IMMPACT XXIII - Central Sensitization/Somatosensory Amplification and Multiple Comorbidities

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IMMPACT-XXIII

Research Design Considerations for Chronic Pain Clinical Trials Addressing Central Sensitization/Somatosensory Amplification and Multiple Comorbidities

Friday, July 26, 2019
8:00 a.m. to 2:53 p.m.

The Westin Georgetown
Washington, DC

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

DR. KATZ: Good morning, everyone. For those of you that I don't know, which I think there are very few of you, my name is Nathaniel Katz. I have a very easy and pleasant job this morning, which is to introduce some of my favorite people who are speakers this morning, and I would like to begin with Dr. Srinivasa Raja.

Where are you, Raj? There you are. Everybody I think knows Raj. He's been one of the most longstanding and prolific contributors to the pain field, I would say, someone who I've had the pleasure of learning a great deal from over the years and counting as a professional friend. He'll be speaking to us, introducing the first session.

Thank you, Raj.

Presentation - Srinivasa Raja

DR. RAJA: Good morning, everyone. Yesterday, we started with an incredible journey, almost a full decade journey from the start of the reports of central sensitization to 2019, where we

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have these clinical pain syndromes and overlapping pain conditions.

The task I was given was a simple task of summarizing all of this work and coming up with a design for a clinical study in the next 45 minutes.

(Laughter.)

DR. RAJA: When Bob or Dennis sends me an email or asks me to talk at this meeting, I usually say yes because I think of it as an exercise for my aging brain.

(Laughter.)

DR. KATZ: Then, as I started researching this area and figuring out what I should be saying and summarizing some of this work, I started getting a little worried because I thought I was seeing signs of the shrinking of that brain, especially in the prefrontal cortex and maybe in the hippocampal regions, because I ended up having more questions than answers.

Fortunately for me, I had Helen Keller who was comforting me by telling me that it's okay to have questions. When you have these kinds of

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questions, then you say how do you go about talking to this erudite audience? So like Charlie, I kind of asked Lucy for some advice, and Lucy gave me this advice. "If life seems to have more questions than answers, try to be the one who asks the questions."

(Laughter.)

DR. RAJA: So I think in my presentations, I will provide some perspective, but I also will be asking quite a few questions, hoping that the collective expertise here will answer those questions.

We heard this phrase from Clifford yesterday, "What's in the name?" And I think I have to differ from Shakespeare who said, "A rose by any other name would smell as sweet." So maybe it's true for a rose, but in researching this topic that we're discussing in the last 24 hours, what I came across is this list of names for this condition. This is not an extensive list. It's central sensitivity syndrome; centralized chronic pain; overlapping chronic pain conditions; chronic

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widespread; chronic primary pain; fibromyalgia-ness; nociplastic pain; and many more.

Looking at Steve, I feel like we are in this field where CRPS was more than two decades ago, before things like reflex sympathetic dystrophy, causalgia, Sudeck's atrophy, et cetera, and a single name came up for that. So I think the first thing is the name does matter, and if different specialties refer to those conditions by different names, I think the field will take a lot more longer to progress.

What are you talking about? Is this a condition? Is this a disease? Is it a disorder? Is this a syndrome? Each of those have special meanings. I personally thing that we are dealing with a syndrome, a collection of signs or symptoms that characterize or suggest a particular disease.

You also heard from Roger and several others that this central sensitization has maybe associate overlapping pain conditions. If there's one thing during my long association with Bob Dworkin, that is if you need to make an impact in a field, you

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have to have an appropriate acronym. And that acronym should have at least a word that has some action in it, and it has to have one or more letters that are replicated or duplicated, and it's better if you have a logo that goes with it.

So here's my suggestion, CCOPSS or chronic centralized overlapping pain sensitization syndromes --

(Laughter.)

DR. RAJA: -- and here's the logo that goes with that.

(Laughter.)

DR. RAJA: So the question is why this IMMPACT meeting? What prompted Bob to say that we need to have a 2-day session to consider these conditions such as central sensitization and some somatosensory amplification? One hypothesis I had was maybe there is possibly a central common mechanism for these conditions that is different from acute or chronic thing conditions such as inflammatory on neuropathic pain states. So maybe the central sensitization that occurs in these

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disorders is different from the central sensitization which we know occurs after inflammation or after neuropathic pain. There's some suggestion, based on twin studies, that they may be a greater genetic influence for these chronic overlapping conditions.

An inference of that is that treatment effectiveness in central sensitization syndromes may be unique and may be different from other chronic pain conditions. And hence, if you want to design a study, it should be appropriate for those therapies.

I've long been interested in neuropathic pain, that's been married, and the poster child for the central sensitization syndrome is fibromyalgia. I started by looking at are there differences in terms of drugs that work for these two conditions?

As you've already heard, partly yesterday, the FDA approved drugs for fibromyalgia, duloxetine, pregabalin, and milnacipran, and they are also approved for neuropathic pain states such as diabetic neuropathy, chronic musculoskeletal

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pain; and in terms of pregabalin for diabetic neuropathy, postherpetic neuralgia and spinal cord injury pain. Although milnacipran, I couldn't find a study that's specifically looking at neuropathic pain, at least preclinical studies seem to suggest it's effective in neuropathic pain states as well.

We also heard about other drugs or treatments such as ketamine infusions, which work in about 60 percent of fibromyalgia patients but is also effective in neuropathic pain patients, and studies to show that CBT is also effective in fibromyalgia and neuropathic pain and osteoarthritis. Drugs that are not effective in neuropathic pain states are also not useful in fibromyalgia. An example is NSAIDs, and the Cochrane review suggests that NSAIDs are not effective in treatment of fibromyalgia.

Here are the treatments that are effective for neuropathic pain and are also effective for the poster child condition, fibromyalgia. One can say maybe the drug response or dose-response curves for these two conditions may be different. Thanks to

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Lesley, we have this study where she looked at studies of a single drug, pregabalin, post-diabetic neuropathic pain, postherpetic neuralgia, and fibromyalgia, and this shows the global impression of change is fairly similar in PHN and fibromyalgia in terms of percent responders. Also, the change in sleep quality is similarly effective in both neuropathic pain states and fibromyalgia.

One can then ask the question, is this primarily an issue of assay sensitivity. The trial designs are not sensitive enough to differentiate central sensitization from other conditions such as neuropathic pain?

We've talked about this amplification that occurs in central sensitization and is there difference between neuropathic pain and other central sensitization syndromes, nearly an extent of the magnitude of the amplification or the extent anatomically in terms of where the amplification occurs, such that in post-op pain, maybe the amplifier is turned on slightly, in neuropathic pain, a little bit more, and central sensitization

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or fibromyalgia, it is set to a maximum.

An ultimate explanation may be there's a totally different mechanism for the central sensitization that occurs in neuropathic pain versus the central sensitization syndromes such as chronic overlapping pain conditions.

In developing a clinical study, the basics of it is to define the population that you're interested in, which is the reference population. You have an objective or a primary question that you're interested in. Design the study by picking a study population, including inclusion/exclusion criteria, and then figure out the outcome measures you'd be interested in.

If you have it in a tabulated format, what I hope to do is to pick certain aspects of this one-on-one study design, that is what should be the reference population and what should be the study population; how do they allocate randomly; and maybe the assessment outcome measures.

What should be the reference population for central sensitization and centralized pain? One

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

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

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

They were comparing normal subjects with

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

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

We talked about quite a bit yesterday as to

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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is a Revised Fibromyalgia Impact Questionnaire. So here is a tool that not only can diagnose this condition but also correlate symptomatically with a degree of symptoms. So maybe we'll find out whether it comes out as a tool in the future.

The other question that comes to mind, we had some discussions yesterday, the question of whether we should include or exclude in a study patients with multiple comorbidities such as fatigue, mood disturbances, sleep disturbances, and cognitive changes.

If you are a lumper, you might say that this is part and parcel of fibromyalgia, and they may have a shared mechanism or it's secondary to a consequence of the widespread pain, and that pain relief will also result in improvement of these different factors. If you're prone to be a splitter, you might say this may confound your results, and the interpretation of the results may be difficult.

In the drug study pregabalin in fibromyalgia patients, many of these patients also had

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osteoarthritis, and Charles Argoff did some retrospective analyses on these studies, whereas some patients with fibromyalgia also had osteoarthritis, and looked at dose-response curves, and clearly showed that regardless of all the patients with osteoarthritis or not, the pregabalin was effective in reducing the pain of fibromyalgia.

But the more relevant question that was unanswered is what was the effect of the treatment of pregabalin on the osteoarthritic pain in these patients with fibromyalgia? So you don't know from the study is the drug equally a factor in treating fibromyalgia, and also a factor in treating the osteoarthritis.

The other aspect is that the patients with fibromyalgia are a heterogeneous group. In this study, it looked at more than 1200 patients with fibromyalgia and classified them using cluster analysis into 5 different clusters. Cluster 1 is those who had high pain had severe mental and physical impairment. Cluster 2 had high pain but predominantly physical impairment. There were

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other clusters where there were more mental impairment and less pain.

Then they looked at the efficacy of duloxetine in these different clusters, and the bottom line is that the mental impairment, based on the scales they used, was most attuned to comorbidity, and it influenced the outcome of the drug therapy compared to physical impairment. The better treatment effect of duloxetine they observed are those who had physical impairment and high pain, but not necessarily the high mental impairment.

So the reason for bringing this study is just to say that, fibromyalgia, there are different clusters and there are different degrees of physical and mental impairment, and the efficacy of a drug may vary depending on the complexity of these different conditions.

When we go into a clinical trial, we randomize patients. Sometimes we just do simple randomizations where the whole sample is then distributed into equal groups, a treatment group or

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a placebo group. If there are subtypes or strata, then the population may be divided into subgroups, and then the randomization occurs within each subgroup.

Given the complexity of these central sensitization conditions, my suggestion is to be able to get meaningful information, that we may have to stratify these patients and use the proportional stratified random sampling tool. And the pros of such a strategy would be that it accurately will reflect and represent the population of patients that we are studying, that it will have greater position and may require a smaller sample size and may save money, and may allow us to do subgroup analysis subsequently.

The cons obviously are defining the strata is critical. It requires the ability to classify our patients into subgroups a priori before we randomize those patients. Therefore, it could be more complex to organize, and the analysis may be somewhat more challenging.

The more important question that we may have

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to decide is if we stratify, what are the relevant strata? Should it be those patients who are predominantly a single primary pain pathology or multiple pain conditions? Are these patients who have predominantly, quote/unquote, "centralized pain" where the periphery contributes less to their overall pain or is it a combination of both peripheral and central mechanisms?

These patients who have comorbidities, is it the degree of physical versus psychological features? One would have to then appropriately power these to determine differences across the strata.

In any study, you have a primary question that you are interested in answering. I can think of two questions here. One, is drug A effective in patients with central sensitization syndrome regardless of their primary pain presentation? So regardless of where they are, irritable bowel syndrome, or fibromyalgia, or osteoarthritis, is the drug equally effective across conditions where there is central sensitization?

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The second question could be, drug B, does it help understand the neurobiology of central sensitization? That is, are the mechanisms of central sensitization different from neuropathic pain? Does this drug work specifically on those patients who have central sensitization that is different or somewhat unique in some way compared to other conditions such as neuropathic pain?

To answer question A, you may enroll all patients with central sensitization regardless of their primary pain pathology and presentation and study the efficacy of the drug at multiple pain sites.

For question B, you may enroll all patients with central sensitization, but stratify them based on whether there is solitary or multiple pains and compare these patients with a patient group of neuropathic pain states so you can do a comparison of whether these drugs are better or more effective in central sensitization conditions compared to neuropathic pain.

So we've talked about study designs

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primarily from a perspective of randomized control trials. I liked the cartoon that says, "Do you know about any RCTs that provide evidence that we should use RCTs?" The question, in looking at people who know more about clinical trial designs than I do, I came across these two cohorts that carefully conducted observational studies may provide more evidence than poor RCTs.

Unfortunately, a perfect trial can only exist in our imagination. Maybe RCTs may not be the best or only solution, and maybe a multicenter trial with large registries of patients may be also a useful tool in studying the central sensitization syndromes.

What are the outcome measures that we should be studying in these patients? Obviously, a long time back, the IMMPACT II suggested 6 core outcome domains such as pain, physical functioning, emotional functioning, global impression of change, symptoms and adverse events, and participant disposition.

These are appropriate for studies in central

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sensitization, as for any other pain condition. The other outcome measure that's been used in fibromyalgia studies, particularly -- and I know Ian and Lesley had used it in some of their studies -- is the Fibromyalgia Impact Questionnaire, which I'll talk about in the next slide. Others have talked about symptom clusters, and obviously other measures could be QST measures such as temporal summation and CPM, or conditioned pain modulation, imaging, and other biomarkers.

So these could all be outcome measures. At this stage, I'm going to just touch on the IMPACT questionnaire. This was initially brought about in the end of the last century, but then revised subsequently. It consisted of 21 questions, and it was shown that it could separate fibromyalgia patients from rheumatoid arthritis, SLE, or healthy controls.

Subsequently, in the revision, there were four other new symptom measures that were introduced such as memory, tenderness, balance, and sensitivity. There are 21 items across the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(No response.)

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

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

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

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

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

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

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

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Claudia in the next presentation.

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

(Applause.)

DR. KATZ: Thank you very much, Raj.

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

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

Presentation - Claudia Campbell

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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measure that tries to get at general sensitivity as opposed to central sensitivity.

Several groups have done profiling and tried to do cluster analyses to try and get at these differences. Yvonne Lee and colleagues, I believe out of Dave Williams' lab, found these three distinct clusters where -- oh, I should point out, on the X-axis, you have these more physiological variables, and on the Y-axis you have your more psychosocial variables. On the X-axis more is worse, and on the Y-axis, less is worse.

The first cluster has the lowest pain, lowest swollen counts, least psych issues, while the third group has the highest objective findings, but more moderate psych issues, whereas the second group, they have the lowest objective findings but the highest widespread pain inventory and the most psych issues.

What I thought was interesting here is that they're all reporting around the same level of pain. Everybody's reporting around a 3 out of 10 on the BPI. But they do have quite different psych

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variables, and how those factors are associated with their clinical findings are different.

Almeida and colleagues did something similar with pressure pain threshold testing. What I thought was interesting here was that they used pressure pain at a number of different potty [ph] sites, so they weren't just targeting specific areas where people had pain. You can see that folks in this first cluster have high pain sensitivity and the worst psychosocial distress. Not surprisingly, those folks had the most pain and the worst disability with their musculoskeletal pain.

I added this last night because I felt like we were talking a bit about OPPERA, and somebody had asked about clusters that OPPERA has looked at. Of course, they have an enormous data set, and it probably won't surprise anybody to know those with global symptoms. So they've got all this stuff.

Most of the TMD patients fell into this group. Those healthy folks that were in this group were vastly more likely to develop TMD and other

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symptoms as opposed to those in the adaptive cluster, which were characterized more by higher prevalence and healthy folks and less pain. Interestingly, there is another cluster, the pain sensitive cluster. They had the highest QST findings, but not as high on the psychosocial and physiological symptoms as I might have suspected.

The terms seem different. How might we measure one versus the other, and do we really need to measure them both? It feels obligatory to say something about chicken and egg and which comes first. There has been quite a bit of discussion about that here. The literature seems fairly convincing that psychobehavioral factors do seem to contribute to the risk of developing pain and likely maintaining it.

OPPERA and other studies, there's been well over two dozen QST studies looking at postoperative pain and trying to understand how those physiological alterations might predict the development of pain, while other studies have challenged that idea and say that, well, these

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preexisting sensitivity issues may modify and perpetuate pain, but may not actually initiate them.

I'm interested in laboratory pain testing. We talked a little bit about capsaicin yesterday. We did this laboratory study in healthy folks where we put capsaicin on the back of the hand. Capsaicin is the active ingredient in hot chili peppers. It produces this burning sensation that increases over about 30 minutes.

If you measure pain and catastrophizing repeatedly, you can do what's called a cross-lagged panel analysis. While it's not a test that I would say specifically addresses causality, you can try to understand what proceeds and try to get a temporal understanding of some variables.

You can look at how pain changes from early to mid, and then mid to late, and how that's associated with catastrophizing changes. We've been talking about catastrophizing a lot. We know it's a potent predictor or potently associated with pain outcomes. In this particular study, we did

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

They compared emotional awareness and

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expression therapy. If you're not familiar with that, you can think of the Feats of Strength in Seinfeld or Festivus, where you kind of get out your emotions with your family, anger, and it's more productive than that, but that's the idea. Anyway, they did not find substantial difference in most pain outcomes compared to CBT, but they did find that emotional awareness and expression therapy improved

self-reported pain reduction and very much improvement on Global Impression of Change Scale.

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

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

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

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

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

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

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

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

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

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

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

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amount of healthcare utilization as the low CS group.

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

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

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So is there value in being able to show there isn't widespread or peripheral somatosensory amplification? Should we just be getting those CS variables when we're talking about a QST battery? If we're going to recommend that for folks, do they only need to be doing temporal summation and conditioned pain modulation?

It turns out they're pretty closely related, more so in chronic pain patients than healthy controls. If you have this continuous measure of central sensitization from those CS QST variables versus general QST sensitivity, you see they are pretty highly correlated.

Now, we were really interested in opioids, of course, sickle cell disease. If you split the group into those on chronic long-term opioid therapy versus not, not surprisingly, you see a lot of differences in pain, proportion of days reporting a crisis, and crisis pain. I was wondering if they are just generally sensitive; they're sensitive to everything no matter what we do and what we look at.

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But that wasn't the case, and I think some of the value in trying to get some of these other QST variables can go to show that kind of difference. The folks on chronic opioid therapy had a higher central sensitivity index, but not general sensitivity. They were pretty much the same on those variables with their non-chronic opioid therapy counterparts. It seems like there's something maybe special about that.

I wanted to come back to this quantifying QST a little bit. This is in a different cohort. This is knee osteoarthritis folks, and this is what their QST data looked like. That's a lot of data. We ended up averaging that into those CS variables and those that were QST variables not including the CS. I like that as a way to condense these kind of data and think about them a little bit differently.

The other method for doing that, we've talked a little bit. I think Rob showed a Yarnitsky's pain modulation profile and how that could be used. So I went ahead and calculated that in some of our data. Looking at taking temporal

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summation, if they summate, they get a 1; if they don't summate and stay the same, they get a zero; and if they habituate, they get a negative 1. Doing the same thing with CPM, if it's efficient, they get a negative 1, and you have to reverse it.

I was curious to see how those measures stacked up and how they were similar. Again, in Rob's total knee replacement data, we found a higher correlation in central sensitivity index with this pain modulation profile, not surprisingly, that's what we found with general sensitivity.

I was curious what mapped on closer to pain in this group, so trying to understand BPI, widespread pain inventory, symptom severity, and it seems like -- well that doesn't seem like. The only variable that was associated with those was this measure of general sensitivity. The central sensitivity did not map on as I might have thought. So it does seem like there's value in trying to understand general sensitivity as opposed to just these temporal summation and CPM variables.

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I'm not going to get in much to the point about samples. Raj just spoke very nicely on how we might do that. I will say just from a practical sense, it will be a whole lot easier to recruit, make things more generalizable, and probably much more meaningful to include folks that have these overlapping pain conditions instead of just our treatment of choice or our disorder of choice. Now, whether funding bodies, reviewers, and FDA are going to be on board with that, hmmm, but it does seem like stratifying those groups, as Raj was mentioning, makes a whole lot of sense.

Should we subgroup or classify participants in any kind of way? We know that QST has been associated with outcomes for a lot of different medications and suggest analgesic benefit. There have been a number of reviews there. I should mention that all of these measures were not specific to central sensitization, so it wasn't just temporal summation and CPM that was used in all of these different trials.

Quantifying sensory function might be

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

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

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

We've been talking about a whole lot of

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

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

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

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

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

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

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pedometer or something like that for some amount of time.

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

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

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

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it, on a continuum. I've been wondering if the distribution of those factors matter, and if there's any kind of meaningful way to put it together.

I was wondering if we can take a note from our cardiovascular colleagues. They've had a lot of, I don't know, I think success in getting to the lay public about what the risk factors are for cardiovascular disease. Maybe I'm just responding to the nice rainbow-ness of their information, but I was wondering about the way we present data, and we typically don't present it, I don't think, in a very user-friendly fashion.

So I was wondering, well, if we have all these baseline factors, and we kind of bend them into some logical things, so clinical pain, function, laboratory markers, some kind of sensitivity, and then our space variables, is there a way to show an additive effect? So this person has 20 of these issues while this person only has 3, and is there a way to make sense of that?

I was just playing around with this. It

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might be completely outside the scope of this meeting, but it just got me thinking, well, when I read one of these papers, I usually don't know if something got a little worse for one pain area or got a little better for another, or some of those space variables improved over time.

When I think about trying to see what kind of recommendations we would make or what kind of advice I would ask of you all experts, I'd be curious to know if we are at the point where we think we can reliably subgroup people and treat them differently or if we're still at the point of, well, let's phenotype everything and see what shakes out later.

It feels like somewhere in between might be right. What predictors, what outcomes? Is everything both? Should we recommend using QST? QST is my bread and butter; that's what we do in the lab. I'm really interested in it, but I'm sort of an egghead like that, and I don't know if it makes sense to really be having our clinical colleagues trying to do that kind of thing,

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especially when we heard yesterday we're not really at N of 1 anything.

How should we present data if people are going to do it? Is there a way to reduce that to make it more meaningful and compelling? Is there a better way to show what variables are impacted by others and vice versa? I want to thank all of my colleagues, collaborators, mentors, and you all for your attention. Thanks.

(Applause.)

DR. KATZ: Thank you very much, Claudia, for a very thoughtful and comprehensive presentation.

It is time for a break, so why don't we go ahead and take that break, and we'll resume promptly at 10:00.

(Whereupon, at 9:28 a.m., a recess was taken.)

DR. KATZ: Hello again, everybody. Thanks so much for being here promptly at 10-ish. Our next presentation will be given by Dr. Lesley Arnold, who I've had the pleasure of collaborating with on a number of different trials in

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fibromyalgia and who has been, as you probably all know, one of the major contributors to clinical research in fibromyalgia for a number of years now.

That will be our next presentation, then after that, we'll have time for discussion.

Presentation - Lesley Arnold

DR. ARNOLD: Thank you. It's been a pleasure to be here, and I've learned a lot from all of you over the last couple of days. As many of you know, I spend a lot of my time doing clinical trials in patients with chronic pain, especially fibromyalgia, so I'll be mostly speaking from my experience in working with these patients. We have made a lot of progress in identifying new treatments for patients with chronic pain, but I'm hoping that what we're learning about centralized pain will advance our studies and open up more treatment options for our patients.

I thought before I got into dealing with this problem of comorbidities, I'd thought I'd share with you a typical day in the clinic with you, just to give you an idea of what we're talking

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

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

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

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

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

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

My next patient was a single woman. She had

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

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

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

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pain, which we know affects cognition.

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

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

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

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it really affects the prognosis long term. It definitely adversely affects it.

So that's something else to think about when you're thinking about including a patient in a clinical trial, how do we address that problem? Do we exclude people who have PTSD? Does it affect the prognosis? Yes, it does. So again, something to think about when we're trying to decide what patients to include in a clinical trial.

My next patient is an 18-year-old woman. She had participated in one of our juvenile fibromyalgia studies. She decided to stay with me as a patient, so I've been seeing her for many years. She had migraine as a comorbid pain condition, but she also had very severe psychiatric comorbidity. Her depression led to suicidality and multiple psychiatric hospitalizations, so she has struggled some, mostly, with regard to the comorbidity of depression.

Finally, my last two patients, I had a 74-year-old woman and one of my existing patients. She also struggles with overweight. She has more

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significant medical comorbidity with regard to diabetes, neuropathic pain, and coronary artery disease. She also has osteoarthritis, so, again, multiple sources of pain and also comorbid depression.

Then finally, another new patient referred by a rheumatologist, a younger woman with just a one-year history of symptoms. She also had problems with obesity and spinal disease, and then she had a couple of the chronic overlapping pain conditions, irritable bowel syndrome and TMD. She had an eating disorder as a psychiatric comorbid condition, which is a little less common in the fibromyalgia population but it does occur.

I hope that gives you an idea of what we're dealing with when we're talking about comorbidity and how that can impact our clinical trials.

These are some of the more common chronic overlapping pain conditions that I see in my patients: irritable bowel, chronic headache, interstitial cystitis, temporomandibular disorder, chronic pelvic pain, and low back pain. There are

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some other ones, but these are the most common that I see.

Again, as we've been talking about, they may be linked by some common pathophysiologic problem, but as we've seen with my patients in the clinic, they have other comorbid conditions that are associated with pain: osteoarthritis, degenerative disc disorder, spinal stenosis, and is very challenging sometimes to figure out what is contributing to their pain experience and how to target our treatments.

Neuropathies are very common in the population, radiculopathies, and we've heard about other rheumatologic disorders. Ehler-Danlos we heard about yesterday. That's a very common problem in my patient population. Then again, the issue with obesity, sleep disorders, especially obstructive sleep apnea, and then depression and anxiety, all of which are associated with pain.

Over the years, we've worked to design clinical trials in fibromyalgia to help advance the field, and we have had success. We have three

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FDA-approved treatments, but we still need to do more work, and we need to expand access to treatments for all patients with these pain disorders. But there's an effort usually in a clinical trial to reduce heterogeneity if we can, and to try to focus, at least in the fibromyalgia group, on patients who have fibromyalgia as what we think is their primary pain problem.

This is a typical, cut right out of one of our trials, exclusion criteria. It says, "pain due to diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, prior surgery, complex regional syndrome, or other source of pain."

By other, it's not really specified, and does not specifically exclude those other chronic overlapping pain conditions. But it's up to the investigator's judgment because it says "in the investigator's opinion, the presence of these other pain conditions would confound or interfere with the assessment of the subject's fibromyalgia pain or require excluded therapies during the participation."

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

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

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

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

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

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

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

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

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

We typically exclude suicidality for obvious reasons and then also substance-use disorders. We're faced now with a new problem of people taking cannabinoids as these become legal in many states. It's becoming a challenge of how to manage that in

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

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

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

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again, in a clinical trial, we're trying to look for a signal, so we do try to reduce the variability in the population as much as we can.

Then generally, patients, as far as other medical comorbidities, have to be reasonably stable. Other medical diseases, sleep apnea, all of these things, have to be treated and stable, so in general, the clinical trial population is going to be healthier and less severely affected.

Coming back to then how we view comorbidities when we're looking at our outcome measures, we heard a lot about this earlier today. How are we assessing outcomes, and are we taking all these sources of pain into account when we assess pain severity?

Typically, in a fibromyalgia trial and other chronic pain trials, pain severity is the primary outcome measure. It's typically average pain severity usually measured once daily, in the evening or in the morning, depending on the trial. It's a simple numeric rating scale, 0 to 10, no pain, to 10 being worst pain, or pain as bad as you

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can imagine.

That's all we're giving patients. In some cases, there is some education provided how to rate that, but in most cases, not. I've had patients come to me during a clinical trial and they'll say, "Well, I know I'm here for fibromyalgia pain, but I wasn't sure. Was I supposed to rate my headache with that? I had this knee pain from my arthritis. Am I supposed to rate that, too, when I'm measuring my pain severity?"

So there's a lot of confusion out there, and I suspect a great deal of variation in the pain scores based upon how patients view this. So I think we need to do a better job of figuring out how the presence of these comorbid disorders can affect pain ratings. Maybe there's a way to develop some consensus around that so that when we have a clinical trial, we're educating the sites on how to present these scales and teach them how to use the scales. We might have a better effect if we do that, but I think it's an open question.

When we design these trials, one idea -- and

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this is what we're kind of trying to address -- is centralized pain disorder. You think about fibromyalgia as representing centralized pain that is the end of the continuum, and that these other chronic overlapping pain conditions might be related based upon the presence of this centralization.

I'm quoting Dan here from his slide set earlier yesterday that the phenotype is quite clear: multifocal pain and other CNS symptoms, and in some cases, hypersensitivity to other sensory stimuli. We know that, and that actually is how we define fibromyalgia.

This was an effort to educate primary care clinicians on how to diagnose fibromyalgia and how to simplify it for the clinician. It really emphasizes the chronic widespread pain or chronic multisite pain, however you define it, and then fatigue and sleep disturbance.

In this triad, we were trying to educate our fellow clinicians that If you see this in the clinic, think about fibromyalgia as a possible

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diagnosis. And of course, these other symptoms are very important to assess, but the idea was to just have them focus in on these three symptoms, and that might improve the recognition of fibromyalgia in the clinic.

Through the work at AAPT, we took that and tried to create a little more simplified diagnostic criteria for fibromyalgia that included multisite pain, moderate or severe sleep problems, or fatigue, and then symptoms present for at least 3 months. This is, again, an effort to try to improve recognition of fibromyalgia in the clinical setting, and we were able to reduce the number of painful sites to 9 possible sites, and then 6 out of these 9 would be a positive result.

This would be fibromyalgia at the end of the continuum, but as we've seen, it may also be useful to look at a more continuous measure. As Dan has proposed and has been doing for other trials, adding a sum measure of fibromyalgia, whether it be syndromal or subsyndromal, might be important in picking out those patients who have centralized

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

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

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

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

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

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

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

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

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

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

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

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

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

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There are a lot of other issues to consider. We've talked about some of these. Catastrophizing has come up a fair amount. In my clinical experience, we looked longitudinally at different factors that predicted outcome and controlled for all of these different factors: medications used; presence of opioids; whether patients were obese or not; whether they use opioids; a lot of factors.

The only thing that really predicted a poor prognosis was the presence of catastrophizing at the beginning of the study. But the problem is the patients who entered our study already had pain, so I don't know when the catastrophizing started, if they had it before they developed pain, or if it developed after they developed pain.

Nonetheless, it seems to be a sign of a poor prognosis, so maybe we need to identify this in a clinical trial, which we've never really done. We've never looked at this in a medication clinical trial, to my knowledge, one of the big programs for indication. Maybe we need to. Maybe we need to consider that in our inclusion/exclusion criteria.

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There are a lot of other factors that go into designing a trial such as lifestyle factors, stressors, disability, we discussed, and then function. I just want to bring you back to the function piece because we do assess function in our clinical trials, but it's usually one of the secondary outcomes.

I think we can do a little bit better with that, maybe. We've worked on developing response indices that include function potentially as a primary outcome. Some of the trials in the past have tried to do that. I think we need to do that a little bit better, and maybe include indices that have functioned as part of it, and then also includes not just pain but maybe sleep, and fatigue, and some of these other very important symptoms so that we really get a good feel of how a drug is working on these multiple domains of fibromyalgia, because we know this condition has a profound impact on people's lives; socioeconomic consequences. We've tried to track these in some of our trials, but I think we can do better.

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In summary, fibromyalgia is a prototypic centralized pain state. The assessment for the presence of fibromyalgia symptoms, that is centralized pain, may be important in trials of all chronic pain disorders. Identifying these overlapping pain conditions and tracking their response to treatment may be helpful in establishing new therapies.

For example, TMD, we really haven't done a lot of medication clinical trials in that condition, and maybe adding some outcomes, again, in an early-stage program, we might get some cues that a new medication might work for these other COPCs; and phenotyping, based on the presence of comorbidity, and using some of these more advanced techniques, might help to identify individuals that are more likely to respond to a particular therapy. Thank you.

(Applause.)

Q&A and Panel Discussion

DR. KATZ: Let me invite all of our speakers from this morning's session to come up and join me

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up here on the panel.

Friedhelm, why don't you come and join us, please, as well? We have an additional member of our panel, Friedhelm Sandbrink, who runs the pain program at the VA, who will be joining us for this discussion.

We have an hour and 15 minutes. What I would like to do is see if we can discipline ourselves to start with clarifying questions about the presentations. So if anybody has any questions or comments about specifically what was presented. I'm not sure how long that will take; probably not that long. Then we can try to move into identifying what the key questions are that we need to answer at this meeting to see if we can come up with some clear answers.

So I'll ask the panelists, while we're going through the initial part of this question and answer, to begin to think about what you think those key questions are and see if we can start to define some answers. I think, Dan, you had your hand up first, and then Ian, and then Lee.

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DR. CLAUW: Yes. This is probably more of a public service announcement than anything else. A couple of years ago, the NIH gave a contract to Bill Maixner and Dave Williams from our group to create a screener for COPCs, and that is almost done. It will be publicly available in the next couple of months. But this will make it a lot easier, in the context of a trial, to screen for all 10 of the chronic overlapping pain conditions in a very short period of time because it asks a couple of leading questions that can say, okay, is it possible the person has irritable bowel? Then it gives the actual criteria for each of the chronic overlapping pain conditions.

So it will be the first time in an easy way that people, at the beginning of a trial, could say which of these 10 COPCs someone has. And I do think this would be an incredibly useful thing in phase 2 of an industry trial because you might then see chronic overlapping pain conditions that you have efficacy or effectiveness, that didn't even anticipate might be something that you would be

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going towards with respect to an indication.

I think when it's super easy to do it, like it will be, I would recommend that people start doing that.

DR. KATZ: I think it's worth taking a minute and diving down that rabbit hole one step further since hopefully, we'll come up with actionable recommendations at this meeting.

Dan, just made a recommendation, which is that -- I'll try to paraphrase it, Dan -- routinely in chronic pain clinical trials, we should include a screener for these chronic overlapping pain conditions so that we can -- if I can expand on what you said -- better characterize our populations at baseline and even determine whether there's an impact of therapy on these conditions that may or may not be the primary focus of the clinical trial.

Is that a reasonable paraphrase?

DR. CLAUW: Perfect.

DR. KATZ: Okay. Who thinks that's a bad idea?

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(Laughter.)

DR. KATZ: Lee Simon. Anybody else think it's a bad idea?

John, you think it's a bad idea?

DR. MARKMAN: I would want to understand -- in a lot of these clinical trials we do now, we have these tools that we incorporate to exclude mimicking disorders. So I guess some of those tools incorporate some of the questions that Dan is talking about, but they're a little more disease specific.

On a peripheral neuropathy trial for idiopathic peripheral neuropathy or diabetic peripheral neuropathy trial, you have a mimicking, overlapping disease tool, which is specific for neuropathy; so osteoarthritis of the foot, peroneal nerve entrapment, blah, blah, blah, but also all of these other disorders.

So I guess the only tension there would be between one which is more tailored to the indexed condition that you're studying versus one that's sort an off-the-rack solution for all trials.

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That's the one tension I see.

DR. KATZ: Okay. Great. I think we can probably all agree that those two goals can live together, and that we'll need to do what we need to do to clarify what the actual primary diagnosis is, and make sure it's not one of these imitating disorders, and at the same time track all of these comorbid conditions.

We're still just focusing on Dan's proposal. Lee, do you want to explain your objection to his proposal?

DR. SIMON: It's not an objection. It would be great to have this evidence that you accrue in academic explorations of experiences to progress and further understand what populations we're looking at. But Dan went so much further to suggest that maybe using it in a phase 2 trial would be helpful.

It might be helpful, or exclusion/inclusion criteria, to define your population better, but it is not an indication. And that's actually one of the issues that we have to discuss; how does one

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put a box around what we're looking at to determine how to define a primary outcome for a disease state?

Industry is interested in getting drugs approved. I can't even imagine, based on what we've heard this morning, how that would happen, based on what we've heard this morning. And yet I really believe in central sensitization and I think it's maybe even driving the argument that chronic pain is a separate chronic disease, but we have to define that better. It's possible that Dan's work would allow us to do that, but academic work, not an industry-sponsored trial yet. That's my objection.

DR. KATZ: Mike, go ahead. Use the mic, please. Oh, and I forgot to remind everyone to say their name first.

DR. ROWBOTHAM: Mike Rowbotham. The screener that is being discussed in the whole presentation yesterday on COPCs is really quite different from what Lesley was saying, which has been my experience recruiting for trials; patients

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come in, and they've got all sorts of things wrong with them.

If you ever want to recruit a patient into your trial, especially fibromyalgia patients, you kind of have to downplay some of those a little bit. And the patients certainly do because they know what the inclusion/exclusion criteria are, and they tailor what they tell you so that they're not going to get kicked out right away.

She may want to comment further on that because that's a really tough issue.

DR. KATZ: Lesley, you were invited to comment further on that.

DR. ARNOLD: Yes, I agree, it's very challenging. I don't think it's just the patients who downplay it. I think some of the investigators -- you know, sometimes we just have to deal with this comorbidity, and we do the best we can. But I was thinking and proposing that maybe we just characterize the patients better and acknowledge that these patients are in our trials, and then find a way to determine, at least at

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early-stage programs, to see if the presence of these comorbidities affect our outcomes are not. They may not.

If these are linked by centralized pain or sensitization, whatever you want to say, maybe they would respond to the same treatments; I don't know. But my proposal is to, well, come out of the closet a little bit about it and just characterize the patients better that we're putting in our trials.

DR. KATZ: So still focusing on the issue of whether we should be tracking these comorbidities in clinical trials, I have John and then Clifford, and then Steven.

DR. FARRAR: I think there's a push and pull here. There are conflicting components to this that I think Lesley raised very well, which is that you can't exclude everybody. You can't find the one person with only centralized sensitization and nothing else because it doesn't even make sense. On the other hand, there are a group of patients that you do want to exclude, people with significant psychiatric abnormalities.

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So I think one of the tasks in front of us with regards to this issue of coexisting problems and comorbidities is trying to decide which of that group need to be excluded because they will add so much variability to the measurements that we do, that we can't determine what actually happens versus the ones we include, as Lesley was just saying, and try and deal with as we go through.

I was struck by something that was presented -- to, I think Dr. Campbell presented it -- with regards to a study that she was looking at where the depression and anxiety measures did not change, whereas some of the pain measures and other measures did change.

I think some of what we are going to need to deal with is to get and look at some of that data to understand whether we can include people with depression, anxiety, or whether we need to measure it. I mean, we certainly need to include them, but the point is how to measure it and how to think about it, and what we decide to do if both of them get better versus one not [sic] getting better and

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one not.
So I think the key issue here is trying to dissociate what we can include, stratify, and look at versus the things that we really can't because of the problems that it would impose on the study.
DR. KATZ: Clifford?
DR. WOOLF: This is a question to the panel, the extent to which the presence of these comorbid features are stable, do they change? When you have your patients -- it looks like a very busy day you had -- when they come back, is the pattern the same for every patient, or for someone who has IBS, does that disappear? In which case, this can make the dynamic nature of that and will add some complexity.
DR. ARNOLD: Well, I think, sadly, things stay pretty much the same over time. There is maybe improved coping and living with symptoms, but as part of my clinic, I included the FIQR, the Fibromyalgia Impact Questionnaire, and they fill it out every time they come. It's disheartening sometimes to see how little symptoms change over

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time. Maybe, again, their coping improves or their adaptation to their symptoms improve. Maybe there's a slight movement of these symptoms. But it's really -- again, my patient population is tertiary care, so you have to keep that in mind. But typically, there's not much movement.
DR. KATZ: Although, Of course, if we don't capture it, we don't really -- there could be -- if there was a 40 percent improvement in something, we would probably never know it. It's hard to figure out if people's symptoms are improved without capturing the data.
DR. BRUEHL: This is talking about Dan's proposed overlapping pain measure, but I'll frame it as a question. The measure seems to be something that would be very detailed and characterizing diagnostic criteria for a whole variety of potential overlapping pain conditions. But listening across all the presentations so far, it sounds like the reason those are important presumably is because they all reflect some underlying mechanism; and that what we're really

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focused on is pain.
I'm wondering if we're over complexifying by trying to do diagnostic criteria for a whole variety of disorders rather than simply focusing on number of pain sites, which would be a surrogate, because if you've got IC, you've got pain in the pelvis. If you've got migraine, you've got pain in the head.
That would show up in a really simple measure. And pragmatically, if you're trying to do trials, would it be easier to say a cutoff out of a number of pain sites at least 4 rather than saying how many in which of the specific conditions you'd have. And I guess I would like comments from the panel as to what they would think of the value of being more simple versus more detailed.
DR. KATZ: I think I'm hearing you ask, in addition to a body map, which was a recommendation that floated up yesterday, what additional information is provided that aids in our understanding of these patients by looking at their medical comorbidities, either as a snapshot in time

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or even past through time?
Does anybody have an answer to that question in terms of what additional information is added by the comorbidities? Dan?
DR. CLAUW: Yes. So again, I was implying that you would use this in addition to a body map, not instead of a body map.
DR. KATZ: Yes.
DR. CLAUW: And the reason that I think it's a good idea is that I think that probably half of those chronic overlapping pain conditions don't even currently have a single approved drug. Many of them are visceral pain conditions that are part of trying to get to a chronic pain indication.
And I do consult with a lot of people in industry, Lee.
DR. SIMON: I know you do.
DR. CLAUW: And I think they have often struggled in phase 2 to figure out what conditions their drugs might be effective, and a lot of them are looking and wondering is there a visceral pain condition my centrally acting analgesic might work

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

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

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

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

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musculoskeletal pain got better, but my IBS didn't get better," or my migraines didn't get better. That would be great. I don't think it necessarily has to be at any particular phase because it's going to be a secondary measure anyway.

But the key thing for picking a good subject from a not so good subject, or a subject you really don't want to have in your trials, is whether or not they can be reliable and understand what it is they're rating as opposed to just giving you this kind of global thing of, "Well, I just don't feel good, so therefore even though my FM pain is better, I'm still not happy," or I still don't feel good, and therefore they rate the drug as ineffective.

DR. KATZ: I totally agree with that.

Lesley, did you want to add anything to that?

DR. ARNOLD: No, I totally agree with that. As I was giving an example of a patient who came back and asked me what she was supposed to be rating all this time, her headaches or not,

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clearly, ideally if a patient can differentiate the different pain disorder sources, that would be ideal, but it might be better to, maybe again as secondary outcomes, specifically ask about their IBS pain or their headache pain to separate it out.

I think most people with fibromyalgia understand the widespread achy nature of the fibromyalgia, and they can focus on that, but it can get a little tricky there, too, because I don't know if their low back pain is related, or I don't know if their joint pain is centralized pain, or a mixture of factors.

I still think the pain severity is an important primary. I think your programs, and educating patients, and teaching them how to use the scale is good in the beginning and maybe adding some more specific questions about other regional pain disorders might be helpful as secondary or exploratory.

DR. KATZ: In our experience developing these training programs, it's amazing how often when you sit there with a sponsor and try to

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finalize a program, that reveals lack of clarity about what the sponsor is actually asking the patient and the question in the first place. So putting together these training programs is useful not only for the patients, but also to clarify what is it exactly that we're trying to elicit.

Rick, you were next. Just say your name into the mic, please.

DR. MALAMUT: Hi. Rick Malamut at Collegium Pharma. I have so much to talk about now --

(Laughter.)

DR. MALAMUT: -- just since I've raised my hand. But I'll start from the beginning, which was John's comment, that totally agree we're going to have to include comorbidities in these studies. It's going to be difficult to find that perfect patient, much less a hundred, much less more for phase 3, who meets our predefined criteria of not having too many comorbidities.

I think it's doable to have them in the study. We may want to set limits as to severity. I agree that maybe severe psychiatric

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conditions -- we have to define that -- may not be the best study patients. Then there are validated scales for some of these; for sleep, for mood, fatigue. It's easy enough to watch those, to attract those, assuming our primary endpoint is a pain outcome. We just have to make sure that our primary endpoint is going to be reliable to make sure the patients can actually reliably tell us that their pain is due to the index condition we're studying.

Then, I have to go back to Lee's comment. I agree with you that some of my colleagues in pharma do try to go too quick, and try to jump from phase 1 to phase 3 without adequate phase 2. Phase 2, as everyone knows in the room, is where studies go to fail. Phase 2 is often thought of as maybe we can use this for registration purposes, but phase 2 is where we learn.

So I would suggest that phase 2 for this type of condition is the most important study we run. It's where we look at our population. We look at our outcomes. We see, okay, are these

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viable? We look for those subpopulations. If we have a patient with fibromyalgia who also has TMD, we look to see, did that patient in the subpopulation analysis get better? Do they do worse? And that all helps to guide us with our patient population for phase 3.

I agree dose is important, but it's a little more than that, and we can talk about biomarkers later.

DR. KATZ: Howard, you were next.

DR. FIELDS: The thing that jumped out at me, particularly in Lesley's talk, was how the patients who were rated high in catastrophizing seemed to do poorly in terms of outcome. That raised to me the issue of is that a comorbidity or is that a feature of the primary condition you're trying to treat? If the latter is the case, you might want to exclude them to have a successful trial, but then it might turn out that the drug isn't that effective clinically.

So I'm kind of glad that we have the particular expertise. I was looking over at you,

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Roger. You seem to raise the possibility that catastrophizing, whatever the neurobiological mechanism is, could actually have a causal role in the condition, or maybe I misunderstood what you said.

DR. FILLINGIM: Well, I think that catastrophizing, along with other psychological factors, could have causal influences on manifestation of the condition and potentially on responses to therapy.

DR. FIELDS: So it's not comorbidity; it's part of the disease being treated.

DR. FILLINGIM: Could be, yes.

DR. FIELDS: Okay. I just raise it because it seems to me to be one of the core problems in clinical trial design.

DR. KATZ: What's the comorbidity versus what's part of the actual disease that we're treating? Yes.

DR. FIELDS: Yes.

DR. KATZ: Roger, did you want to add another comment? You had your hand up.

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DR. FILLINGIM: Yes. I had a question. Mike just brought up, and I think you confirmed, the importance of training participants and retaining the ones who are good participants. Do we have a sense that the presence of multiple overlapping pain conditions, or central sensitization, somatosensory amplification, or catastrophizing is associated with being a bad participant, and thus being at risk of being excluded from trials? Because that seems relevant to the discussion here.

MALE VOICE: What's a bad participant?

DR. KATZ: Roger, you asked. What's a bad participant?

DR. FILLINGIM: Somebody who rates so poorly or fails to meet whatever criterion you selected for being a good participant.

(Laughter.)

MALE VOICE: I don't know what that is.

DR. KATZ: Okay.

MALE VOICE: Probably the biggest problem is inconsistent.

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DR. KATZ: What we do know, or at least what I know about that, is that we actually have looked at catastrophizing as a predictor of pain reporting accuracy in some of the studies that we've done. We have a whole way of defining pain reporting accuracy, which I won't bore you with. The patients who were catastrophizers were actually not bad at reporting their pain accurately, as it turned out. We thought they would be, but they weren't in. In one or two studies where we looked at the Pain Catastrophizing Scale compared to experimental pain reporting consistency, if you will, it was not a bad predictor.

Bob?

DR. DWORKIN: Nat, you recently published that the people who report variable pain during your baseline period seemed to have less internal focus, as I recall, than the people who, to use Jim's phrase, are more consistent. Then my question is, is there any relationship between internal versus external sensory focus and catastrophizing?

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

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

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

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

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there's some additional information that can be gained by measuring comorbidities. We have Dan's tool that will come out eventually. It could used for that purpose.

A number of people mentioned and a number of important potential unintended consequences of that or a caveats, such as how that's going to impact our inclusion/exclusion criteria for these trials once you started revealing that these patients in fact do have comorbidities that we might have been happier to sweep under the rug before, and some other caveats as well. And those caveats need to be considered as well in making that decision.

That's what I got out of that whole conversation. I think we can move on to other questions or comments about the presentations. Ian?

DR. GILRON: Ian Gilron from Queen's in Canada. First of all, thanks to everyone for amazing talks this morning. My question relates to Raj's what's in a name and how it leads to identifying participants for a proposed trial.

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This is not a rant, but let me just unpack it a little bit. It seems to me that the important distinctions here, dealing with central sensitization or whatever we might call it, are do we have sensitization or is the sensory nervous system normal? Is it central versus peripheral sensitization? Is that important? And is there a known source of nociception versus no identifiable source of nociception?

I'm thinking back to what was done in neuropathic pain. For example, in 2008, Rolf-Detlef Treede and Charles Jensen and others were working on a grading system for diagnosing neuropathic pain, using an approach with history, physical, and as needed, special investigations to come up with a designation of probable neuropathic pain likely or -- sorry, definite, probable, or likely neuropathic pain, and I wonder if we need that here.

So my question is must we, or should we, include an objective or at least clinician observed measure to confirm sensitization of the nervous

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system, for example, such as QST patterns compared to population norms as an inclusion criterion for central sensitization?

DR. KATZ: So let's break that down a little bit because, Ian, I think you brought up two kind of companion issues. The first one is, which I think is the big pink elephant in the room, is central sensitization one thing or is it multiple things? And if it's multiple things, what are those multiple things?

That's issue number one, and then a separate issue would be, what is the best way to measure it, or to diagnose it, or what-have-you? I think it might be easier to put the measurement issues aside and just deal with the conceptual categorization first, which is the first thing you brought up; is central sensitization one thing or multiple things? And if so, if it's a multiple, what are those multiple things?

We can debate about names but at least maybe agree on the concepts first. And you actually proposed a classification system, if I was

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listening to you correctly, where you proposed that we could classify these patients based on whether there is or is not an identifiable source of nociception, and whether there is or is not sensitization. And if there is sensitization, is it peripheral or central? That's what I heard you say as an initial kind of draft classification system, if you will.

Maybe start with the speakers first. Maybe start with you, Raj, first. You were specifically called out. Is central sensitization one thing or multiple things? And if it's multiple, what are the subtypes?

DR. RAJA: I think going back to the issue of do we need something along the lines of what the neuropathic group did, I would say, yes, that might be helpful. Again, going back to the analogy of -- and Steve can add to this -- complex regional pain syndrome, we had a whole cluster of names, a whole cluster of symptom complexes. Until they came up with some kind of clear clusters of symptoms, and then signs, and the presence of them

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or not, I think the field was lagging behind because each specialty was calling this differently, and the studies were done differently.

So I think to be able to advance this field, we have to come with kind of a paradigm of sorts, and this paradigm could be initially based on history, based on some exam factors and some biomarkers, whatever it would be. But I think coming up with a protocol and saying these are the likely patients to have central sensitization, or these are definitely the patients, I don't think is going to help advance this field.

DR. KATZ: So you're advocating an effort to try to create more clarity around the typology of central sensitization.

DR. FIELDS: I'm going to vote for multiple.

DR. KATZ: You're going to vote for multiple? What are they? What are the multiple types?

DR. FIELDS: Well, they're in Clifford Woolf's review article. You can have a loss gabaergic inefficient. You can have excitation.

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You can have amplification by descending facilitation. So there are a variety of mechanisms centrally that could give rise to what we observe clinically.

DR. RAJA: That could be the subtypes within a broad group.

DR. KATZ: So let's talk about the subtypes of what we observe clinically. What are those subtypes?

DR. RAJA: Could you get Steve's comment on what he thinks based on what's happened in that --

DR. BRUEHL: I was just going to say, I totally understand Howard's desire to break things out by mechanisms, and I also appreciate Roger's comment about lack of clarity, like disagreement on what the basic concepts are. And there's a big parallel with CRPS, many names, many presumed mechanisms.

I sat in on several expert meetings where the people that knew the most about the mechanisms of CRPS all felt like it was important to have a mechanism-based diagnosis but were basically saying

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we don't know enough about the details of the mechanisms to convincingly argue that we should diagnose based on that.

As a result, what happened was it was more of an umbrella term first, which was designed to get everybody using the same terminology and the same criteria, although, granted, they are probably over inclusive. And then we shrunk it down a little bit with revised criteria, and probably will do that further considering subtypes now that may indeed be mechanism based.

I think in the context of talking about what we're talking about here, there are a lot of parallels. We don't agree on terminology, so I think having that would be valuable so at least everybody's on the same page. When I look at the mechanisms or the indicators of mechanisms we've talked about, what I kind of see are three distinct buckets, and I will throw this out for comment.

One seems to be central sensitization as originally defined, where Clifford was talking about you've got a stimulus and response and you've

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got a hyper responsivness that you see, and maybe QST is the way to best assess that. But that's one bucket that would be that pure traditional central sensitization.

Then separately, we've got a number of body sites, maybe chronic overlapping pain conditions based on diagnostic criteria, and according to Dan's cluster analysis, the general sensitivity issue. All those things seem to hang together. Then separately we have the negative affect catastrophizing issue, which seems to be important and may be related to central sensitivity, but is kind of not really the same thing as the other two.

All of these, of course, may interrelate. I wonder about the best starting places here; whether you start with a broad label, you collect data on all of these buckets, and then get a sufficient number of patients to be able to empirically decide what mechanisms might be supported, or if you go the other way around and say, a priori, we're going to say we think these mechanisms are involved, and that's kind of what we do eventually to come up

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

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

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

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

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and peripheral nerves, and also the interactions of those is important. And of course, not all of those potential mechanisms are operative in every single patient and in every single condition.

But we can provide that simple framework, that there's -- even now, just articulating that there's independent contributions of the brain to creating facilitation, for instance, of amplification is in itself an advance. I mean, it really is a significant step forward.

So I think proposing that type of framework is really an advance that this group can, with the context of, but we don't know, of course, all those mechanisms, and what they are, and how to classify them, and how do they want individual patient, and how to assess. That's where I think the framework idea may hold some water.

DR. KATZ: Thanks. You get speaker's privilege, Lesley.

DR. ARNOLD: Well, thanks. I guess I question the idea of this pure fibromyalgia top-down only because I don't think we know enough

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about peripheral inputs to be able to say that the peripheral input is not also important. I mentioned obesity as an example. It's not an injury, but it's a metabolic change, and that can affect how the brain is functioning.

So I just want to be careful not to separate it like that. I think this framework that Ajay presented is I think a good way to look at it, that there are these multiple possible mechanisms. We don't always know what's operating in an individual patient, but to present this as these are the possible parts to the puzzle is important. I'm very cautious right now of dividing the group just yet until we have more data.

DR. KATZ: Thank you. Simon?

DR. HAROUTOUNIAN: I just wanted to caution ourselves against labeling people as patients who have loss of descending inhibition because I think it really depends on the testing paradigm. When we test descending inhibition in healthy volunteers, we apply some sort of conditioning stimulus, and then look at the response to test stimulus. But

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someone who is in chronic pain, they're already using their, whatever, descending inhibitory control they have, and this additional conditioning stimulus will apply second conditioning pain.

So it might be that we're not able to at least get extra response to sort of second conditioning stimulus rather than we'll label them as someone who's descending inhibition doesn't work. So I think we need to be somewhat careful and not label patients with inability to facilitate descending inhibitory control in a sense. So it depends on the testing paradigm, we should be just careful.

DR. KATZ: Thanks. Mike, you were next.

DR. ROWBOTHAM: I think you'd have a hard time finding a fibromyalgia patient who when they tell you their story doesn't have some sort of inciting event, injury, flu-like illness, sports injury, something that they kind of tied onset of their symptoms to.

One thing I wanted to get back to, and I thought about it just by Vitaly's talk yesterday,

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is there is sensitization, I believe in that, but that's perhaps on top of an underlying tendency that's really a personality trait towards this somatosensory amplification. That would fit with a lot of the genetic data in patients with migraine, where there's heritability and other kinds of things; that you're not really going to be able to medicate that part away. You may be able to medicate away the overlying sensitization, but you're not going to change personality.

So the data that Vitaly was showing yesterday that was really compelling was where you looked at the brain activation, and it was the same, but it was the same based on the percept rather than the same based on the stimulus intensity. I think that's really very important.

Unfortunately, the OPPERA study came close to getting some of that kind of data, but I don't think it really went -- and I'd like to be corrected if I'm not right on this. But it doesn't necessarily go back far enough to get at what the patients were like long before they developed TMD

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

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

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

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

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DR. FARRAR: I'm struck by the problem that we're trying to address and the lack of specificity, if you like, on what it is that we're actually talking about. I'm a strong believer in the centralization process. As Clifford has suggested, and Howard, there might be multiple mechanisms that underlie that.

I'm also very much struck by the fact that the cause may not be the same process that maintains that. My analogy is once the car has wrapped itself around the tree, fixing or doing something with the brakes isn't going to help very much. I guess what I'm struggling with is trying to think, as Ian is saying, about how do we identify the group.

What strikes me is that a couple of people now have said that there is a peripherally maintained chronic pain centralization or chronic pain enhancement; the example given of injecting into the nerve endings of people who've lost limbs, and finding that a lot of their phantom pain can go away.

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My guess is there are two groups. There are the people in which you can do that, and it goes away, and there are people you can try it on, and it doesn't go away, and that might be a proactive way of actually defining certain groups.

Now, I don't know how to do that, but it seems to me that if we could come up with some mechanisms for actually trying to characterize the pain -- Mike's work in postherpetic neuralgia, the capsaicin sensitive versus the capsaicin insensitive, I'm not sure what they are, but it seems to me that at least some thought about ways to not simply measure and gather patient-reported outcomes, but to do some sort of testing to understand -- we had the imaging data yesterday, where given a pressure of 4 on the finger, some people had a much bigger response than others.

So I would just raise that as a question for the group in terms of whether there are ways to think about categorizing our underlying mechanisms in a way that would allow us to better address them.

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DR. KATZ: Sharon Hertz?

DR. HERTZ: I keep hearing about QST, and I'm wondering if there is a thing that everybody is referring to that is the same. And if not, what is the range of what's going on out there and how does that impact understanding the results?

DR. KATZ: Would anybody like to answer Sharon's question about what are people doing out there that they call QST and what's the variability in terms of what's actually done?

DR. FARRAR: Maybe Dr. Campbell. It's your lot.

DR. ARNOLD: I could try. I think there's enormous variability in QST responses. There are a lot of different tasks that people do. We include a battery that covers a lot of different domains and takes about an hour. We could never expect a clinician or somebody that's trying to quantify the person right in front of them to do anything like that; nor do we have normative data. The German Research Network has tried to do some of that work.

I imagine between some of us here in this

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room, we could probably come out with norms, but I still think even if we did that, it would probably be unreasonable to expect somebody to do any kind of deep phenotyping at the outset of a trial. So I think that's tricky. There's huge variability that I think can obscure what you're trying to look at.

Like Dan was saying with some of these pyschosocial and behavioral factors, we can look later on at the end of the trial and see if we can predict outcome based on baseline responses to X, Y, Z QST measure. I don't think we've done as good a job about testing those various factors over time, and I actually had the same complaint over some of our psychosocial, behavioral, and widespread pain questions.

I think we do a fairly decent job getting some of these measures at baseline, but then don't necessarily follow them and look at trends over time to be able to identify who did better and what outcomes that improved.

DR. HERTZ: Just to follow up, there's a lot to choose from. I'm assuming there are different

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systems to run them on. And then we have to wonder about inter-rater or performer reliability. It sounds like -- when I hear conclusions based on QST, I'm not entirely sure what it means. It's like saying, well, we evaluated the patient, and there was no correlate with the evaluation. It's just this box of something that goes into it.

So I'm just wondering if moving forward, there's any interest, or stomach, or ability to consider defining some parameters so that when we look study to study or population to population, we have some idea of what this QST means.

Because when we're trying to think of what might actually be useful and pragmatic in a clinical trial setting, when it comes to this kind of thing, QST in particular and no matter what it's being directed at, everyone and their brother wants to use it because they think it will somehow get them something.

I'm just struck with how large the number of possibilities are that could fall into that box. And with a lack of any consensus on the kinds of

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parameters, the type of testing, and comparing different operating equipment, how are we going to really understand the findings from one study to one study, or from one program to another?

DR. KATZ: Steven?

DR. BRUEHL: Just to address some of those issues, I do get the sense, there is a lot of variety in ways you can do QST, but I think the most commonly used method is the computerized heat pain, which seems to be pretty consistent across a lot of locations, often using exactly the same equipment, at least by the same company.

So I think there is some consistency in that. CPM, we call it CPM, but it is a whole bunch of different procedures, and I don't think there's any consistency on that at all because there are so many permutations of stimuli you can use in that. And I know that there is some work done that show you get very different results, depending on the particular combination of stimuli, whether it's heat and cold, or heat and pressure, or whatever it may be.

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For APS a few years ago, I was asked to review reliability information on these commonly used QST measures, which nobody really talks about. And at that time, it was very clear that tolerance and threshold are both pretty reliable and have good reliability. Temporal summation is not quite as high, but it's still reasonably reliable, and CPM was not very good at all. It made me wonder whether CPM is a state rather than a trait, whereas maybe temporal summation is more something trait-wise that we're assessing.

I just thought I would throw that out. There is a lot of inconsistency, but they can be reliable measures. And in terms of Jim's comment about pragmatic, the temporal summation option using von Frey hairs is very simple to do in a bedside setting.

So that would be very pragmatic. It has been used in several studies, although it doesn't seem like everybody uses the same pressure, and I'm not sure what the data are on reliability of that.

DR. KATZ: We've actually published data on

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the reliability of temporal summation using von Frey filaments in osteoarthritis, which showed that it was pretty reliable. And in that same paper, we published data on the reliability of CPM, showing that it was not that reliable, so there is some data out there.

Yes, Joachim?

DR. SCHOLZ: I have a comment regarding the specificity of these assessments. It seems like the reference could be maybe healthy population, but I don't think that would be adequate because then the outcome would more refer to we define central sensitization as increased pain sensitivity, and that cannot be the objective. It is defined as a particular mechanism.

So our reference should rather be a group of patients who have a painful condition but do not display signs that we consider specific for central sensitization. I think that's where it becomes a little bit tricky, so we would have to think also about methods to rule peripheral sensitization or have a clear understanding of the concept of how

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

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

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

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

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of it in any of those studies is weak. Our values are 0.3, 0.4. You can get statistical significance, but they don't come close to the point that you would use them to make clinical decisions or things like, and that's where I have probably a bigger problem with QST.

I think you can actually circumvent some of the problems of standardization across sites, dealing with inter-rater reliability and normative data. It's just that it simply doesn't -- compared to the patient-reported outcomes or the imaging, where we have all of those in all of our studies, over and over and over again, the QST is not strongly telling us anything.

That's the cautionary note, and I agree with Sharon. It's like part of it is like the validity, and I'd be interested in it, and we still do it to try to infer mechanisms, but I'm just giving this cautionary note that I just don't think it tells you that much that you can't glean with simpler measures.

DR. FARRAR: Specifically on that, as I'm

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also involved in the MAPP program and know about Steve's work, I agree with you that it has not worked well in those situations, but getting to Sharon's perspective, all of MAPP-1, the QST consisted of thumb pressure. It was a single measure. There was no temporal summation studies.

So I'm not disagreeing that it has not worked in the studies that Steve has been involved in. My thought would be that perhaps we just don't understand what we're doing there very well, and that if we're looking for temporal summation as an indication of centralization, then we should do temporal summation, and we should look to see if that's predictive, and I'm not sure that that's been done.

DR. CLAUW: Look at OPPERA.

DR. KATZ: Could you speak into your mic, Dan?

DR. CLAUW: OPPERA did 10 QST measures, and none of them have an odds ratio greater than 2 in predicting anything.

DR. KATZ: Roger?

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DR. FILLINGIM: Well, we've sort of been going back and forth on getting more specific in identifying mechanisms for whatever this thing is we're talking about, or these things, versus looking at a global phenotype or subphenotypes. And those are all different initiatives. I think it relates to this conversation about QST.

So if I want to predict mortality, I can ask people about specific conditions they have, or I could ask them, overall, how healthy do you feel. And how healthy they feel is going to be a better predictor of mortality, I suspect, than really specific questions about their health.

I think we get into the same phenomenon with patient-reported outcomes, which they can subsume a lot of constructs, and each construct may actually have additive predictive value. So that global construct is predictive, but it doesn't tell us much about mechanisms to the extent we might be interested.

Then if we drill down into subphenotypes or methods like QST that we think are a bit closer to

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mechanisms, we sort of keep drilling down, and I suspect we're going to have to find some happy medium somewhere in there. But I think that's some of the tension here.

DR. KATZ: We have a few minutes left to go in this morning's discussion. Does anybody feel prepared to articulate a proposal for how we're going to identify this group of patients with central sensitization, whether it's one thing or more than one thing, what those more than one things are and how to identify them just as an appetizer for the afternoon's discussion?

DR. BRUEHL: I just want to ask a question, which is if we look at the title of this conference, we're talking about central sensitization, somatosensory amplification kind of as a bundled thing, but we've spent a lot of time talking about chronic overlapping pain conditions. I guess what I wonder is, is that something separate from central sensitization or is that one of the components we're considering to be part of that?

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

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

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

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

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What is the degree of centralization? or centralized pain that is part of the component of some of these pain symptoms?

I think that that would help both for putting the patients into the right studies, I guess one as a predictor, but then also, I think it's part of an outcome I guess down the road as well. One reason why I feel it's so important is not just because we are talking about studies in these COPCS; we are also talking about all the other studies that happen, and I think, typically, this is not being assessed.

We do studies in low back pain and in diabetic neuropathy. We do a lot of studies, and often the component of centralized pain is not assessed, so we are missing on the correct phenotyping of all the patients, which I think has an impact on the success of the studies down the road.

DR. KATZ: Well, that seems like a good final comment for the morning. I'd like to thank the panel for participating and for their

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presentations. It's time for lunch.

(Applause.)

(Whereupon, at 11:45 a.m., a lunch recess was taken.)

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

(1:07 p.m.)

Consensus Discussion

DR. DWORKIN: So we're in the home stretch here, and for those of you who have been at IMMPACT meetings before, you know how this works. I just want to start with some thank yous and appreciation, first of all, to all the presenters, as the slide says, for their truly wonderful presentations; to everyone else for their stimulating, lively, provocative and wonderful comments, discussion; to Valorie and Julie outside; and the AV team and the transcription team for another flawless meeting.

Dennis and I will definitely retire at whatever point Valorie retires, and she knows that, and she's promised us that she's going to keep going.

Finally, it's not on the slide because it really does go without saying, to the FDA and to Sharon and Allison because ACTTION wouldn't exist without the FDA. So we wouldn't be here, we

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wouldn't be doing what we've been doing for the last 2 days without the support of Sharon and Allison and the FDA, so thank you.

As a couple of general comments, as all of you I think appreciate by now, Annie has been the rapporteur for this meeting. She's going to draft the manuscript, and you will all be invited to be co-authors on the manuscript; so that's just the way we do things. You don't have to be a co-author. You could send an email back saying I'd rather not be in author; entirely up to you.

We're going to be calling on the speakers for help with drafting certain sections because the presenters obviously had great expertise in certain areas, and we're going to run those particular sections by the speakers before we finalize the draft that we send out to the rest of you. Pain is almost always, if not always, the target journal.

The systematic review that Annie presented is separate. That will be a separate publication, a smaller number of authors, though the main manuscript from this meeting will refer to the

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

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

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

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

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

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

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

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

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

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

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

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

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surgery, trauma, shingles, et cetera. We need to change the slides.

Ian?

DR. GILRON: Just to chase that comment, in the possibility that there might be a phenotype of, call it fibromyalgia-ness, that predisposes to transition to chronic pain, maybe we could tie this in with prevention trials. It could be another area, but it might be relevant to --

DR. DWORKIN: When we get to trial design, let's add that because that is not on the slide.

Is everyone satisfied with how we've evolved in the last five minutes? Steve?

DR. BRUEHL: I am, and I'm just wondering if maybe in the paper it would be useful to have a Venn diagram with chronic primary pain and then chronic central sensitization syndrome, or whatever we call it, overlapping to some degree just to kind of show visually that we do think there's some overlap, but there are going to be conditions that aren't covered by chronic primary pain. I don't know if we want to highlight the IASP issue and all

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that.

DR. DWORKIN: You took the words out of my mouth.

DR. BRUEHL: If we do need to, I think a diagram might be helpful.

DR. DWORKIN: One of the other ACTTION groups is doing, and we've never done this before, a Delphi poll. It strikes me that your suggestion for that Venn diagram would be an impetus for Delphi poll to see how much of us agree with highlighting chronic primary pain, and how many of us think like let's just leave it aside. So we'll take that under advisement.

Dan?

DR. CLAUW: I think that is one of the most effective ways to leave it aside by doing what several people have just suggested and say central sensitization can occur in acute pain, in chronic primary pain, in all the other kinds of pain, but then we don't have to take on the controversy.

The only other thing I would recommend is, please, let's not us invent yet another term. If

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the term doesn't exist -- no one really uses the term, although I happen to agree that it's a good term, "sensitivity," like "chronic," or for that matter, "somatosensory amplification." We already have four terms that we have to live with in this field, and for us in IMMPACT to introduced yet --

DR. DWORKIN: So that's a vote for centralized pain.

DR. CLAUW: I don't care which one. It's a vote against chronic central sensitivity because that doesn't yet exist -- people aren't writing about that.

DR. WOOLF: I would argue against centralized pain because that has a very specific meaning, is that it implies the autonomous, which may be just a small part of the whole package.

DR. DWORKIN: And you like central sensitivity? Is that better, Clifford?

DR. WOOLF: That's better.

DR. CLAUW: Well, why don't we just use central sensitization? Why do we have to use a new term?

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MALE VOICE: All pain is central. I mean, it just is.

DR. DWORKIN: Mike?

DR. ROWBOTHAM: Pain with somatosensory amplification?

DR. DWORKIN: We have like I think five different terms on the --

MALE VOICE: We'll never -- we can spend until 5:00 on this.

DR. DWORKIN: I know. I know.

Howard, can I call on you to get me out of this jam?

DR. FIELDS: I didn't realize that you were in a jam.

(Laughter.)

DR. DWORKIN: Get us; get us out of this jam. I was in a jam because I didn't know what to say.

DR. FIELDS: I couldn't agree more with Dan. The last thing we need is a new term. We've got more than enough terms.

DR. DWORKIN: So you would be happy with

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

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

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

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

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

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

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

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

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somebody with interstitial cystitis, and they have a degree of fibromyalgia-ness. That's just a little kind of convoluted way of saying what I was going to say and what I think Lesley means.

DR. CLAUW: The advantage of going that direction -- and it would be cool if we can agree on this because it might be a little bit more controversial. But then you could basically say that negative affect is another thing that can span a number of chronic pain conditions with or without central sensitization.

MALE VOICE: And we know that's for sure.

DR. CLAUW: But that's for sure. Catastrophizing can -- but I really think it's -- the one thing that I probably feel the most strongly about is don't have the core definition of this include affect, include cognition, because this is something that can clearly occur in people that don't catastrophize, people that are not depressed.

DR. DWORKIN: We're going to get to that.

DR. CLAUW: Right. But I think that RDoC

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thing does that nicely for us. If we say this is the framework we're going to use -- like some people with chronic pain have negative affect; some have catastrophizing; some have central sensitization, but we don't say that these always occur together because they don't.

DR. DWORKIN: I love that. John?

DR. FARRAR: Clifford and I had a conversation at lunch about the fact that there are multiple mechanisms and other things that go on here, but also about the fact that it seems to me that what we want to define is that it's sensitization of the pain relevant structures in the brain. And I know that there's a big gray line between that and other things, but what Dan's talking about in terms of catastrophizing, depression, et cetera, is more a limbic process, I think. It's more a cortical interpretation.

I don't know how to divide those, but somebody looking at this could say, well, central sensitization, or essentially, everything is central. Depression is central. This is central.

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DR. DWORKIN: I have a list of possible aspects of the phenotypes definition, so let's look at that when we get to it because it is exactly what Dan's talking about.

Some of you that IASP has introduced a new term, "nociplastic pain."

(Groans from audience.)

(Laughter.)

DR. DWORKIN: And this is pain that isn't either nociceptive, as you can see from the definition that I highlighted at the bottom of the slide -- pain that isn't nociceptive, and isn't neuropathic, and is still pain or something. And clearly, Howard votes that we just not use the word "nociplastic" in this article, and we make believe -- we don't think it's relevant to what we're talking about, and I'm happy to completely leave it out of the article.

Dan?

DR. CLAUW: Let me give you the reasons that I don't think that's a good idea to do. I want to first say that we are the only ones that wrote a

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letter to the editor that said this is a stupid --

(Laughter.)

DR. CLAUW: I've gone on record and print in saying this name is stupid; we believe it to be stupid. But then I got put on the IASP committee that's going to define this.

(Laughter.)

DR. CLAUW: And there are some people on that committee that have no idea what they're talking about. And it would really be helpful because this committee is dragging on so long. The biggest thing right now that I'm fighting in this committee is a lot of the people in this committee will not allow non-pain symptoms to be part of the definition of anything the IASP puts out, and that's going to make the definition of nociplastic pain incredibly -- it's going to be something like pain that is greater than one would expect. But it's like something that would be impossible to quantify, or to put into diagnostic criteria, or anything like that.

So I think that this discussion that's

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occurred over the last day and a half is like infinitely better than the IASP committees that get together by email or trying to work out some of these types of things. I think it would be really helpful to lay all these things out and just say nociplastic is one of the things that's been thrown out there, but then still say what we want to say.

DR. DWORKIN: Well, I think we all would be in your debt if you would write those 4 sentences for Annie and us.

DR. CLAUW: I'll write those 4 sentences. I'd be happy to write those 4 sentences.

DR. DWORKIN: And even 5 would be fine.

DR. CLAUW: Yes, maybe 5.

DR. DWORKIN: Does everyone agree we can move on from nociplastic pain? I see a lot of heads banging up and down. Okay.

Let me just go back to the overview slide. I think we're done with bullet 1 of this outline. Does everyone think that we've taken care of mechanisms, types, central sensitization?

(Affirmative nods.)

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DR. DWORKIN: Okay. Clinical trial objectives and design. So this is really what this meeting is about. We spent a lot of time thinking about this over the last evening and morning. One way I was thinking about how we could do this is there really have been 2 threads or themes for the last day and a half.

One is how do we optimize the design of clinical trials for patients with one of the chronic overlapping pain conditions? FM, TMD, IBS, IC/PBS, with, as Lesley just said, fibromyalgia being the kind of exemplar COPC.

What are the things that we've talked about in the last day and a half that really allow us to propose ways of optimizing the design going forward of clinical trials of fibromyalgia, IBS, et cetera? Clearly, I think the biggest contribution is that we're seeing within those patients, some of them -- maybe all FM patients, but some of the others have a certain phenotype that it sounds like we're now calling a central sensitization phenotype.

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So one set of clinical trial objectives -- and we're really talking about efficacy, randomized clinical trials probably with phase 2 and phase 3 -- is to optimize the design of clinical trials of one or another chronic overlapping pain conditions by identifying a phenotype that needs to be examined at baseline in those patients, and maybe would be an inclusion criteria. We're not going to study you in our clinical trial of IBS unless you have the central sensitization phenotype.

Another way of thinking about, it seems to me, the clinical trial objective -- and this is a little bit more novel, and this has been a theme, too -- can we do a clinical trial where we enroll patients with one of several different either COPCs or other conditions that we've been talking about for the last day and a half, where we think central sensitization plays an important role in at least some reasonably sized minority of patients.

I put down some examples: obviously OA, RA, musculoskeletal low back pain, CRPS, and headache.

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And Simon pointed out to me -- and I think this is true -- that we could even include -- actually, Simon's left. We can even click neuropathic pain patients here because we don't necessarily believe that all patients with diabetic peripheral neuropathy have central sensitization as their primary or predominant mechanism.

So that would be a trial that where it gets you randomized is having a phenotype, that we are going to define, irrespective of which of these kind of classic etiology based diagnoses you have.

Lee?

DR. SIMON: Is the attempt of that design and carrying it out to develop a treatment for the phenotype or is it to develop a treatment for one of the specific causal events? Because I don't know how you develop a drug for a phenotype.

DR. DWORKIN: This goes back to Mitchell Max's -- he had an article in 1990.

DR. SIMON: That's right.

DR. DWORKIN: This is mechanism-based treatment. If you think central

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sensitization -- Mitchell thought if central sensitization is an important mechanism, you are going to treat patients who have that as an important mechanism of their pain with some agent that you think attenuates the sensitization. And it doesn't matter whether you're diagnosed as FM, or OA, or PHN.

DR. SIMON: So the purpose of that design, as you've described it, is to develop a therapeutic of some sort or another for the phenotype.

DR. DWORKIN: Phenotype mechanism, because even earlier than 1990 Mike and Howard were talking about segmenting, if you will, PHN patients into one of three different mechanism-based groups, and at least one of those three PHN groups had central sensitization as a primary mechanism.

So no one's ever really thought this way, that you could enroll a PHN patient, for whom the mechanism of his or her pain was primarily central sensitization, in the same trial as an OA patient for whom -- that's why I said this is a very novel approach.

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A flip forward, just to illustrate -- and I'm not a hundred percent sure about this. Lisa LaVange, who is a biostatistician, who's head of the Office of Biostatistics at CDER for 6 years, and now she's at UNC, and Janet Woodcock published an article about a year ago in the New England Journal of Medicine on master protocols, including basket and umbrella designs.

So I was thinking this is sort of like the second bullet, right? Different diseases, and you look at the patients with these different conditions -- OA, postherpetic neuralgia, FM -- and you phenotype them that their primary underlying mechanisms of pain is central sensitization, and you enroll them in this basket trial and treat them with -- what would be the example? Duloxetine or milnacipran, or some triple reuptake inhibitor that we haven't developed yet.

Now, that's a very different approach. This kind of basket trial, obviously, is a very different approach than the first item here, which is just optimizing the design of future IBS or FM

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trials.

Ajay?

DR. WASAN: Maybe you want to add in a label for sensitization as a primary or secondary mechanism of the pain syndrome. For instance, acute pain is a good example, acute postsurgical pain. You could argue that the sensitization is a secondary mechanism on top of the tissue injury generated pain.

So that gives you more flexibility and freedom, and it also gets to the same point of sensitization is operative to more or less degrees in a whole variety of situations.

DR. DWORKIN: I think I understand your point, but that makes it complex because that patient might have a kind of primary mechanism that is not sensitization, so then you're treating a secondary, presumably less important mechanism. But that could still be making an important contribution to their pain, so yes.

DR. WASAN: Well, that being the central sensitization points.

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DR. DWORKIN: Dan?

DR. CLAUW: I like both of those top two things. So I hope we're not talking about these in some way being mutually exclusive because I think that they're both -- and I think the manuscript could flush out because there are different reasons that you would do the top bullet versus the second bullet.

DR. DWORKIN: I was hoping you would like both of them, because I think what makes the manuscript better is that we talk about both of these two very different pathways, optimizing and then doing something novel that hasn't been done yet, but it certainly seems possible, the kind of mechanism-based targeted treatment. And this slowly moves into biomarker-based treatment and precision medicine. We're in that pathway.

Rick?

DR. MALAMUT: It's doable. We did this back at AstraZeneca a hundred years ago, in which we enrolled a population of patients who we believed had mechanical hyperalgesia, and our tools, we were

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using brush allodynia and punctate hyperalgesia. The tools may be more sophisticated now if MRI is ready or QST is agreed on, but it was doable.

The key for us, though, would be -- if we go down this road in a phase 2 study, in which we're not studying FMS or PHN, we're studying a mechanistic base -- is, is that going to be a viable indication? So at least from my point of view, we would want to talk with FDA and say, hey, this is what we're proposing, an indication, and this is the study we're proposing. This helps because at least you're providing a way to do that.

DR. DWORKIN: Obviously, I can't speak for FDA, but I think I can almost speak for NIH. Sorry, I'm going the wrong way. The NIH EPPIC-Net, the phase 2 clinical trials network that most of you know a lot about, they're very bullish -- from Francis Collins on down, they are very bullish about basket trial designs, umbrella designs, and master protocols in general.

So even if this is not there yet for FDA, it's very close to being there for NIH. I'd be

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really surprised if there wasn't a phase 2 clinical trial of this design occurring within the next 24 to 36 months.

DR. WOOLF: As you get rid of centralized.

DR. ROWBOTHAM: So these designs are pretty standard in cancer therapy.

DR. DWORKIN: Yes.

DR. ROWBOTHAM: [Indiscernible - off mic].

DR. DWORKIN: In fact, the examples in the Woodcock and LaVange article are primarily oncology. A couple of other, pulmonary, I think. I may not be remembering that.

I don't know that there's anything to discuss about the last two bullets. Jim mentioned pharmacologic in Richmond this morning, I believe, and I personally thought that was a really cool idea, designing a trial where you have an enrichment phase, and you identify the patients who putatively have central sensitization as a primary mechanism, and you might confirm it by seeing if they respond to a drug that you think targets central sensitization like milnacipran.

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So I thought it would be kind of interesting to at least in the draft of the manuscript have a paragraph about the potential for pharmacologic enrichment, and we could also say something about enriched enrollment standard, enriched enrollment randomized withdrawal designs. IMMPACT's already been there. We've got articles, and there are many articles in the field about ERW designs, but there's much less in the chronic pain field about the possibility of pharmacologic enrichment.

Nat?

DR. KATZ: One of the bullets that's not there is whether we want to make recommendations related to central sensitization for people doing clinical trials who couldn't care less about central sensitization, but who's doing a regular old trial in chronic low back pain, or a regular old trial in osteoarthritis. We have recommendations for how patients should be characterized or potentially outcomes captured that would even make those trials more informative.

DR. DWORKIN: So think about when you see

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the next slides about the phenotype outcome measures. I have more slides coming up about exactly those issues.

DR. KATZ: It still feels like the outline is incomplete in that regard. If we are going to have a section on clinical trial objectives and designs, then we could have a subsection called clinical trial objectives and design issues in relation to chronic pain studies in general.

DR. DWORKIN: Okay. That would be the third bullet on this slide. Raj?

DR. RAJA: I'll just say, you're talking about pharmacological enrichment and central sensitization. Rather milnacipran, I would think ketamine as one of the probable drugs to test.

DR. DWORKIN: Yes, definitely, effusion, whatever you know, yes, absolutely. Dan?

DR. CLAUW: Just for completeness, and I think this is probably what Nat's getting at as well, I do think it's important to also say that even if you are not trying to identify the people with central sensitization, you may want to screen

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because you may want to exclude them. If you have a more peripherally-based target, you may want to identify the people you don't want to put in your subsequent trials because you see that there's a lack of responsiveness.

DR. KATZ: Yes. Wouldn't it be nice to know that you didn't have 80 percent of your patients in group A with central sensitization and 20 percent in group B with central sensitization when you're doing that, versus placebo?

DR. DWORKIN: So Dan, you would suggest if I'm going to do a trial -- I'm not -- of intra-articular hyaluronic acid for a knee OA, I should exclude the OA patients with predominant central sensitization because we can't imagine that HA --

DR. CLAUW: That would be exactly like a Samumed program, where I showed that this is an intra-articular injection, a Wnt inhibitor, that it works way better in the OA patients without widespread pain than it does in the --

DR. DWORKIN: So the third bullet on this

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side that we've just added, Annie's just added, is kind of Nat Katz and Dan Clauw's recommendation for other pain trials, and we'll get to this.

We'll have a paragraph at various places, that might be two or three paragraphs, about stratification, and we talked about stratification on and off during the meeting; stratified allocation when that's reasonable; stratified randomization, and we'll get to analyses, stratified analysis of subgroups.

So we'll talk about stratification. I don't know that we need to discuss it here. You'll see those paragraphs. That will be fairly straightforward. I'm a fan of an article that Tom Permutt, a statistician at the FDA, published about the different types of stratification about 10 years ago, so that article will be cited.

We talked about this. All right. This is my phenotype slide. Dennis and I tried to listen really carefully to all the wonderful presentations, and this is not, at this point obviously, meant to be a proposed diagnostic

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criteria for the presence of central sensitization, but it seemed to be the key things that people mentioned in their presentations and in the discussion.

Widespread pain as assessed by a body map, we've talked about that, Lesley and Dan; the history of multiple comorbid chronic pain conditions, and obviously one assessment approach would be the Maixner Williams screener that we heard about this morning; and disproportionate pain. It's not clear to me how you assess that, but it seems to me that there should be something on a physical exam that could give the evaluating clinician some sense of disproportionate pain that isn't QST. I don't know what --

DR. WASAN: There is [indiscernible] - off mic] validated things, the pain behavior indices. This goes way back to Waddell, but then it's updated with the PROMIS pain behavior scale. So there's a variety of identified pain behaviors.

DR. DWORKIN: I think that's patient report. How about a physical exam, Ajay? Is there anything

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on a physical exam that tells you, and Dan, and Lesley, and Raj, and Nat that the patient has disproportionate pain?

DR. WASAN: Well, you observe pain behaviors. It is an exam. It's not just self-report. Yes, you can have self-report, but you can observe those behaviors, and that's part of your exam. You document that.

DR. DWORKIN: Steve, and then Dan.

DR. BRUEHL: I was just thinking of the CRPS, we tried [indiscernible - off mic] in some way, and obvious would be the pinprick hyperalgesia and allodynia. I think Clifford mentioned that earlier I think in this context.

But Mike, I was thinking back to you mentioning a variety of traditional neuropathic pain conditions that are going to be associated with allodynia and hyperalgesia, yet you were arguing that they're primarily peripheral. It may cause problems if we include something like that in there, unless we're certain it's not really a peripheral [indiscernible] issue.

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

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

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

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

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Mike?
DR. ROWBOTHAM: I agree with Howard on "disproportionate," that word. But something that should be brought up and flipped around is patients who have elaborated examinations, it could be collapsing weakness to minimal stimuli, elaborated gait, sensory loss, basically impossible, all those things that neurologists look for on neuro exams to see if you can really trust your examination. So if you see a patient with signs of elaboration on their exam, then you kind of just have to start all over.
DR. DWORKIN: That's something very different.
Howard, you won. Dan agreed to 4 sentences or so on nociplastic pain. Will you write those 4 sentences?
DR. ROWBOTHAM: [Indiscernible - off mic]?
DR. DWORKIN: Yes.
DR. ROWBOTHAM: Yes.
DR. DWORKIN: And it's really exclusion in some ways.

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(Crosstalk.)
DR. WASAN: The other term for what he's describing is called exaggerated pain behaviors. This is part of a well-accepted terminology. Neurology may have a slightly different terminology, but it's the same thing I mentioned, and we should put it in there, not disproportionate pain, but --
DR. FIELDS: Exaggerated is more on the diagnostic side.
DR. WASAN: So just call it pain behaviors.
(Crosstalk.)
DR. WASAN: You just call it pain behaviors, and include all the things like Mike said.
DR. DWORKIN: I promise that you will get at least three or four opportunities to criticize what Mike writes. I promise.
DR. BRUEHL: It seems like some are arguing to include that as a criterion for this and others saying it's an inclusion. Which is it?
DR. DWORKIN: It's more an exclusion.
DR. BRUEHL: Okay.

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DR. DWORKIN: It's to not be confused in evaluating symptoms, and perhaps signs, by these kind of exaggerated --
DR. SCHOLZ: But it also comes back to the question of what's the reference, because you may have a patient with a pain condition who is not central sensitization. So they still have abnormal pain behavior or pain sensations, but it's not central sensitization, so you cannot compare with your physiological situation.
DR. WASAN: It's part of the phenotype. We're just talking about sensitization as a downstream consequence of a whole variety of possible inputs. We're talking about identifying these folks clinically, and that is typical, whether you call it the signs and symptoms that Mike mentioned or whether you put it in the category of pain behaviors, which are the same, actually description of the same events. I mean, it is a known defined construct.
DR. SCHOLZ: Well, the problem is with terms like exaggerated or disproportionate, to what?

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What's your comparison?
DR. DWORKIN: How about I propose we wait and see what Mike comes up with.
DR. WASAN: Okay, fine.
DR. DWORKIN: We'll have 4 or 5 sentences from Mike, and we'll see whether the other individuals in the room agree with him.
The next bullet is really a bunch of questionnaires that patients fill out, and I just put down various ones that we heard a lot about over the last two days: The Pill, the ACR-90 Somatization Scale; the fibromyalgia survey that Dan and Chad Brummett use; the Central Sensitization Inventory; my favorite, Barsky Somatosensory Amplification Scale.
It's my favorite because we 30 years ago showed that patients with high somatosensory amplification scores, shingles patients with high scores are more likely to develop PHN 3 to 6 months later. But obviously, these are all measures that are assessing a kind of -- one imagines an underlying construct of somatosensory sensory

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amplification not only of painful stimuli, but as we've heard, loud noises, sounds, bright colors, odors, who knows what?

I don't know. I think, Steve, you asked this question that given all of these measures -- and it could have been a longer list -- are we going to be able to recommend one of them? And I think, no.

DR. BRUEHL: I actually had a comment on this, and I'm not familiar with all of these very well. But the CSI I know has been used quite a bit. My take on it from what was presented here, and my little bit of reading of the literature, is that those studies are heavily weighted towards fibromyalgia samples. I think the problem, probably in some of these other measures as well, is that that's probably also true.

I'm wondering, if we're talking about a cross-diagnostic construct, and we've shown that CSI is elevated in fibromyalgia compared to controls, I would really like to see, before we recommend a specific measure, evidence that some of

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these other overlapping pain conditions have the same elevations on this measure of central sensitization.

DR. DWORKIN: Well, we know TMD does. So it's not only fibromyalgia, it's TMD.

DR. BRUEHL: Well, the same cross-cutting. So maybe MAPP has this information, but I think that would help to be able --

DR. DWORKIN: I've got two samples of shingles patients for the somatosensory amplification scale.

I think what I'm hearing you saying -- I wasn't expecting anyone to say this, but maybe we really do need to think about somehow getting a systematic review done of sensory amplification measures, these and all the others we identify, with respect to how they were developed, what's their content, what do we know about reliability, validity, assay sensitivity in clinical trials, if they're ever used in clinical trials.

DR. BRUEHL: That would be a great use.

DR. CLAUW: And there are some studies now

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that are doing that along with doing QST for other non-painful sensory stimuli, which would actually then help say, okay, if we're really trying to get at some underlying biological construct, then the questionnaires that match up best with QST might be the ones that we gravitate to.

But I would agree with you. I think taking that and saying that that might be useful to screen and put a couple of things. But again, our group hypothesizes that the people with central sensitization that don't have chronic overlapping pain conditions don't have nearly as much pan-sensory sensitivity as the ones -- like an OA patient with central sensitization or an RA patient.

I think that's still an unanswered question, so I don't think we should -- as Steve's saying, I don't think we should imply as part of the construct.

DR. DWORKIN: I think Dan just made a proposal, which is the first three bullets on this slide would be -- and they obviously have to be

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rewritten -- the way we propose the phenotype is identified, and the bottom three bullets are more a research agenda, not only the QST or fMRI and metabolomics, but even which questionnaire would really add value.

Certainly, Dan you said a moment ago that fatigue, sleep, mood, cognitive abnormalities are not defining of the phenotype.

DR. CLAUW: If you look at the 2001 fibromyalgia measure that we've used a lot, that has two elements. It has a widespread-ness of pain, and the other, there's the fatigue, memory problems, and sleep disturbance. They each contribute about 50 percent variance in predicting poor outcomes to surgery, poor outcomes to opioids.

So no, I don't mind in any way, but they're separate. They load on separate factors. That was the factor analytic paper of Andrew Schrepf, that someone presented this morning. They're separate factors, so you have to assess them separately or just say I'm not going to look at -- but what's been called space, or fatigue, sleep, mood,

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

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

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

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

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Ajay?
DR. WASAN: I would support Dan because the unique thing about these, and what's mentioned in that bullet point, is that many of those have been shown to be causal of central sensitization, not just associated. We know that poor sleep and experiments that induce poor sleep create more sensitization on QST and other measures.
We know the same thing with mood, that you can worsen someone's mood, and you have worsening QST outcomes, and you have neural correlates in the brain, and fMRI are those types of things. So there's a causal component here to sensitization that is different than just being an associated symptom.
DR. DWORKIN: The other thing to think about -- and Lesley didn't highlight it in her talk this morning -- but the ACTTION APT [ph] criteria for fibromyalgia, which was just published in the last couple of months, do highlight as part of the diagnostic criteria -- and Dan was an author also -- fatigue and sleep.

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So we actually have an ACTTION precedent, if you will, of including fatigue and sleep in part of the definition of a chronic pain condition. Jim?
DR. RATHMELL: So why not just move it to important coexisting considerations that will affect response to treatment?
DR. DWORKIN: No, that's what Roger thinks, but Dan and presumably Lesley disagree.
DR. RATHMELL: So even though it's uncommon, you would exclude any people who met the first three criteria and didn't have the fifth there.
DR. CLAUW: Well, I guess I wasn't thinking that the first three, that you had to have all three in order to diagnose this because there will be people that you don't even have all three. So I was thinking that these were just more, if you see this, this is supportive of the -- so maybe we're thinking differently about how to -- because a lot of criteria, you have to have column A plus B as supportive. And I'd be very okay with the B being supportive, being fatigue, memory problems, sleep disturbance, and sensory sensitivity.

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DR. FIELDS: The key is that it's a symptom, in a symptom complex. So you're using it to make a diagnosis. If you have it, it increases your confidence in the diagnosis.
DR. CLAUW: Exactly, and you're just helping people get more comfortable.
DR. FIELDS: My guess is with the sleep, it's maybe asking the patients as opposed to doing the SLEEP study. If you did a sleep study, you might find that it's a universal component of what we're calling this condition. I don't know what they call it.
DR. DWORKIN: So could we do something? I mean this is sort of the DSM-3, 4, 5 model, that we list those four, the bullets 1, 2, 3, and 5, as the kind of core features of central sensitization in chronic or acute pain patients, and that we kind of recommend at least 3 of those 4 would be required to have confidence that the patient has this mechanism phenotype.
Is 3 or 4 a solution?
DR. FIELDS: What do you think about moving

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catastrophizing down next to cognitive abnormalities?
DR. DWORKIN: I don't know what catastrophizing was, which is why I wasn't sure where to put it. It is cognitive.
Raj?
DR. RAJA: It's less likely to be effective because widespread pain is an essential criteria, so you have to have some criteria there, which is essential, and then you can have a secondary X of Y. There are certain which you really want as essential criteria.
DR. DWORKIN: We could say you have to widespread pain in two of the remaining three.
Roger and then Clifford.
DR. FILLINGIM: I just think conceptually there are several things on the list that we think reflect central sensitization. That includes widespread pain, multiple comorbid chronic pains, disproportionate pain, or whatever that is, and maybe sensory amplification. The others don't look like they result from central sensitization. In

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fact, Ajay was making the reverse case, that they cause central sensitization. That's an important distinction to me.

What I'm thinking this list is about is if somebody is centrally sensitized, what phenotype does that produce, not what factors led to their central sensitization.

DR. DWORKIN: Clifford, did you have your hand up?

DR. WOOLF: I just think we're at risk here of defining central sensitization purely on the basis of fibromyalgia. Yes, that is part of the spectrum, but it's not the entire spectrum. Yes, there may be widespread pain, but, again, I go back to postoperative pain where it's not widespread, it's secondary. Hyperalgesia typically is in a limited [indiscernible].

I just think, yes, we got to capture the fibromyalgia for sure, but we've got to recognize that every feature that is present in fibromyalgia is going to be present in other clinical manifestations that include central sensitization.

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DR. CLAUW: If we do that, and I'm okay with that, then we have to eliminate number 2, and put that over on the other side, because someone with osteoarthritis with superimposed central sensitization doesn't have COPCs. They got osteoarthritis. They developed central sensitization.

I'm okay with that, but then let's just make sure that we put things in the right bucket. Then we'd have 1 and 2 as required -- 1 and 3 as required, and 2 and 4 and 3 as suggestive. But we can't have 2 as required because it doesn't occur in the people with OA or RA that develops central --

DR. DWORKIN: Is that our way forward, 1 and 3 required, 2 and 4 as frequently co-occurring but not required?

Mike?

DR. ROWBOTHAM: I think we can come up with a testing scheme with a variety of permutations to say presence or absence of central sensitization. But I echo what was just said. When you talk about

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fatigue, sleep, mood, cognition, it's hard to see how those directly follow from central sensitization.

DR. DWORKIN: So there's an emerging consensus that 1 and 3 would be required; 2 and 4 frequently co-occurring, but kind of not pathognomonic because there are patients who won't have it. I'm also getting the sense that ACTTION might have to consider over the next several months having a smaller meeting to come up with evidence-based diagnostic criteria for central sensitization as an important mechanism in acute and chronic pain, but that would be a smaller meeting probably at the O'Hare Hilton.

Kushang?

DR. PATEL: This is a minor point, but for the paper, can we give the exact definition of widespread pain according to different body maps that is acceptable? I can think of several different definitions.

DR. DWORKIN: We're going to start with the fibromyalgia APT [ph] criteria, where it was 6 out

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of 9? There was one other hand, and then we'll move on.

DR. BRUEHL: I'm sorry. We do 6 out of 9, that again, all these people with fairly constrained centralized pain, like OA, would not qualify.

DR. CLAUW: That's a threshold for fibromyalgia --

DR. DWORKIN: For fibromyalgia.

DR. CLAUW: -- and a threshold for central sensitization.

DR. BRUEHL: I mean, it's simply having one pain location with one additional one or not. I don't know what the answer is to that.

DR. DWORKIN: All of multisite pain; I don't know.

DR. BRUEHL: Yes, multisite pain.

DR. DWORKIN: Raj?

DR. RAJA: Sorry. I'm just thinking back on what Clifford said, that we need to include the whole spectrum, and then if you use widespread pain in postoperative pain, it's not necessarily

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

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sensitized, but it's not fibro. It's not the whole body.
DR. RAJA: No, but I can give the example of postherpetic neuralgia, where patients have allodynia and hyperalgesia. There is central sensitization, but it's not widespread. It's often dermatomal. So I think widespread may not fit the criteria.
DR. DWORKIN: John?
DR. FARRAR: No, go ahead.
DR. DWORKIN: No.
(Laughter.)
DR. DWORKIN: I talk only when you guys have nothing to say.
(Crosstalk.)
DR. FARRAR: I'm wondering whether something along the lines of the wider the spread, the more likely -- the higher the likelihood of it. The reason I'm bringing that up is --
(Laughter.)
DR. FARRAR: -- if you're interested
(Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dan?

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

DR. DWORKIN: I agree.

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

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evaluated, but it's not --

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

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

DR. DWORKIN: We will replace it, yes.

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

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

DR. KLEYKAMP: Okay.

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

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

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

DR. KLEYKAMP: Okay.

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

DR. DWORKIN: To the next, yes. Catastrophizing gets moved to the droids.

DR. KLEYKAMP: All right.

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

(Laughter.)

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

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Dan?

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

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

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

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

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

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

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

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

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DR. BRUEHL: Yes, but what we're talking about is potentially a clinical trial where the entry criterion is meeting this centralized pain phenotype, so you'd almost have to have some pain criterion. I thought when it said impact domains, that that's what it was talking about, was the pain intensity associated with central sensitization phenotype.

DR. CLAUW: Just to make it [indiscernible - off mic].

DR. BRUEHL: Yes, please.

DR. CLAUW: You're looking at central sensitization in knee osteoarthritis patients and you're looking at the degree to which that resolves after knee arthroplasty. I know this well because we have a lot of these ongoing studies.

If you don't separately rate pain intensity at the knee and all the other places in the body, you can't tell if the central sensitization got better because people, depending on the rate at which their knee is healing, they're sometimes rating their knee pain, they're sometimes rating

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their overall pain, but you really have a hard time figuring out what their most severe pain is and knowing what got better with the intervention.

So in fibromyalgia, asking a summary measure is fine because people hurt all over, but we do a lot of work with these regional pain conditions like OA and RA, and if you don't ask the intensities at different regions, or at least big body region, 7 body regions, you really get in a lot of trouble afterwards because one part of the pain got a lot better from the intervention, but other components didn't.

DR. BRUEHL: So you don't even need a global pain measure in most cases.

DR. CLAUW: In something like fibro, I would use a global pain measure because that's how people tend to write their -- but even Lesley was talking about examples where the woman's rating or headache or whatever, and not knowing what to rate or things like that. I think that it is helpful just because we're into these studies, and you see so many different times where it's hard to know what the

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patient was rating.

If you don't collect that data -- and again, I think we don't want to do a map where we're rating 45 sites, but rating 7 different sites, we do that now, and it just adds like 5 or 10 seconds to the burden because it only comes up to rate if they check a site in that area of the body.

DR. BRUEHL: Or maybe we could make it just more clearer, because I assumed, when you were talking about having the impact factors assessed, that that was a pain rating that in my head, I immediately thought, "Well, it's a central sensitization rating," which there really isn't one; I understand that. But I think maybe we need to be very specific.

DR. DWORKIN: Yes.

DR. BRUEHL: When you were assessing pain to identify this, you need to independently assess the intensity.

DR. DWORKIN: The reason I went back is depending on what kind of trial you're doing, an optimized trial of IBS, or of TMD versus the kind

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of basket trial where you might include in one trial patients with IBS and TMD and FM, the way you do your primary pain rating is obviously going to differ and meaning to say that. I think that's very important.

Any other comments about outcome measures? Raj?

DR. RAJA: Just a question -- going back to your, quote/unquote, "essential criteria," do the outcome measures capture those essential criteria?

DR. DWORKIN: I think they do. I know I looked at that at some point.

DR. RAJA: So you said 1 and 3 were going to be --

DR. DWORKIN: So we have to add, if allodynia and hyperalgesia are now specifically listed in 3, there should be a reassessment of allodynia, hyperalgesia also as an outcome measure.

DR. RAJA: That's where I'm heading. Thank you.

DR. DWORKIN: Yes, absolutely. Dan?

DR. CLAUW: Just for completeness, maybe in

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the last slide, the outcome measures, we should put one of the options people could use that COPC screener. You had it in a different place, but you may want to map that forward to outcome measures.

DR. DWORKIN: Okay. Right. So basically, we have to make sure that the outcome measure list includes the baseline phenotyping measures.

DR. CLAUW: Right.

DR. DWORKIN: Absolutely. Chris?

MS. VEASLEY: I've been intentionally quiet most of this meeting, but feel like I need to say something around outcome measures. The pain field in general has been very slow to bringing patients into the process of developing measures. And like Simone asked the question yesterday, do we know what patients think is important with these conditions? And we both have not done this for individual pain conditions, nor have we done it for people who have multiple pain conditions.

Particularly when it comes to outcomes, I think in terms of research recommendations, that needs to be added. There are some individual

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efforts, like with the FDA in TMD, right now to look at actually bringing patients into the process, and actually asking them what's important to them in terms of outcome measures, and including that. But in terms of this as well, I think it's a very important recommendation.

DR. DWORKIN: Thank you, because if there were no other questions, the next thing -- are there any other questions? Ewan?

(Laughter.)

DR. McNICOL: Sorry. You mentioned the outcome measures, fatigue and sleep. If I remember right, those were both outcome measures from IMMPACT I and IMMPACT II. So are you suggesting that we look at them differently or use different measurements?

DR. DWORKIN: Right. No, if they're in the IMMPACT I and II article, then I was just not forgetting -- I mean, I wasn't remembering. That's right. To the extent that they were recommended as secondary, or depending on the circumstance, outcome measures, that's really captured in the

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first bullet. Thank you.

So it's about two 2:45, and what I was going to say is we didn't realize that usually the last thing we do, the second afternoon, is to spend 15 or 20 minutes talking about a research agenda. Chris just mentioned getting some patient input, I think not only about outcome measures but about research design more generally.

So we could spend another 15 to 20 minutes on coming up with a bunch of bullets for a research agenda. We have some: risk factor or longitudinal studies of chronic pain transition, prevention studies, et cetera. The alternative is Dennis and I could thank you all for participating, and you could all send me emails with research agenda bullets.

John?

DR. FARRAR: I think I was daydreaming at the time and need to bring up just one other quick issue, which is that you went over analysis as though it were a minor point, and I realized that we need to do lots of things.

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I mentioned to you at the break that one of the issues in the analysis is the assessment of the effect and whether things are done as responder analyses or other things. The reason that I bring that up is that in situations where you have a poor definition of the group that you're studying -- and I would suggest that no matter how close we get to understanding centralized pain, the likelihood of defining the group we want is likely to be 50/50, meaning that you're going to have 50 percent of people who have what you're trying to have and 50 percent who might not.

We don't know what the numbers will be ultimately, but in every study I've ever done, there are groups who have the capability of responding and people who don't. All I would say is that in the analysis component of this, there needs to be at least a short description of the fact that there are ways to approach data and data analysis that improved the likelihood of discovering or being able to find those smaller groups as opposed to simply looking at standard

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

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

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

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

better and can be done, and maybe give you some better -- it's a nice research agenda thing.

DR. DWORKIN: If something gets replicated, I don't care whether it's in psychiatry, neurology, or pain, I'd love to see the article. But yes, I'm all in favor of doing it, absolutely.

Okay. Do people want to spend another 20 minutes on developing a research agenda or has everybody had enough and wants to catch the nearest Uber to the airport or the train station?

MALE VOICE: Bar.

DR. DWORKIN: What?

MALE VOICE: Bar.

DR. CLAUW: You can give the people that want to say and go over the research agenda the ability to do that.

(Laughter.)

Adjournment

DR. DWORKIN: I saw a lot of faces just staring at me, but one very vigorous no. So on the basis of the one very vigorous no that was kind of let's get out of here as soon as possible, Dennis

and I would like to thank you all for your participation. This was a great meeting. You will be seeing this manuscript over and over again until you're sick of it and us, and safe flights home everybody, and see you at the next IMMPACT meeting.

(Applause.)

(Whereupon, at 2:53 p.m., the meeting was adjourned.)

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