question related to
 3 that. Many of you have done studies in
 4 fibromyalgia and chronic overlapping conditions.
 5 The question is -- well, a bad patient could be one
 6 whose likelihood of dropping out of the study is
 7 high because of whatever reason.
 8 Do we know if this is a factor in what
 9 influences maintaining that patient across the
 10 study?
 11 DR. KATZ: The retention rates in the
 12 fibromyalgia studies have been pretty good, I
 13 think. No?
 14 DR. RAJA: But have they excluded those high
 15 catastrophizers?
 16 DR. KATZ: Oh, I see; catastrophizing per se
 17 rather than -- it doesn't seem like widespread pain
 18 itself is a reason for people dropping out because
 19 the fibromyalgia patients, they don't seem to drop
 20 out for much. But in terms of catastrophizing per
 21 se, I don't know the answer.
 22 Does anybody know whether catastrophizing is

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1 a predictor of a dropout?
 2 DR. WASAN: There's no data on that.
 3 DR. KATZ: Okay.
 4 DR. WASAN: Just as far as I can -- Rob, do
 5 you agree? I haven't seen a single thing.
 6 DR. EDWARDS: Along those lines I think it
 7 has emerged from the placebo literature that the
 8 expectation of a negative outcome has a big
 9 influence on actually the outcome being negative.
 10 One might expect that a catastrophizer would be
 11 pessimistic about the outcome.
 12 There was a recent article, actually, from
 13 Fabrizio Benedetti I was talking about with someone
 14 yesterday, where they were looking at injections
 15 for set joint pain, either lidocaine or saline.
 16 Saline was the placebo. People that thought they
 17 got the active drug, even if they had the placebo,
 18 were the ones that did well. There was a bigger
 19 effect of expectation than there was of the local
 20 injection.
 21 So it seems like it's a conundrum. If
 22 catastrophizing is really a feature of the disease

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1 and has a negative influence on the outcome of your
 2 treatment, you've got to figure out a way to deal
 3 with that particular problem. One possibility is
 4 just asking people whether they think they got the
 5 active treatment. If you think they got it or they
 6 think they didn't, you might group those together
 7 and look at the difference with the medication.
 8 That's what they did in that study that
 9 turned out to be very useful, so that's something
 10 to think about in terms of an analysis of the
 11 outcome. If you don't do that, then you're going
 12 to introduce a lot of variability based on people's
 13 expectations.
 14 DR. KATZ: Right. Luana?
 15 DR. COLLOCA: It's interesting that we don't
 16 have too many papers exploring the relationship
 17 between catastrophizing and expectancy, but this is
 18 a great point because it is not so demanding in
 19 terms of cost, and any clinical trial can be
 20 complemented with this measurement that can be
 21 extremely important to help us in interpreting
 22 data, but maybe also stratifying the patient when

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1 we run clinical trials.
 2 DR. KATZ: I have to say that I see
 3 pharmaceutical companies increasingly incorporating
 4 measures of masking, if you will, or expectation in
 5 their clinical trials often because they
 6 expect -- no pun intended -- that they're going to
 7 be asked to evaluate whether side effects, for
 8 example, caused on masking, which in turn was
 9 responsible for the treatment benefit that was
 10 observed. So they need to have that data on hand
 11 in order to address that question. I wouldn't say
 12 it's universally done, far from it, but I see it
 13 increasingly done.
 14 Ian and then Ajay.
 15 DR. GILRON: Should I move on?
 16 DR. KATZ: Okay. Let me actually summarize
 17 where we are with this topic on measuring
 18 comorbidities, and then we can move on to if there
 19 any other clarifying questions about the
 20 presentations.
 21 It sounds like there's a general support for
 22 the idea of measuring not only a body map, but also

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1 there's some additional information that can be
 2 gained by measuring comorbidities. We have Dan's
 3 tool that will come out eventually. It could used
 4 for that purpose.
 5 A number of people mentioned and a number of
 6 important potential unintended consequences of that
 7 or a caveats, such as how that's going to impact
 8 our inclusion/exclusion criteria for these trials
 9 once you started revealing that these patients in
 10 fact do have comorbidities that we might have been
 11 happier to sweep under the rug before, and some
 12 other caveats as well. And those caveats need to
 13 be considered as well in making that decision.
 14 That's what I got out of that whole
 15 conversation. I think we can move on to other
 16 questions or comments about the presentations.
 17 Ian?
 18 DR. GILRON: Ian Gilron from Queen's in
 19 Canada. First of all, thanks to everyone for
 20 amazing talks this morning. My question relates to
 21 Raj's what's in a name and how it leads to
 22 identifying participants for a proposed trial.

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1 This is not a rant, but let me just unpack
 2 it a little bit. It seems to me that the important
 3 distinctions here, dealing with central
 4 sensitization or whatever we might call it, are do
 5 we have sensitization or is the sensory nervous
 6 system normal? Is it central versus peripheral
 7 sensitization? Is that important? And is there a
 8 known source of nociception versus no identifiable
 9 source of nociception?
 10 I'm thinking back to what was done in
 11 neuropathic pain. For example, in 2008,
 12 Rolf-Detlef Treede and Charles Jensen and others
 13 were working on a grading system for diagnosing
 14 neuropathic pain, using an approach with history,
 15 physical, and as needed, special investigations to
 16 come up with a designation of probable neuropathic
 17 pain likely or -- sorry, definite, probable, or
 18 likely neuropathic pain, and I wonder if we need
 19 that here.
 20 So my question is must we, or should we,
 21 include an objective or at least clinician observed
 22 measure to confirm sensitization of the nervous

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1 system, for example, such as QST patterns compared
 2 to population norms as an inclusion criterion for
 3 central sensitization?
 4 DR. KATZ: So let's break that down a little
 5 bit because, Ian, I think you brought up two kind
 6 of companion issues. The first one is, which I
 7 think is the big pink elephant in the room, is
 8 central sensitization one thing or is it multiple
 9 things? And if it's multiple things, what are
 10 those multiple things?
 11 That's issue number one, and then a separate
 12 issue would be, what is the best way to measure it,
 13 or to diagnose it, or what-have-you? I think it
 14 might be easier to put the measurement issues aside
 15 and just deal with the conceptual categorization
 16 first, which is the first thing you brought up; is
 17 central sensitization one thing or multiple things?
 18 And if so, if it's a multiple, what are those
 19 multiple things?
 20 We can debate about names but at least maybe
 21 agree on the concepts first. And you actually
 22 proposed a classification system, if I was

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1 listening to you correctly, where you proposed that
 2 we could classify these patients based on whether
 3 there is or is not an identifiable source of
 4 nociception, and whether there is or is not
 5 sensitization. And if there is sensitization, is
 6 it peripheral or central? That's what I heard you
 7 say as an initial kind of draft classification
 8 system, if you will.
 9 Maybe start with the speakers first. Maybe
 10 start with you, Raj, first. You were specifically
 11 called out. Is central sensitization one thing or
 12 multiple things? And if it's multiple, what are
 13 the subtypes?
 14 DR. RAJA: I think going back to the issue
 15 of do we need something along the lines of what the
 16 neuropathic group did, I would say, yes, that might
 17 be helpful. Again, going back to the analogy
 18 of -- and Steve can add to this -- complex regional
 19 pain syndrome, we had a whole cluster of names, a
 20 whole cluster of symptom complexes. Until they
 21 came up with some kind of clear clusters of
 22 symptoms, and then signs, and the presence of them

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1 or not, I think the field was lagging behind
 2 because each specialty was calling this
 3 differently, and the studies were done differently.
 4 So I think to be able to advance this field,
 5 we have to come with kind of a paradigm of sorts,
 6 and this paradigm could be initially based on
 7 history, based on some exam factors and some
 8 biomarkers, whatever it would be. But I think
 9 coming up with a protocol and saying these are the
 10 likely patients to have central sensitization, or
 11 these are definitely the patients, I don't think is
 12 going to help advance this field.
 13 DR. KATZ: So you're advocating an effort to
 14 try to create more clarity around the typology of
 15 central sensitization.
 16 DR. FIELDS: I'm going to vote for multiple.
 17 DR. KATZ: You're going to vote for
 18 multiple? What are they? What are the multiple
 19 types?
 20 DR. FIELDS: Well, they're in Clifford
 21 Woolf's review article. You can have a loss
 22 gabaergic inefficient. You can have excitation.

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1 You can have amplification by descending
 2 facilitation. So there are a variety of mechanisms
 3 centrally that could give rise to what we observe
 4 clinically.
 5 DR. RAJA: That could be the subtypes within
 6 a broad group.
 7 DR. KATZ: So let's talk about the subtypes
 8 of what we observe clinically. What are those
 9 subtypes?
 10 DR. RAJA: Could you get Steve's comment on
 11 what he thinks based on what's happened in that --
 12 DR. BRUEHL: I was just going to say, I
 13 totally understand Howard's desire to break things
 14 out by mechanisms, and I also appreciate Roger's
 15 comment about lack of clarity, like disagreement on
 16 what the basic concepts are. And there's a big
 17 parallel with CRPS, many names, many presumed
 18 mechanisms.
 19 I sat in on several expert meetings where
 20 the people that knew the most about the mechanisms
 21 of CRPS all felt like it was important to have a
 22 mechanism-based diagnosis but were basically saying

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1 we don't know enough about the details of the
 2 mechanisms to convincingly argue that we should
 3 diagnose based on that.
 4 As a result, what happened was it was more
 5 of an umbrella term first, which was designed to
 6 get everybody using the same terminology and the
 7 same criteria, although, granted, they are probably
 8 over inclusive. And then we shrunk it down a
 9 little bit with revised criteria, and probably will
 10 do that further considering subtypes now that may
 11 indeed be mechanism based.
 12 I think in the context of talking about what
 13 we're talking about here, there are a lot of
 14 parallels. We don't agree on terminology, so I
 15 think having that would be valuable so at least
 16 everybody's on the same page. When I look at the
 17 mechanisms or the indicators of mechanisms we've
 18 talked about, what I kind of see are three distinct
 19 buckets, and I will throw this out for comment.
 20 One seems to be central sensitization as
 21 originally defined, where Clifford was talking
 22 about you've got a stimulus and response and you've

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1 got a hyper responsiveness that you see, and maybe
 2 QST is the way to best assess that. But that's one
 3 bucket that would be that pure traditional central
 4 sensitization.
 5 Then separately, we've got a number of body
 6 sites, maybe chronic overlapping pain conditions
 7 based on diagnostic criteria, and according to
 8 Dan's cluster analysis, the general sensitivity
 9 issue. All those things seem to hang together.
 10 Then separately we have the negative affect
 11 catastrophizing issue, which seems to be important
 12 and may be related to central sensitivity, but is
 13 kind of not really the same thing as the other two.
 14 All of these, of course, may interrelate. I
 15 wonder about the best starting places here; whether
 16 you start with a broad label, you collect data on
 17 all of these buckets, and then get a sufficient
 18 number of patients to be able to empirically decide
 19 what mechanisms might be supported, or if you go
 20 the other way around and say, a priori, we're going
 21 to say we think these mechanisms are involved, and
 22 that's kind of what we do eventually to come up

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1 with what the proper label is.
2 Sorry for the length of that.
3 DR. KATZ: For the moment, would people
4 agree that central sensitization and the presence
5 of some kind of peripheral injury, a nerve injury
6 or osteoarthritis of the knee or what-have-you, is
7 a different subtype than people with, let's say,
8 pure fibromyalgia, where they have widespread pain
9 and hypersensitivity without any obvious peripheral
10 injury?
11 Would people agree that those are -- at
12 least how separable they are in terms of the
13 realities of measurements is another thing, but are
14 they conceptually different? Yes; so that's two
15 subtypes.
16 I had Ian, and then Mike.
17 DR. GILRON: I'm just wondering -- just
18 coming back to Howard's comment of parsing this
19 out, and maybe Clifford can help -- for example, if
20 someone has loss of descending inhibition as a
21 predominant mechanism for their widespread pain, is
22 that actually central sensitization per se or is it

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1 just impaired inhibition?
2 DR. KATZ: Clifford?
3 DR. GILRON: I don't know if that semantic
4 is important.
5 DR. WOOLF: To take a slightly different
6 take of this, it seems to me we want to try and
7 capture enough information so that we can identify
8 who responds to different treatment modalities.
9 Again, unfortunately, that's a chicken and egg.
10 Once we have different treatment modalities that do
11 act on different aspects of this phenomenon, that
12 may help us identify the differences that exist in
13 outpatients.
14 We don't know enough, I think it's fair to
15 say, at the moment, mechanistically, about the
16 underpinnings of these different forms of
17 centralized pain to be able to say which one is
18 disinhibition, which one is facilitation, which one
19 is predominantly spinal cord, and which one is in
20 the higher brain centers. But if we see patterns
21 of differential responsiveness to this treatment
22 versus that, that may actually help inform us in a

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1 way.
2 I would add that definitely to the mix as
3 part of the way in which we classify who responds
4 to what or what kinds of patients respond with
5 which particular therapist and what aspects of
6 their pain or response? Is it only the tactile
7 allodynia or is it some other aspect of pain?
8 DR. KATZ: So are you saying that you think
9 that loss of inhibition is a salient enough
10 phenomenon that contributes to these clinical
11 features that it's worth characterizing if we're
12 doing a study, and we're attempting to understand
13 the impact of a treatment on central sensitization?
14 DR. WOOLF: What I'm saying is I don't think
15 we know enough now in terms of being able to
16 identify an individual patient if they have
17 disinhibition versus any other mechanisms.
18 DR. KATZ: I see.
19 DR. WOOLF: But as part of our attempt to do
20 that, whether functional imaging or other
21 techniques may enable us to identify what is the
22 predominant mechanism, I think that part of that

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1 may be treatment response. So it's not just using
2 this to identify treatment response, but it's
3 actually that treatment response itself may help
4 give us mechanistic insight.
5 DR. KATZ: Right. Actually, Ajay, you had
6 your hand up earlier, and I lost track of you, and
7 then I have Simon. Who else wants else wants to
8 get in the queue? Mike and Jim; everybody wants to
9 talk. Go ahead.
10 (Laughter.)
11 DR. KATZ: I'll just go by the rows.
12 DR. WASAN: First of all, I'm Ajay Wasan.
13 Secondly is that I agree with Steve and even some
14 of the comments from Clifford and others, that it's
15 just too much to say we should be able to classify
16 it by mechanism. But I think we can propose a
17 framework that is an advance that allows,
18 subsequently, to fill in some of these mechanisms.
19 For instance, I think that this concept that
20 there is somatosensory amplification, a feature of
21 many chronic pain syndromes, that they're
22 independent contributions of brain, of spinal cord,

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1 and peripheral nerves, and also the interactions of
 2 those is important. And of course, not all of
 3 those potential mechanisms are operative in every
 4 single patient and in every single condition.
 5 But we can provide that simple framework,
 6 that there's -- even now, just articulating that
 7 there's independent contributions of the brain to
 8 creating facilitation, for instance, of
 9 amplification is in itself an advance. I mean, it
 10 really is a significant step forward.
 11 So I think proposing that type of framework
 12 is really an advance that this group can, with the
 13 context of, but we don't know, of course, all those
 14 mechanisms, and what they are, and how to classify
 15 them, and how do they want individual patient, and
 16 how to assess. That's where I think the framework
 17 idea may hold some water.
 18 DR. KATZ: Thanks. You get speaker's
 19 privilege, Lesley.
 20 DR. ARNOLD: Well, thanks. I guess I
 21 question the idea of this pure fibromyalgia
 22 top-down only because I don't think we know enough

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1 about peripheral inputs to be able to say that the
 2 peripheral input is not also important. I
 3 mentioned obesity as an example. It's not an
 4 injury, but it's a metabolic change, and that can
 5 affect how the brain is functioning.
 6 So I just want to be careful not to separate
 7 it like that. I think this framework that Ajay
 8 presented is I think a good way to look at it, that
 9 there are these multiple possible mechanisms. We
 10 don't always know what's operating in an individual
 11 patient, but to present this as these are the
 12 possible parts to the puzzle is important. I'm
 13 very cautious right now of dividing the group just
 14 yet until we have more data.
 15 DR. KATZ: Thank you. Simon?
 16 DR. HAROUTOUNIAN: I just wanted to caution
 17 ourselves against labeling people as patients who
 18 have loss of descending inhibition because I think
 19 it really depends on the testing paradigm. When we
 20 test descending inhibition in healthy volunteers,
 21 we apply some sort of conditioning stimulus, and
 22 then look at the response to test stimulus. But

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1 someone who is in chronic pain, they're already
 2 using their, whatever, descending inhibitory
 3 control they have, and this additional conditioning
 4 stimulus will apply second conditioning pain.
 5 So it might be that we're not able to at
 6 least get extra response to sort of second
 7 conditioning stimulus rather than we'll label them
 8 as someone who's descending inhibition doesn't
 9 work. So I think we need to be somewhat careful
 10 and not label patients with inability to facilitate
 11 descending inhibitory control in a sense. So it
 12 depends on the testing paradigm, we should be just
 13 careful.
 14 DR. KATZ: Thanks. Mike, you were next.
 15 DR. ROWBOTHAM: I think you'd have a hard
 16 time finding a fibromyalgia patient who when they
 17 tell you their story doesn't have some sort of
 18 inciting event, injury, flu-like illness, sports
 19 injury, something that they kind of tied onset of
 20 their symptoms to.
 21 One thing I wanted to get back to, and I
 22 thought about it just by Vitaly's talk yesterday,

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1 is there is sensitization, I believe in that, but
 2 that's perhaps on top of an underlying tendency
 3 that's really a personality trait towards this
 4 somatosensory amplification. That would fit with a
 5 lot of the genetic data in patients with migraine,
 6 where there's heritability and other kinds of
 7 things; that you're not really going to be able to
 8 medicate that part away. You may be able to
 9 medicate away the overlying sensitization, but
 10 you're not going to change personality.
 11 So the data that Vitaly was showing
 12 yesterday that was really compelling was where you
 13 looked at the brain activation, and it was the
 14 same, but it was the same based on the percept
 15 rather than the same based on the stimulus
 16 intensity. I think that's really very important.
 17 Unfortunately, the OPPERA study came close
 18 to getting some of that kind of data, but I don't
 19 think it really went -- and I'd like to be
 20 corrected if I'm not right on this. But it doesn't
 21 necessarily go back far enough to get at what the
 22 patients were like long before they developed TMD

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1 or any of these other COPC grouping of conditions.
 2 DR. KATZ: Thanks. I have Jim Rathmell
 3 next.
 4 DR. RATHMELL: I think it's mostly been
 5 said, but I want to restate, let's be pragmatic
 6 about how at the bedside you're going to be able to
 7 characterize some of these things. There are these
 8 tests that can sort out the inhibition versus
 9 amplification, and are we really going to insert
 10 those into the clinical trials as the paradigm for
 11 selecting people, or is it just going to be
 12 additional information?
 13 I think we're getting to a point where I'm
 14 getting foggy on how you would actually select the
 15 patient for characterization. But one of the
 16 things that Clifford just said is interesting, is
 17 you could say based on their initial response to
 18 therapy, X, Y, or Z during an enrichment period,
 19 you could label them mechanistically because of the
 20 response to an individual drug and say we think
 21 this is the mechanism, and then carry forward from
 22 there; so if you're trying to select based on their

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1 response, or you may even screen them with a panel
 2 of different drugs to select the ones that respond
 3 to drug X, Y, or Z because of the mechanism that
 4 underlies that. That would be an interesting
 5 paradigm.
 6 DR. KATZ: Dan, you actually were next in
 7 the queue.
 8 DR. CLAUW: If I could just respond to a
 9 couple of things. One, first of all, there's
 10 absolutely no evidence that this is a personality
 11 disorder, so I'm just going to push back very
 12 strongly on that, but that's not the main point
 13 that I want to make.
 14 The main point that I want to make is I just
 15 want to agree with the fact that even though our
 16 group does a lot of imaging, QST, and things like
 17 that, we've published a lot of studies where we
 18 take individuals with fibromyalgia, we do QST and
 19 imaging, we give them a treatment, and we then go
 20 back and see what predicted what worked.
 21 In many cases, we are at an a priori
 22 hypotheses about the imaging findings that would

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1 predict responsiveness, and we were right, but we
 2 have never been able to go back afterwards and say,
 3 okay, now we see this group of responders; let's go
 4 back and look at their clinical symptoms. It would
 5 have been easily collected at the point of care or
 6 in a trial, and tried to say which subset.
 7 That was the same with all the fibromyalgia
 8 studies, registration trials that were done with
 9 pregabalin and duloxetine. Even though we
 10 intuitively thought the people with more depression
 11 would respond to duloxetine, and the people with
 12 more sleep problems would respond to pregabalin.
 13 It was very difficult, actually, to ever see that
 14 you could, a priori, based on the predominant
 15 symptom or anything, predict who was going to
 16 respond to the treatment.
 17 So I'm just saying that even though I love
 18 these mechanistic studies, I don't think any of
 19 them are ready to be embedded into clinical trials
 20 because, again, the clinical trials, at least for
 21 the foreseeable future, are going to be looking at
 22 PROs or things like that, or QST. But again, QST

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1 doesn't do it. It's not strong enough.
 2 DR. KATZ: I have Ian, and then John Farrar,
 3 and then Sharon Hertz.
 4 DR. GILRON: Just coming back to a
 5 diagnostic test or a diagnostic process for this,
 6 I'm hearing comments that this is a little bit
 7 contrived, and to hang our hat on something like
 8 that would be difficult given our understanding the
 9 complexity of that.
 10 Within this room, I think we can all
 11 appreciate that and would probably have some
 12 consensus on knowing who we're looking for when we
 13 see them, that this looks like who we're talking
 14 about, but coming up with a definition,
 15 particularly if we get to, at some point down the
 16 road, labeling indication -- to get to the point of
 17 how we're going to define our inclusion criteria.
 18 I feel like we have the need to at least
 19 come up with some sort of clinician observed
 20 measure that is more than just history or
 21 self-report measures.
 22 DR. KATZ: John?

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1 DR. FARRAR: I'm struck by the problem that
2 we're trying to address and the lack of
3 specificity, if you like, on what it is that we're
4 actually talking about. I'm a strong believer in
5 the centralization process. As Clifford has
6 suggested, and Howard, there might be multiple
7 mechanisms that underlie that.
8 I'm also very much struck by the fact that
9 the cause may not be the same process that
10 maintains that. My analogy is once the car has
11 wrapped itself around the tree, fixing or doing
12 something with the brakes isn't going to help very
13 much. I guess what I'm struggling with is trying
14 to think, as Ian is saying, about how do we
15 identify the group.
16 What strikes me is that a couple of people
17 now have said that there is a peripherally
18 maintained chronic pain centralization or chronic
19 pain enhancement; the example given of injecting
20 into the nerve endings of people who've lost limbs,
21 and finding that a lot of their phantom pain can go
22 away.

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1 My guess is there are two groups. There are
2 the people in which you can do that, and it goes
3 away, and there are people you can try it on, and
4 it doesn't go away, and that might be a proactive
5 way of actually defining certain groups.
6 Now, I don't know how to do that, but it
7 seems to me that if we could come up with some
8 mechanisms for actually trying to characterize the
9 pain -- Mike's work in postherpetic neuralgia, the
10 capsaicin sensitive versus the capsaicin
11 insensitive, I'm not sure what they are, but it
12 seems to me that at least some thought about ways
13 to not simply measure and gather patient-reported
14 outcomes, but to do some sort of testing to
15 understand -- we had the imaging data yesterday,
16 where given a pressure of 4 on the finger, some
17 people had a much bigger response than others.
18 So I would just raise that as a question for
19 the group in terms of whether there are ways to
20 think about categorizing our underlying mechanisms
21 in a way that would allow us to better address
22 them.

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1 DR. KATZ: Sharon Hertz?
2 DR. HERTZ: I keep hearing about QST, and
3 I'm wondering if there is a thing that everybody is
4 referring to that is the same. And if not, what is
5 the range of what's going on out there and how does
6 that impact understanding the results?
7 DR. KATZ: Would anybody like to answer
8 Sharon's question about what are people doing out
9 there that they call QST and what's the variability
10 in terms of what's actually done?
11 DR. FARRAR: Maybe Dr. Campbell. It's your
12 lot.
13 DR. ARNOLD: I could try. I think there's
14 enormous variability in QST responses. There are a
15 lot of different tasks that people do. We include
16 a battery that covers a lot of different domains
17 and takes about an hour. We could never expect a
18 clinician or somebody that's trying to quantify the
19 person right in front of them to do anything like
20 that; nor do we have normative data. The German
21 Research Network has tried to do some of that work.
22 I imagine between some of us here in this

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1 room, we could probably come out with norms, but I
2 still think even if we did that, it would probably
3 be unreasonable to expect somebody to do any kind
4 of deep phenotyping at the outset of a trial. So I
5 think that's tricky. There's huge variability that
6 I think can obscure what you're trying to look at.
7 Like Dan was saying with some of these
8 psychosocial and behavioral factors, we can look
9 later on at the end of the trial and see if we can
10 predict outcome based on baseline responses to X,
11 Y, Z QST measure. I don't think we've done as good
12 a job about testing those various factors over
13 time, and I actually had the same complaint over
14 some of our psychosocial, behavioral, and
15 widespread pain questions.
16 I think we do a fairly decent job getting
17 some of these measures at baseline, but then don't
18 necessarily follow them and look at trends over
19 time to be able to identify who did better and what
20 outcomes that improved.
21 DR. HERTZ: Just to follow up, there's a lot
22 to choose from. I'm assuming there are different

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1 systems to run them on. And then we have to wonder
2 about inter-rater or performer reliability. It
3 sounds like -- when I hear conclusions based on
4 QST, I'm not entirely sure what it means. It's
5 like saying, well, we evaluated the patient, and
6 there was no correlate with the evaluation. It's
7 just this box of something that goes into it.
8 So I'm just wondering if moving forward,
9 there's any interest, or stomach, or ability to
10 consider defining some parameters so that when we
11 look study to study or population to population, we
12 have some idea of what this QST means.
13 Because when we're trying to think of what
14 might actually be useful and pragmatic in a
15 clinical trial setting, when it comes to this kind
16 of thing, QST in particular and no matter what it's
17 being directed at, everyone and their brother wants
18 to use it because they think it will somehow get
19 them something.
20 I'm just struck with how large the number of
21 possibilities are that could fall into that box.
22 And with a lack of any consensus on the kinds of

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1 parameters, the type of testing, and comparing
2 different operating equipment, how are we going to
3 really understand the findings from one study to
4 one study, or from one program to another?
5 DR. KATZ: Steven?
6 DR. BRUEHL: Just to address some of those
7 issues, I do get the sense, there is a lot of
8 variety in ways you can do QST, but I think the
9 most commonly used method is the computerized heat
10 pain, which seems to be pretty consistent across a
11 lot of locations, often using exactly the same
12 equipment, at least by the same company.
13 So I think there is some consistency in
14 that. CPM, we call it CPM, but it is a whole bunch
15 of different procedures, and I don't think there's
16 any consistency on that at all because there are so
17 many permutations of stimuli you can use in that.
18 And I know that there is some work done that show
19 you get very different results, depending on the
20 particular combination of stimuli, whether it's
21 heat and cold, or heat and pressure, or whatever it
22 may be.

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1 For APS a few years ago, I was asked to
2 review reliability information on these commonly
3 used QST measures, which nobody really talks about.
4 And at that time, it was very clear that tolerance
5 and threshold are both pretty reliable and have
6 good reliability. Temporal summation is not quite
7 as high, but it's still reasonably reliable, and
8 CPM was not very good at all. It made me wonder
9 whether CPM is a state rather than a trait, whereas
10 maybe temporal summation is more something
11 trait-wise that we're assessing.
12 I just thought I would throw that out.
13 There is a lot of inconsistency, but they can be
14 reliable measures. And in terms of Jim's comment
15 about pragmatic, the temporal summation option
16 using von Frey hairs is very simple to do in a
17 bedside setting.
18 So that would be very pragmatic. It has
19 been used in several studies, although it doesn't
20 seem like everybody uses the same pressure, and I'm
21 not sure what the data are on reliability of that.
22 DR. KATZ: We've actually published data on

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1 the reliability of temporal summation using von
2 Frey filaments in osteoarthritis, which showed that
3 it was pretty reliable. And in that same paper, we
4 published data on the reliability of CPM, showing
5 that it was not that reliable, so there is some
6 data out there.
7 Yes, Joachim?
8 DR. SCHOLZ: I have a comment regarding the
9 specificity of these assessments. It seems like
10 the reference could be maybe healthy population,
11 but I don't think that would be adequate because
12 then the outcome would more refer to we define
13 central sensitization as increased pain
14 sensitivity, and that cannot be the objective. It
15 is defined as a particular mechanism.
16 So our reference should rather be a group of
17 patients who have a painful condition but do not
18 display signs that we consider specific for central
19 sensitization. I think that's where it becomes a
20 little bit tricky, so we would have to think also
21 about methods to rule peripheral sensitization or
22 have a clear understanding of the concept of how

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1 central sensitization can look clinically. I don't
 2 think that's precisely defined yet.
 3 DR. KATZ: Can you speak a little bit closer
 4 into your mic? It's hard to hear you, your last
 5 sentence.
 6 DR. SCHOLZ: Okay. I don't think we have a
 7 clear understanding of the clinical concept, how
 8 can central sensitization look in a patient other
 9 than just increased sensitivity. I'm not quite
 10 convinced that I have heard that during our
 11 discussion.
 12 DR. KATZ: Sharon, did those comments
 13 address your question?
 14 DR. HERTZ: Somewhat, yes.
 15 DR. KATZ: I think the answer is you're
 16 right. There are a lot of things going on there
 17 with no clear standards. And you're suggesting
 18 that it would be useful to have such standards, and
 19 I think the group heard your suggestion.
 20 DR. CAMPBELL: Just to add one thing. Going
 21 off of what Steve mentioned, those static tests, so
 22 threshold, tolerance, do seem to be more stable and

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1 trait like, but I think Yarnitsky and some other
 2 folks have suggested that these tests that are
 3 potentially more central sensitivity related, like
 4 temporal summation and conditioned pain modulation,
 5 might be more malleable and potentially more
 6 responsive to treatment, and might be -- I don't
 7 want to say better -- different measures you could
 8 use to potentially get at some of that.
 9 DR. KATZ: Sharon, would it help you folks
 10 to have some kind of a review handy that outlined
 11 what the techniques are that have been -- like
 12 Steve's review, what are the specific techniques,
 13 how exactly are they done, and what is the
 14 reliability of the specific technique as it's done?
 15 Would that be useful information for you?
 16 DR. HERTZ: No --
 17 (Laughter.)
 18 DR. HERTZ: -- because --
 19 DR. KATZ: Then I won't bother.
 20 DR. HERTZ: -- I mean, yes and no. What's
 21 useful is what's going to be actually done out
 22 there. I don't want to direct a large project to

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1 occur if it's not going to be consistent with
 2 anybody's approach -- I don't want to create work
 3 that's not going to be then utilized -- I mean, it
 4 will be interesting. I'd like to read it, but I
 5 don't know if that's the reason to do all that
 6 work.
 7 DR. KATZ: Mike?
 8 DR. ROWBOTHAM: I just wanted to comment to
 9 Dan that I was not implying this is a personality
 10 disorder. I was talking about personality traits;
 11 so not personality disorder as in what used to be
 12 called the somatoform disorders or somatization
 13 disorder and now are called, in DSM-5, somatic
 14 symptom disorder. I'm just talking about enduring
 15 underlying personality traits that are likely to
 16 remain pretty constant over many years.
 17 DR. KATZ: Clifford?
 18 DR. WOOLF: To address Sharon's question
 19 about the utility of QST, at least I think I
 20 remember correctly, there's a paper by Ralf Baron
 21 and Roy Freeman, claiming that patients with
 22 tactile allodynia were the ones who responded to

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1 pregabalin, and those who didn't did not. To me,
 2 that is where you could get value from these kinds
 3 of measurements. It helps identify responders.
 4 DR. KATZ: And those were done with simple
 5 bedside techniques in that particular study, yes.
 6 Simon?
 7 DR. HAROUTOUNIAN: We just did the same
 8 thing prospectively in trying to see patients with
 9 baseline mechanical sensitivity [indiscernible] to
 10 respond to pregabalin, and they didn't. We just
 11 published it in Pain.
 12 (Laughter.)
 13 DR. KATZ: Dan?
 14 DR. CLAUW: I want to give another anti-QST.
 15 Steve Hart in our group leads the QST for three big
 16 NIH networks, the MAPP and two other big networks
 17 studies, a thousand people in the MAPP and hundreds
 18 in the other networks. All the things that people
 19 have said are true. There are issues of
 20 reliability and norms and things like that, but
 21 that's not what bothers me about QST.
 22 What bothers me is that the predictive power

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1 of it in any of those studies is weak. Our values
2 are 0.3, 0.4. You can get statistical
3 significance, but they don't come close to the
4 point that you would use them to make clinical
5 decisions or things like, and that's where I have
6 probably a bigger problem with QST.
7 I think you can actually circumvent some of
8 the problems of standardization across sites,
9 dealing with inter-rater reliability and normative
10 data. It's just that it simply doesn't -- compared
11 to the patient-reported outcomes or the imaging,
12 where we have all of those in all of our studies,
13 over and over and over again, the QST is not
14 strongly telling us anything.
15 That's the cautionary note, and I agree with
16 Sharon. It's like part of it is like the validity,
17 and I'd be interested in it, and we still do it to
18 try to infer mechanisms, but I'm just giving this
19 cautionary note that I just don't think it tells
20 you that much that you can't glean with simpler
21 measures.
22 DR. FARRAR: Specifically on that, as I'm

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1 also involved in the MAPP program and know about
2 Steve's work, I agree with you that it has not
3 worked well in those situations, but getting to
4 Sharon's perspective, all of MAPP-1, the QST
5 consisted of thumb pressure. It was a single
6 measure. There was no temporal summation studies.
7 So I'm not disagreeing that it has not
8 worked in the studies that Steve has been involved
9 in. My thought would be that perhaps we just don't
10 understand what we're doing there very well, and
11 that if we're looking for temporal summation as an
12 indication of centralization, then we should do
13 temporal summation, and we should look to see if
14 that's predictive, and I'm not sure that that's
15 been done.
16 DR. CLAUW: Look at OPPERA.
17 DR. KATZ: Could you speak into your mic,
18 Dan?
19 DR. CLAUW: OPPERA did 10 QST measures, and
20 none of them have an odds ratio greater than 2 in
21 predicting anything.
22 DR. KATZ: Roger?

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1 DR. FILLINGIM: Well, we've sort of been
2 going back and forth on getting more specific in
3 identifying mechanisms for whatever this thing is
4 we're talking about, or these things, versus
5 looking at a global phenotype or subphenotypes.
6 And those are all different initiatives. I think
7 it relates to this conversation about QST.
8 So if I want to predict mortality, I can ask
9 people about specific conditions they have, or I
10 could ask them, overall, how healthy do you feel.
11 And how healthy they feel is going to be a better
12 predictor of mortality, I suspect, than really
13 specific questions about their health.
14 I think we get into the same phenomenon with
15 patient-reported outcomes, which they can subsume a
16 lot of constructs, and each construct may actually
17 have additive predictive value. So that global
18 construct is predictive, but it doesn't tell us
19 much about mechanisms to the extent we might be
20 interested.
21 Then if we drill down into subphenotypes or
22 methods like QST that we think are a bit closer to

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1 mechanisms, we sort of keep drilling down, and I
2 suspect we're going to have to find some happy
3 medium somewhere in there. But I think that's some
4 of the tension here.
5 DR. KATZ: We have a few minutes left to go
6 in this morning's discussion. Does anybody feel
7 prepared to articulate a proposal for how we're
8 going to identify this group of patients with
9 central sensitization, whether it's one thing or
10 more than one thing, what those more than one
11 things are and how to identify them just as an
12 appetizer for the afternoon's discussion?
13 DR. BRUEHL: I just want to ask a question,
14 which is if we look at the title of this
15 conference, we're talking about central
16 sensitization, somatosensory amplification kind of
17 as a bundled thing, but we've spent a lot of time
18 talking about chronic overlapping pain conditions.
19 I guess what I wonder is, is that something
20 separate from central sensitization or is that one
21 of the components we're considering to be part of
22 that?

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1 DR. KATZ: Anyone on the panel want to
 2 answer that?
 3 DR. FILLINGIM: So the answer is yes.
 4 (Laughter.)
 5 DR. KATZ: Yes what?
 6 (Laughter.)
 7 DR. KATZ: Can you expand on that one-word
 8 answer a little bit, Roger?
 9 (No response.)
 10 DR. KATZ: Sorry. No answer. Personally, I
 11 think that -- actually, Dan, why don't you answer
 12 that question? Chronic overlapping pain
 13 conditions, are they part of the definition of
 14 central sensitization or are they just patient
 15 characteristics that we want to track as we're
 16 performing clinical trials? What is its role on a
 17 conversation about central sensitization?
 18 DR. CLAUW: If I had to define them, I would
 19 say that these are clinical conditions that overlap
 20 a great deal with each other, both in individuals
 21 and families, and seem to have shared mechanisms
 22 and prominent central nervous system mechanisms. I

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1 think central sensitization is playing a role in
 2 all of the chronic overlapping pain conditions, but
 3 I think it also plays a role in any chronic pain
 4 state. There's a subset of people with any chronic
 5 pain condition that have central sensitization.
 6 So I think the only thing that really sets
 7 the COPCs apart from any number of other pain
 8 conditions are that maybe the central factors are
 9 more front and center in those conditions. But
 10 again, you take any of the COPCs, and you can
 11 identify, again, 20 percent of people with
 12 interstitial cystitis that clearly have just a
 13 bladder problem; that they don't have anything that
 14 would look like central sensitization. You can
 15 identify 15 percent of people with
 16 temporomandibular disorder that clearly have a TMJ
 17 joint problem.
 18 So within any of those cohorts, there are
 19 people that have very strong peripheral factors
 20 that are playing a role, that these are terms that
 21 have been used historically to merely indicate pain
 22 in a location of the body. So it sort of goes

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1 without saying that not all of that would have the
 2 same underlying cause.
 3 But I think that's how the COPCs sort of
 4 came to be because we saw that these were
 5 clustering individuals; that they seem to respond a
 6 lot better to these central nervous system acting
 7 therapies, and that there was familial
 8 coaggregation.
 9 Not that these are all purely central
 10 problems because if you take any one of them and
 11 look at it, you're going to identify at least 20
 12 percent of any of the COPCs in which there's a very
 13 peripheral phenotype, and another where there's an
 14 intermediate phenotype that's more regional pain,
 15 not fully widespread pain. So in any of the COPCs,
 16 it's probably only half of the people that have
 17 mainly central sensitization.
 18 DR. KATZ: Well, in an effort to wrap up, do
 19 any of the speakers have any final comments?
 20 DR. RAJA: I think the one comment -- what
 21 I'm hearing is, clinically, this is not a single
 22 disease; it's a spectrum of disorders. If you're

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1 going to study these patients, personally I think
 2 we need to somehow stratify these patients. And
 3 the question is what are the strata? Are they
 4 based on physical function in terms of number of
 5 pain states? Is it going to be based on
 6 psychosomatic comorbidities or is it based on
 7 catastrophizing or so?
 8 What are the different strata that are
 9 important in these patients? I think that's going
 10 to help us provide probably some more meaningful
 11 information.
 12 DR. KATZ: Friedhelm, were you going to add
 13 something?
 14 DR. SANDBRINK: Yes. I'm a little bit
 15 struck by what Dan just said. There are these 15
 16 to 20 percent, even in our chronic overlapping pain
 17 syndromes, who seem to have pretty much isolated
 18 pain. I think maybe one particular aspect of how
 19 to move forward is truly -- and, Lesley, you
 20 articulated very clearly -- to come up with some
 21 kind of measure of how much centralized pain is
 22 present in this patient.

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1 What is the degree of centralization? or
 2 centralized pain that is part of the component of
 3 some of these pain symptoms?
 4 I think that that would help both for
 5 putting the patients into the right studies, I
 6 guess one as a predictor, but then also, I think
 7 it's part of an outcome I guess down the road as
 8 well. One reason why I feel it's so important is
 9 not just because we are talking about studies in
 10 these COPCS; we are also talking about all the
 11 other studies that happen, and I think, typically,
 12 this is not being assessed.
 13 We do studies in low back pain and in
 14 diabetic neuropathy. We do a lot of studies, and
 15 often the component of centralized pain is not
 16 assessed, so we are missing on the correct
 17 phenotyping of all the patients, which I think has
 18 an impact on the success of the studies down the
 19 road.
 20 DR. KATZ: Well, that seems like a good
 21 final comment for the morning. I'd like to thank
 22 the panel for participating and for their

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1 presentations. It's time for lunch.
 2 (Applause.)
 3 (Whereupon, at 11:45 a.m., a lunch recess
 4 was taken.)
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1 AFTERNOON SESSION
 2 (1:07 p.m.)
 3 Consensus Discussion
 4 DR. DWORKIN: So we're in the home stretch
 5 here, and for those of you who have been at IMMPACT
 6 meetings before, you know how this works. I just
 7 want to start with some thank yous and
 8 appreciation, first of all, to all the presenters,
 9 as the slide says, for their truly wonderful
 10 presentations; to everyone else for their
 11 stimulating, lively, provocative and wonderful
 12 comments, discussion; to Valorie and Julie outside;
 13 and the AV team and the transcription team for
 14 another flawless meeting.
 15 Dennis and I will definitely retire at
 16 whatever point Valorie retires, and she knows that,
 17 and she's promised us that she's going to keep
 18 going.
 19 Finally, it's not on the slide because it
 20 really does go without saying, to the FDA and to
 21 Sharon and Allison because ACTION wouldn't exist
 22 without the FDA. So we wouldn't be here, we

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1 wouldn't be doing what we've been doing for the
 2 last 2 days without the support of Sharon and
 3 Allison and the FDA, so thank you.
 4 As a couple of general comments, as all of
 5 you I think appreciate by now, Annie has been the
 6 rapporteur for this meeting. She's going to draft
 7 the manuscript, and you will all be invited to be
 8 co-authors on the manuscript; so that's just the
 9 way we do things. You don't have to be a
 10 co-author. You could send an email back saying I'd
 11 rather not be in author; entirely up to you.
 12 We're going to be calling on the speakers
 13 for help with drafting certain sections because the
 14 presenters obviously had great expertise in certain
 15 areas, and we're going to run those particular
 16 sections by the speakers before we finalize the
 17 draft that we send out to the rest of you. Pain is
 18 almost always, if not always, the target journal.
 19 The systematic review that Annie presented
 20 is separate. That will be a separate publication,
 21 a smaller number of authors, though the main
 22 manuscript from this meeting will refer to the

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1 systematic review for the background it provides.
 2 I'll answer any questions before moving
 3 ahead in a second. As we go through the next
 4 couple of hours, I think there's an important thing
 5 that we've learned over the years, and that is that
 6 what we say in these manuscripts sort of can be put
 7 into three different buckets.
 8 Some of the IMMPACT publications are
 9 recommendations, recommended outcome measures for
 10 chronic pain clinical trials. Some of them are
 11 recommended considerations, the difference being,
 12 clearly, that there wasn't enough of a consensus to
 13 say we recommend the brief pain inventory for all
 14 clinical trials of chronic pain, and recommended
 15 considerations, obviously, is a softer kind of
 16 recommendation. We recommend that you consider
 17 using, for example, the BPA for chronic pain
 18 clinical trials.
 19 Then when we really wimp out, we can't get
 20 consensus on a recommendation or even a recommended
 21 consideration, what do we do? We have a research
 22 agenda. So for the rest of the afternoon, you

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1 should think about -- in terms of having the
 2 discussion proceed and getting done in two hours,
 3 we'll sort through as we distribute drafts and
 4 revisions, et cetera of the manuscript, whether we
 5 feel there's enough of a consensus to make a
 6 recommendation, or whether it's really a softer
 7 recommended consideration, or whether, for example,
 8 quantitative sensory testing really goes into the
 9 research agenda bucket, and we'll get to that,
 10 obviously.
 11 Any questions about anything I said before I
 12 move forward? Dennis, did I leave out anything?
 13 (Dr. Turk gestures no.)
 14 DR. DWORKIN: All right.
 15 We tried to do our best to come up with an
 16 outline for the manuscript, and this is the outline
 17 at the 30,000-foot level, the proposed outline.
 18 What you guys are supposed to do for the next two
 19 hours is to criticize this, amend it, and slice and
 20 dice it. So what we've left off, of course, is the
 21 first two sections are going to be introduction and
 22 methods, and that goes without saying. This is

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1 really the meat of the manuscript. The last
 2 section would be something like discussions and
 3 conclusions.
 4 This is a proposal for the meat of the
 5 consensus recommendations, or recommended
 6 considerations, from this meeting. We're going to
 7 spend time talking about each of these sessions
 8 unless we run out of time; an initial section on
 9 the kind of meaty issues that we've been talking
 10 about throughout the last two days, central
 11 sensitization and centralized pain; mechanisms;
 12 types; the role of peripheral drive; descending
 13 inhibition and other spinal processes; and the
 14 brain.
 15 I'll say something about terminology in a
 16 minute. We clearly could spend the next two hours,
 17 I think, talking about mechanisms and types of
 18 central sensitization and centralized pain. What I
 19 would like to propose is that for that initial
 20 section of the manuscript, that Annie -- and I'm
 21 going to respectfully leave Dennis out of
 22 this -- and I plagiarize the publications by

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1 Clifford and Dan that were background reading, and
 2 that we work with Clifford and Dan to finalize the
 3 two or three or four paragraphs of that section of
 4 mechanisms, types of sensitization, sensitivity,
 5 and centralized pain; unless -- we have enough
 6 people behaving like demagogues in this city, so I
 7 don't want to be another demagogue --
 8 (Laughter.)
 9 DR. DWORKIN: -- unless someone wants to say
 10 something more because we did run out of time at
 11 various panel discussions about this kind of
 12 challenging part of the article, and we obviously
 13 spent a lot of time talking about it this morning.
 14 But one way of moving forward is to kind of
 15 say let's leave it to Bob and Annie and Dan and
 16 Clifford to pull three or four, or however many
 17 paragraphs together, and we'll all take a look at
 18 what that looks like.
 19 Raj?
 20 DR. RAJA: Just a question. Does the
 21 quote/unquote overlapping pain syndromes come under
 22 the same bucket or is that a different bucket?

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1 FEMALE VOICE: Please use the microphone.
 2 DR. RAJA: Sorry. Raja from Johns Hopkins.
 3 The issue is whether -- we've talked about these
 4 chronic overlapping pain syndromes. Is that part
 5 of the central sensitization bucket or is it a
 6 different bucket by itself?
 7 DR. DWORKIN: Well, there could be an
 8 initial discussion here. I think it gets
 9 highlighted further down the outline, and we'll get
 10 to that. I have more slides.
 11 DR. BRUEHL: Bob, I think that is kind of
 12 the distinction between the mechanisms and presumed
 13 markers of those mechanisms, right?
 14 DR. DWORKIN: And we'll get to that.
 15 DR. BRUEHL: Okay.
 16 DR. DWORKIN: Any other comments? Yes,
 17 Mike.
 18 DR. ROWBOTHAM: Mike Rowbotham. Is there
 19 going to need to be some sort of operational
 20 definition for when we consider sensitization?
 21 DR. DWORKIN: Yes. Let's defer that to item
 22 number 3, though item 2 starts to bleed into it. I

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1 think we're going to have to say something, because
 2 we're talking about the design of clinical trials,
 3 about how we identify, diagnose, define, whatever,
 4 patients we're enrolling in the clinical trials,
 5 but I don't know that it belongs this early in the
 6 article.
 7 What about this terminology thing? On the
 8 agenda for this meeting and throughout most of the
 9 last two days, we've talked about chronic
 10 centralized pain conditions. I think it was Raj
 11 this morning who suggested that he liked the word
 12 "syndromes" better than conditions. And I thought
 13 one of your slides, Raj, had an interesting -- the
 14 word "sensitivity" was used rather than
 15 sensitization. And I thought that was kind of
 16 interesting, too, because sensitization, to me at
 17 least, has a connotation of some active sensitizing
 18 going on, whereas sensitivity could be something
 19 you're born with.
 20 So I think we have to make a
 21 decision -- this is something I'm not sure we can
 22 defer -- about what we're really calling either the

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1 condition or group of conditions that we're talking
 2 about in this article. One possibility is chronic
 3 centralized pain conditions, which was what was on
 4 the agenda. Another possibility, maybe a little
 5 bit more agnostic, is chronic central sensitivity
 6 syndromes, but this gets us right into IASP.
 7 As many of you know, IASP has worked with
 8 the World Health Organization on ICD-11. And now,
 9 officially, in ICD-11, is my understanding, there
 10 is a diagnosis of chronic primary pain. So another
 11 decision that we have to make, I think this
 12 afternoon, is what do we all think about chronic
 13 primary pain? Is that what we're talking about?
 14 One could imagine an reviewer of this manuscript
 15 saying, "What are you guys doing? We already have
 16 chronic primary pain."
 17 This is how chronic primary pain is defined,
 18 and I mentioned this. I think we talked about this
 19 yesterday. Chronic primary pain is defined as pain
 20 in one or more anatomical regions that persists for
 21 longer than 3 months. It is associated with
 22 significant emotional distress or functional

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1 disability, and the symptoms are not better
 2 accounted for by another diagnosis.
 3 I don't think that's what we've been talking
 4 about for the last day and a half. Does anyone --
 5 DR. CLAUW: Don't you think that's what they
 6 meant?
 7 DR. DWORKIN: They didn't say it, though.
 8 Yes, I do think --
 9 DR. CLAUW: I strongly feel that's what
 10 was --
 11 DR. DWORKIN: That is what they meant. Dan
 12 was reading my slides in advance over my shoulder
 13 because here's the evidence of what Dan just said.
 14 We could have easily prepared this exact
 15 same slide, which comes from a recent article in
 16 Pain, and instead of having chronic primary pain at
 17 the top, we could have had chronic centralized
 18 pain. It is what they meant. I think the reason
 19 we can set their terminology aside is there's
 20 nothing in it about central sensitization, central
 21 sensitivity, and all of those processes and
 22 mechanisms that we've been talking about for the

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1 last day and a half.
2 DR. BRUEHL: Having worked with some of
3 these IAS people before, my suspicion is they
4 intentionally did not use that because they want to
5 avoid implying mechanisms when we don't have any
6 certainty that those are -- that's really what's
7 going on.
8 DR. SCHOLZ: I was actually on the
9 classification task force, and the decision was not
10 to use mechanisms as a criteria for classification.
11 So we are free to do with central sensitization,
12 whatever we please.
13 DR. DWORKIN: Well, I feel like a decision
14 has just come from on high --
15 (Laughter.)
16 DR. DWORKIN: I mean, wow! Thank you,
17 Joachim. If Joachim thinks that we can go ahead,
18 as we've been discussing for the last day and a
19 half -- I mean, obviously, we have to put a
20 sentence or two in the article saying why we're not
21 using this -- I don't want to say what I think
22 about it -- this bucket, and rather we're using

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1 centralized pain where we have some notion of
2 mechanisms, we're going to have a sentence or two
3 in it. There's going to be a chance that the
4 article will get rejected from Pain because it's
5 felt that we're defining a new pain condition that
6 IASP has not defined, and we'll take that chance.
7 Ajay?
8 DR. WASAN: We're about to turn the
9 somatosensory amplification term as sort of a
10 process, and maybe that avoids some of these
11 political pitfalls and gets away from identifying
12 the mechanism per se, but it talks about it as a
13 process that goes on that could involve these
14 multiple other mechanisms.
15 DR. DWORKIN: Let's come back to that when
16 we get to the phenotype because that's actually an
17 interesting possibility.
18 Mike?
19 DR. ROWBOTHAM: From the way this slide is
20 laid out, essentially everything we've been talking
21 about would fit into this chronic primary.
22 DR. DWORKIN: Yes. But as Joachim said,

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1 there's nothing here, even hypothesis, about
2 underlying mechanism.
3 DR. ROWBOTHAM: Right. So you could say
4 we're talking about a subtype of chronic primary
5 pain in the sense that we're insisting that there
6 being some sensitivity or sensitization components,
7 but that otherwise, including the overlapping pain
8 syndromes, fit into this.
9 DR. DWORKIN: I love it. We're looking at a
10 group of conditions within the larger umbrella
11 category of chronic primary pain, where we have
12 reason to think central sensitization or
13 sensitivity is an important mechanism.
14 Simon?
15 DR. HAROUTOUNIAN: The only caveat might be
16 that there might be conditions that do fit our
17 criteria that are outside the chronic primary pain.
18 So if we're thinking about neuropathic pain with
19 central sensitization component, it falls outside
20 this particular bucket. We just need to think
21 whether we're just talking about a subset of this
22 or a subset of maybe all sorts of chronic pain

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1 syndromes.
2 DR. DWORKIN: That's brilliant, and we'll
3 get to that in one of the other slides. As you
4 know, a PHN patient, where the mechanism we believe
5 is central sensitization, wouldn't be in this
6 bucket but could be in our pocket.
7 Clifford?
8 DR. WOOLF: I would argue very strongly that
9 we don't lock ourselves entirely on the chronic
10 side. Central sensitization, the most robust
11 manifestation of it is, for example, post-surgical
12 pain or the acute post-traumatic pain, where you
13 get secondary hyperalgesia, et cetera, et cetera.
14 They've locked themselves into chronic. There is
15 an element of the involvement of central
16 sensitization in chronic pain, but definitely in
17 acute.
18 DR. DWORKIN: I'm all for that. I think we
19 can easily, in the article, say that our examples
20 or discussion will mostly involve chronic
21 conditions, but that pretty much everything we say
22 would also apply to a patient 7 days, 30 days after

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1 surgery, trauma, shingles, et cetera. We need to
2 change the slides.
3 Ian?
4 DR. GILRON: Just to chase that comment, in
5 the possibility that there might be a phenotype of,
6 call it fibromyalgia-ness, that predisposes to
7 transition to chronic pain, maybe we could tie this
8 in with prevention trials. It could be another
9 area, but it might be relevant to --
10 DR. DWORKIN: When we get to trial design,
11 let's add that because that is not on the slide.
12 Is everyone satisfied with how we've evolved
13 in the last five minutes? Steve?
14 DR. BRUEHL: I am, and I'm just wondering if
15 maybe in the paper it would be useful to have a
16 Venn diagram with chronic primary pain and then
17 chronic central sensitization syndrome, or whatever
18 we call it, overlapping to some degree just to kind
19 of show visually that we do think there's some
20 overlap, but there are going to be conditions that
21 aren't covered by chronic primary pain. I don't
22 know if we want to highlight the IASP issue and all

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1 that.
2 DR. DWORKIN: You took the words out of my
3 mouth.
4 DR. BRUEHL: If we do need to, I think a
5 diagram might be helpful.
6 DR. DWORKIN: One of the other ACTION
7 groups is doing, and we've never done this before,
8 a Delphi poll. It strikes me that your suggestion
9 for that Venn diagram would be an impetus for
10 Delphi poll to see how much of us agree with
11 highlighting chronic primary pain, and how many of
12 us think like let's just leave it aside. So we'll
13 take that under advisement.
14 Dan?
15 DR. CLAUW: I think that is one of the most
16 effective ways to leave it aside by doing what
17 several people have just suggested and say central
18 sensitization can occur in acute pain, in chronic
19 primary pain, in all the other kinds of pain, but
20 then we don't have to take on the controversy.
21 The only other thing I would recommend is,
22 please, let's not us invent yet another term. If

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1 the term doesn't exist -- no one really uses the
2 term, although I happen to agree that it's a good
3 term, "sensitivity," like "chronic," or for that
4 matter, "somatosensory amplification." We already
5 have four terms that we have to live with in this
6 field, and for us in IMMPACT to introduced yet --
7 DR. DWORKIN: So that's a vote for
8 centralized pain.
9 DR. CLAUW: I don't care which one. It's a
10 vote against chronic central sensitivity because
11 that doesn't yet exist -- people aren't writing
12 about that.
13 DR. WOOLF: I would argue against
14 centralized pain because that has a very specific
15 meaning, is that it implies the autonomous, which
16 may be just a small part of the whole package.
17 DR. DWORKIN: And you like central
18 sensitivity? Is that better, Clifford?
19 DR. WOOLF: That's better.
20 DR. CLAUW: Well, why don't we just use
21 central sensitization? Why do we have to use a new
22 term?

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1 MALE VOICE: All pain is central. I mean,
2 it just is.
3 DR. DWORKIN: Mike?
4 DR. ROWBOTHAM: Pain with somatosensory
5 amplification?
6 DR. DWORKIN: We have like I think five
7 different terms on the --
8 MALE VOICE: We'll never -- we can spend
9 until 5:00 on this.
10 DR. DWORKIN: I know. I know.
11 Howard, can I call on you to get me out of
12 this jam?
13 DR. FIELDS: I didn't realize that you were
14 in a jam.
15 (Laughter.)
16 DR. DWORKIN: Get us; get us out of this
17 jam. I was in a jam because I didn't know what to
18 say.
19 DR. FIELDS: I couldn't agree more with Dan.
20 The last thing we need is a new term. We've got
21 more than enough terms.
22 DR. DWORKIN: So you would be happy with

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1 something like central sensitization pain; nothing
 2 new about that.
 3 DR. FIELDS: I like the idea of having a
 4 primary, well-established diagnosis, let's say
 5 fibromyalgia, or some other condition like
 6 interstitial cystitis with evidence of
 7 sensitization. Opposed to creating a new
 8 diagnostic entity that groups a bunch of things
 9 together, we take the entities that are already
 10 there and then say with or without sensitization.
 11 DR. DWORKIN: All right. So I'm hearing
 12 three different possibilities, and maybe in the
 13 interest of moving forward, we just defer this as
 14 possibly a Delphi poll, or you guys will send me an
 15 email telling me what you think.
 16 What we started with on the agenda is
 17 centralized pain. Another possibility would be
 18 central sensitivity, and the third possibility is
 19 just sticking with central sensitization as some
 20 kind of adjective qualifier
 21 John?
 22 DR. FARRAR: Just a very small point, which

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1 is that I think it's been pointed out several
 2 times, as Howard was just doing, that many of the
 3 comorbid conditions that we're looking at can have
 4 a centralized component or not. So I worry that
 5 calling it centralized pain suggests that there are
 6 two pains, and I don't think we want to imply that.
 7 So I would argue strongly for not calling it a pain
 8 separate from the other ones that we've got. Yes;
 9 I'm beginning to see the problems with that as
 10 well. I leave it to you. Never mind.
 11 (Laughter.)
 12 DR. DWORKIN: Thank you.
 13 So nociplastic pain -- I'm sorry.
 14 Sharon, did you have your hand up?
 15 DR. HERTZ: Yes. Let's be careful that we
 16 don't use terminology that's going to get confused
 17 with central pain syndromes like thalamic pain. I
 18 just don't want this to start becoming --
 19 DR. DWORKIN: We would have a sentence very
 20 early in the article that we're not talking about
 21 central neuropathic pain, for example, associated
 22 with stroke, spinal cord injury, multiple

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1 sclerosis. Yes, that's critically important.
 2 Lee?
 3 DR. SIMON: Just out of curiosity, if we do
 4 what Howard is suggesting, which is a nice
 5 compromise, it does eliminate the possibility that
 6 somebody might develop a chronic pain syndrome
 7 without being actually being able to be categorized
 8 based on vulvodinia with chronic pain, or chronic
 9 sensitization, or fibromyalgia with chronic
 10 sensitization.
 11 For those people that think there might be a
 12 chronic pain disease and the right person can be
 13 stimulated by something else leading to afferent
 14 input that leads to chronic pain, you aren't living
 15 that as a possibility.
 16 DR. DWORKIN: But I think that's going to be
 17 a thread throughout the article. As I understand
 18 it, there are some patients with fibromyalgia and
 19 IBS who don't have centralized pain, central
 20 sensitization.
 21 DR. SIMON: Right.
 22 DR. DWORKIN: There are more patients with

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1 OA who don't have that, but in both of those
 2 diagnostic categories, it can exist and it may not
 3 be there.
 4 DR. SIMON: But turn it around. Is it
 5 possible that you had something that caused you
 6 to like what Clifford was referring to due to an
 7 acute pain syndrome. It's then gone, but yet, you
 8 still are having chronic pain. That's an
 9 independent event without -- it's possibly
 10 stimulated by some afferent input, but that
 11 afferent input is not there any longer.
 12 DR. DWORKIN: Right, and that's the first
 13 bullet here.
 14 DR. SIMON: Okay.
 15 DR. DWORKIN: We're going to have a
 16 discussion --
 17 DR. SIMON: Just want to be sure.
 18 DR. DWORKIN: -- about the role of
 19 peripheral drive and that you can also have this in
 20 its absence. Absolutely.
 21 DR. SIMON: Exactly.
 22 DR. DWORKIN: That's that for bullet.

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1 Steve?
2 DR. BRUEHL: I'm thinking that given this
3 discussion, it would be very helpful early on to
4 explicitly state that we are not proposing a
5 discreet diagnostic entity; that this is really
6 more of a phenotype that's cross-diagnostic. That
7 seems to be kind of what the discussion is.
8 DR. DWORKIN: Dan's raising his hand, but
9 I'm hoping he's going to agree with you.
10 DR. CLAUW: I'm totally going to agree --
11 DR. DWORKIN: Terrific.
12 DR. CLAUW: -- and I'm going to suggest that
13 we use the same kind of thinking that the RDoC in
14 NIMH has used. In NIMH, six or seven years ago,
15 they basically said we see these mechanisms that
16 cross 10, 20 different psychiatric conditions, and
17 instead of studying them as one-offs in between,
18 we're going to look for these themes.
19 This would almost be like a central
20 sensitization -- or whatever term, and I prefer
21 that because I think it's the least charged -- can
22 occur in acute pain, in chronic primary pain, but

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1 it's basically a mechanism that can be superimposed
2 upon any other disease that we take care of. Then
3 I think we stay away from some of the traps, where
4 people are, because I think that really is what
5 we're talking about. It can be in any of our pain
6 conditions, in acute and chronic. It's never in
7 all of them in any disease.
8 DR. DWORKIN: Well, and we call it central
9 sensitization. If you and Clifford and Howard are
10 fine with that, boy, anyone who isn't fine with
11 that can leave for the airport early.
12 (Laughter.)
13 DR. FIELDS: That's kind of why I suggested
14 what I suggested, which is we keep the diagnostic
15 entities that we have and add in plus or minus.
16 DR. DWORKIN: Central sensitization.
17 DR. FIELDS: We're almost at a consensus.
18 We should see how many people vote against that.
19 DR. DWORKIN: They can't. I'm not going to
20 let them.
21 (Laughter.)
22 DR. DWORKIN: Lesley?

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1 DR. ARNOLD: One thing about that -- Lesley
2 Arnold -- is fibromyalgia as being at the end of
3 the continuum, and that is really the prototypic
4 central sensitization disorder. I can't think of a
5 fibromyalgia patient who doesn't have --
6 MALE VOICE: We just heard that someone says
7 they --
8 DR. DWORKIN: I thought Dan said there are
9 some fibro patients --
10 DR. CLAUW: Almost all the other chronic
11 overlapping pain conditions you can clearly
12 identify people that don't have central
13 sensitization? It's harder to do that in
14 fibromyalgia because it's defined by widespread
15 pain. There's certainly a ton of fibromyalgia
16 patients that have ongoing nociceptive pain and
17 neuropathic pain that contributes to their overall
18 pain.
19 DR. DWORKIN: Then that's the end of the
20 continuum --
21 DR. ARNOLD: That's the end of the
22 continuum. And you can almost say that --

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1 DR. DWORKIN: -- with postherpetic neuralgia
2 maybe being the other end of the continuum.
3 MALE VOICE: You've to be on board, Lesley.
4 DR. ARNOLD: Yes, I'm on board. I was just
5 saying, though, that you could actually even make
6 the case that fibromyalgia is central
7 sensitization, by a different name.
8 MALE VOICE: Not yet. I don't think you can
9 make that case yet. It's possible.
10 DR. ARNOLD: It's possible.
11 DR. WASAN: I was just going to say we
12 obviously could just put a qualifier on the fibro
13 that is maybe redundant with the term "central
14 sensitization." Then I would just, again, echo the
15 research as the main criteria. You may even want
16 to put a little more in the introduction about
17 that, because that has provided very helpful and
18 useful research agenda going forward.
19 DR. DWORKIN: I think that's a great idea.
20 I completely agree. I think it's a great idea.
21 DR. FIELDS: In agreement with that, it kind
22 of gets around this issue of saying, well, here's

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1 somebody with interstitial cystitis, and they have
 2 a degree of fibromyalgia-ness. That's just a
 3 little kind of convoluted way of saying what I was
 4 going to say and what I think Lesley means.
 5 DR. CLAUW: The advantage of going that
 6 direction -- and it would be cool if we can agree
 7 on this because it might be a little bit more
 8 controversial. But then you could basically say
 9 that negative affect is another thing that can span
 10 a number of chronic pain conditions with or without
 11 central sensitization.
 12 MALE VOICE: And we know that's for sure.
 13 DR. CLAUW: But that's for sure.
 14 Catastrophizing can -- but I really think
 15 it's -- the one thing that I probably feel the most
 16 strongly about is don't have the core definition of
 17 this include affect, include cognition, because
 18 this is something that can clearly occur in people
 19 that don't catastrophize, people that are not
 20 depressed.
 21 DR. DWORKIN: We're going to get to that.
 22 DR. CLAUW: Right. But I think that RDoC

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1 thing does that nicely for us. If we say this is
 2 the framework we're going to use -- like some
 3 people with chronic pain have negative affect; some
 4 have catastrophizing; some have central
 5 sensitization, but we don't say that these always
 6 occur together because they don't.
 7 DR. DWORKIN: I love that. John?
 8 DR. FARRAR: Clifford and I had a
 9 conversation at lunch about the fact that there are
 10 multiple mechanisms and other things that go on
 11 here, but also about the fact that it seems to me
 12 that what we want to define is that it's
 13 sensitization of the pain relevant structures in
 14 the brain. And I know that there's a big gray line
 15 between that and other things, but what Dan's
 16 talking about in terms of catastrophizing,
 17 depression, et cetera, is more a limbic process, I
 18 think. It's more a cortical interpretation.
 19 I don't know how to divide those, but
 20 somebody looking at this could say, well, central
 21 sensitization, or essentially, everything is
 22 central. Depression is central. This is central.

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1 DR. DWORKIN: I have a list of possible
 2 aspects of the phenotypes definition, so let's look
 3 at that when we get to it because it is exactly
 4 what Dan's talking about.
 5 Some of you that IASP has introduced a new
 6 term, "nociplastic pain."
 7 (Groans from audience.)
 8 (Laughter.)
 9 DR. DWORKIN: And this is pain that isn't
 10 either nociceptive, as you can see from the
 11 definition that I highlighted at the bottom of the
 12 slide -- pain that isn't nociceptive, and isn't
 13 neuropathic, and is still pain or something. And
 14 clearly, Howard votes that we just not use the word
 15 "nociplastic" in this article, and we make
 16 believe -- we don't think it's relevant to what
 17 we're talking about, and I'm happy to completely
 18 leave it out of the article.
 19 Dan?
 20 DR. CLAUW: Let me give you the reasons that
 21 I don't think that's a good idea to do. I want to
 22 first say that we are the only ones that wrote a

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1 letter to the editor that said this is a stupid --
 2 (Laughter.)
 3 DR. CLAUW: I've gone on record and print in
 4 saying this name is stupid; we believe it to be
 5 stupid. But then I got put on the IASP committee
 6 that's going to define this.
 7 (Laughter.)
 8 DR. CLAUW: And there are some people on
 9 that committee that have no idea what they're
 10 talking about. And it would really be helpful
 11 because this committee is dragging on so long. The
 12 biggest thing right now that I'm fighting in this
 13 committee is a lot of the people in this committee
 14 will not allow non-pain symptoms to be part of the
 15 definition of anything the IASP puts out, and
 16 that's going to make the definition of nociplastic
 17 pain incredibly -- it's going to be something like
 18 pain that is greater than one would expect. But
 19 it's like something that would be impossible to
 20 quantify, or to put into diagnostic criteria, or
 21 anything like that.
 22 So I think that this discussion that's

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1 occurred over the last day and a half is like
 2 infinitely better than the IASP committees that get
 3 together by email or trying to work out some of
 4 these types of things. I think it would be really
 5 helpful to lay all these things out and just say
 6 nociplastic is one of the things that's been thrown
 7 out there, but then still say what we want to say.
 8 DR. DWORKIN: Well, I think we all would be
 9 in your debt if you would write those 4 sentences
 10 for Annie and us.
 11 DR. CLAUW: I'll write those 4 sentences.
 12 I'd be happy to write those 4 sentences.
 13 DR. DWORKIN: And even 5 would be fine.
 14 DR. CLAUW: Yes, maybe 5.
 15 DR. DWORKIN: Does everyone agree we can
 16 move on from nociplastic pain? I see a lot of
 17 heads banging up and down. Okay.
 18 Let me just go back to the overview slide.
 19 I think we're done with bullet 1 of this outline.
 20 Does everyone think that we've taken care of
 21 mechanisms, types, central sensitization?
 22 (Affirmative nods.)

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1 DR. DWORKIN: Okay. Clinical trial
 2 objectives and design. So this is really what this
 3 meeting is about. We spent a lot of time thinking
 4 about this over the last evening and morning. One
 5 way I was thinking about how we could do this is
 6 there really have been 2 threads or themes for the
 7 last day and a half.
 8 One is how do we optimize the design of
 9 clinical trials for patients with one of the
 10 chronic overlapping pain conditions? FM, TMD, IBS,
 11 IC/PBS, with, as Lesley just said, fibromyalgia
 12 being the kind of exemplar COPC.
 13 What are the things that we've talked about
 14 in the last day and a half that really allow us to
 15 propose ways of optimizing the design going forward
 16 of clinical trials of fibromyalgia, IBS, et cetera?
 17 Clearly, I think the biggest contribution is that
 18 we're seeing within those patients, some of
 19 them -- maybe all FM patients, but some of the
 20 others have a certain phenotype that it sounds like
 21 we're now calling a central sensitization
 22 phenotype.

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1 So one set of clinical trial
 2 objectives -- and we're really talking about
 3 efficacy, randomized clinical trials probably with
 4 phase 2 and phase 3 -- is to optimize the design of
 5 clinical trials of one or another chronic
 6 overlapping pain conditions by identifying a
 7 phenotype that needs to be examined at baseline in
 8 those patients, and maybe would be an inclusion
 9 criteria. We're not going to study you in our
 10 clinical trial of IBS unless you have the central
 11 sensitization phenotype.
 12 Another way of thinking about, it seems to
 13 me, the clinical trial objective -- and this is a
 14 little bit more novel, and this has been a theme,
 15 too -- can we do a clinical trial where we enroll
 16 patients with one of several different either COPCs
 17 or other conditions that we've been talking about
 18 for the last day and a half, where we think central
 19 sensitization plays an important role in at least
 20 some reasonably sized minority of patients.
 21 I put down some examples: obviously OA, RA,
 22 musculoskeletal low back pain, CRPS, and headache.

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1 And Simon pointed out to me -- and I think this is
 2 true -- that we could even include -- actually,
 3 Simon's left. We can even click neuropathic pain
 4 patients here because we don't necessarily believe
 5 that all patients with diabetic peripheral
 6 neuropathy have central sensitization as their
 7 primary or predominant mechanism.
 8 So that would be a trial that where it gets
 9 you randomized is having a phenotype, that we are
 10 going to define, irrespective of which of these
 11 kind of classic etiology based diagnoses you have.
 12 Lee?
 13 DR. SIMON: Is the attempt of that design
 14 and carrying it out to develop a treatment for the
 15 phenotype or is it to develop a treatment for one
 16 of the specific causal events? Because I don't
 17 know how you develop a drug for a phenotype.
 18 DR. DWORKIN: This goes back to Mitchell
 19 Max's -- he had an article in 1990.
 20 DR. SIMON: That's right.
 21 DR. DWORKIN: This is mechanism-based
 22 treatment. If you think central

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1 sensitization -- Mitchell thought if central
 2 sensitization is an important mechanism, you are
 3 going to treat patients who have that as an
 4 important mechanism of their pain with some agent
 5 that you think attenuates the sensitization. And
 6 it doesn't matter whether you're diagnosed as FM,
 7 or OA, or PHN.
 8 DR. SIMON: So the purpose of that design,
 9 as you've described it, is to develop a therapeutic
 10 of some sort or another for the phenotype.
 11 DR. DWORKIN: Phenotype mechanism, because
 12 even earlier than 1990 Mike and Howard were talking
 13 about segmenting, if you will, PHN patients into
 14 one of three different mechanism-based groups, and
 15 at least one of those three PHN groups had central
 16 sensitization as a primary mechanism.
 17 So no one's ever really thought this way,
 18 that you could enroll a PHN patient, for whom the
 19 mechanism of his or her pain was primarily central
 20 sensitization, in the same trial as an OA patient
 21 for whom -- that's why I said this is a very novel
 22 approach.

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1 A flip forward, just to illustrate -- and
 2 I'm not a hundred percent sure about this. Lisa
 3 LaVange, who is a biostatistician, who's head of
 4 the Office of Biostatistics at CDER for 6 years,
 5 and now she's at UNC, and Janet Woodcock published
 6 an article about a year ago in the New England
 7 Journal of Medicine on master protocols, including
 8 basket and umbrella designs.
 9 So I was thinking this is sort of like the
 10 second bullet, right? Different diseases, and you
 11 look at the patients with these different
 12 conditions -- OA, postherpetic neuralgia, FM -- and
 13 you phenotype them that their primary underlying
 14 mechanisms of pain is central sensitization, and
 15 you enroll them in this basket trial and treat them
 16 with -- what would be the example? Duloxetine or
 17 milnacipran, or some triple reuptake inhibitor that
 18 we haven't developed yet.
 19 Now, that's a very different approach. This
 20 kind of basket trial, obviously, is a very
 21 different approach than the first item here, which
 22 is just optimizing the design of future IBS or FM

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1 trials.
 2 Ajay?
 3 DR. WASAN: Maybe you want to add in a label
 4 for sensitization as a primary or secondary
 5 mechanism of the pain syndrome. For instance,
 6 acute pain is a good example, acute postsurgical
 7 pain. You could argue that the sensitization is a
 8 secondary mechanism on top of the tissue injury
 9 generated pain.
 10 So that gives you more flexibility and
 11 freedom, and it also gets to the same point of
 12 sensitization is operative to more or less degrees
 13 in a whole variety of situations.
 14 DR. DWORKIN: I think I understand your
 15 point, but that makes it complex because that
 16 patient might have a kind of primary mechanism that
 17 is not sensitization, so then you're treating a
 18 secondary, presumably less important mechanism.
 19 But that could still be making an important
 20 contribution to their pain, so yes.
 21 DR. WASAN: Well, that being the central
 22 sensitization points.

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1 DR. DWORKIN: Dan?
 2 DR. CLAUW: I like both of those top two
 3 things. So I hope we're not talking about these in
 4 some way being mutually exclusive because I think
 5 that they're both -- and I think the manuscript
 6 could flush out because there are different reasons
 7 that you would do the top bullet versus the second
 8 bullet.
 9 DR. DWORKIN: I was hoping you would like
 10 both of them, because I think what makes the
 11 manuscript better is that we talk about both of
 12 these two very different pathways, optimizing and
 13 then doing something novel that hasn't been done
 14 yet, but it certainly seems possible, the kind of
 15 mechanism-based targeted treatment. And this
 16 slowly moves into biomarker-based treatment and
 17 precision medicine. We're in that pathway.
 18 Rick?
 19 DR. MALAMUT: It's doable. We did this back
 20 at AstraZeneca a hundred years ago, in which we
 21 enrolled a population of patients who we believed
 22 had mechanical hyperalgesia, and our tools, we were

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1 using brush allodynia and punctate hyperalgesia.
 2 The tools may be more sophisticated now if MRI is
 3 ready or QST is agreed on, but it was doable.
 4 The key for us, though, would be -- if we go
 5 down this road in a phase 2 study, in which we're
 6 not studying FMS or PHN, we're studying a
 7 mechanistic base -- is, is that going to be a
 8 viable indication? So at least from my point of
 9 view, we would want to talk with FDA and say, hey,
 10 this is what we're proposing, an indication, and
 11 this is the study we're proposing. This helps
 12 because at least you're providing a way to do that.
 13 DR. DWORKIN: Obviously, I can't speak for
 14 FDA, but I think I can almost speak for NIH.
 15 Sorry, I'm going the wrong way. The NIH EPPIC-Net,
 16 the phase 2 clinical trials network that most of
 17 you know a lot about, they're very bullish -- from
 18 Francis Collins on down, they are very bullish
 19 about basket trial designs, umbrella designs, and
 20 master protocols in general.
 21 So even if this is not there yet for FDA,
 22 it's very close to being there for NIH. I'd be

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1 really surprised if there wasn't a phase 2 clinical
 2 trial of this design occurring within the next
 3 24 to 36 months.
 4 DR. WOOLF: As you get rid of centralized.
 5 DR. ROWBOTHAM: So these designs are pretty
 6 standard in cancer therapy.
 7 DR. DWORKIN: Yes.
 8 DR. ROWBOTHAM: [Indiscernible - off mic].
 9 DR. DWORKIN: In fact, the examples in the
 10 Woodcock and LaVange article are primarily
 11 oncology. A couple of other, pulmonary, I think.
 12 I may not be remembering that.
 13 I don't know that there's anything to
 14 discuss about the last two bullets. Jim mentioned
 15 pharmacologic in Richmond this morning, I believe,
 16 and I personally thought that was a really cool
 17 idea, designing a trial where you have an
 18 enrichment phase, and you identify the patients who
 19 putatively have central sensitization as a primary
 20 mechanism, and you might confirm it by seeing if
 21 they respond to a drug that you think targets
 22 central sensitization like milnacipran.

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1 So I thought it would be kind of interesting
 2 to at least in the draft of the manuscript have a
 3 paragraph about the potential for pharmacologic
 4 enrichment, and we could also say something about
 5 enriched enrollment standard, enriched enrollment
 6 randomized withdrawal designs. IMMPACT's already
 7 been there. We've got articles, and there are many
 8 articles in the field about ERW designs, but
 9 there's much less in the chronic pain field about
 10 the possibility of pharmacologic enrichment.
 11 Nat?
 12 DR. KATZ: One of the bullets that's not
 13 there is whether we want to make recommendations
 14 related to central sensitization for people doing
 15 clinical trials who couldn't care less about
 16 central sensitization, but who's doing a regular
 17 old trial in chronic low back pain, or a regular
 18 old trial in osteoarthritis. We have
 19 recommendations for how patients should be
 20 characterized or potentially outcomes captured that
 21 would even make those trials more informative.
 22 DR. DWORKIN: So think about when you see

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1 the next slides about the phenotype outcome
 2 measures. I have more slides coming up about
 3 exactly those issues.
 4 DR. KATZ: It still feels like the outline is
 5 incomplete in that regard. If we are going to have
 6 a section on clinical trial objectives and designs,
 7 then we could have a subsection called clinical
 8 trial objectives and design issues in relation to
 9 chronic pain studies in general.
 10 DR. DWORKIN: Okay. That would be the third
 11 bullet on this slide. Raj?
 12 DR. RAJA: I'll just say, you're talking
 13 about pharmacological enrichment and central
 14 sensitization. Rather milnacipran, I would think
 15 ketamine as one of the probable drugs to test.
 16 DR. DWORKIN: Yes, definitely, effusion,
 17 whatever you know, yes, absolutely. Dan?
 18 DR. CLAUW: Just for completeness, and I
 19 think this is probably what Nat's getting at as
 20 well, I do think it's important to also say that
 21 even if you are not trying to identify the people
 22 with central sensitization, you may want to screen

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1 because you may want to exclude them. If you have
2 a more peripherally-based target, you may want to
3 identify the people you don't want to put in your
4 subsequent trials because you see that there's a
5 lack of responsiveness.
6 DR. KATZ: Yes. Wouldn't it be nice to know
7 that you didn't have 80 percent of your patients in
8 group A with central sensitization and 20 percent
9 in group B with central sensitization when you're
10 doing that, versus placebo?
11 DR. DWORKIN: So Dan, you would suggest if
12 I'm going to do a trial -- I'm not -- of
13 intra-articular hyaluronic acid for a knee OA, I
14 should exclude the OA patients with predominant
15 central sensitization because we can't imagine that
16 HA --
17 DR. CLAUW: That would be exactly like a
18 Samumed program, where I showed that this is an
19 intra-articular injection, a Wnt inhibitor, that it
20 works way better in the OA patients without
21 widespread pain than it does in the --
22 DR. DWORKIN: So the third bullet on this

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1 side that we've just added, Annie's just added, is
2 kind of Nat Katz and Dan Clauw's recommendation for
3 other pain trials, and we'll get to this.
4 We'll have a paragraph at various places,
5 that might be two or three paragraphs, about
6 stratification, and we talked about stratification
7 on and off during the meeting; stratified
8 allocation when that's reasonable; stratified
9 randomization, and we'll get to analyses,
10 stratified analysis of subgroups.
11 So we'll talk about stratification. I don't
12 know that we need to discuss it here. You'll see
13 those paragraphs. That will be fairly
14 straightforward. I'm a fan of an article that Tom
15 Permutt, a statistician at the FDA, published about
16 the different types of stratification about 10
17 years ago, so that article will be cited.
18 We talked about this. All right. This is
19 my phenotype slide. Dennis and I tried to listen
20 really carefully to all the wonderful
21 presentations, and this is not, at this point
22 obviously, meant to be a proposed diagnostic

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1 criteria for the presence of central sensitization,
2 but it seemed to be the key things that people
3 mentioned in their presentations and in the
4 discussion.
5 Widespread pain as assessed by a body map,
6 we've talked about that, Lesley and Dan; the
7 history of multiple comorbid chronic pain
8 conditions, and obviously one assessment approach
9 would be the Maixner Williams screener that we
10 heard about this morning; and disproportionate
11 pain. It's not clear to me how you assess that,
12 but it seems to me that there should be something
13 on a physical exam that could give the evaluating
14 clinician some sense of disproportionate pain that
15 isn't QST. I don't know what --
16 DR. WASAN: There is [indiscernible] - off
17 mic] validated things, the pain behavior indices.
18 This goes way back to Waddell, but then it's
19 updated with the PROMIS pain behavior scale. So
20 there's a variety of identified pain behaviors.
21 DR. DWORKIN: I think that's patient report.
22 How about a physical exam, Ajay? Is there anything

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1 on a physical exam that tells you, and Dan, and
2 Lesley, and Raj, and Nat that the patient has
3 disproportionate pain?
4 DR. WASAN: Well, you observe pain
5 behaviors. It is an exam. It's not just
6 self-report. Yes, you can have self-report, but you
7 can observe those behaviors, and that's part of
8 your exam. You document that.
9 DR. DWORKIN: Steve, and then Dan.
10 DR. BRUEHL: I was just thinking of the
11 CRPS, we tried [indiscernible - off mic] in some
12 way, and obvious would be the pinprick hyperalgesia
13 and allodynia. I think Clifford mentioned that
14 earlier I think in this context.
15 But Mike, I was thinking back to you
16 mentioning a variety of traditional neuropathic
17 pain conditions that are going to be associated
18 with allodynia and hyperalgesia, yet you were
19 arguing that they're primarily peripheral. It may
20 cause problems if we include something like that in
21 there, unless we're certain it's not really a
22 peripheral [indiscernible] issue.

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1 DR. DWORKIN: This is part of a
2 multidimensional kind of phenotype.
3 Dan, do you ever do pinprick with
4 fibromyalgia patients?
5 DR. CLAUW: No.
6 DR. DWORKIN: Is there anything or do we
7 delete this bullet?
8 DR. CLAUW: No, I wouldn't delete it. I
9 think you could put something like signs or
10 symptoms of allodynia or hyperalgesia. The
11 symptoms include things like does it bother you if
12 you wear tight clothing? Does it bother you to sit
13 in a chair for a long period? Does it bother you
14 if a blood pressure cuff's inflated? Those are
15 symptoms that help discriminate.
16 Then if someone wants to go a little bit
17 further and do like a clinical test, there have
18 been a couple articles published of using a blood
19 pressure cuff as a poor man's quantitative sensory
20 test. It's in every exam room, and it's not a
21 terrible thing. I'm not necessarily suggesting
22 that people have to do that, but you could give a

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1 list of -- and you could say, even QST. You could
2 say that signs or symptoms of allodynia, and then
3 in parentheses, here are some symptoms. Here are
4 some signs. If you happen to have quantitative
5 sensory testing, cool, you can do that.
6 I would leave it there, but just give people
7 options about, given the clinical setting they're
8 in, the degree to which they try to assess that.
9 DR. DWORKIN: Does anyone disagree with
10 disproportionate pain as assessed by signs and
11 symptoms of allodynia and hyperalgesia, and in
12 parentheses, "also QST when available"?
13 DR. FIELDS: I think the term
14 "disproportionate" is absurd on the face of it
15 because if it's something that is a symptom or a
16 sign of a disease, by definition, it's not
17 disproportionate. So there's no need for that
18 term. It's confusing, it's subjective, and it
19 could be used to say, well, okay, this patient's
20 pain is proportionate, so they don't have this
21 condition. So I would just get rid of it. It's
22 not as bad as nociplastic, but it's pushing it.

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1 (Laughter.)
2 DR. CLAUW: Does anyone disagree with
3 Howard? I agree with him. I just love the word
4 "disproportionate," and I wanted to use it
5 somewhere on a slide. But I think he's right. We
6 don't need disproportionate with signs and symptoms
7 of --
8 DR. CLAUW: [Indiscernible - off mic] -- and
9 hyperalgesia; it's not disproportionate. It's the
10 pain to normally non-painful --
11 (Crosstalk.)
12 DR. DWORKIN: This will be the easiest
13 consensus of the year.
14 DR. FIELDS: The next bullet, sensory
15 amplification, has all the correct aspects of
16 what's implied by that term.
17 DR. CLAUW: Those are different. Those are
18 symptoms. Those are surveys and symptoms looking
19 at sensory amplification other than pain.
20 DR. FIELDS: Pain's not a symptom?
21 DR. CLAUW: I'm just saying that I think
22 it's still okay to have that as a separate bullet

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1 point and say allodynia, all the different ways you
2 might be able to assess --
3 DR. DWORKIN: Howard, this is the
4 patient-reported questionnaire bullet, so signs and
5 symptoms would be more in the history physical
6 exam.
7 DR. RATHMELL: I would take signs out of it.
8 There are no signs. What's a sign? It's
9 objective. So even if you're stimulating them,
10 their response is still somewhat subjective.
11 DR. CLAUW: Even QST is not a sign at some
12 level.
13 DR. RATHMELL: It's symptoms of.
14 DR. DWORKIN: Let the record not show that
15 Dr. Rathmell is a stickler.
16 MALE VOICE: Symptoms based on the
17 [indiscernible - off mic].
18 DR. DWORKIN: No, I know. I know. Let's
19 defer until manuscript whether we remove the word
20 "signs." But of course you're right, Jim, that
21 it's all by patient report, even QST, so it's not
22 really a sign.

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1 Mike?

2 DR. ROWBOTHAM: I agree with Howard on

3 "disproportionate," that word. But something that

4 should be brought up and flipped around is patients

5 who have elaborated examinations, it could be

6 collapsing weakness to minimal stimuli, elaborated

7 gait, sensory loss, basically impossible, all those

8 things that neurologists look for on neuro exams to

9 see if you can really trust your examination. So

10 if you see a patient with signs of elaboration on

11 their exam, then you kind of just have to start all

12 over.

13 DR. DWORKIN: That's something very

14 different.

15 Howard, you won. Dan agreed to 4 sentences

16 or so on nociplastic pain. Will you write those 4

17 sentences?

18 DR. ROWBOTHAM: [Indiscernible - off mic]?

19 DR. DWORKIN: Yes.

20 DR. ROWBOTHAM: Yes.

21 DR. DWORKIN: And it's really exclusion in

22 some ways.

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1 (Crosstalk.)

2 DR. WASAN: The other term for what he's

3 describing is called exaggerated pain behaviors.

4 This is part of a well-accepted terminology.

5 Neurology may have a slightly different

6 terminology, but it's the same thing I mentioned,

7 and we should put it in there, not disproportionate

8 pain, but --

9 DR. FIELDS: Exaggerated is more on the

10 diagnostic side.

11 DR. WASAN: So just call it pain behaviors.

12 (Crosstalk.)

13 DR. WASAN: You just call it pain behaviors,

14 and include all the things like Mike said.

15 DR. DWORKIN: I promise that you will get at

16 least three or four opportunities to criticize what

17 Mike writes. I promise.

18 DR. BRUEHL: It seems like some are arguing

19 to include that as a criterion for this and others

20 saying it's an inclusion. Which is it?

21 DR. DWORKIN: It's more an exclusion.

22 DR. BRUEHL: Okay.

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1 DR. DWORKIN: It's to not be confused in

2 evaluating symptoms, and perhaps signs, by these

3 kind of exaggerated --

4 DR. SCHOLZ: But it also comes back to the

5 question of what's the reference, because you may

6 have a patient with a pain condition who is not

7 central sensitization. So they still have abnormal

8 pain behavior or pain sensations, but it's not

9 central sensitization, so you cannot compare with

10 your physiological situation.

11 DR. WASAN: It's part of the phenotype.

12 We're just talking about sensitization as a

13 downstream consequence of a whole variety of

14 possible inputs. We're talking about identifying

15 these folks clinically, and that is typical,

16 whether you call it the signs and symptoms that

17 Mike mentioned or whether you put it in the

18 category of pain behaviors, which are the same,

19 actually description of the same events. I mean,

20 it is a known defined construct.

21 DR. SCHOLZ: Well, the problem is with terms

22 like exaggerated or disproportionate, to what?

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1 What's your comparison?

2 DR. DWORKIN: How about I propose we wait

3 and see what Mike comes up with.

4 DR. WASAN: Okay, fine.

5 DR. DWORKIN: We'll have 4 or 5 sentences

6 from Mike, and we'll see whether the other

7 individuals in the room agree with him.

8 The next bullet is really a bunch of

9 questionnaires that patients fill out, and I just

10 put down various ones that we heard a lot about

11 over the last two days: The Pill, the ACR-90

12 Somatization Scale; the fibromyalgia survey that

13 Dan and Chad Brummett use; the Central

14 Sensitization Inventory; my favorite, Barsky

15 Somatosensory Amplification Scale.

16 It's my favorite because we 30 years ago

17 showed that patients with high somatosensory

18 amplification scores, shingles patients with high

19 scores are more likely to develop PHN 3 to 6 months

20 later. But obviously, these are all measures that

21 are assessing a kind of -- one imagines an

22 underlying construct of somatosensory sensory

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1 amplification not only of painful stimuli, but as
2 we've heard, loud noises, sounds, bright colors,
3 odors, who knows what?
4 I don't know. I think, Steve, you asked
5 this question that given all of these
6 measures -- and it could have been a longer
7 list -- are we going to be able to recommend one of
8 them? And I think, no.
9 DR. BRUEHL: I actually had a comment on
10 this, and I'm not familiar with all of these very
11 well. But the CSI I know has been used quite a
12 bit. My take on it from what was presented here,
13 and my little bit of reading of the literature, is
14 that those studies are heavily weighted towards
15 fibromyalgia samples. I think the problem,
16 probably in some of these other measures as well,
17 is that that's probably also true.
18 I'm wondering, if we're talking about a
19 cross-diagnostic construct, and we've shown that
20 CSI is elevated in fibromyalgia compared to
21 controls, I would really like to see, before we
22 recommend a specific measure, evidence that some of

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1 these other overlapping pain conditions have the
2 same elevations on this measure of central
3 sensitization.
4 DR. DWORKIN: Well, we know TMD does. So
5 it's not only fibromyalgia, it's TMD.
6 DR. BRUEHL: Well, the same cross-cutting.
7 So maybe MAPP has this information, but I think
8 that would help to be able --
9 DR. DWORKIN: I've got two samples of
10 shingles patients for the somatosensory
11 amplification scale.
12 I think what I'm hearing you saying -- I
13 wasn't expecting anyone to say this, but maybe we
14 really do need to think about somehow getting a
15 systematic review done of sensory amplification
16 measures, these and all the others we identify,
17 with respect to how they were developed, what's
18 their content, what do we know about reliability,
19 validity, assay sensitivity in clinical trials, if
20 they're ever used in clinical trials.
21 DR. BRUEHL: That would be a great use.
22 DR. CLAUW: And there are some studies now

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1 that are doing that along with doing QST for other
2 non-painful sensory stimuli, which would actually
3 then help say, okay, if we're really trying to get
4 at some underlying biological construct, then the
5 questionnaires that match up best with QST might be
6 the ones that we gravitate to.
7 But I would agree with you. I think taking
8 that and saying that that might be useful to screen
9 and put a couple of things. But again, our group
10 hypothesizes that the people with central
11 sensitization that don't have chronic overlapping
12 pain conditions don't have nearly as much
13 pan-sensory sensitivity as the ones -- like an OA
14 patient with central sensitization or an RA
15 patient.
16 I think that's still an unanswered question,
17 so I don't think we should -- as Steve's saying, I
18 don't think we should imply as part of the
19 construct.
20 DR. DWORKIN: I think Dan just made a
21 proposal, which is the first three bullets on this
22 slide would be -- and they obviously have to be

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1 rewritten -- the way we propose the phenotype is
2 identified, and the bottom three bullets are more a
3 research agenda, not only the QST or fMRI and
4 metabolomics, but even which questionnaire would
5 really add value.
6 Certainly, Dan you said a moment ago that
7 fatigue, sleep, mood, cognitive abnormalities are
8 not defining of the phenotype.
9 DR. CLAUW: If you look at the 2001
10 fibromyalgia measure that we've used a lot, that
11 has two elements. It has a widespread-ness of
12 pain, and the other, there's the fatigue, memory
13 problems, and sleep disturbance. They each
14 contribute about 50 percent variance in predicting
15 poor outcomes to surgery, poor outcomes to opioids.
16 So no, I don't mind in any way, but they're
17 separate. They load on separate factors. That was
18 the factor analytic paper of Andrew Schrepf, that
19 someone presented this morning. They're separate
20 factors, so you have to assess them separately or
21 just say I'm not going to look at -- but what's
22 been called space, or fatigue, sleep, mood,

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1 cognitive, that's very well established to be part
2 of this.
3 DR. DWORKIN: So you would move that up and
4 say --
5 DR. CLAUW: Move that up, and then have the
6 bottom two be sort of optional or research agenda.
7 DR. DWORKIN: Comments on Dan's proposal,
8 that bullets 1, 2, 3, and 5 are relatively defining
9 of the phenotype of central sensitization, and
10 bullets 4 and the last one, obviously, kind of need
11 further research. Anybody want to disagree with
12 that, comment on it? I saw some hands. Mike?
13 DR. ROWBOTHAM: I just wanted to add to it,
14 but I can wait.
15 DR. DWORKIN: Okay. Roger?
16 DR. FILLINGIM: I guess I wasn't thinking
17 that fatigue and sleep and mood and cognitive
18 abnormalities are part of this central
19 sensitization. They may frequently accompany it.
20 They certainly frequently occur in the absence of
21 it, but I wouldn't put catastrophizing or any of
22 those in the same bucket as things like sensory

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1 amplification, or whatever kind of pain this is.
2 It's clearly not disproportionate or exaggerated,
3 but some other kind of pain.
4 I don't like the idea of these non-pain
5 related symptoms being part of a classification of
6 central sensitization that we're describing in the
7 context of pain.
8 DR. DWORKIN: So you would consider those
9 kind of frequently co-occurring but not in any way
10 required as part of the phenotype; that you would
11 say if you had 1, 2, and 3, that identifies the
12 phenotype, and 5 frequently occurs in concert with
13 the phenotype.
14 Dan?
15 DR. CLAUW: I disagree because, again, we
16 have data that that construct in the MAPP and in
17 all these studies that we've done predicts a fair
18 amount of variance. And if you look at cluster 3
19 in AFRA [ph], it's loaded with it.
20 DR. FILLINGIM: Yes, but predicting variance
21 doesn't mean it's part of --
22 DR. CLAUW: Well, predicting variance and

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1 non-responsive as a treatment, so it is sort of
2 -- that's more implying mechanism. It's not just
3 showing a cluster, it's --
4 DR. FILLINGIM: Well low education level
5 would predict responsiveness to treatment. Should
6 we add that? I guess I'm just thinking, at some
7 point, we're going to have all of the brain and the
8 subjective life of the human in here, and we've
9 moved pretty far from pain.
10 DR. FARRAR: It relates to what I said
11 before, which is that I think the critical
12 components, the depression, the catastrophizing,
13 the justification, is part of the control that we
14 exert over what we experience in the environment,
15 but it's not what we're interested in studying
16 here.
17 It will definitely affect the outcome in
18 some way, shape, or form. We need to measure it as
19 part of clinical studies that we do in order to
20 understand its relationship, but I don't think it
21 defines -- and I agree with Roger. I don't think
22 it's part of the definition of this phenotype.

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1 DR. DWORKIN: So Dan, if someone had 1, 2,
2 and 3, but didn't have fatigue, sleep, et cetera,
3 you would still diagnose them as having
4 fibromyalgia, central sensitivity, right?
5 DR. CLAUW: Yes, except how often does that
6 occur?
7 DR. DWORKIN: Right. So I'm thinking like
8 someone with severe major depression often will
9 have early morning awakening, but may not. So it
10 doesn't define major depression, but it's almost
11 always there. Is this sort of similar with the
12 fatigue and sleep? It's almost always there in
13 someone who has a predominant central
14 sensitization --
15 DR. CLAUW: That's part of the criteria for
16 major depressive disorder
17 DR. DWORKIN: Well, it's --
18 DR. CLAUW: Sorry. But I --
19 (Crosstalk.)
20 DR. DWORKIN: Well, then you'd be going in a
21 different direction; 3 from column A and at least 1
22 from column B. We could go in that direction.

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1 Ajay?

2 DR. WASAN: I would support Dan because the

3 unique thing about these, and what's mentioned in

4 that bullet point, is that many of those have been

5 shown to be causal of central sensitization, not

6 just associated. We know that poor sleep and

7 experiments that induce poor sleep create more

8 sensitization on QST and other measures.

9 We know the same thing with mood, that you

10 can worsen someone's mood, and you have worsening

11 QST outcomes, and you have neural correlates in the

12 brain, and fMRI are those types of things. So

13 there's a causal component here to sensitization

14 that is different than just being an associated

15 symptom.

16 DR. DWORKIN: The other thing to think

17 about -- and Lesley didn't highlight it in her talk

18 this morning -- but the ACTION APT [ph] criteria

19 for fibromyalgia, which was just published in the

20 last couple of months, do highlight as part of the

21 diagnostic criteria -- and Dan was an author

22 also -- fatigue and sleep.

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1 So we actually have an ACTION precedent, if

2 you will, of including fatigue and sleep in part of

3 the definition of a chronic pain condition. Jim?

4 DR. RATHMELL: So why not just move it to

5 important coexisting considerations that will

6 affect response to treatment?

7 DR. DWORKIN: No, that's what Roger thinks,

8 but Dan and presumably Lesley disagree.

9 DR. RATHMELL: So even though it's uncommon,

10 you would exclude any people who met the first

11 three criteria and didn't have the fifth there.

12 DR. CLAUW: Well, I guess I wasn't thinking

13 that the first three, that you had to have all

14 three in order to diagnose this because there will

15 be people that you don't even have all three. So I

16 was thinking that these were just more, if you see

17 this, this is supportive of the -- so maybe we're

18 thinking differently about how to -- because a lot

19 of criteria, you have to have column A plus B as

20 supportive. And I'd be very okay with the B being

21 supportive, being fatigue, memory problems, sleep

22 disturbance, and sensory sensitivity.

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1 DR. FIELDS: The key is that it's a symptom,

2 in a symptom complex. So you're using it to make a

3 diagnosis. If you have it, it increases your

4 confidence in the diagnosis.

5 DR. CLAUW: Exactly, and you're just helping

6 people get more comfortable.

7 DR. FIELDS: My guess is with the sleep,

8 it's maybe asking the patients as opposed to doing

9 the SLEEP study. If you did a sleep study, you

10 might find that it's a universal component of what

11 we're calling this condition. I don't know what

12 they call it.

13 DR. DWORKIN: So could we do something? I

14 mean this is sort of the DSM-3, 4, 5 model, that we

15 list those four, the bullets 1, 2, 3, and 5, as the

16 kind of core features of central sensitization in

17 chronic or acute pain patients, and that we kind of

18 recommend at least 3 of those 4 would be required

19 to have confidence that the patient has this

20 mechanism phenotype.

21 Is 3 or 4 a solution?

22 DR. FIELDS: What do you think about moving

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1 catastrophizing down next to cognitive

2 abnormalities?

3 DR. DWORKIN: I don't know what

4 catastrophizing was, which is why I wasn't sure

5 where to put it. It is cognitive.

6 Raj?

7 DR. RAJA: It's less likely to be effective

8 because widespread pain is an essential criteria,

9 so you have to have some criteria there, which is

10 essential, and then you can have a secondary X of

11 Y. There are certain which you really want as

12 essential criteria.

13 DR. DWORKIN: We could say you have to

14 widespread pain in two of the remaining three.

15 Roger and then Clifford.

16 DR. FILLINGIM: I just think conceptually

17 there are several things on the list that we think

18 reflect central sensitization. That includes

19 widespread pain, multiple comorbid chronic pains,

20 disproportionate pain, or whatever that is, and

21 maybe sensory amplification. The others don't look

22 like they result from central sensitization. In

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1 fact, Ajay was making the reverse case, that they
 2 cause central sensitization. That's an important
 3 distinction to me.
 4 What I'm thinking this list is about is if
 5 somebody is centrally sensitized, what phenotype
 6 does that produce, not what factors led to their
 7 central sensitization.
 8 DR. DWORKIN: Clifford, did you have your
 9 hand up?
 10 DR. WOOLF: I just think we're at risk here
 11 of defining central sensitization purely on the
 12 basis of fibromyalgia. Yes, that is part of the
 13 spectrum, but it's not the entire spectrum. Yes,
 14 there may be widespread pain, but, again, I go back
 15 to postoperative pain where it's not widespread,
 16 it's secondary. Hyperalgesia typically is in a
 17 limited [indiscernible].
 18 I just think, yes, we got to capture the
 19 fibromyalgia for sure, but we've got to recognize
 20 that every feature that is present in fibromyalgia
 21 is going to be present in other clinical
 22 manifestations that include central sensitization.

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1 DR. CLAUW: If we do that, and I'm okay with
 2 that, then we have to eliminate number 2, and put
 3 that over on the other side, because someone with
 4 osteoarthritis with superimposed central
 5 sensitization doesn't have COPCs. They got
 6 osteoarthritis. They developed central
 7 sensitization.
 8 I'm okay with that, but then let's just make
 9 sure that we put things in the right bucket. Then
 10 we'd have 1 and 2 as required -- 1 and 3 as
 11 required, and 2 and 4 and 3 as suggestive. But we
 12 can't have 2 as required because it doesn't occur
 13 in the people with OA or RA that develops
 14 central --
 15 DR. DWORKIN: Is that our way forward, 1 and
 16 3 required, 2 and 4 as frequently co-occurring but
 17 not required?
 18 Mike?
 19 DR. ROWBOTHAM: I think we can come up with
 20 a testing scheme with a variety of permutations to
 21 say presence or absence of central sensitization.
 22 But I echo what was just said. When you talk about

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1 fatigue, sleep, mood, cognition, it's hard to see
 2 how those directly follow from central
 3 sensitization.
 4 DR. DWORKIN: So there's an emerging
 5 consensus that 1 and 3 would be required; 2 and 4
 6 frequently co-occurring, but kind of not
 7 pathognomonic because there are patients who won't
 8 have it. I'm also getting the sense that ACTION
 9 might have to consider over the next several months
 10 having a smaller meeting to come up with
 11 evidence-based diagnostic criteria for central
 12 sensitization as an important mechanism in acute
 13 and chronic pain, but that would be a smaller
 14 meeting probably at the O'Hare Hilton.
 15 Kushang?
 16 DR. PATEL: This is a minor point, but for
 17 the paper, can we give the exact definition of
 18 widespread pain according to different body maps
 19 that is acceptable? I can think of several
 20 different definitions.
 21 DR. DWORKIN: We're going to start with the
 22 fibromyalgia APT [ph] criteria, where it was 6 out

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1 of 9? There was one other hand, and then we'll
 2 move on.
 3 DR. BRUEHL: I'm sorry. We do 6 out of 9,
 4 that again, all these people with fairly
 5 constrained centralized pain, like OA, would not
 6 qualify.
 7 DR. CLAUW: That's a threshold for
 8 fibromyalgia --
 9 DR. DWORKIN: For fibromyalgia.
 10 DR. CLAUW: -- and a threshold for central
 11 sensitization.
 12 DR. BRUEHL: I mean, it's simply having one
 13 pain location with one additional one or not. I
 14 don't know what the answer is to that.
 15 DR. DWORKIN: All of multisite pain; I don't
 16 know.
 17 DR. BRUEHL: Yes, multisite pain.
 18 DR. DWORKIN: Raj?
 19 DR. RAJA: Sorry. I'm just thinking back on
 20 what Clifford said, that we need to include the
 21 whole spectrum, and then if you use widespread pain
 22 in postoperative pain, it's not necessarily

Page 237

1 widespread pain. So even number 1 may not be an
2 essential criteria.
3 DR. BRUEHL: So postoperatively,
4 disproportionate pain would be the only thing you
5 could use to say somebody has central
6 sensitization, right?
7 DR. CLAUW: Or allodynia. Most of those
8 people do have some allodynia and hyperalgesia in
9 the region where they have chronic postoperative
10 pain.
11 DR. BRUEHL: That's what I meant.
12 DR. CLAUW: Yes, so you could use that other
13 thing, too. But yes, it wouldn't be widespread.
14 DR. DWORKIN: We may have to carve out acute
15 postoperative pain and treat that a little
16 differently than all of the chronic pain
17 conditions.
18 DR. WOOLF: It's beyond the site of injury,
19 but not the whole body.
20 DR. DWORKIN: Right.
21 DR. CLAUW: That's what's seen in a lot of
22 these people, though. It's spread regionally, it's

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1 sensitized, but it's not fibro. It's not the whole
2 body.
3 DR. RAJA: No, but I can give the example of
4 postherpetic neuralgia, where patients have
5 allodynia and hyperalgesia. There is central
6 sensitization, but it's not widespread. It's often
7 dermatomal. So I think widespread may not fit the
8 criteria.
9 DR. DWORKIN: John?
10 DR. FARRAR: No, go ahead.
11 DR. DWORKIN: No.
12 (Laughter.)
13 DR. DWORKIN: I talk only when you guys have
14 nothing to say.
15 (Crosstalk.)
16 DR. FARRAR: I'm wondering whether something
17 along the lines of the wider the spread, the more
18 likely -- the higher the likelihood of it. The
19 reason I'm bringing that up is --
20 (Laughter.)
21 DR. FARRAR: -- if you're interested
22 (Laughter.)

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1 DR. CLAUW: You didn't hear [indiscernible -
2 off mic].
3 DR. DWORKIN: I do like that word.
4 (Laughter.)
5 DR. FARRAR: Just because we talked before
6 about the need to try and make the group as
7 homogeneous as possible when we're studying it. So
8 if you included people with a little bit of extra
9 pain in the leg, then the question of whether
10 you're talking about a spinal mediated
11 centralization or a more broad sensitization might
12 be an interesting issue. I'm not saying we have to
13 require, but a sentence or two that just specifies,
14 it might be useful to focus on those.
15 DR. DWORKIN: Steve?
16 DR. BRUEHL: Just thinking, a lot of the
17 purpose of doing this is to enable better clinical
18 trials, and it seems to me like most of the
19 clinical trials that would use this would be
20 targeting chronic pain rather than acute
21 postoperative pain. So I think it would make sense
22 to kind of tailor this more for the chronic pain

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1 setting, although I agree that the acute pain --
2 DR. DWORKIN: The same way we're going to
3 have two kind of pathways in terms of the type of
4 the clinical trial, we can also separate out to
5 some extent acute pain because there are different
6 issues. Mike?
7 DR. ROWBOTHAM: A lot of the protocols for
8 showing that there were sensory abnormalities
9 extending outside the area where you would expect,
10 based on the site of injury, those protocols have
11 been pretty well worked out. So there's lots of
12 literature that you can site showing how they
13 demonstrate that and how it responds to different
14 treatments. The same thing with postherpetic
15 neuralgia, there's enough literature that you can
16 say that it's spread beyond where it could possibly
17 have reflected the initial zoster reactivation.
18 DR. CLAUW: When you see it -- for example,
19 in rheumatoid arthritis, the way we see it is it's
20 in areas that are not typically affected by
21 rheumatoid arthritis. There are certain joints
22 that are affected by RA and certain -- but I think

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1 we can try to come up with something along those
 2 lines, that it's pain outside the distribution that
 3 you would expect to see --
 4 DR. DWORKIN: Expected, yes.
 5 DR. CLAUW: -- with that particular disease
 6 or injury.
 7 DR. DWORKIN: And give examples; give these
 8 examples.
 9 DR. CLAUW: Yes. It doesn't have to be
 10 widespread, but it's outside the distribution you
 11 would expect to see --
 12 DR. DWORKIN: Examples from RA and PHN would
 13 be helpful.
 14 Can we move on? Anybody? John, last word?
 15 DR. FARRAR: Last word, disproportionately
 16 the last word. I think we need to be carefully,
 17 and maybe this comes up under your
 18 inclusion/exclusion section. To be clear whether
 19 we're talking about a peripherally maintained
 20 sensitization, if you like, the description of the
 21 injection of stumps from people who've had missing
 22 limbs, where the pain gets much better with the

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1 injection into a neuroma.
 2 Some statement about needing to try to treat
 3 other things that to see whether it's, whether it's
 4 just the 20 percent who have RA, and RA pain all
 5 over the place, or who have arthritis, but it's
 6 arthritis in joints. So I'm wondering how to couch
 7 that, and I'm not sure what to do.
 8 DR. DWORKIN: Well, the whole issue of
 9 whether there's peripheral drive there or not, we
 10 said we would talk about early on in the article
 11 because it's more conceptual. Is the question
 12 you're raising whether we need to think about that
 13 diagnostically, that we want to somehow partition
 14 this phenotype into those patients where there's
 15 some evidence of peripheral drive and those
 16 patients where the centralization, if you will,
 17 seems independent?
 18 That wasn't the discussion I was hearing.
 19 The sense I had was that we're not there yet; that
 20 if the patient has central sensitization pain, no
 21 one seemed to think it was critically relevant to
 22 do a clinical trial to figure out which of those

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1 patients have a peripheral component and which
 2 don't.
 3 DR. FARRAR: What I'm suggesting is that at
 4 least there be -- not just at the beginning of the
 5 article but where we talk about the phenotype, that
 6 there be a sentence or two about that phenomenon so
 7 that people can be aware and maybe consider that in
 8 the --
 9 DR. DWORKIN: Yes, we could put this
 10 decision in, something like why we're not requiring
 11 kind of interrogation of possible peripheral drive.
 12 Friedhelm, sorry.
 13 DR. SANDBRINK: I'm sorry. One last word.
 14 Clinically, we often try to differentiate between
 15 multifocal pain or multisite pain where there's
 16 generalized pain; at least that's when I see a
 17 patient. So somebody who has truly what seems to
 18 be relatively localized headache, shoulder pain,
 19 neck pain, low back pain, but really not pain all
 20 over, at least in my diagnostic impression, I do
 21 make a differentiation for that.
 22 DR. DWORKIN: So I think it has already been

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1 suggested that instead of the word "widespread,"
 2 that "multisite" might be a little better. Does
 3 anyone disagree with that, multisite instead of
 4 widespread?
 5 (No response.)
 6 DR. DWORKIN: All right. You made a
 7 decision.
 8 Lesley?
 9 DR. ARNOLD: I was just going to say that we
 10 looked at that question when we were developing the
 11 criteria and the different ways of defining
 12 widespread pain, and we learned that it can be
 13 easily defined as multisite, not just in the
 14 traditional 1990 approach, so the multisite was
 15 what we went with.
 16 DR. DWORKIN: Exactly.
 17 DR. ARNOLD: We were talking about defining
 18 widespread pain. I mean, it is on a continuum, so
 19 that's why I think you could put starting with
 20 beyond the site of injury up to the end of the
 21 continuum, again, fibromyalgia --
 22 DR. DWORKIN: Right, is fibromyalgia.

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1 DR. ARNOLD: -- where you have 6 out of 9 or
 2 however you want to define it. So it is a
 3 continuum, but at the very least beyond the site of
 4 injury, if you will.
 5 DR. DWORKIN: Maybe this really will be the
 6 last word. Nat?
 7 DR. KATZ: So multisite means 2 or more
 8 sites?
 9 DR. DWORKIN: There was a suggestion that,
 10 yes, in some patients, it might only be one
 11 additional site.
 12 DR. ARNOLD: Like I said, on the continuum,
 13 and then we have to decide where.
 14 DR. KATZ: If you have osteoarthritis in
 15 both knees, then you have multisite pain?
 16 DR. ARNOLD: Uh-huh.
 17 DR. KATZ: How about both knees and a
 18 shoulder?
 19 DR. DWORKIN: And presumably you'd have to
 20 have a couple of others of these phenotypic
 21 characteristics.
 22 DR. CLAUW: In most of the big data sets

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1 we've looked at, three is a better demarcation --
 2 DR. DWORKIN: Than two.
 3 DR. CLAUW: -- to say that it's something
 4 different because there are so many people that
 5 have two sites of pain without having this process.
 6 If you're counting sites, I'm not necessarily
 7 advocating that, but if you're trying to set a
 8 threshold, 2 wouldn't be central sensitization; 3
 9 or more would be.
 10 DR. DWORKIN: Saying like the cutoff could
 11 be somewhere in the 2, 3, 4 realm --
 12 DR. CLAUW: And besides that it's a
 13 continuum.
 14 DR. DWORKIN: -- and that this is a research
 15 agenda question.
 16 DR. KATZ: So this is a requirement for the
 17 identification of this syndrome or just one -- you
 18 could central sensitization without multisite pain?
 19 DR. DWORKIN: I think we said that 1 and 3
 20 were required, and 2 and 4 were often.
 21 I think what we're sort of dancing around is
 22 whether this article is actually going to propose

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1 diagnostic criteria for central sensitization pain.
 2 I think going into this meeting, none of us really
 3 thought we'd end up with actually having to come up
 4 with diagnostic criteria, because if we thought
 5 that, we would have made sure there was some kind
 6 of literature review of all of these bullets, which
 7 we haven't done.
 8 So I think we're going to have to figure out
 9 one of two pathways going forward. We either
 10 finesse this in the article by being a little
 11 vague, by, as Lesley said, it's a continuum of
 12 sites from zero to many, and we're not quite sure
 13 where the best cutoff is, and it might depend on
 14 the type of pain, et cetera. So maybe we could
 15 finesse it.
 16 The other path is that we have another
 17 meeting where we actually prepare to come up with
 18 specific criteria for the diagnosis for central
 19 sensitization. I think this decision I don't feel
 20 able to make right now, but we need to, as a group,
 21 consider do we just finesse it to the greatest
 22 extent possible we can or do we want to have a

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1 meeting in the O'Hare Hilton? I'm on purpose
 2 making this not very desirable.
 3 (Laughter.)
 4 DR. DWORKIN: So let's move forward.
 5 DR. BRUEHL: I'm sorry. You mentioned this,
 6 so I have to respond to it. Using the wording
 7 "diagnostic criteria" creates problems because of
 8 the multi-diagnosis issue. We're adding another
 9 one that overlaps multiple --
 10 DR. DWORKIN: Yes. I think part of
 11 finessing this article might be to say that we want
 12 to propose a way --
 13 (Crosstalk.)
 14 DR. DWORKIN: -- an approach for identifying
 15 a phenotype.
 16 DR. BRUEHL: Yes.
 17 DR. DWORKIN: -- without it being specific
 18 criteria because we don't have the evidence base to
 19 propose specific criteria.
 20 DR. BRUEHL: Isn't criteria for identifying
 21 a phenotype? We just don't call it a diagnostic.
 22 DR. DWORKIN: I agree, yes. Nobody

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1 disagrees with that.
 2 What?
 3 DR. FIELDS: Agree strongly.
 4 DR. DWORKIN: I agree strongly, and Howard
 5 agrees strongly.
 6 I think this might be my last slide. We had
 7 a lot of discussion this morning about medical and
 8 psychiatric comorbidities. I thought the best way
 9 of summarizing that discussion is we don't know
 10 whether these are the droids we're looking for or
 11 not, and it depends on the specific clinical trial
 12 and its objectives.
 13 I think in many cases these are the droids
 14 we're looking for, and we want to know about the
 15 effect of the treatment, not only on the index
 16 condition phenotype but on some additional
 17 conditions, but in other circumstances, we might
 18 want to exclude those droids.
 19 Unless someone disagrees -- and obviously
 20 we're going to leave out the Star Wars quote in the
 21 article -- I think we're going to say it really
 22 depends on the clinical trial objectives and the

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1 extent to which comorbidities are excluded, or
 2 actually the other extreme would be to be made a
 3 secondary target of the treatment valuation. Does
 4 your treatment benefit the fibromyalgia but also
 5 the IBS, and the tension type headache?
 6 Does that seem a reasonable approach?
 7 Because I think we'll be here all through the
 8 weekend if we try to decide that we're either
 9 studying the comorbidities or excluding them. I
 10 don't think there's a right answer, one size fits
 11 all.
 12 DR. RATHMELL: Medical and psychiatric
 13 comorbidities are common. Think about it.
 14 DR. DWORKIN: Exactly. So this is a
 15 strongly recommended consideration. We're not
 16 recommending to do or do not, but we think an
 17 investigator has to agonize over how they're going
 18 to deal with the medical and psychiatric
 19 comorbidities.
 20 DR. FARRAR: I think it might be useful to
 21 comment on the fact that from an exclusion
 22 perspective, the issue is whether the patient has

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1 the capability to participate actively in a study
 2 so that somebody who's psychotic and all that -- I
 3 mean, my point is that there's going to be a line
 4 in each of these that is going to result in an
 5 exclusion.
 6 DR. DWORKIN: So for this bullet, number 4,
 7 and for 5, what we really tried to highlight in
 8 preparing these slides, is the issues that are
 9 specific to central sensitization. Now, there's
 10 there's a long list. Of course, we all know of
 11 other inclusion/exclusion criteria, but this seemed
 12 to be the one that was foremost in terms of its
 13 relevance to the types of trials we're talking
 14 about.
 15 So let's dispense with bullet 6. I think
 16 it's important for IMMPACT and ACTION to be at the
 17 cutting edge, if you will, and to talk about things
 18 that haven't been talked about in previous
 19 recommendations. So the statisticians and
 20 methodologists in our group will write several
 21 paragraphs about estimands and modern approaches to
 22 dealing with missing data, particularly given that

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1 these patients might have higher rates of AEs than
 2 other patients, and the right and wrong way to do
 3 subgroup analyses and address multiplicity.
 4 So I don't think we need to talk about 6,
 5 unless anyone wants to, because it will be in the
 6 article. It will be a section. It will be up to
 7 date, state of the art. It will be different than
 8 anything in previous IMMPACT articles. But in the
 9 remaining time, and we have quite a bit of time,
 10 what we do have to discuss is outcome measures. I
 11 think we've gotten to, pretty much, every aspect of
 12 recommendations or recommended considerations for
 13 clinical trials, except our outcomes.
 14 Raj?
 15 DR. RAJA: Just a question on 4. I think
 16 apart from just saying that medical and psychiatric
 17 comorbidities can occur, based on my reading of the
 18 literature and what I've heard is they may also in
 19 some way influence the outcome or at least -- I
 20 think that concept may need to be brought in; that
 21 that needs to be considered.
 22 DR. DWORKIN: Right. And that does go right

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1 down to the bottom of the slide because one could
 2 imagine a subgroup analysis, ideally prespecified,
 3 where you compare the patients who have multiple
 4 comorbidities with the ones who don't, and you
 5 would have had a prediction about which group the
 6 treatment would work better in; absolutely. There
 7 are things on all of the slides that are potential
 8 moderators of treatment efficacy, and we need to
 9 highlight that.

10 Dan?

11 DR. CLAUW: One suggestion would be you
 12 might want to put catastrophizing under 4 because
 13 it fits probably better under 4 than it does where
 14 it was before. It was clumped next to sensory
 15 before, and that's not really where it belongs.

16 DR. DWORKIN: I agree.

17 DR. CLAUW: And this is really an RDoC
 18 thing. Any chronic pain patient can have anxiety,
 19 depression, catastrophizing that always has a
 20 negative influence on outcomes. It's nothing that
 21 is specific to centralized pain or central
 22 sensitization. So let's just say that it's being

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1 evaluated, but it's not --

2 DR. DWORKIN: So we're taking
 3 catastrophizing out of this slide and moving it to
 4 the next slide. Thank you. As you can see, I
 5 didn't know what to do with it.

6 DR. KLEYKAMP: Bob, just for my
 7 clarification so I'm on the same page before we
 8 move, can I double-check this slide, what we've
 9 decided? So multisite pain, that's the term for
 10 now we're going to use, and this other -- I'm not
 11 going to say the disproportionate -- that will not
 12 be in there, but this other --

13 DR. DWORKIN: We will replace it, yes.

14 DR. KLEYKAMP: Those are two primary
 15 considerations, and then additional considerations
 16 that are important, as you've diagnosed, or design
 17 treatments.

18 DR. DWORKIN: Well 2 and 4 become -- no, 2
 19 and 5 become almost always important in the
 20 phenotype, but not required for the phenotype.
 21 We'll work on it together.

22 DR. KLEYKAMP: Okay.

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1 DR. DWORKIN: And then, the sensory
 2 amplification bullet and the last bullet are sort
 3 of more we need more data, more research, and
 4 catastrophizing gets moved over to the next slide.

5 DR. KLEYKAMP: So history of multiple
 6 comorbid chronic pain conditions and this fatigue,
 7 sleep, mood, those are very important but not --

8 DR. DWORKIN: And we will come up with
 9 language, yes.

10 DR. KLEYKAMP: Okay.

11 DR. BRUEHL: No, but we were talking about
 12 moving catastrophizing to fatigue --

13 DR. DWORKIN: To the next, yes.

14 Catastrophizing gets moved to the droids.

15 DR. KLEYKAMP: All right.

16 DR. DWORKIN: Okay. Outcome measures. I
 17 think this is my last slide; it is. Depending on
 18 how much time we spend on outcome measures is when
 19 you get to go home.

20 (Laughter.)

21 DR. DWORKIN: That wasn't meant to be any
 22 kind of a bias.

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1 Dan?

2 DR. CLAUW: Can I suggest nixing the FIQR?
 3 It's a terrible outcome measure. Let me read a
 4 couple items of the FIQR in case you didn't know
 5 how terrible it was.

6 "Prepare a homemade meal, no difficulty,
 7 very difficult; vacuum, scrub, or sweep floors;
 8 lift and carry a bag of groceries; arrange bed
 9 sheets." Need I say more? It's a terrible outcome
 10 measure. It's only ever been used in fibromyalgia.
 11 It shouldn't be more broadly used for this
 12 construct. There's just nothing about it that is
 13 good.

14 DR. DWORKIN: So Dennis and I do our very
 15 best to make everybody happy, so how about this?
 16 That we take the FIQR off this list, but we have a
 17 sentence somewhere in this section that gives its
 18 long history of use in fibromyalgia clinical
 19 trials, that for a fibromyalgia trial, the
 20 investigator could consider it?

21 DR. CLAUW: Yes, but that's different. I
 22 don't think that's really what we're talking about

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1 here, but that's okay.
 2 DR. DWORKIN: NO, no, but that's the point
 3 of this list. The point of this list is for you to
 4 say what you said and for us to kind of deemphasize
 5 it.
 6 Are you okay with that, Lesley?
 7 DR. ARNOLD: Absolutely.
 8 DR. DWORKIN: Okay. We've solved the FIQR.
 9 DR. TURK: We dealt with this in the
 10 IMMPACT I or II, whichever one it was, which is
 11 when there are specifically identified measures for
 12 certain disorders, you should use those. When you
 13 don't have those is when you use --
 14 DR. CLAUW: When you have a disease-specific
 15 functional status measure, you should use that.
 16 DR. TURK: Yes, exactly.
 17 DR. CLAUW: Above and beyond, perhaps a
 18 generic measure. I'm okay with that. Instead of
 19 calling out the FIQR and making it seem like --
 20 DR. DWORKIN: That was my mistake, putting
 21 it there. The others are more general, administer
 22 the body map again and to see if the number of

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1 regions has decreased. Whatever sensory
 2 amplification measure you might or might not have
 3 decided to use at baseline, give it again and see
 4 if patients are less bothered by mosquito bites;
 5 fatigue, sleep, obviously.
 6 This is the point I think Lesley really made
 7 quite clear. If comorbidities are not exclusion
 8 criteria, then let's make some effort to see
 9 whether the treatment also has a benefit on pain
 10 intensity and maybe pain interference of the
 11 comorbid IBS, or TMD, or tension type headache.
 12 Anything missing? So Dan wants FIQR off
 13 this list. Anything to add? Anything else to go
 14 off it? Howard?
 15 DR. FIELDS: I was just thinking, do you
 16 think under outcome measures, it's premature to
 17 identify some as primary and others as necessarily
 18 secondary outcome measures?
 19 DR. DWORKIN: I think what we'd say is
 20 something like for most circumstances, a measure of
 21 pain intensity for the specific condition being
 22 studied will be the primary measure, and that these

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1 would be secondary. A lot of sentences begin
 2 saying, "depending on the circumstances."
 3 Clifford?
 4 DR. WOOLF: Something potentially missing
 5 for research agenda is whether the presence of
 6 central sensitization represents a risk factor for
 7 chronicity or --
 8 DR. DWORKIN: Yes. We should have -- and
 9 this would go in the research agenda section. I
 10 guess Claudia discussed this a lot, kind of the
 11 extent to which what we've been discussing, is
 12 there a risk factor for chronicity or a kind of
 13 risk factor for maintenance of the chronic pain
 14 longer than it would otherwise be? And that kind
 15 of transitions quite easily into prevention trials,
 16 which we haven't talked about, but I think deserves
 17 at least several sentences, if not a paragraph.
 18 So risk factors for the acute to chronic
 19 pain transition -- which I think you all know, NIH
 20 has lots of money from a common fund initiative, to
 21 say, acute to chronic pain initiative. So there
 22 should be a paragraph in this article, and

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1 prevention follows on from that.
 2 Steve?
 3 DR. BRUEHL: I had a question about the pain
 4 intensity interference in comorbid conditions. So
 5 what we have is a phenotype that is
 6 cross-diagnostic, and part of characterizing that
 7 phenotype is to ask for pain intensity. And
 8 because it's, by definition, almost multisite, all
 9 you can ask is what's your overall pain intensity.
 10 I'm thinking whatever we get as a pain
 11 intensity for the phenotype, and then we're saying
 12 now go to the individual components of that and ask
 13 for the pain associated with the individual
 14 components, I'm just not sure what that's asking.
 15 DR. DWORKIN: Well, setting aside
 16 fibromyalgia, where I think it does get a little
 17 tricky, if you're doing a clinical trial of TMD and
 18 the primary outcome is TMD associated pain, you
 19 could also -- if I'm understanding Lesley's point
 20 correctly and if the patient has IBS, you could
 21 have them rate their IBS pain on a separate pain
 22 rating.

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1 DR. BRUEHL: Yes, but what we're talking
2 about is potentially a clinical trial where the
3 entry criterion is meeting this centralized pain
4 phenotype, so you'd almost have to have some pain
5 criterion. I thought when it said impact domains,
6 that that's what it was talking about, was the pain
7 intensity associated with central sensitization
8 phenotype.
9 DR. CLAUW: Just to make it [indiscernible -
10 off mic].
11 DR. BRUEHL: Yes, please.
12 DR. CLAUW: You're looking at central
13 sensitization in knee osteoarthritis patients and
14 you're looking at the degree to which that resolves
15 after knee arthroplasty. I know this well because
16 we have a lot of these ongoing studies.
17 If you don't separately rate pain intensity
18 at the knee and all the other places in the body,
19 you can't tell if the central sensitization got
20 better because people, depending on the rate at
21 which their knee is healing, they're sometimes
22 rating their knee pain, they're sometimes rating

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1 their overall pain, but you really have a hard time
2 figuring out what their most severe pain is and
3 knowing what got better with the intervention.
4 So in fibromyalgia, asking a summary measure
5 is fine because people hurt all over, but we do a
6 lot of work with these regional pain conditions
7 like OA and RA, and if you don't ask the
8 intensities at different regions, or at least big
9 body region, 7 body regions, you really get in a
10 lot of trouble afterwards because one part of the
11 pain got a lot better from the intervention, but
12 other components didn't.
13 DR. BRUEHL: So you don't even need a global
14 pain measure in most cases.
15 DR. CLAUW: In something like fibro, I would
16 use a global pain measure because that's how people
17 tend to write their -- but even Lesley was talking
18 about examples where the woman's rating or headache
19 or whatever, and not knowing what to rate or things
20 like that. I think that it is helpful just because
21 we're into these studies, and you see so many
22 different times where it's hard to know what the

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1 patient was rating.
2 If you don't collect that data -- and again,
3 I think we don't want to do a map where we're
4 rating 45 sites, but rating 7 different sites, we
5 do that now, and it just adds like 5 or 10 seconds
6 to the burden because it only comes up to rate if
7 they check a site in that area of the body.
8 DR. BRUEHL: Or maybe we could make it just
9 more clearer, because I assumed, when you were
10 talking about having the impact factors assessed,
11 that that was a pain rating that in my head, I
12 immediately thought, "Well, it's a central
13 sensitization rating," which there really isn't
14 one; I understand that. But I think maybe we need
15 to be very specific.
16 DR. DWORKIN: Yes.
17 DR. BRUEHL: When you were assessing pain to
18 identify this, you need to independently assess the
19 intensity.
20 DR. DWORKIN: The reason I went back is
21 depending on what kind of trial you're doing, an
22 optimized trial of IBS, or of TMD versus the kind

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1 of basket trial where you might include in one
2 trial patients with IBS and TMD and FM, the way you
3 do your primary pain rating is obviously going to
4 differ and meaning to say that. I think that's
5 very important.
6 Any other comments about outcome measures?
7 Raj?
8 DR. RAJA: Just a question -- going back to
9 your, quote/unquote, "essential criteria," do the
10 outcome measures capture those essential criteria?
11 DR. DWORKIN: I think they do. I know I
12 looked at that at some point.
13 DR. RAJA: So you said 1 and 3 were going to
14 be --
15 DR. DWORKIN: So we have to add, if
16 allodynia and hyperalgesia are now specifically
17 listed in 3, there should be a reassessment of
18 allodynia, hyperalgesia also as an outcome measure.
19 DR. RAJA: That's where I'm heading. Thank
20 you.
21 DR. DWORKIN: Yes, absolutely. Dan?
22 DR. CLAUW: Just for completeness, maybe in

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1 the last slide, the outcome measures, we should put
2 one of the options people could use that COPC
3 screener. You had it in a different place, but you
4 may want to map that forward to outcome measures.
5 DR. DWORKIN: Okay. Right. So basically,
6 we have to make sure that the outcome measure list
7 includes the baseline phenotyping measures.
8 DR. CLAUW: Right.
9 DR. DWORKIN: Absolutely. Chris?
10 MS. VEASLEY: I've been intentionally quiet
11 most of this meeting, but feel like I need to say
12 something around outcome measures. The pain field
13 in general has been very slow to bringing patients
14 into the process of developing measures. And like
15 Simone asked the question yesterday, do we know
16 what patients think is important with these
17 conditions? And we both have not done this for
18 individual pain conditions, nor have we done it for
19 people who have multiple pain conditions.
20 Particularly when it comes to outcomes, I
21 think in terms of research recommendations, that
22 needs to be added. There are some individual

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1 efforts, like with the FDA in TMD, right now to
2 look at actually bringing patients into the
3 process, and actually asking them what's important
4 to them in terms of outcome measures, and including
5 that. But in terms of this as well, I think it's a
6 very important recommendation.
7 DR. DWORKIN: Thank you, because if there
8 were no other questions, the next thing -- are
9 there any other questions? Ewan?
10 (Laughter.)
11 DR. McNICOL: Sorry. You mentioned the
12 outcome measures, fatigue and sleep. If I remember
13 right, those were both outcome measures from
14 IMMPACT I and IMMPACT II. So are you suggesting
15 that we look at them differently or use different
16 measurements?
17 DR. DWORKIN: Right. No, if they're in the
18 IMMPACT I and II article, then I was just not
19 forgetting -- I mean, I wasn't remembering. That's
20 right. To the extent that they were recommended as
21 secondary, or depending on the circumstance,
22 outcome measures, that's really captured in the

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1 first bullet. Thank you.
2 So it's about two 2:45, and what I was going
3 to say is we didn't realize that usually the last
4 thing we do, the second afternoon, is to spend 15
5 or 20 minutes talking about a research agenda.
6 Chris just mentioned getting some patient input, I
7 think not only about outcome measures but about
8 research design more generally.
9 So we could spend another 15 to 20 minutes
10 on coming up with a bunch of bullets for a research
11 agenda. We have some: risk factor or longitudinal
12 studies of chronic pain transition, prevention
13 studies, et cetera. The alternative is Dennis and
14 I could thank you all for participating, and you
15 could all send me emails with research agenda
16 bullets.
17 John?
18 DR. FARRAR: I think I was daydreaming at
19 the time and need to bring up just one other quick
20 issue, which is that you went over analysis as
21 though it were a minor point, and I realized that
22 we need to do lots of things.

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1 I mentioned to you at the break that one of
2 the issues in the analysis is the assessment of the
3 effect and whether things are done as responder
4 analyses or other things. The reason that I bring
5 that up is that in situations where you have a poor
6 definition of the group that you're studying -- and
7 I would suggest that no matter how close we get to
8 understanding centralized pain, the likelihood of
9 defining the group we want is likely to be 50/50,
10 meaning that you're going to have 50 percent of
11 people who have what you're trying to have and 50
12 percent who might not.
13 We don't know what the numbers will be
14 ultimately, but in every study I've ever done,
15 there are groups who have the capability of
16 responding and people who don't. All I would say
17 is that in the analysis component of this, there
18 needs to be at least a short description of the
19 fact that there are ways to approach data and data
20 analysis that improved the likelihood of
21 discovering or being able to find those smaller
22 groups as opposed to simply looking at standard

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1 means and averages.
2 DR. DWORKIN: Maybe I misunderstood you.
3 Could you be more specific? What I'm hearing you
4 say now is that we phenotype patients, and
5 presumably into phenotype positive, phenotype
6 negative. But we don't do that with perfect
7 reliability.
8 DR. FARRAR: Correct.
9 DR. DWORKIN: So the fact that we don't
10 phenotype patients with perfect reliability means
11 that if we're looking for a phenotype by outcome
12 interaction, we're less likely to find it, and need
13 a larger sample size, et cetera. Then you said
14 there are ways to address that. For example, what?
15 DR. FARRAR: The issue is if you look at the
16 data as a continuous variable, and you have only a
17 smaller number of people who actually have the
18 phenotype, and never mind that there are three
19 mechanisms that could underlie the phenotype, then
20 you tend to wash out people who get dramatic
21 responses. In 20 percent of the patients, you get
22 a dramatic response. You may not see that.

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1 We've talked about this at other IMMPACT
2 meetings, and in terms of the analysis component of
3 this, instead of just estimands, missing data, and
4 subgroups, I think it's key that we refer back to
5 some of the other work that we've done in terms of
6 how to look at understanding the data in a way that
7 looks at the levels of responders and other things,
8 so that we don't miss being able to find small
9 groups of patients who have dramatic effects.
10 DR. DWORKIN: Sure. If what's you're saying
11 is there should be secondary data mining attempts
12 to look to see if whether a subgroup of real best
13 responders can be identified; sure. But as you and
14 I know from going back 15 years, Pfizer has never
15 been able to identify demographic or clinical
16 predictors of who responds to pregabalin and
17 replicate it. It's not that there haven't been
18 attempts to say this works, but it's never been
19 replicated; and likewise, Eli Lilly with
20 duloxetine; and likewise, opioid; and actually in
21 psychiatry, likewise oral antidepressants.
22 So being able to identify and replicate a

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1 predictor, a moderator, really, of treatment
2 outcome, I'm all on board with trying to do it, but
3 nobody's ever succeeded.
4 DR. FARRAR: No, no. I agree with that. I
5 guess what I'm saying is that one way of designing
6 a trial is to design it based on a continuous
7 measure with a mean value outcome. Another way of
8 designing it is to say I want to look for a
9 percentage of patients who have a clinically
10 relevant response; however you define that. It
11 increases the sample size, but it allows you to
12 identify smaller groups of patients who respond;
13 not preidentify them, but it allows you to get a
14 positive trial where sometimes you might need it.
15 DR. DWORKIN: ACTION has a paper that I
16 think will come out soon, where we conclude, on the
17 basis of a bunch of pretty sophisticated analyses
18 that Omar [ph] spearheaded, the notion in the pain
19 field that response is bimodal, is an artifact of
20 the way in which those data were analyzed. And if
21 you analyze the data correctly, at least for
22 chronic neuropathic and musculoskeletal pain,

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1 response is not bimodal, but it looks much more
2 like a normal distribution.
3 Now it could still be that with certain
4 treatments and certain conditions, there is a kind
5 of bimodal response, of robust response and blah,
6 but it doesn't exist in the way that people have
7 argued it does. It's an artifact of poor data
8 analysis. But this is getting into the weeds.
9 DR. FARRAR: It is.
10 DR. DWORKIN: Ajay?
11 DR. WASAN: Because of all those failures of
12 secondary analysis, one thing you could put in this
13 section and suggest is that if the sample sizes
14 were large enough -- and certainly there is some
15 movements with anti-[indiscernible], if they get
16 these aggregated large data sets together -- is
17 consider using causal inference statistics, which
18 would be a different approach, which may get to a
19 little more causal issues, which we all want to.
20 Those are things like your Bayesian network
21 analysis, CART with decision tree, some things like
22 that that just haven't been done, which now are

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1 better and can be done, and maybe give you some
2 better -- it's a nice research agenda thing.
3 DR. DWORKIN: If something gets replicated,
4 I don't care whether it's in psychiatry, neurology,
5 or pain, I'd love to see the article. But yes, I'm
6 all in favor of doing it, absolutely.
7 Okay. Do people want to spend another 20
8 minutes on developing a research agenda or has
9 everybody had enough and wants to catch the nearest
10 Uber to the airport or the train station?
11 MALE VOICE: Bar.
12 DR. DWORKIN: What?
13 MALE VOICE: Bar.
14 DR. CLAUW: You can give the people that
15 want to say and go over the research agenda the
16 ability to do that.
17 (Laughter.)
18 Adjournment
19 DR. DWORKIN: I saw a lot of faces just
20 staring at me, but one very vigorous no. So on the
21 basis of the one very vigorous no that was kind of
22 let's get out of here as soon as possible, Dennis

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1 and I would like to thank you all for your
2 participation. This was a great meeting. You will
3 be seeing this manuscript over and over again until
4 you're sick of it and us, and safe flights home
5 everybody, and see you at the next IMMPACT meeting.
6 (Applause.)
7 (Whereupon, at 2:53 p.m., the meeting was
8 adjourned.)
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<p>[</p> <p>[Indiscernible (7)] 206:8;212:11; 215:8;216:17;217:18; 239:1;261:9</p> <p>[indiscernible] (4) 156:9;211:16; 212:22;233:17</p> <p>[ph] (5) 46:6;226:19; 229:18;235:22;271:18</p> <p>[sic] (1) 104:22</p>	<p>accomplished (1) 111:9</p> <p>according (2) 132:7;235:18</p> <p>account (1) 85:14</p> <p>accounted (1) 176:2</p> <p>accrue (1) 100:13</p> <p>accuracy (2) 120:4,6</p> <p>accurately (2) 28:11;120:8</p> <p>achy (1) 114:7</p> <p>acid (1) 209:13</p> <p>acknowledge (1) 102:21</p> <p>acknowledged (1) 83:11</p> <p>ACR-90 (2) 17:19;220:11</p> <p>acronym (2) 8:1,2</p> <p>across (20) 6:19;14:6;15:7; 18:21;23:10;29:12,21; 31:6;32:22;38:3,14; 39:11,13,16;56:21; 90:7;106:19;121:9; 150:10;157:8</p> <p>act (2) 34:10;134:11</p> <p>actigraph (1) 68:7</p> <p>actigraphy (3) 34:10,14;55:11</p> <p>acting (3) 108:22;109:3;163:6</p> <p>action (1) 8:3</p> <p>actionable (1) 98:8</p> <p>activation (1) 140:13</p> <p>active (5) 48:8;49:21;122:17; 123:5;174:17</p> <p>actively (1) 251:1</p> <p>activities (1) 24:21</p> <p>ACTION (7) 167:21;182:6; 229:18;230:1;235:8; 251:16;271:15</p> <p>actual (5) 44:15;54:2;97:13; 100:5;118:18</p> <p>actually (61) 23:21;48:2;51:12;</p>	<p>52:7,10,16;53:4; 65:20;66:15;87:12; 100:21;104:6;109:4, 20;110:11,20;112:16; 115:2;116:8;118:3; 120:2,7;122:9,12; 124:16;127:21; 133:22;134:22;136:3, 5;141:14;142:6; 143:13;145:4;146:5,8; 147:10;148:13; 149:14;151:22; 154:21;157:7;159:16; 161:11;177:8;178:16; 187:7;192:5;200:2; 219:19;221:9;223:2; 230:1;246:22;247:3, 17;250:2;266:2,3; 269:17;270:20</p> <p>acute (17) 8:20;180:12,17; 182:18;188:7;189:22; 190:6;203:6,6;231:17; 235:12;237:14; 239:20;240:1,5; 259:18,21</p> <p>adaptation (1) 106:2</p> <p>adaptive (1) 47:1</p> <p>add (16) 104:4;105:14; 113:17;118:21; 128:18;135:2;153:20; 164:12;181:11; 190:15;203:3;224:5; 225:13;227:6;258:13; 264:15</p> <p>added (5) 46:14;108:3;210:1, 1;265:22</p> <p>adding (4) 88:20;95:11; 114:16;248:8</p> <p>addition (2) 107:18;108:6</p> <p>additional (10) 96:3;107:19;108:3; 125:1;139:3;141:12; 236:13;245:11; 249:16;254:15</p> <p>additive (2) 69:19;159:17</p> <p>address (11) 77:5;84:8;87:1; 124:11;145:2;146:21; 150:6;153:13;155:18; 252:3;269:14</p> <p>addresses (1) 48:14</p> <p>adds (1) 263:5</p> <p>adequate (3)</p>	<p>111:2;116:14; 152:11</p> <p>adjective (1) 185:20</p> <p>adjourned (1) 274:8</p> <p>Adjournment (1) 273:18</p> <p>administer (2) 22:1;257:21</p> <p>admit (1) 41:1</p> <p>adulthood (1) 58:3</p> <p>advance (8) 72:17;79:21;129:4, 12;136:17;137:9,12; 176:12</p> <p>advanced (1) 95:15</p> <p>advantage (1) 193:5</p> <p>adverse (1) 31:20</p> <p>adversely (3) 75:15;77:2;82:9</p> <p>advice (4) 6:3,4;41:8;70:9</p> <p>advise (1) 67:5</p> <p>advisement (1) 182:13</p> <p>advising (1) 57:7</p> <p>advocating (2) 129:13;246:7</p> <p>AEs (1) 252:1</p> <p>affect (15) 15:20;60:5,6;75:15; 77:6;82:9;86:16; 103:2;132:10;138:5; 193:9,17;194:3; 227:17;230:6</p> <p>affected (4) 83:9;85:9;240:20, 22</p> <p>affects (3) 76:1;77:1,2</p> <p>afferent (5) 13:11;14:20; 187:13;188:10,11</p> <p>Affirmative (1) 197:22</p> <p>AFRA (1) 226:19</p> <p>afternoon (4) 40:12;169:22; 175:12;267:4</p> <p>afternoon's (1) 160:12</p> <p>afterwards (2) 143:2;262:10</p>	<p>again (50) 14:19;17:16,17,21; 20:4;23:7;33:12,16; 37:9;38:12;63:7; 71:18;73:21;76:8; 77:7;78:3;79:3,16; 81:16;82:2,21;84:20; 85:1;88:11;91:19; 92:3,10,17,95:11; 106:1,4;108:5;114:3; 128:17;134:9;143:20, 22;157:13;162:10,11; 192:14;223:9;226:15; 233:14;236:4;244:21; 257:22;258:3;263:2; 274:3</p> <p>against (4) 138:17;183:10,13; 190:18</p> <p>agenda (17) 169:22;170:9; 174:8;175:4;185:16; 192:18;224:3;225:6; 246:15;259:5,9;267:5, 11,15;273:2,8,15</p> <p>agent (1) 201:4</p> <p>aggregated (1) 272:16</p> <p>aging (1) 5:10</p> <p>agnostic (1) 175:5</p> <p>ago (11) 7:4;33:9;43:16; 97:3;151:1;189:14; 202:6;204:20;210:17; 220:16;224:6</p> <p>agonize (1) 250:17</p> <p>agree (36) 100:3;102:14; 113:16,19;115:14,22; 116:12;117:7;122:5; 127:21;131:14;133:4, 11;136:13;142:15; 157:15;158:2;182:10; 183:2;184:19;189:9, 10;192:20;193:6; 197:15;215:3;217:2; 220:7;223:7;227:21; 240:1;248:22;249:3,4; 253:16;271:4</p> <p>agreed (2) 205:3;217:15</p> <p>agreement (1) 192:21</p> <p>agrees (1) 249:5</p> <p>ahead (8) 62:21;71:14; 101:15;110:8;136:9; 169:3;177:17;238:10</p>
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