ACTTION IMMPACT XXIV - Pragmatic and Comparative Effectiveness Clinical Trials of Pain Treatments

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ACTTION

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

IMMPACT-XXIV

Research Design Considerations for Pragmatic and Comparative Effectiveness Clinical Trials of Pain Treatments

Virtual Meeting

Friday, October 23, 2020

12:00 p.m. to 4:30 p.m.

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P R O C E E D I N G S

(12:00 p.m.)

Introductions and Meeting Objectives

DR. TURK: Welcome back to the second day of the IMMPACT XXIV meeting. I'm just going to review with you the housekeeping details that we used yesterday just to refresh anybody's memory for those. To remind you of what the program was, for today it's going to start with the discussion of patient sources and eligibility criteria; choosing study sites; concomitant and rescue medications; and outcome domains. Those will be discussed by four presentations. There will then be a break, and there will be a panel discussion.

At the end of that panel discussion, we'll switch to the consensus discussion about what specific recommendations can be made for pragmatic and comparative effectiveness clinical trials of pain treatment. This is really the most important session of the two days. That's when we try to take the information we've obtained from the presentations and from discussions to try to begin

to guide what this manuscript will look like. There will be some coverage of summarizing certain points by those panelists.

For general housekeeping, just to remind you, questions can be submitted throughout the meeting by clicking on the "Ask a Question" button located in the engagement panel. After each presentation, five minutes have been allocated to answer any questions requesting clarification of information presented. Remember, those are the times to ask clarifying questions, but all other questions should be addressed in the panel discussions.

Each panel will include the presenters as well as two moderators. To participate in the consensus discussion, click on the "Consensus Discussion" button in the engagement panel. You will be directed to a new meeting page.

Per the updated policy that I mentioned yesterday about publication, to be a co-author, you should be attending both days of the meeting and at least 6 hours. To require additional information

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regarding that policy, you can contact Valorie Thompson at the email site that's up there. A list of the IMMPACT XXIV meeting participants and the two-day agenda can be found by clicking on either the "Meeting Participants" or the "Agenda" buttons within the engagement panel.

Please complete the post-meeting evaluation, which can be found by clicking on the "Feedback Forms" button in the engagement panel. As I said yesterday, and I reiterate again, we really want to learn from this meeting about what was the most effective and efficient way to conduct these types of meetings. So therefore, letting us know what was useful, what wasn't useful, and recommendations you would have, all of that would be useful information for us.

I want to thank you, and now we'll begin with the second day formally with presentations, and I'll introduce the moderators.

As you could see from the description of what we're going to be covering today in the agenda, we've moved from yesterday, in which we

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were covering some general principles, general concepts, and some examples of different programs that had been developed while looking at comparative effectiveness trials jobs or pragmatic trials, today we're going to be focusing on some of the details or logistics of what goes on in having to conduct those types of studies, specifically looking at things like how do you select patients and how do you decide upon outcome measures. Those are all important things in any clinical trial, but there are some unique characteristics that are important when we think about pragmatic and these types of trials that people are going to use.

Now, joining me in this session as the moderator, I'm delighted to have Dr. Karen Sherman. Dr. Sherman is a senior investigator at the Kaiser Permanente Washington Health Research Institute. She has a tremendous background in doing these types of trials, and she brings a lot of experience, knowledge, and insight to them. Karen's going to be helping us in moderating this particular session and potentially even throwing in

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some questions for us.

Now I'm going to introduce our first presentation this morning. He's a good friend, Dr. John Markman. Dr. Markman is a professor of neurosurgery and neurology. He is director of the Neuromedicine Pain Management Center and the director of Translational Pain and Research Program at the University of Rochester. Dr. Markman is going to start this off by discussing patient sources and eligibility as far as how we acquire, or enlist, or enroll, or get volunteers for these particular types of trials. So John is going to lead us off for the first talk of this session.

Presentation - John Markman

DR. MARKMAN: Good afternoon, everyone. I'd like to thank Dr. Dworkin, Dr. Turk, and all of you for tuning in for this presentation as part of this important IMMPACT XXV meeting. It's an honor to be here as always. My talk today is on Patient Sources and Eligibility Criteria. I've subtitled it, The Promis(e) and the Perils, and perhaps some of you will immediately get the double entendre of

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the PROMIS. But I will talk about both the opportunities here but also what I think are some substantial risks of this really important topic. These are my other relationships and disclosures.

I want to start with this image of something which I think all of the participants at this meeting -- the influential academics, the industry leaders, the powerful regulators -- probably all have in common. This is something which in America, and I think in the developed world, we all have a lot of stuff. This is something which we all know quite a bit about, I suspect. I certainly do. This is the junk drawer.

I want to begin by asking what do the electronic health record and the drunk drawer in your house, or maybe even your office or your garage, have in common? Just like the electronic record, the junk drawer is brimming with important things that you need to get by. It's old cords for that last laptop you had or maybe your current one; maybe the matches, or the highlighter, or the indelible marker, or the perfect Allen wrench size

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for that new piece of furniture which you've had.
But in the same way, the electronic record has all of this information, which is so critical at certain times, in there, but sometimes you can barely even open it, just like the junk drawer. You can't get into it, as you know, for those of us who use it every day. Oftentimes, you can't remember when you put it in there or you worry that someone else put it in there and didn't put it back, or took it out and didn't put it back.
So there's this crowded, brimming repository, the junk drawer, but it's not particularly well organized and hard to access, and I think this has important implications for the topic of my talk, this metaphor, of patient sources and eligibility criteria.
My talk, as I said, is broken into two components, The Promise and The Perils. The Promise is, I think, the following: that clinical effectiveness research or pragmatic trials with regard to study population allow you to maximize the external validity. You can include in your

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study the entire population, which the results will ultimately be generalized, hopefully.
So instead of using a trial of post-herpetic neuralgia as a proxy for everything that burns and tingles anywhere in the body as we currently do, you can design your trial so that you're not using a single condition as the lens or the lever through which you're going to try and extrapolate all the information. So that's the opportunity here.
So the take-home message of this talk is the eligibility criteria of your CER or your pragmatic study should identify a group that reflects that population that's ultimately going to be exposed, whether they're all in a certain age range, or they all have a certain sensory feature, or they all are going to get a certain treatment sequence or one or two treatments sequences. But the goal is to try and have that approximated.
Here's the simple formula. CER equals PRO plus EHR. That's really what we're talking about at this meeting. Clinical effectiveness research is the patient-reported outcomes, which are a

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mainstay of pain treatment because that's the gold standard of assessment, is self-report, and the information in the electronic health record.
The beauty of the electronic health record, as you know, is it really holds so many things: the encounter information; when it happened; who was in the room; what type of physician or other provider was in the room; the medications that were ordered; the procedures that were ordered or performed; the surgical history or medical history; and the problem listed. I think not in all systems, but in the future, it will also include the billing and authorization and all that information.
To get at that, though, for a system that's integrated, as they all are now, and large, for the most part, it's tricky. It's a real challenge to design and get into the world of the patients, in a large system with hundreds of thousands or millions of patients, and figure out the ones who have a chronic pain problem that's relevant to the question that you want to ask.

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I'm going to focus in this talk on chronic pain. I do think that some of these CER challenges and these medical record information extrapolation challenges, or extraction challenges, which I'm going to talk about today are much simpler and easier to execute for acute pain trials after, say, a surgery or a fracture, than they are for chronic pain just because it's harder to identify the patients of interest with a chronic pain syndrome because oftentimes there's no discrete onset from which to start from moment zero to query the record, the broad vast drawer, if you will.
This is a study from the 2010 time frame, which I relied on in designing a cluster randomized trial with my colleagues here. There weren't really many studies to look at, at the time, for doing a CER study in the Epic system to go in and query and find a filter for the chronic pain patients. So we relied on this one, which is actually very helpful.
This is a study by Tian, which says, "Using the electronic health records to identify patients

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with chronic pain in a primary care setting." Our study was, again, trying to be done in a primary care setting because we wanted to see how practice was done broadly across providers of varied professional formation and the types of questions we wanted to ask that were most relevant. We're looking for the broadest possible population, not a chronic pain subspecialist population.

What these investigators found is that if you just relied on the ICD-9 diagnosis at the time, now ICD-10, it really wouldn't be successful at finding the patients you were looking for unless you combined that with two other elements in the system. One was there analgesic medication and specifically short-acting opioids, and the other was the patient's pain score.

So when you took those three things -- the pain score; the ICD-9 diagnosis, osteoarthritis of the knee, post-herpetic neuralgia, tension-type headache, whatever that may have been; plus the medication used; plus the pain score at the time of that episode of care, that visit -- all of a sudden

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you had a filter which worked when they went back and did a series of corroborating steps to confirm that those, in fact, were the patients who had chronic pain when folks who took care of them every day looked at the charts. So this algorithm, if you will, really helped us in designing a cluster randomized trial to identify the chronic pain patients across hundreds of thousands of visits.

I think the notion of eligibility criteria for these studies, especially when they're done in silico, if you will, really relies on developing algorithms such as this one to identify who the chronic pain patients are and picking discrete data elements that you can aggregate to identify the population of interest. And again, the population of interest here is the one which will maximize the external validity of the results you have and the question you're asking.

This is a recent study, which is the sort of updated version of the previous one I just showed you. This is just very recently done in the Journal of Pain by some illustrious investigators.

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They were tackling a more difficult problem, even than the one I described; not just finding patients with chronic pain but, really, they wanted to think about ways to use filters to determine eligibility to, I think, get at a more difficult construct.

I picked this paper because I do think this is a type of study population which would be very difficult to identify, potentially, using our old single-site, single-investigator style of doing clinical research in an efficacy trial, if you will, at a bunch of sites across the country.

It could be done, but it can be done much more efficiently, looking for these, quote/unquote, "multiple overlapping pain conditions" to the electronic health record, or a query where you could just go in and see who had the six, or five, or two overlapping syndromes on their problem list, or using other techniques to see which descriptors or locations in the body conform with those other types of problems.

These investigators looked at ICD-10 codes and did a study of overlapping pain conditions

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which are familiar to all, conditions such as fibromyalgia. Some include chronic low back pain, or vulvodynia, or tension-type headache even. But the fact is that these are syndromes for which the risks and the natural histories seem to overlap, and this was an attempt to create an ICD-10 filter that would allow the design of trials in the future, where you could really examine a whole constellation of syndromes, which kind of come together, instead of picking one of them, a fibromyalgia study perhaps or a vulvodynia study, and just studying that condition.

So I think this is an interesting opportunity for the inclusion criteria and eligibility criteria for these future trials perhaps. So again here, the study of COPCs, or these chronic overlapping pain conditions, collectively rather than indexed conditions in isolation, is in its infancy. But tools like this one for eligibility may in fact accelerate it, and it may be done in a more facile way, if you will, in the new electronic record using CER techniques.

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This is a recent CER trial which got an enormous amount of attention, which I was struck by. This was a study of the Effect of Opioid Versus Non-Opioid Medication on Pain-Related Function in Patients with Chronic Low Back Pain or Hip and Knee Osteoarthritis; so again, a broader population, taking two of the largest pain populations in the universe, chronic low back pain and osteoarthritis of the hip and knee, and putting them together.

This was a study conducted through the VA and looked at patients over 12 months. What they wanted to do is approximate the patients in the Minneapolis VA system more broadly who are being treated for chronic pain, and they wanted to ask the question about whether pain-related function was improved by opioids to a greater extent than non-opioid analgesics.

One thing that struck me about this study, which you'll note here, is that the authors talked about the design of this study, a pragmatic design, and they talked about its advantages. They say,

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"First, enrolled patients had characteristics similar to those of patients receiving opioids in VA primary care, including patients with depression."

The interesting thing about this study, when I looked at it, was that they had screened around 4,485 patients and they excluded 4,220 of them. So even though this was said to be a representative sample, I was struck by the fact that virtually every patient who was screened was excluded, and these are patients who all had hip and knee OA and back pain, for the most part.

So when you go back and read this paper, you find out that patients who were on chronic opioids were ineligible for this study, and you also learn a couple of other things which make you question whether this really is going to be easily extrapolated and representative of a broader population when you're excluding 95-plus percent of the patients who are screened for this study.

So I think that just because something is done as a pragmatic design or a CER study, it does

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not necessarily mean that it will be germane to all the world of patients asking the question of opioids versus non-opioid medications because so many patients are excluded either because they had prior exposure to an opioid or some other criteria. But they did include patients with severe depression and PTSD because they thought those patients often do receive these medications.

So I think it's interesting that, again, the promise here of being broadly extrapolated is not always realized or, I think in fact if you look closely, may not always be as useful as it may seem on its face in terms of helping one make a decision about a broad population of patients.

Just a little bit more about the promise, as many of you know, the CHOIR registry is a tool which is developed and cultivated through Stanford, UPMC, Dr. Wasan, and others, who've really led the way in this. I think that these -- and I'm sure you've heard quite a bit about them already over these past two days -- are excellent in using this cross-sectional path modeling for developing

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hypotheses. We've learned that fatigue as measured by PROMIS is a mediator of physical function and pain interference, and the social role satisfaction mediates pain and anger.

So we've come away with these new hypotheses, which I think has been very useful. But I do think that the PROMIS tool, as I've seen it in my own institution and elsewhere, when it's broadly deployed also has some challenges, and I'll talk more about those in a moment. But the promise here, really, is that creating a dashboard such as this one, that records the key information with regard to pain interference and mood using a computer-adapted technology, allows for an efficient way for patients to record the totality of their experience.

This is the idea of Ajay Wasan's or Sean Mackey's junk drawer, which looks incredibly well organized on this sheet, and you know where everything is. You know where the pencil is, and you know where the scissors are, and you know where the rubber bands are. So you know where the pain

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intensity is, and you know where the opioids are, and you know what part of the body is affected. So you have disparate pieces of information which are all together.

We tried to do this here in the pre-CHOIR or right around the time CHOIR was first being introduced using a different jerry-rigged methodology, which used a scraping tool for the electronic medical record called i2b2. That would go into Epic, scrape the information out that we wanted, and put it into REDcap for our clinical trials.

So we tried to design a cluster randomized, controlled pragmatic trial using a simple pain assessment tool, where instead of asking patients of their pain intensity alone, what we asked them was whether their pain was tolerable, in addition to the numeric rating score. We wanted to see if pain tolerability was aligned with pain intensity and perhaps could open a conversation for patients about their chronic pain experience and give them more satisfaction. In fact, the primary endpoint

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of this study was the patient's satisfaction with the communication with their prescriber.

Again, this was a very large study across a few hundred primary care practices, where the cluster randomized ambitions for some of the other questions which we were hoping to answer really fell apart in the execution. Again, it spoke to the challenge of patient eligibility.

One of the ways we enrolled patients in this trial was through the patient portal. So a patient had to go into the portal of the electronic medical record prior to their visit and answer some information, and then post hoc could do the same. It just turns out that in that day and age -- and I think this has evolved somewhat but it's still a challenge -- the amount of use of the portal wasn't robust enough to support our goals in terms of execution for this clinical trial, and I'll talk a little bit more about why that was such a challenge.

I just want to say one piece about the

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execution of a clinical trial like this, a pragmatic trial which is conducted completely in the electronic health record. The people who do this trial are probably different from the people who do a trial in a research center, or an academic site, or a for-profit standing commercial research site because you're probably not going to have a former nurse from the cardiac care unit or the emergency room, who's now become a nurse clinical coordinator as part of your team, conducting this trial in an important way, because it's not like you can just walk over to their office and say, "Well, how many subjects do we have today? Any bites? Do we have anybody who's reasonable for this trial? Let's screen them."

Basically, what you get is a tranche of a couple terabytes of data every once in a while, and you sift through it, and you try and decide whether the answers are in there, and whether you got the right stuff, and whether that tranche of terabytes lines up with the information that was pulled out of the previous one. So you don't really have the

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same feel for conducting a trial in this format that you might if you were conducting it as an investigator on a site, and looking at individual subjects as they come through, a classic efficacy pivotal trial.

I think this is really important. The screening is totally different, as I talked about with these filters. It's really done in the background, and I think that's a problem if you don't have a good handle on how your filter is working. So it's really important to test your filter and make sure you're getting the patients you think you're getting.

This is one thing that we actually learned that was very successful. We used the Tian filter for this trial, and as I'll show you in a moment, it really worked in a sense that when you look at the diagnosis family here from these group of patients, they really look like the kinds of patients I would expect to see in a chronic pain population.

The vast majority of them had chronic

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musculoskeletal pain and disease of the spine. Well, we would expect that, based on the epidemiology, to be the highest groups in terms of prevalence. There is a significant chunk with diabetic neuropathy and other neuropathic pain conditions. We would expect that to be a significant but smaller epidemiologic chunk. We'd expect there to be a group that have headache syndromes, which is fairly sizable, and that's the case here with about 15 percent. Then there's a potpourri of other conditions which are in the lower numbers.

We rolled these up into these different groupings of 6 diagnoses families from the ICD codes. I think this gave us some confidence in the face validity of this method of using this filter, and we also interestingly found that the pain tolerability question aligned very well with the pain intensity on the numeric rating scale; that is that the increase in intensity of pain did kind of match, especially in the more severe ranges, with the decrement in pain tolerability.

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What's interesting is that there are many patients who have moderate to severe pain who find their pain tolerable, who may not need treatment, or at least that may be a conversation to be having. I think that was something we learned and we're continuing to explore.

So just a bit more about the perils, and then we'll be all done. The electronic health record as I know it is inconsistently used. As I mentioned, patients may or may not access the patient portal. Clinicians may or may not enter all the information which you think is relevant, and that's a real challenge.

I think that there's also a growing reluctance as a secular trend in our society, but also in our hospitals and our offices, of patients being extremely worried of providing extraneous information about themselves. If I'm here because these first three fingers are numb on my hand and I have carpal tunnel syndrome, I don't want you to ask me if I'm sad every day of the month, or I don't want you to ask me if I'm having some other

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psychic challenge. In fact, if you do that, I just may not answer that question. I may put the iPad in the waiting room down, I may walk out of the office, or I may be really angry at you for asking me that.

I think that in a world of good intentions and good will, it would seem like, well, this person is just trying to understand it. But I think there's a difference between asking a human being a question about how their life is going and making them fill out 7, or 4, or 6 questions on an iPad, especially when they're doing that all day long at Starbucks, and Chipotle, and every other vendor or large institution they're interacting with.

So I think there's a real wariness now to share this information, and I think it's growing. We're seeing rates of interaction with our PROMIS tool on iPads plummet. That was part of the reason I really liked the pain tolerability question because I thought it was a single question as opposed to this attempt to sort of wrap your arms

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around the entire experience of the patient. It was a single question to the patient, which if they were coming for a pain problem, had to be relevant to why they were there, and it was the springboard to a conversation and building a therapeutic alliance.

I think one of the challenges is if you ask a question on an iPad and you never follow up with a patient, you're just opening a set of doors for that patient, which may be disturbing and upsetting, which may make their pain worse, which may make their function worse, or just may be unsettling for them. And I think that we're prone to doing this more and more by asking a lot of questions, because we can, using technology. But again, I think it's counter-therapeutic, and I think that over time it may erode patients' willingness to engage in what otherwise could be a very powerful technology, to be included in ongoing studies in their clinical record.

I also just want to point out two other challenges. One is that documentation in the

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medical record is not just documentation by clinicians. It might be at a site in a clinical trial for an efficacy study. There's increasingly attempts to maximize the complexity of documentation in the clinical record, especially pain problems on the outpatient side, to maximize revenue or to maximize other examples. So the EHR may not be the real world; it may be its own world.

Here's an example for you, a distortion which is happening in the electronic health record at my own institution. We have found that the U.S. News & World Report's rankings relied extremely heavily on the Elixhauser Comorbidity Index. I have no idea what this was until I went to Grand Rounds last week. But it turns out that if you include certain codes, if patients have unacceptable, or bad, or difficult outcomes, that kind of puts some shade around that issue in the sense of explaining why this bad outcome occurred, potentially.

The way that your ranking is affected by this, the U.S. News & World Report system, is that

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if you're seeing high, complex, super sick patients, as this coding identifies, then whatever mortality is documented in your facility or other adverse events are documented in your facility are counter-balanced by the fact that you're seeing the most difficult complex patients; you're not just doing the simple appendectomy that was diagnosed early.

This has become an incredibly important driver of U.S. News and World Report rankings. What happens is that we look around the country and see other institutions which are soaring in the ratings on U.S. News and World Report and by other measures and have invested heavily in documentation specialists. What documentation specialists focus on -- our hospital has about 9 or 10, other hospitals have 40 or 50 or 100 -- they focus on maximizing the complexity of the encounter, adding in or rechanging the language, or finding ways to stimulate providers to change the language, through which they describe the interaction.

This is just a single example, but what I'm

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showing you is that there are other agendas which are driving the information in the electronic health record, which may, again distort how we can ask questions about a study population because they may be made to look sicker or different because they're serving some other agenda that the institution or the folks paying for the EHR have.

I just want to finish, again, with this comment about patients and their reluctance to share their information. This is an extraordinary book by Dr. Professor Zuboff on The Age of Surveillance Capitalism. The idea here is that patients are more and more concerned about providing information, which I do think is useful as clinicians and that you want to understand how someone is functioning or how they feel about their pain.

The idea that we're collecting this information as part of a clinical effectiveness research study, patients know that in de-identified -- or in some identified -- ways that is being repackaged and resold to insurance

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companies, and device companies, and other entities, which is happening around our country through these systems and is a dangerous prospect, and one which makes them clam up in a way that it would make any of us do that.

So I think that this is a real concern about eligibility and defining these populations for CER, and also for the ethics of it in helping patients understand that they are participating in large experiments, even if they just signed a waiver of consent -- that they sign with all the other user agreements when they walked in the emergency room, or walked in the hospital, or your office -- to use the portal, for example. But buried in there is the fact that they're part of some larger CER experiment. I do think that we are going to have to have ways to communicate this with patients and help them understand the risks, and more and more, explain to them how their eligibility and, yet, how their protection may go hand in hand.

I look forward to your questions, and I hope this was helpful in moving our conversation forward

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and ultimately producing a powerful IMMPACT publication, which will influence the way these clinical trials are done in chronic pain in the years ahead. So thank you all for your attention, and I look forward to speaking further.

DR. SHERMAN: Thank you so much, John, for a very, very stimulating presentation. We're now open for questions. Because of Dr. Markman's schedule, we're going to allow 10 minutes for questions, as he may not be able to make the panel later.

I'd like to start out with a question for you, John. I study chronic low back pain, and I don't always study the highest impact patients, so I would find your idea of recruiting patients based on pain scores, plus medications, plus diagnoses quite problematic because a lot of my patients will be using over the counters and that sort of thing.

I just wonder if you can comment on that. It sounds like you work with a more serious population. So just to get the ball rolling, I'd like to hear your thoughts on using the EHR for

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more of, say, a primary care kind of focus rather than opioids in particular, for example.

DR. MARKMAN: Karen, that's a great question. I think that Dr. DeBar's presentation yesterday leads me to my answer to your question, which I thought was excellent. She made the point that in these studies, the medical assistant, who often is part of the patient encounter in an outpatient setting, is a much more important player than they might otherwise be in other types of studies because they're sort of facilitating the sharing of the PRO information.

As you know, within Epic or many of these systems, the medication reconciliation component of the encounter is something which is entirely brokered in most places -- not always, but often -- by the medical assistant, and it's in that part of the encounter where that information is being shared because they're often asking the patients how many Advil do you take a day, or how much St. John's-wort do you take in October versus in the spring? I think that's where we tend to get

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that information, and it tends to be supplemented through something that the medical assistant puts in the record.

That's one experience we had. In fact, in the study that I mentioned here, the next phase of the study is really to see what happens when the medical assistant asks the pain tolerability question rather than doing it through the portal because I think that in this type of CER and pragmatic research, the medical assistant is moving into a more pivotal role because they tend to be able to, I think, in some ways curate some of the information on the PRO side that's going into the EHR.

So I hope that answers your question, but I think that's maybe one wrinkle that could begin to get to this issue of self-directed care and how it's documented.

DR. SHERMAN: Thank you very much.

We now have a question from Ian Gilron. It's a bit long. He thanks the organizers and presenters for an excellent meeting and he

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appreciates your talk very much. He loves your example of the seemingly pragmatic trial that excludes so many patients. It illustrates many of the conflicts we can encounter conducting future pragmatic studies.

He wonders, for example, if it could be that eligibility criteria in the study were defined in order to allow for valid comparisons between two different groups rather than just being extremely broad, and wonders moving forward, although the PRECIS-2 tool gives the impression that more pragmatism is better, do you think that different pragmatic features of a pragmatic trial need to be individualized to the specific research question of each study? Could you just elaborate on that for a bit?

DR. MARKMAN: I think, yes. Obviously, a brilliant question from Ian, as always, and thank you for the kind words. Yes, I think the pragmatic trial has to be tailored and the question has to be shaped in a very ad hoc way, whereas I think with an efficacy trial, we're asking oftentimes much

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more regimented questions; does this meet the John Farrar 30 percent reduction in pain intensity standard relative to another therapy or relative to some other gold standard which was not created from a composite or an amalgam of data? I think the reality is what is clinically meaningful and how to interpret that I think is going to be a little bit more sui generis for each pragmatic trial.

Also, I thought the comment by Ajay Wasan yesterday was particularly important, and I think this is underlying my answer to Ian's question, the idea that you need a modicum of efficacy to really enter into the pragmatic trial question. I think you need to feel like the efficacy box has been at least partially checked, maybe with a light pencil, before you really venture down the pragmatic trial route. I thought that was a really important point and, again, gets to this issue where we're trying to fill in all sorts of things with the pragmatic study, but you're not necessarily trying to answer what I think of as a very standardized question about efficacy.

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DR. SHERMAN: Great. Thank you very much.

It looks like nobody else has questions here in the box, so let me throw something out. Thinking about your dream study that's pragmatic, what would you like to do that you think the electronic health record doesn't quite allow you to do yet, and how would you like it to shift so that you can do that ideal study?

DR. MARKMAN: Interesting. That's a great, hard question. I kind of want to jump out this imaginary window right here; it's such a hard question. But let me just say, in honor of Ian, because he asked the last question, I think one of the most important sets of questions I think pragmatic trials can answer have to do with combinations of therapy. Ian is obviously one of the thinkers who's challenged us the most to think about how different treatments interact, both pharmacologic but also nonpharmacologic.

I think the kinds of questions that, really, this type of study can answer, in a way that really no other kind of study can answer, is how do we

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compare combinations of treatments or combinations plus sequences? Because I still think some of the essential questions about how to titrate medications or how to titrate them in combination are completely unanswered.

Again, these studies are particularly useful for clinicians faced with patients trying to make decisions. This is not trying to answer the binary question of does it work or not work by some threshold of efficacy compared to placebo. So I think for those types of questions, I really think the comparisons of treatment sequence and combinations is the key thing.

What has to happen in the electronic record I think is a more complicated answer. I think it's more about what has to happen to me and people like me. I found this to be one of the most challenging studies we ever did, and I think that if I were to throw myself into doing this all the time, I would really need to become more educated in how to be a study monitor for my own study.

When you put a filter in, or in this case

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where we used the i2b2, it's a little disconcerting when you run the same query and you start getting different results, and you don't understand why, and there's no easy way to troubleshoot that. For someone like me who can barely use Google Docs, the idea that I'm going to sit there and all of a sudden go through 5 terabytes and look for the differences in the data polls is really hard.

So I think what has to happen is my skills would need to come up in terms of my ability to access the information, but I also think a lot of work has to be done on the data management end to make people like myself, or the next generation of researchers, have a way of interpreting the information that's, frankly, easier. I think it is really a whole different set of skills and very difficult to analyze the information that you get when you're just pulling massive quantities of data from Epic, for example.

DR. SHERMAN: Great. Well, thank you very much again for an outstanding presentation and quite enlightening and thoughtful answers to some

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difficult questions that were provided. You've kicked off the morning in an outstanding way. Thank you again.

DR. MARKMAN: Thank you so much. I also just want to thank Valorie and her team as well, and Bob and Dennis. I just think this has been innovative and slightly heroic in the execution, and I'm honored to be a part of it as always. But I just want to acknowledge what a feat this is to pull this off. So as ever, thank you all so much. I appreciate it.

DR. SHERMAN: So it's now my very great honor to introduce Dr. John Farrar. He told me that the toughest thing was actually to say his name correctly. I'm sure I did not. Nonetheless, he's a very superb researcher and neurologist and epidemiologist at the University of Pennsylvania, and I'm sure his talk is going to be most interesting.

Presentation - John Farrar

DR. FARRAR: I'm John Farrar, and I'm at the University of Pennsylvania in the Department of

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Epidemiology, Anesthesia, and Neurology. I've been asked to talk today about choosing sites and investigators as part of the process of setting up clinical trials. Starting with my conflicts of interest, I do consulting for a number of organizations entirely about clinical trial design and have grant funding from NIH and a contract with FDA.

What I'll be talking about today is defining the issues and problems in selecting sites, and we'll talk about some criteria for selecting sites, and then some other considerations and conclusions. I just want to start off by saying that there is no absolute right and wrong here, and there are no exact definitions that will help you to select only good sites. But I'm hopeful that this presentation will help you think through how you might want to select different sites and have a more functional clinical trial as a result.

So let's start by defining assay sensitivity. You've heard some of this before, but it's defined by the International Conference on

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Harmonisation as "a property of clinical trials defined as the ability to distinguish an effective treatment from a less effective or ineffective intervention." I think this is important because we really need to think about all the components that go into a trial of which site selection is only one. Our primary focus when we're trying to achieve assay sensitivity is a reduction of the unintentional variability and bias in all aspects of the trial, and then the consideration of the role of the placebo-treated group response in the trial design.

Starting with what a clinical trial looks like, you've seen this before. Obviously, we're talking about the population of interest carried through to randomization into two treatment groups, following it with measurement and blinding, an analysis, and then interpretation. If you think about it, the site investigators are really involved in who enrolls in the trial and remembering that not everyone in the population is willing to enroll in a trial. The other component

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of it is that there are ways to avoid some of the problems that can occur with multicenter trials by having a central enrollment and randomization component that would be built into the clinical trial design in this location.

There are a number of different ways in which site selection has been thought about, and obviously pain management is not the only group that considers how to pick their sites. This is a statement from ASCO on the attributes of exemplary clinical trial sites, and they talk about the diversification, meaning a broad group of individuals not simply from one sex, one race, or one age, with a high accrual activity, previous participation in the clinical trial development process, and a group that maintains high educational standards.

This is an interesting issue. Obviously, ASCO very often targets academic centers, but they're really interested in people who continue to keep up with the medical literature. There's quality assurance, multidisciplinary involvement in

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the clinical trial process, and then, clinical trial awareness.

Another way of thinking about this is a survey of attitudes that was conducted in Europe. These are two of the columns in this paper, and the reference is here for your benefit. The investigator-driven activities that they were interested in was investigator interest in the trial, which is a very important component; previous experience with similar studies working with being able to include the trial in the workload that they are up against; and the recruitment and retention track record, which is a key component of what we need to look at, and then some evidence of involvement in publication.

Hospital/unit information is here, which you can review. It is not particularly pertinent to what we're looking at now, although academic centers certainly can be part of the clinical trials that we're interested in.

So what do we want to do in terms of recruitment? You've heard some of this already

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this morning with regard to the patient characteristics, but from the perspective of the site selection, we need to really think about the homogeneity of the population that we're looking at. While we're not interested in a completely homogeneous population, as we said a diverse population is better, we are interested in accuracy of the diagnosis. The patients enrolled ought to have the disease of interest and be of the character appropriate for the trial design.

How long the patients have had the disease, variation in this can be quite useful, and clearly patients with very long histories of disease perhaps are less likely to respond; baseline disease level, how much process or pain do they have at the enrollment; prior treatment and failures, which can be a significant issue in trying to enroll patients; and then psychopathology or psychological issues involved in patients that might be interested in enrolling and considering how to deal with those or to exclude patient. Obviously, the reason for the patient participating

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is a big part of that, and we need to really look at why patients are participating, understanding that there are a growing number of professional patients, and those can be sometimes problematic.

The other issue for a site is clearly the likelihood of study completion for the patients involved, and we'll talk some more about that as we go along. Site and investigator considerations include the role of the financial incentive in participation. If the finances are the primary driving factor, this could potentially lead to bias in the patients that are enrolled and needs to be considered.

In consideration of academic versus private practice, an interesting study that's listed here found that in depression studies, academic sites provided a larger separation of placebo and treatment effect. We know that a placebo response is a big issue in pain trials as well, and this may be important for us to consider.

Then there are issues of higher or lower recruitment sites, and a study by Irving found that

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higher recruitment sites tended to have higher placebo rates. This is not true of all sites, but it was a general finding and needs to be considered in thinking about how we pick sites. Then there are professional recruitment centers, and these are a growing number of groups across the country who basically make their living or have set up centers to handle clinical trials and are willing to try and recruit and work with any kind of patient population.

In terms of thinking about the components related to those characteristics, obviously as I said, the financial incentives are important and we need to be careful to design those incentives to appropriately provide incentive for screening, enrollment, and completion of the study; not simply getting patients into the study. We need to assure that the centers can accurately diagnose patients, and this very often requires that the investigators involve be expert in the area that we're studying.

Accuracy of previous treatment history, we need to know whether they have performed well in

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the past and that they collect history appropriately. An accurate and honest assessment of baseline pain intensity, and we'll talk a little bit more about this in a minute. Accurate and honest assessment of the willingness to participate. What I mean by this is that the patient shouldn't be cajoled into trying to participate when they're not really interested and could lead to more dropout.

Then there's the actual involvement of the investigator in the patient enrollment and study process. Having a good research coordinator is key, but the investigator has to take an active role and be willing to commit time and have time to be able to do those things.

In a paper recently written as part of the ACTTION and IMMPACT initiative on improving the conduct of clinical trials, a couple of interesting facts were looked at. One is that recent industry-sponsored trials include between 35 and 153 sites, which is quite a large potential number, and that the average number of participants

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recruited per site ranged from 3.5 up to about 11. This is the average per site. Clearly, there are sites that have recruited more than this. Then interestingly, site recruitment rates were independently associated with the placebo response as we talked about before in this article by Irizarry in 2009.

In thinking about the site selection criteria that we ought to be looking at, obviously, the number of sites we're going to need is going to be determined by the population prevalence of the target condition that we're looking at, and things that are rare will require a broader number of sites.

We should include sites with the track record of producing high-quality data. They need to be highly experienced clinical investigators and staff, as I've said, to make the right diagnosis and to know how to properly conduct a trial. They need to have the requisite resources areas to see the patients, the appropriate equipment to examine if there is special equipment that's needed.

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Site visits by the investigators who were planning the trial is an important component to confirm the experience and quality, so those are worthwhile. A little bit of prevention up front with problems identified on site visits can go a long way to improving the conduct of the trial.

You want to look for any previous citations by the FDA or others of the investigator that might tend to dissuade you from using that investigator in the trial, and you need to be cautious, especially later in trials, about implementing strategies to accelerate the recruitment or adding less-experienced sites.

As we know, recruitment is one of the biggest issues in these trial processes, and we're very often encouraged to try and increase the number of sites in order to improve recruitment. But one of the things that has been found is that participants enrolling towards the end of trials tend to demonstrate a smaller treatment effect.

How do you go about assessing sites and investigators? You want to have some idea about

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the interest of the group in the clinical trial topic. Groups that have patient populations that have the disease of interest are probably better, rather than those that have to go recruit, but both can play a role in active recruitment.

How many subjects have they previously recruited? Have they previously been involved in trials and how well have they done? Then, a record of the subject completion of the study, a really important component is not only how many do they get into the trial but how many of those patients ultimately complete all steps in the trial. It's that component that is actually probably the most important.

You want a record of study completeness. No site is perfect, but they ought to have a pretty good record of completing data collection accurately and the transfer of that data, as well as a rapid response to queries as they come about in the review of that data. Any recent changes in the investigators or staff might be a tip-off of additional training or there may be other

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considerations to think about, and then the willingness of the staff and the investigator to attend and pay attention to orientation meetings because we're coming to understand that training and understanding of how to conduct trials needs to be conveyed to even experienced staff because every trial is different.

In terms of assessing sites, one of the big issues sometimes considered is factors in the placebo group response. One of the issues is that larger placebo group responses for a particular site can be a result of some issues that are of concern, and these include encouraging or overstating the patient baseline. "I know, Ms. Smith, you're saying that your pain is a 3 today, but last week it was a 4, and wouldn't it be closer to a 4 today?" You want to avoid those kinds of discussions in recruiting patients.

An overly enthusiastic coordinator who presents the study in a very positive light might have the effect of creating a larger placebo effect. One of the ways of dealing with this is to

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have a standardized approach to how the coordinators discuss the study with the patient. You clearly want coordinators who are really actively involved and want to do the study, but we have to be careful about how things are presented.

Poor control for professional patients, we know that there's a growing issue of patients who are involved in clinical trials. Some of them may actually be involved in more than one trial at the same time, which is clearly inappropriate. There are some mechanisms now to help deal with some of these, but it's an issue that ought to be discussed with the sites.

For sites with lower placebo group responses, which is a good thing, probably, we have to be a little bit careful and make sure that they are not just recruiting only more severe cases. We know that more severe cases tend to have a lower placebo response, or it can, so one way of dealing with that is to look at the active treatment groups and to understand how those compare, and to understand that lower recruiting sites may also be

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recruiting only more severe disease.

In thinking about other things to consider, to reduce the site variability, staff training to standardize interactions as we've discussed and a centralized process for enrollment and decision-making. Consider for instance having a direct upload to the central site of the screening data such as the 7-day pain diary so that the analysis of that can be done centrally and not by the individual sites.

Pre-randomization run-in is a very important component to making sure that patients enrolled will be likely to complete the trial since they will have gone through all of the data collection; and then setting appropriate incentives, as we've talked about before, to make sure that we encourage all steps in the appropriate recruitment of patients; and then an ongoing monitoring for the validity of data.

I want to cover just two more things here that might be of use, and one of them is the statistical issues in site selection. One of the

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issues is homogeneity of patients within a site. We tend to pick sites in different areas in the country to try and get a broad sample of patients, including socioeconomic status, race, and sex. The treatment approaches to the disease of interest might be standardized in the individual site but different across sites, and that treatment approach might affect the results in a way that could be detrimental if we don't have a full set; and then location factors, urban center and a rural center can be very different.

Design approaches to mitigate the effect, sites ought to be block-randomized, which means that you get both treatment and placebo patients from all sites. Then statistically, there are three different ways to approach the sites. One is to ignore them, and that's not a preferred way, but you'd be surprised how often this happens. You need to model them perhaps as a fixed effect or model them as a random effect, depending on the statistical process that you're going to use to analyze the data.

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I'll finish with this, which is just to give you a few additional references of interest. One of them is on improving site selection in clinical trials, a standardized objective multistep method. Again, this is not specific to pain studies and may give you some ideas about how to go about selecting sites.

There's an optimizing clinical trial recruitment via deep learning that's interesting. We're beginning to apply informatic processes to be able to analyze the results of multiple clinical trials across multiple sites to come up with the criteria that might best suit specific clinical trial types, and this is just the beginning of that process.

Predicting enrollment of investigation centers, this is, again, looking at criteria that might help enrollment. Then this last one, which is an example of others that have been done, is actually looking at industry sponsors, looking at investigators, and looking at sites and seeing what they think is an important way to do this.

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So with that, I'll stop and see if there are any questions.

DR. TURK: Excellent presentation, John. Thank you very much for calling our attention to the numerous issues that are important in selecting clinical sites.

Before we go to questions, I remember that you said that you had a point or two that you wanted to clarify, so let me give you the opportunity to do that before we go to formal questions.

DR. TURK: Thank you, Dennis. Actually, this applies directly to the question that was put up by Dan Cherkin, which is that the presentation was really focused somewhat more on issues related to evaluating treatments. One of the things that is clear in thinking about my overall presentation and listening to yesterday's presentation is that there are some additional factors to mention.

If we look at the combination of John Markman's presentation and mine, John really focused on the selection of patients using cluster

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randomization and health records, which is clearly the way in which many of these studies are done. Looking at David Hohenschurz-Schmidt's presentation yesterday, only 9 percent of the studies done that were considered pragmatic included the placebo group, but over 50 of those studies included active controls.

I think the primary feature here that is missing is the consideration of cluster randomization in the selection of sites. Especially when you're studying usual care or when you're using sites, you need to understand what the standard of care is at those sites because the addition of additional care is going to be needed to be differentiated from what is different between the sites.

If you're using multiple sites, as was explained yesterday by Bob Kerns with regards to the Yale effort and using VAs around the country, it's going to be very important to make sure that the patient populations at those sites are cared for in a similar fashion, either matching sites to

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normalize those or accounting for differences in the way they are cared for in usual care in order to be able to differentiate what we're actually finding.

The other thing that was key in terms of what Bob said yesterday was that many of the studies that we're going to want to do are going to look at behavioral changes and perhaps nonpharmacologic approaches to the care of patients.

If there are studies that we want to do that are looking at pharmacologic changes, then we do need to get specific participation of each patient, and we can potentially randomize, if they're blinded, not so much by site but within site, in which case a lot of the comments that I made are directly applicable.

I think the primary issue here is to remember that pragmatic trials are not just about selecting the patients but are about making sure that the sites can adequately maintain care with those patients in order to be able to get the

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primary outcomes. In particular, with comparisons with a standard of care, how do you keep patients who are receiving a standard of care in a trial if you're required to get consent from them as opposed to using standardized data?

Then lastly, I would just say that one of the biggest issues in pain studies is phenotyping. John Markman talked briefly about how to use ICD-9 codes and other things, but we all know that the coding systems that are used in clinical care do not adequately phenotype our patients. So if we're designing trials, we may want to include other things -- patient-reported outcomes or different kinds of measures -- to help us define the patient populations we're actually enrolling.

So I'll stop there, Dennis.

DR. TURK: Thanks, John.

Let me just make two points before we go on, and that is, a number of questions have come in and we're not going to be able to handle all of those at this particular point, whereas with John Markman, because he wasn't going to be able to be

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in the panel, we went into some detail on some of those.

So some of the questions that you've asked and that people are asking, we may have to save for the panel discussion. Really, what we're hoping for after the presentation is more clarifying questions. So let me just throw out this one, and then I think we're going to have to move on.

John, what you presented was, as I said, very comprehensive and applies to randomized-controlled trials or efficacy trials, and I'm wondering do you see any unique things from what you presented about sites and site selection that are unique to when you're doing pragmatic types of trials. Most of what you're saying sounds fairly general to any trial, and I wondered was there any insight that you had about some specific aspects that were important for these types of comparative effectiveness trials.

DR. FARRAR: Well, I think the primary issue is that comparative effectiveness trials really generally work with centers and with groups. It

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may be a hospital group, it may be an academic center with multiple hospitals, and it's very unlikely to be using large practices or standard of care in a private setting.

However, there is a bias that we inject when we do that because, clearly, the majority of patients who are cared for are not cared for in academic centers or in large hospital settings, so we need to be very cognizant of the fact that we ought to figure out a way to include those sites.

The trouble is that the selection of those sites is going to include a lot of upfront work to make sure that their patient population is appropriate for the study we're interested and that their ability to maintain the patient population and complete the study is adequately supported by either previous experience or adequate training for the trials.

DR. TURK: Great.

As I said, there were a number of other questions that have been coming in, and we're going to have to save those for the panel because we need

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to stay on a reasonable schedule. So let me switch gears now to introduce our next presenter.

The next presenter is going to be Dr. Michael Rowbotham. Dr. Rowbotham is an adjunct professor of anesthesia and emeritus professor of neurology at the University of California, San Francisco. He's an attending neurologist at the University of California San Francisco Pain Management Center.

One thing I just want to say about all of these speakers that we're going to be having today, they not only are eminently known for the research and the quality of their studies, but also they all have clinical experience in working with patients. So they sit on both sides, and they know what it's like from the clinical perspective as well as from the research perspective.

Dr. Rowbotham's topic is going to be on concomitant and rescue treatments, which are commonly the consideration that must be taken into account if, in fact, we hope to be able to have some reasonable judgment and statements about the

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efficacy of a particular treatment.
Dr. Rowbotham, I'll turn this over to you.
Presentation - Michael Rowbotham
DR. ROWBOTHAM: Hi. My name is Michael Rowbotham at UCSF, and the title of my talk is Concomitant and Rescue Treatments. The first issue is where are we right now with regard to concomitant and rescue medications in prospective controlled clinical trials. I want to review several things at the beginning before we get into the specific trial aspects.
I want to talk about the Belmont report, which is what guides human subjects research committees and vulnerable populations and the issues around the ethics of placebo-controlled trials and some of the risks. For example, too many or inappropriate concomitant medications are a risk and too much or too little in the way of rescue medications poses a different set of risks.
I want to note that clinicaltrials.gov does a very nice job of providing summaries of clinical trial protocols, including sites where the studies

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are going to be conducted, but it doesn't list concomitant or rescue medications. This is true also when results are reported on clinicaltrials.gov. And just to jump ahead a little bit, only a small minority of clinical trial publications actually analyze and fully report this data.
The IRB review and informed consent is guided by the Belmont report of 1979 and it has three main elements. The first is respect for persons. The researchers are to acknowledge the autonomy of their research patients and to protect us with diminished autonomy. Beneficence is an obligation, and that includes both not harming research participants and to make a good effort, maximize possible benefits, and to minimize possible harms to research patients.
Third is justice, which really means who ought to receive the benefits of research and who ought to bear its burden; for example, studies conducted entirely in developing countries for medications that will only be available in advanced

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Western countries. Then subject selection, that it can't just be easy availability or subjects who are potentially in a compromised position or who are easily manipulated.
Vulnerable populations has a specific definition in the ICH guidelines, and it means those with a diminished capacity to consent or a willingness to accept very high risks in their search for a cure. Undue influences on the willingness would be highlighting benefits associated with participation in the study or the threat of retaliation in case of refusal to participate. This includes prisoners, detainees, medical students, lab personnel, and any employees of the pharmaceutical industry.
Other vulnerable populations include patients with incurable diseases. One can include patients with chronic pain in that category, especially for the ones where suffering is great and treatments are particularly limited. For example, complex regional pain syndrome and central post-stroke pain come to mind. Persons in nursing

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homes, minors, and those who are impoverished or incapable of consenting are also vulnerable populations.
Placebo and sham control clinical trials can be justified under certain circumstances. The goal of these studies is to determine both safety and efficacy of an experimental treatment. A placebo group reduces overall harm by reducing the total number of subjects required to prove that a treatment is both safe and efficacious. So the harm is lessened because fewer people are exposed to the potential harm.
Now, when it comes to concomitant medications and therapies, requiring subjects to discontinue all potentially analgesic medications may increase their pain, sometimes very substantially. That's a disincentive to participation in the study, clearly increases anxiety on the part of potential subjects, and it may increase dropout significantly before the experimental treatment actually starts.
Now with opioids, there are special

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considerations. Opioid tapering as an entry criteria can be difficult, especially if a patient is required to either taper off completely or to reduce their dose to a low preset amount. Opioid tapering can proceed at different rates in different patients. It depends on their willingness to accept withdrawal symptoms and potentially increased pain. In some patients, it might be very slow, requiring many weeks to taper to the desired level, and the protocol may not allow such a slow taper.

When it comes to opioids as a concomitant medication, it's important to consider what's the maximum does they've been on in the past. Some patients have been on very high doses of opioids in the past and they're probably not very good potential research subjects. Most trials that do allow opioids will require patients to be certainly much less than 100 morphine equivalents a day and usually at 30 to 60 maximum per day. When using opioids as a rescue medication, the decision has to be made whether or not to allow very weak opioids,

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such as low doses of codeine or hydrocodone, and whether or not to allow them to take very small doses or more substantial doses.

The other thing to consider with concomitant medications is medications that might duplicate the mechanism of action of the experimental medication is obviously a problem, and potential drug interactions with the experimental compound is also an issue. Of course, additive adverse events makes it particularly difficult to fully assess the safety of the experimental treatment.

Rescue analgesics are a difficult balancing act. A highly effective rescue drug reduces the treatment effect size, which makes statistical analysis difficult. It confounds the results if the active group uses less rescue but has no difference in pain scores from the control group. Of course, a completely ineffective rescue may violate the minimize possible harm obligation in the Belmont report.

Acetaminophen or paracetamol is frequently used as a rescue, even though nearly all chronic

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pain patients have tried it. Subjects can at least feel like they're able to take something, even though they know already that it's not very effective for their pain. I've already mentioned drug interactions with the experimental therapy, and of course you don't want adverse events from the rescue medication.

In current guidance available to us, the World Medical Association Declaration of Helsinki prohibits offering patients an intervention that is less effective than the best proven intervention. What that means is that patients entering, let's say, a phase 2A or a phase 2B trial of an experimental medication, it raises some ethical issues recruiting them to be in that study if they've not even tried well-established medications for their pain problem, especially if those medications have received regulatory agency approval from the FDA or EMEA.

The Consolidated Standards of Reporting Trials, or CONSORT, guidelines makes no mention of rescue medication. To quote from one of the older

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IMMPACT meetings the publication from 2010, quote, "If rescue analgesia is permitted, it is important to record and report the amount used by subjects, which may be greater in the placebo group in a trial of an efficacious treatment and should be considered in analyzing and interpreting the data."

Rescue and concomitant analgesics in placebo-controlled trials, a very important publication came out earlier this year by a group in Norway. The background that they gave was that in their search of 265 trials, they found that the proportion of trials utilizing a rescue medication has tripled to a level of 55 percent of trials in the past 20 years.

In their analysis, they looked at 83 trials for low back pain and 182 trials for neuropathic pain. In 43 percent of the trials, patients had to stop their usual analgesics before study initiation and also restricting non-analgesic medications that are often used for pain. That would include all antidepressants, anticonvulsants that can be used for pain -- so drugs like gabapentin or

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pregabalin -- but also sodium channel blocking antidepressants such as carbamazepine, and then also restricting non-analgesic medications that are also used by pain patients such as benzodiazepines.

Forty-eight percent of the trials allowed all or some concomitant analgesics. Only 10 percent didn't specify at all how prestudy analgesics were to be handled. Forty-four percent of the trials permitted rescue medication. Only 10 percent prohibited them completely, and the rest, it just was unclear; it wasn't adequately reported. Stand-alone paracetamol was more common in neuropathic pain trials, three-quarters of them. Strong opioids were more common in low back pain trials, but still a relatively small percentage, 28 percent, and 16 percent of trials permitted both continuing the usual analgesics, as well as rescue analgesics.

Continuing from this study, 38 percent of the trial reports didn't say if rescue use was quantified, 53 percent did not explicitly say if rescue used was an outcome measure, and only

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19 percent of trial reports fully included rescue medication use. Of the 126 trials allowing usual analgesics, 56 percent did not report on the actual intake. Of the 72 trials permitting rescue medication but prohibiting prestudy analgesics, 67 percent, two-thirds, did not quantify rescue medication use.

Still, more questions. If two patients report equal baseline pain intensity, one who's been taking significant doses of strong opioids and the other taking no analgesics, are they truly comparable? What if the concomitant medications include analgesic but non-opioid medications such as gabapentin and duloxetine? There's also the belief that multiple concomitant medications plus rescue analgesic medication decreases the potential effect size.

I note that Nat Katz in 2005 reported that trials restricting concomitant medications or rescue medications were more likely to report positive results. Why is that? Could it be subject selection, so that patients entering those

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trials had a different set of expectations around the effect of the study medication or because there was less confounding noise in the data from allowing these other medications?

This is a long list of rescue medication recommendations from the 2020 paper in Pain. For example, was rescue medication permitted? For what reason? Providing the brand and generic names, the allowed doses and frequency, the consequences for research patients of exceeding the allowed dosage, would they be withdrawn from the trial? Would they be considered a treatment failure in the intent-to-treat analysis?

Were there specific procedures, and how were the rescue medications or concomitant medications delivered; by prescription or were they over the counter? Who paid for these medications and how are they quantified? Was it by use or no use; days taking rescue medication; or other ways?

How was the consumption assessed? Was it by the patient self-report or by pill counts conducted by the investigator team? Was it used as an

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outcome? And if so, was it a primary or co-primary outcome? Was it a secondary outcome or was it an explorative outcome?

Was there a prespecified statistical analysis plan for this, especially if it was used as an outcome measure? Was the rescue consumption in each treatment arm reported? What's the statistical analysis, and was there anything in the discussion about whether the rescue medication might have influenced the trial results?

Here's a start at some recommendations. During the pre-treatment baseline period, especially if a placebo run-in period is included, don't have a different regimen of concomitant medications or rescue medications. It's not a good time to be making a change at the end of the baseline period. Also, the baseline period is a good time to ensure that subjects are able to carefully report and record all their medication use because this comes before exposure to the risk of the investigational treatment. Patients who are not good or inconsistent at recording other

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medication use may have the same difficulty when it comes to the investigational medication, so that's a red flag.

How do you consistently document concomitant medications and rescue medication use? Some kind of a standardized approach to incorporating into the statistical plan is needed. There are some older publications by White and others about how this can be done. Should this become a part of the standard CONSORT statement, and should it become a requirement for posting the study on clinicaltrials.gov?

Now, as an aside, when it comes to pragmatic trials or in-practice trials, as opposed to what we're talking about today, with randomized-controlled trials, you of course can't control for concomitant medications in the practice setting, and there's certainly no rescue medications because patients are using their usual medications in the course of their medical care. However, one can select subjects to include in a pragmatic trial based on their usual medication use for their pain

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problem.

That's the end of my talk. Thank you very much for listening.

DR. SHERMAN: Thank you, Michael, for a very interesting presentation. To sort of kick things off, a lot of your presentation seemed like it would be extremely important in an efficacy trial, but I'm curious how you would think about these specifically in the context of comparative effectiveness trials or pragmatic trials, which is slightly different from each other. So that would be a great kickoff question.

DR. ROWBOTHAM: Thank you, Karen. I thought a lot about that when I Was preparing this slide deck because there isn't very much information in the pragmatic trials literature on this, and as my presentation showed, it's really come very late in placebo-controlled trials.

I think one way of looking at this is to screen patients to see who fits into prespecified parameters, and that may be the kind of problem that was referred to in one of the earlier

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sessions, where thousands of patients were examined for their electronic records, but only a small number were actually included in the trial. So that may have been looking at specific medication characteristics.

Now, for looking at rescue medication, it's a little more difficult if it's a completely in-practice trial, where the investigators aren't necessarily going to be interacting directly with their patients. It's a little easier for concomitant trials. But if the study is, let's say, a cluster randomized trial and there is some kind of difference in the protocols from one site to another, then you can at least set parameters on what might be considered the equivalent of rescue medication use in those studies.

DR. SHERMAN: Okay. Thank you.

A question that's just come up from Bob Kerns, he's asking whether these recommendations should apply for nonpharmacologic trials?

DR. ROWBOTHAM: I would think so. They should be applied. For example, if the patients

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are usual medical treatment versus, let's say, yoga, or mindfulness, or acupuncture, then, again, you'd want to know in both patient groups how their usual medications are changing, their concomitant medications, especially analgesic medication use. So to the greatest extent possible, you'd want to include these in clinical trials that are pragmatic, independent of whether or not it's a pharmacologic or a nonpharmacologic therapy that's being studied.

DR. SHERMAN: It's interesting, Michael, because we're doing a study right now of acupuncture as a treatment for chronic low back pain in older adults. We'll be starting recruitment for the trial in January. As a pragmatic trial, people do what they do, and with back pain, as older adults, they may take more at times and less at other times. That's just sort of the background in which we're conducting our trial, but also the background in which primary care providers might make recommendations for acupuncture in the future.

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Do you have any specific comments on what kinds of things you think we might want to collect data on to monitor that kind of stuff, with that being, maybe in some ways, a more extreme end of a pragmatic trial but still quite realistic?

DR. ROWBOTHAM: When it comes to an experimental drug therapy where the investigational products have been custom manufactured and it's in very limited supply, you may do things like use SMART pills or SMART pill bottles to document intake. But when you come to usual, in practice, where patients may be using over-the-counter medications as well as prescription medications, especially if you have situations where two family members are sharing medications, let's say tramadol or a weak opioid -- hopefully, they're not sharing strong opioids -- you don't really have an easy way of quantifying how much they're using and when they're using it unless you go to the extraordinary effort and expense of coming up with SMART pill bottles or other kinds of electronic means to record when they're using those. You'd have to

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actually supply all their concomitant medications as well and have them turn in their usual supply at the beginning of the trial.

Likewise, for nonpharmacologic therapies, if patients are engaging in specific exercises in addition to acupuncture, or going to yoga classes, or things like that, how do you quantify that in any kind of meaningful way that it can be used as an outcome measure?

DR. SHERMAN: Yes. In our particular case, we asked them about those things, but they are some of the sloppier areas of usual practice, particularly with older adults, where they may be using more over the counters and that kind of thing.

I think probably we need to move on now, but thank you. That was a very, very interesting and provocative presentation and food for thought for the future as more methodology gets developed for pragmatic trials, how to think about concomitant medications in a more rigorous manner.

DR. ROWBOTHAM: Thank you.

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DR. SHERMAN: It's my great pleasure to introduce our final speaker for this particular session, and that's Dr. Matt Bair, who's on internist and associate professor at Indiana University School of Medicine. He also is a practitioner and conducts research at the VA in Indianapolis Center for Health Information and Communication, and also at Regenstrief Institute at IU.

So welcome Matt to talk about outcome domains, measures, and sources of data.

Presentation - Matthew Bair

DR. BAIR: Good afternoon. My name is Matt Bair, and I'm a core investigator at the VA HSR&D Center for Health Information and Communication, Regenstrief Institute, and an associate professor of medicine at Indiana University School of Medicine in Indianapolis. The outline for my presentation, I'll briefly discuss and review the PRECIS-2 tool, look at outcome domains, specific measures, and a variety of data considerations in the context of pragmatic clinical trials.

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In 2015, BMJ publication by Loudon and colleagues introduced a PRECIS-2 tool as a tool to design trials for clinical trialists. In brief, this was an upgrade from the 2009 original tool, which had 10 domains that was originally published by Thorpe and colleagues. It measures a variety of criteria from explanatory attitude, which is under ideal situations, to more pragmatic attitudes or usual care situations.

The PRECIS-2 is a well validated and improved version of the original tool. It has 9 domains and each domain or criteria is scored on a 5-point Likert continuum, from 1 being very explanatory or ideal conditions to 5, very pragmatic usual care conditions. This tool can be used by trialists to more easily consider whether their design decisions more closely match their intended purposes and goals.

This is a picture of the tool as depicted in a wheel with all the 9 criteria in the periphery of design decisions that we make as trialists and, again, scored on a 1 to 5 scale. This is an

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example of how a trial might score on each of these 9 domains. For this specific example, this is a fairly pragmatic trial because as you go closer to the hub, it's more explanatory, and closer to the periphery is more pragmatic.

Our own personal experience with the tool, we use this tool to organize our discussion regarding the study design of a planned tool, and this helped us to determine the extent of consensus among a group of study investigators. We had a two-day study investigator meeting at the Virginia Commonwealth University, and before the meeting, we read and reviewed these criteria. Then our research team made judgments of our planned study regarding each criteria to reflect our initial, ideal, and final study design perceptions.

In the end, we had a final study design, which was more explanatory than the preliminary plan, and this was a useful tool in which we achieved consensus through this process. We concluded that using and applying the PRECIS principles were useful for detailing points of

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discussion related to trial design; for making revisions to the design to be consistent with our project goals; and to achieve consensus through this process. We think that this could prove useful and valuable for other trial researchers.

Now, getting more into the meat of the topic and, again, guided by the PRECIS-2, talking about the criteria of primary trial outcome, again this can be on a continuum from explanatory to pragmatic. On the explanatory aim, a primary trial outcome might be much more of a direct consequence of a specific pain intervention, it's usually more disease or condition oriented, and it looks at underlying mechanisms. On the pragmatic end of the spectrum, these may be measures that are objectively or subjectively assessed. They're typically more clinically meaningful and more patient important.

What do we consider in terms of pragmatic outcomes and follow-up? Usually we're considering outcomes of longer term for trials of chronic pain conditions. Again, these are clinically meaningful

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to study participants. Typically, the follow-up is of a lower intensity that more typifies usual clinical practice, and the outcomes may also come from existing data without patient contact at all.

Considering selecting pain outcomes, there are several pain trial general considerations in whether to use objective outcomes or subjective patient-reported outcomes. From previous IMMPACT group recommendations, we know that there are multiple important outcome domains to assess in pain clinical trials, and there are other considerations when we look at measures specifically, looking at how responsive they are, what's the degree of respondent burden with these assessments, and how easily or uneasy is an integration into clinical workflow.

Looking at key outcome domains, I think we can make strong arguments from previous groups, especially the IMMPACT, that these are four very important key domains to assess in a pain clinical trial: pain intensity, pain interference, physical function, and pain-related change. This is

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consistent with previous IMMPACT guidelines for pain trials and looked at core domains for clinical trials of chronic pain treatment efficacy and effectiveness, looking at some core domains to assess, published by Dr. Turk and IMMPACT colleagues back in 2003.

Another study by Dr. Turk and colleagues looked at what do patients view as most relevant in terms of their pain outcomes. What's interesting is not only do they rate pain relief as important, but other factors as well as highly important, such as fatigue, enjoyment of life, emotional well being, et cetera. So not only do they want their pain relieved, but they want these other domains to be improved as well in a pain trial.

Given the frequency of comorbidities in patients with chronic pain, there are other highly relevant outcome domains to consider such as depression, anxiety, and sleep. Other relevant outcomes, again, depending on the goals of the trial, may include work disability, medication use or healthcare utilization, and health-related

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quality of life or well being. Given specific trials, there may be other important domains such as catastrophizing, self-efficacy, and pain coping that may be assessed.

In terms of specific measures within each of these domains, there are many different measures for pain intensity. These are certainly commonly used measures and representative of many pain intensity measures, although certainly not an exhaustive list, including the Numeric Rating Scale; Brief Pain Inventory, the subscale for intensity; and the Multidimensional Pain Inventory or MPI. In terms of other measures specific to the pain interference domain, the Patient Reported Outcomes Measurement Information System, or PROMIS; interference items are useful, the BPI Pain Interference Subscale, the PEG, which is derived from the BPI; and the MPI, as well as the Graded Chronic Pain Scale.

We have moved in our pragmatic trials to the PEG item largely because it was validated in primary care. It's ultra brief, only involving

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3 items in the primary care setting, which lends itself to pragmatic trials and trying to integrate within a clinical workflow. It's also advantageous because there's an intensity item. There's a well-being item, as well as an interference item with activity.

In terms of measuring physical function, there are many physical function scales out there. We've gravitated to the PROMIS physical function 4-item that looks at function across four different specific tasks. In the literature and through many of our trials, we've used a lot of these different specific physical function measures, such as Roland Morris Disability Questionnaire and the Oswestry Disability Index, which is most commonly used in low back pain trials.

Specific to osteoarthritis is the Western Ontario McMasters Osteoarthritis Index or the WOMAC. More generally, we've also sometimes used the Medical Outcome Study SF-36 Bodily Pain Subscale because it only involves two items; so again, an ultra brief that assesses severity and

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interference.

In terms of a specific measure related to pain-related change, a commonly recommended item is the Patient-Reported Global Impression of Change or PGIC. There are many different response sets for the PGIC. This is the one that we commonly use that looks at change on a scale of 7, 1 to 7.

Again, recognizing that depression is often overlapping with chronic pain, we feel it's important to assess depression in pain clinical trials: the PROMIS depression scale, the Patient Health Questionnaire or PHQ-9, or the much briefer PHQ-2. There's good evidence for the Beck Depression Inventory, the Profile Mood States, as well as the Hospital Anxiety and Depression Scale. Anxiety is often frequent in our patients that are trial participants with chronic pain, so assessment of anxiety is viewed as important; A couple OF measures here, including the Generalized Anxiety Disorder 7-item scale, GAD-7 or the GAD-2, as well as the HADS.

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We've also done ultra brief measures, looking at the PHQ-4 scale here, where it's assessing depression as well as anxiety concurrently, pulling 2 items from the PHQ-9 and 2 items from the GAD-7 to give a 4-item scale of depression and anxiety symptoms. We also recognize that sleep is a big problem in our patients with chronic pain, so assessment of sleep. Certainly, there are very good sleep measures in the literature that are used. We have gravitated to a much briefer assessment of sleep with the PROMIS Sleep 4-item scale.

This is a nice table that summarizes core domains and measures recommended by other expert groups regarding pain research. On the far left, we see the domain of interest, and then across the top, we're looking at these five expert groups from the NIH Research Task Force on low back pain, the IMMPACT group, the COMET group, the VA Evidence-Based Synthesis Program Report, and the VA Work Group. If you look at a specific domain such as pain intensity, they list in this table a

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specific measure, as well as the number of items of that measure in parentheses.

Just to highlight the VA work group led by Kurt Kroenke and Bob Kerns that I was fortunate to be a participant in, we generally recommended and gravitated towards brief and ultra brief measures, which might be more amenable to include in a pragmatic clinical trial and, again, reduce some of that respondent burden and potential interruption of clinical workflow.

Just a brief pivot to looking at reporting of pragmatic trials, the CONSORT extension document published in BMJ in 2008 looked at extending the checklist of items for reporting of pragmatic trials. It talked about 8 of 22 items from the original CONSORT statement that are unique to pragmatic trials. What's more relevant to my presentation is looking at the section on outcomes or item number 6.

When we're reporting, according to the standard CONSORT description, our outcome should be clearly-defined primary and secondary outcome

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measures, and when applicable, any methods used to enhance the quality of measurements, such as multiple observations or training of the assessors. The extension for pragmatic trials reads that when we report, we should explain why we choose these outcomes, and when relevant, the length of follow-up are considered important to those who will use the results of these trials.

So switching now to a variety of data considerations, especially in the area of the quality and completeness of clinical data for research, we need to ask what is the availability of data for research? Are there potential gaps in the data that could be a real problem with missingness or missing data in our analysis? We should also consider how consistent measurement of data is. We need to acknowledge that there might be significant heterogeneity of data across electronic health records and health systems that are involved in our clinical trials.

Other things we should consider as trialists and researchers is asking what is the origin of the

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data that we're collecting; why and how the data were collected; and gleaning information on the data's reliability and its meaningful use for research purposes.

I think it's very important, especially in the early planning phases, that we consider these data issues. We want to know is this feasible. These data collection methods, are they feasible? Are there going to be problems with availability of data, missing data, and gaps in the data? Can our data collection methods used for clinical purposes be repurposed for research?

We know that there are many different data sources we can use for our clinical trials, from patient-reported outcomes to patient-generated data such as actigraphy or step counts, et cetera, and clinical data derived from electronic health records. We can use administrative or claims data, or even registry data in our trials.

What should we consider when selecting a data source? We want to first and foremost know is the data source suitable to answer our specific

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trial question or questions. We may acknowledge that a single source may not be sufficient, so we should use hybrid data sources or a combination of sources, acknowledging that if we do use a combination or multiple sources, this will typically require more planning and greater expense of our trial.

Other data quality and completeness considerations, as Dr. DeBar mentioned in her initial talk, many pragmatic trials are working towards embedded electronic data capture, or EDC, embedded in the electronic health record or the use of brief electronic case report forms, or CRFs, which are automatically collected for trials. These are beneficial potentially because they may improve or reduce costs. These methods may improve efficiency of data collection. They may reduce patient and provider burden, and they may move the trial to give it a greater degree of pragmatism.

While these are exciting methods and promising methods, there are also several potential challenges using these methods, and using these

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methods may require early strategic agreements with sites, EHR platforms or vendors, and healthcare systems. There may be unique challenges using different EHR platforms that we need to acknowledge and anticipate, and we have to anticipate any potential interruption of clinical workflow. Certain, we should also be careful and aware that there might be information security risks using electronic data capture platforms.

In terms of best practices for data quality and some of the recommendations from expert groups, begin with a minimal set of core data elements. We want these core data elements to answer our primary and secondary questions for a given trial. Then if we do add additional data elements, we want to plan and anticipate how these additional data elements may affect clinical workflow.

For best practices, working towards integrating the electronic data capture systems into clinical workflow and being aware and managing information security risks. In terms of best practices related to study design, we as

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researchers and clinical trialists, we want to try and design our trials close to the standard of care. Again, this may reduce those potential gaps in the data that is collected. We want to do our best to limit the number of assessments, again, to reduce burden but also to simulate clinical practice as much as possible, and we want to identify what is needed to capture the primary outcome.

In terms of some best practices for data collection issues, again, it's recommended that we do our best to minimize participant burden in the context of data collection. We want to minimize provider burden and we want to identify and use a collection device or mode of collection most desirable for participants, which may involve a computer-facilitated hardcopy assessment or using a mobile device. Sometimes we consider using multiple collection modes, assuming that it's okay with the budget.

Switching a little bit to study monitoring, we need to acknowledge that there may be

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variability in the data quality across these data collection methods, there may be data gaps, and there may be delays in the availability of data for a study monitoring group or a safety committee, for example. This can really have important implications for trials with safety outcomes. For a trial that's looking at adverse events related to opioid treatment, this might be really important if there are data gaps.

Pragmatic trials are often moving towards a centralized monitoring approach or model. There are newer trials that are looking at a risk-based monitoring model, where they come up with predefined indicators of risk to participant safety or indicators of data integrity issues or trial conduct. If those predefined indicators are met, then it triggers a more in-depth evaluation.

Some summary points about data and the data considerations, it really all starts with good design and discussion of these data considerations right up front. We want to really focus on the primary outcome and how we can best capture that

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outcome with our data. As researchers, we want to try and continue to innovate and iterate on the best data capture strategies and try to evolve to more technology-based data capture in our trials.

Some overall summary points from my presentation, we talked about pain trialists can use the PRECIS-2 tool to consider whether their design decisions match their intended purpose of a trial. We talked and prioritized some key outcome domains in pain clinical trials such as pain intensity, interference, physical functioning pain, and pain-related change. Given the frequency of comorbid conditions, there certainly are other highly relevant outcomes to consider.

I generally highlighted briefer measures to be used for the outcome domains of priority and of interest, again, in the context of pragmatic trials. We discussed multiple considerations for data quality and completeness, and I highlighted some best practices for data quality and completeness as well.

I want to thank you for the opportunity to

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talk with you today, and I look forward to the discussion of some of the points I raised and other issues that we may discuss later on. Thank you very much.

DR. SHERMAN: Thank you very much for a very fascinating presentation, Matt. We have time for a few questions, and I'd like to start off with a question that's always plagued me as a low back pain researcher, and that is that patients tend to focus on pain, but as clinicians and researchers, we know that, actually, most of our treatments do a bit better job working on the function part, especially when we're looking at the nonpharmacologic therapies.

So I'd like you to comment on that with regard to the outcome measures you recommend and thinking about that in the context of pragmatic trials.

DR. BAIR: Yes, Karen, thank you. Thank you very much for the great question. I might start with, traditionally in clinical trials, pain intensity is generally the primary outcome. I

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think there's been a shift within the field where function and pain interference is gaining more traction as a primary outcome. At least personally, in our trials, that's where we're sort of gravitating towards as our primary outcome, is a interference function scale.

DR. SHERMAN: Great. Thank you.

Thinking about the challenges that we have in getting patients to fill anything out, even a 3-item questionnaire, does that argue for a special PRO data collection mechanism for a pragmatic trial or are you still playing with them in the context of primary care? How do you think about?

DR. BAIR: We certainly acknowledge patient and provider burden and do our best to limit it. That's why we've moved towards brief and very brief measures. We've actually found that patients, actually, really, at least within the VA, enjoy talking about pain and answering questions about pain, so we haven't experienced the patient burden of things as much as provider burden and provider engagement in our trials.

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We're still finding ways to try and engage primary care providers or actually the participants in a trial, how to better engage them because they are swamped. They have multiple convening demands and they don't need anything more on their plate.

DR. SHERMAN: So from that perspective, does that argue that some of the other domains that are important, like sleep and mood and things, are things that primary care providers actually don't want to know about at that time? Does that make you less enthusiastic about asking those questions or how do you think about that?

DR. BAIR: Yes, it's a great question. It's a real balancing act, isn't it? I think what's important to patients -- and from Dr. Turk's previous [inaudible - audio break], we've seen fatigue, sleep, and well being are very important to patients. But you bring up a good point. What are providers actually going to do with that data? Do they want the data? They've already received, at least in the primary care setting, a lot of data, and what do they want? Do they really to see

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sleep data?

I would argue if a patient is bringing it up to them that sleep is a big problem, that raises the level of awareness of a primary care provider to try and address.

DR. SHERMAN: Well, thank you very much.

We have a comment about the value of the PRECIS-2, but I think that would actually be fantastic for kicking off the next session, which is the discussion. In the meantime, we have a five-minute break for everybody, and we'll see you back here in five minutes. So thank you again, Matt, for a great presentation, and to all the speakers for this session for a very, very stimulating afternoon.

(Whereupon, a recess was taken.)

Panel Discussion

DR. TURK: That was an excellent set of presentations, really very stimulating and getting down to some of the specific details of what we really need to be doing as we think about these different types of trials.

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We're going to have a panel discussion now, but one person to add to the panel that has not been among the speakers is Penney Cowan. Penney is the executive director and founder of the American Chronic Pain Association, and she's been interested in working with individuals who have chronic pain and their significant others. Importantly, she doesn't use the word "patient" because she wants us to focus on these as people.

Penney, we're delighted to have you as part of this particular panel.

A number of questions have come in, and Karen Sherman and I are going to take turns trying to cover these and trying to go back to some we may have missed.

Karen, do you want to take the first one?

DR. SHERMAN: Sure. Here's a very interesting question. "Throughout the meeting, starting yesterday, we heard about the value of the PRECIS-2 tool that adds to help us understand any particular trial, how pragmatic it is or how efficacious because trials aren't one thing or

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another."

This individual wonders whether it would be beneficial if there was a self-assessment and justification of study-specific PRECIS-2 scores by domain within the methods of pragmatic study. So I'll just open this up to the panel and see what you all think.

DR. BAIR: I'll start, Karen.

Excellent question, very intriguing. We've personally found value in trial design and discussion, and I personally find it useful to review trials and proposals. But I think the question gets at potentially extending the CONSORT statement even more for pragmatic trials in the methods and providing justification for different criteria that are used in the design and the methods. I'm certainly in favor of that. I don't know how to move forward, but that's a really intriguing idea.

DR. FARRAR: I might comment as well. I think one of the advantages of the PRECIS tool is that it makes the point that there is no black and

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white line between efficacy studies or primary studies and pragmatic studies. It's obviously a combination, and every study is a combination based on how it's set up.

Also, as has been said several times this afternoon, it depends on the study design. It depends on the question you want to try and answer. The studies, as presented yesterday by Bob Kerns and others -- Karen, you were just talking about doing an acupuncture study -- there are studies that are looking at adding on therapy to a standard of care, and that's obviously very different than trying to go into a large group of patients and randomize them to two different kinds of pain medications or different from maybe setting up a process of working one's way through the treatment paradigm for back pain to see if we can improve overall care.

So in addition to simply trying to specify where our trials fit in this sphere, I think it's also very important to think about how those differences will affect the way in which we'll

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design the trial, the way in which we'll select the sites, the methods we'll use to select the sites, and how we go about structuring and actually conducting the trial. But at the end of the day, we have to be able to collect good data as outcome, and we need to get reasonably complete data. So I think it's going to be important to keep those things in mind.

DR. TURK: Let me take the next question. This came in from Dr. Howard Fields. Howard, thank you for this. This was a question that came back a little bit earlier on, and I'm not sure if anyone wants to take this on because I don't think John Markman's here, and he was sort of the one this came up from.

Howards says, "It's pretty clear that a given diagnosis with objective criteria can either result in pain or no pain, for example, carpal tunnel. Low back pain, there's no correlation between imaging and pain. How do you deal with the issue in a clinical trial when you're trying to come up with the appropriate patients to include in

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these particular studies?"
I'm not sure whom might want to take that on.
DR. ROWBOTHAM: I can attempt to answer Howard's question. One is there may be a specific ICD code that adds pain to structural abnormalities. That's one clue. The other -- and this is done in some national databases like in Denmark where they have a prescription database for everybody as part of the national health care -- is where you can look for patients based on whether or not they're getting any prescribed medication.
So let's say if a patient has a herniated disc and low back and they're also getting opioids, you could try and exclude other pain diagnoses by looking at the codes. And if you find that there aren't any other ones in the patients receiving opioids, you could infer that they're receiving the opioids for a diagnosis of low back pain. But it is a lot of work, a lot of extra work, especially if the pain diagnosis doesn't have a separate code or that code is missing from the electronic health

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record.
DR. FARRAR: I'd make another point here, which is that many of the pragmatic trials we try are focused on trying to understand how to treat the patients as being seen by primary care physicians and in the medical circumstance. My answer to Howard is that the purpose of the studies that he's talking about is to try and understand what causes pain and what doesn't, and what leads to issues needing to be treated and what doesn't.
I think the approach of pragmatic trials is really focused on the patient who comes to the doctor saying my back hurts, and it's not going to catch the patients who have significant back pain on an MRI or CT scan but who don't have pain. Now, that's completely reasonable if the target is how do I treat the patient who's got pain as opposed to trying to understand the reasons for the underlying pain and what to do about it.
Would you agree with that, Michael?
DR. ROWBOTHAM: Yes. I was just thinking of another thing as you were answering. One thing

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that is a problem in pain clinics is even in a setting like that, standardized questions or simple questionnaires are often not collected from patients. Sometimes the best information you get is from readouts on a pump, an intrathecal pump, or use patterns for spinal stimulation. So even with our pain colleagues, the clinicians, it's hard to get them to collect relatively standardized data from their patients.
DR. SHERMAN: I'll take the next question, which is also one from a bit earlier that came in a little late. This is for John Farrar from Bob Kerns, suggesting that "a significant challenge to recruiting sites in pragmatic trials is that some of those that are maybe under-resourced but also very important for the population, they may not be academically affiliated, or they might be in more rural areas serving very vulnerable individuals, so they may have chronic pain and high-impact chronic pain in particular, but that makes it more difficult to engage them in the way that you talked about in your nice presentation."

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Dr. Kerns would like you to comment on this.
DR. FARRAR: Yes. This is a key issue in any trial design, which is that the internal validity of the design depends on treating the patients who are actually enrolled in an appropriate way to compare groups, either the standard of care and a new treatment or two different treatments.
What Bob's talking about is the ability to extend beyond the patient population that we normally use to other populations. The honest truth -- and you probably know this more than I -- is that you need to end up going and selling what you want to do in some of these locations.
If we can design the trials in a way that's simple enough and straightforward enough, without too much procedural difficulties for smaller environment practices to participate, we ought to be able to get data. But it does mean that we have to be careful in interpreting our results and interpreting them clearly to the group that were included in the trial, and that we really ought to

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work hard to try and extend important treatments out to other areas to be sure that they work as effectively there.

DR. TURK: Let me take the next question. Since Bob Kerns seems to on a roll, I'll give him another opportunity, although there are several more from him.

Bob said, "I tend to agree with Michael's answer, the caveat that obtaining reliable data about medication use could be burdensome and challenging. And I would say it's not only about medication use, but it's also about all types of other alternative treatments that people are taking as concomitant treatment or trying on their own.

"So how do you deal with the problems of the reliability of determining what other treatments patients are receiving in addition to, but not just, medication and other alternatives that they may be using?"

DR. ROWBOTHAM: Yes, this is an age-old question. I still have my prospective new patients fill out a long pain questionnaire, and Howard

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knows all about this because we worked on it together many years ago. Some patients just refuse to do it, but most are very happy to do it. It includes things like a body diagram and a listing of all the physicians that they see and all their concomitant medications.

Really, a lot of the clinical interview time is spent going over that questionnaire and trying to really pin it down; so you see this doctor; what do you see him or her for; do they prescribe any medications? Then going back through their prior treatments is even more difficult. They may not remember anything they've taken before. If you ask them if they've taken an antidepressant for their pain, they may not remember the name of it. They may be very vague on how long they took it for or how high a dose they were getting.

So historical data is pretty difficult to get. Hopefully, when you start some kind of a prospective new treatment, even if it's in the setting of a pragmatic trial, you have to set the baseline right then, and then do your best to try

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and collect the data with each patient visit. That's where scribes, physicians assistants, and other kinds of staff in the clinic really are very helpful.

It's also a place where we're assisted by the fact that for many different diseases, the treatment environment is quite standardized. For example, there may be a special diabetes clinic, or if a patient is being treated with opioids in some healthcare systems, probably not enough of them, those patients are enrolled into a special clinic where their opioid prescribing is consolidated and they're assessed very carefully at each clinic visit.

DR. TURK: Let me just follow up on that. With the advent of electronic medical records, at least maybe we will be able to have better information regarding prescribed medication, they being prescribed to other treatments that are available, and not rely on the patient's memory of what they have received, what they tried to do, and how much they took of these things. Now, it

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doesn't mean people took the medication the way they were supposed to, but at least we know what they were prescribed.

DR. ROWBOTHAM: Yes. I'd actually like to get the opinion of the other panelists on this one. I find electronic health records to be just really a thorn in my side. It is so hard to get information out of them. They just go on and on and on with regurgitated information, and very often the patient comes in and their medication list is just regurgitated from the last visit, and you don't really know if the questions were asked again.

I mean, I've seen examples where the neurological exam at the initial evaluation keeps appearing over and over again and looks like the neurologist has done this complete evaluation every single time, and you know of course that they haven't; and you have to look at the attending notes, if it's a teaching clinic or something else, at the end to realize that they may have only spoken to the patient and not done any examination

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or just done a very limited examination.
So the electronic health record could have all that data in it, this kind of softer, more subjective data, but it often just doesn't. I'd be curious as to what everybody else thinks about it and if they've got the same rant as I just gave.
DR. BAIR: I'll just start, Mike. We've generally looked at concomitant treatments, co-interventions during trials, and I have to confess it is not real pragmatic because we've done, like you guys do, you and Howard, a baseline treatment questionnaire, so that's self-report, patient self-report. But then during the conduct of a trial, we'll do a combination of either the EHR to look at medications, as Dr. Turk was suggesting, and consultations for different nonpharmacologic treatments. We even do a hand, chart review.
So it's very burdensome, time-intensive, and not very pragmatic. But we've also been pressed by journals that they want to know about these confounding co-interventions and are they the

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explanation of the results were seeing. So we're being pushed by journal editors and reviewers to provide that data, so we've done a hybrid self-report and EHR query.
DR. FARRAR: Michael, I think that's a key point, and I say over and over again that the EHR does not stop the -- and in fact it encourages the copying of data over and over again. I'm sure you've had the example where somebody shows up with the neurologic exam saying normal and they're in a wheelchair because they can't walk.
But there seems to be three separate points here, and let me address them very briefly. One is the complexity of the medical record. We had actually a data informatics group that's working very hard to come up with text, interpretive procedures, and learning diagrams in terms of trying to understand and be able to access that data that doesn't do what Matt was just saying, which is hand-review all of those. That does not get rid of the issue that you brought up, which is that we really don't know when medicines were

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started or stopped because the medical record, people don't take the time to fill that out accurately, so it's somewhat hard to know.
Then the third issue, which was brought up in one question by Sean Mackey in terms of thinking about how to recruit patients and the databases, the CHOIR system that he put together captures, really, quite an extensive amount of information, but it's about a very limited population. In our own clinic, we collect certain outcomes on all the patients that we see in the pain clinic, but that doesn't include the patients that go to primary care, where that's not the routine.
I would actually ask Matt whether in his experience he's been able to get even a small amount of data, a PEG or anything, collected on a majority of patients seen in primary care.
DR. BAIR: No. We have the NRS, so it's routinely collected in clinical practice. There is a push within the VA by pain research and pain clinicians to implement the PEG routinely, but right now that's implemented in certain pain

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clinics or rehab clinics but not routinely yet, but that's the push.
MS. COWAN: Can I add something to this conversation? What I have found recently is that a lot of healthcare systems have patient portals, where we go in and actually review all that information before we even have our appointment. Now with COVID and the need for those virtual visits, they call you ahead of time, and somebody in the office goes over all that.
So the provider already has all that information. I'm not sure how that works in the clinical trials, but I know that in a couple big healthcare systems here in the area where I live, that's exactly what they're doing. So everybody has already reviewed it before you even get there. The other thing is that a lot of times the information that they put down, depending on the person, is not correct.
I just wanted to add that, that medical records are great, and if you're going to two different healthcare systems you have a crossover

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that they don't know. They don't have access to your information either, so that's another problem.

DR. ROWBOTHAM: I don't think this is a surprise to anybody who works with the electronic health record, but they really were originally built as billing systems, and they work very well for that. They're great for organizing lab tests, imaging, and those kinds of things.

For clinical reports, they're pretty good for procedure records or surgical records, but when it comes to routine follow-up visits, for collecting the kind of data that we're interested in -- pain, concomitant medication, and how they're actually using the medications that have been prescribed and maybe even filled -- the records really start to break down.

MS. COWAN: I would agree with that.

DR. SHERMAN: Okay. Let's move on to the next question, which is directed to Matt, wondering what you, Matt, think about John Markman's comments about patients being unhappy sharing personal information. Have you seen this as an issue in the

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VA?

DR. BAIR: I can't generalize. Again, my experience is somewhat different in the VA. Most veterans -- again, not all; we can't generalize there and one size fits all -- are pretty open and very brutally honest about their pain experience and want to tell us, so I haven't experienced that. However, from a data security issue, the VA is very particular about data-sharing issues that Dr. Kerns alluded to yesterday, sharing across healthcare systems and sharing outside. That's more at an organizational level, but at an individual, veteran level, I have not actually found that.

DR. SHERMAN: Okay. Thank you.

DR. TURK: Karen, let me take the next question. I want to apologize to people as these come in because they're coming in, in different orders, and sometimes they're related and sometimes not, and sometimes they're duplicates. So we're trying to read through them as best we can. If we don't get to your question, we apologize; we're doing our best.

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This is a question that I guess is to anyone on the panel. "PCORnet, funded by PCORI, contains a standard set of harmonized, EHR variables, where many healthcare systems in the country are funded to maintain and use for pragmatic studies. Any thoughts or experience anyone's had they want to share about using this particular system?"

DR. FARRAR: I can start just to say that we had implemented in our own pain clinic a set of questionnaires targeted at pain, function, depression, and anxiety, and we've used the HEAL Initiative and the network being pushed by NIH to encourage their inclusion in a broader range of health assessments. We've actually had some success with that in that we've got at least a portion of our primary care physicians asking their patients to either go online beforehand, as Penney Cowan was suggesting, and fill in some of these forms.

But to be honest, it's nice that PCORnet has asked these healthcare systems to maintain these measures, but I don't know how successful they've

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been in actually getting them to make a significant dent in getting them answered on a regular basis. I don't know if anybody else has any experience.

DR. BAIR: I personally don't have experience. Certainly, PCORI and others, the VA, DoD, NIH, Pain Collaboratory, and Data Harmonization, issue full support of that. We can have data elements that are first standardized and cross-cutting across our pain trials so that we can potentially compare similar outcome variables and outcomes. I'm fully supportive, but I don't have personal experience with PCORnet.

DR. SHERMAN: Let's move on to another question that was asked by Howard Fields. I can't quite tell when this was asked, but he notes that, "In general, treatments for pain have one of two targets. It's either the underlying nociceptive source or the CNS pain transmission or pain modulation circuits. Do you think the design of clinical trials would benefit by having an underlying mechanistic hypothesis?"

I assume he means pragmatic or comparative

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effectiveness trials. So that's open to anybody who wants to take a stab at that.

DR. FARRAR: So let me start, and then maybe Mike can jump in here. Howard, we all understand and completely agree that in trying to understand and treat pain effectively, we need to understand the underlying mechanisms. But I think that the pragmatic trial and the comparative effectiveness end of things is really trying to get away from the specific underlying etiology towards what's actually seen in practice.

Ideally, we'd have markers that you could send away a panel, like a comprehensive panel of blood work, that would give you an answer to this question, but we don't have that. So I think where we are is thinking about the outcome of the trial and what we're trying to understand. And it seems to me that if you're adding in physical therapy to all of the therapies that are given for back pain or for osteoarthritis, it is overly important to know the specifics of the etiology of the pain. I mean, it would be nice, but it's not the main

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intent.

Obviously if you're studying specific therapies, then knowing what the underlying pathophysiology or the etiology of the pain is would be helpful, but even there, the question that might be asked is does adding this to the full group of patients with back pain make a difference? We may back into understanding whether adding that particular therapy actually explains some of the underlying ideology.

Mike?

DR. ROWBOTHAM: Yes. I have two thoughts about that. One is when it comes to industry-sponsored trials, especially early phase trials, phase 2A, there's always a lot of discussion at the level of the sponsor, and if they bring in any expert advisors, as to what is the right pain syndrome or syndromes to study with this potentially new or first-in-class medication, based on its proposed mechanism of action. So that discussion happens at that level, but those, obviously, are not pragmatic trials.

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When it comes to pragmatic trials, it depends on the intervention you're looking. This is where the discussion earlier about nonpharmacologic therapies gets interesting. For example, let's say that you are treating patients with low back pain with yoga or mindfulness; let's say a combination of yoga and mindfulness because they overlap. So you're attacking the source of the pain transmission in the form of very tight sore muscles, the pain transmission in the periphery that way, but there's also the CNS benefits of the patient relaxing, anxiety reduction, mindfulness, and other kinds of things that you would look at as being in the province of the pain modulation circuits.

To sum up, I think for some medications, if we're doing a pragmatic trial, we may be looking at one and not so much at the other. But when it comes to a number of therapies, especially the nonpharmacologic ones, we're probably looking at both at the same time.

DR. SHERMAN: Yes, I would certainly agree

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with that, Michael. There are a number of theoretical papers on how yoga might work with various types of circuitry, including peripheral and central mechanisms, and the same thing with mindfulness and how they may overlap with each other, and they go into more or less detail. But certainly, the notion of what we call bottoms-up, from the periphery inward, and top-down, from the central nervous system outward, being operative in a variety of non-pharm therapies seems to be at least hypothetically possible.

DR. TURK: Okay. Let's move on to the next question. The PRECIS measure has come up a number of times. Someone -- and I can't tell who asked the question -- said, "Thanks to the presenters, throughout the meeting the value of the PRECIS-2 added interpretation and validity of pragmatic trials has been emphasized. Would it be beneficial if there were a self-assessment and justification of a study-specific PRECIS-2 score by domain within study methods of pragmatic studies?"

DR. BAIR: Yes, Dennis. I think we covered

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that initially, and I am certainly supportive of that. Potentially, it might be an extension to the CONSORT extension for pragmatic trials, where some assessment and justification of PRECIS' criteria would be involved and included in the methods.

DR. SHERMAN: The next question, actually from our comment question from Bob Kerns, follows beautifully off of that. He notes that, "There are going to be protocol papers for the 11 pain management collaboratory trials that are going to be included in an upcoming supplement to the Journal of Pain Medicine. All of them include a PRECIS-2 figure that attempts to convey what the PI thinks is happening in that particular trial." He suggests, "Their experience in these ratings are, of course, objective, and the reliability across trials may not actually be all that great; though, I don't know that a formal study has been done."

So that opens the field a little wider for a few more comments in that area.

DR. BAIR: Bob, that's great to know about this upcoming supplement, first of all, but I'm not

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aware that there's been a look at inter-rater reliability; if they have two raters looking at the same trial and a specific criterion, what the inter-rater reliability is. I assume it's going to be at least moderately correlated. In our experience with PRECIS, we had 11 investigators, and we were fairly consistent in our ratings, but we didn't do a formal inter-rater reliability. It was just sort of by the eyeball test.

DR. FARRAR: I would ask Matt maybe to comment, and maybe Bob can discuss this more in the general session later today. But does it really matter if we know whether it is more pragmatic or less pragmatic? It seems to me that the issue is designing the trial that is ideal for answering the question, and to the degree that we can make it more generalizable and more pragmatic, that's a great idea. But honestly, does it make a huge difference whether it is a little closer or a little further away from the hub on this measure?

I think this is a way of looking at studies that have been done and trying to maybe in

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correlating those studies using a meta-analysis or some other combined analysis to be able to state what kind of trial it was. But in the actual design of the trial, it seems to me you need to design it to answer the question you want to answer, and then put it into a format.

So I'd ask Matt, or Michael, or anyone else, really, about whether we think it matters at the beginning of the trial process to say, okay, I want to do a pragmatic trial, unless that's the right way to answer your question. Karen, I'd ask you, too.

DR. BAIR: Yes, John. I think that's a great question. I think it might matter from maybe David's presentation yesterday, looking at someone that's doing a systematic review and trying to categorize a trial as pragmatic versus not. So it's sort of a systematic review, and researchers that do those, as well as medical librarians when they classify stuff and pin them as what type of trial, that might matter. I agree with you. At the design stage, I think it matters just to

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organize a discussion about different trial dimensions.

DR. FARRAR: Yes, I agree.

DR. SHERMAN: I think there's a value to presenting that information, for example, in a trial protocol of a large -- and particularly maybe for some of the nonpharmacologic trials to really let people know, is this something that's applicable to whatever clinical practice you think you're applying it to or is it so efficacious in ways that would raise your hackles there, that gee, even though they say it's pragmatic, you don't feel confident applying it to your patient population. So I think it could be useful for that.

DR. FARRAR: Yes, in interpreting the trial, and that makes sense. Yes.

DR. TURK: We're going to move on to the next question. This is a question that's directed to John Markman, but he's not here. However, I do believe that it's come up enough times that we can have other people speak to it.

The question says, "A two-part question for

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John Markman. Thank you for bringing up the challenge of the EHR. Most EHRs were not designed for the conduct of pragmatic trials but instead designed to bill and schedule our patients. Those challenges were, in part, the motivation for development of CHOIR as a learning health system in answer to the LHS call from the National Academy of Medicine to have flexible platforms to all capture high-quality data and make it actionable.

"LHS such as CHOIR and others has the ability to conduct pragmatic observational studies and CER studies more easily in the EHR. For instance, we are using CHOIR as a multistate, PCORI, comparative effectiveness trial on compassionate opioid weaning. The trial is integrated into clinical care across multiple systems that couldn't be performed in the EHR. We're also running several comparative effectiveness studies with the Stanford Pain Center at low [ph]."

I'm not sure what "low" is. But I think the question here is we have had discussions about the

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value, the utility, and what the content of electronic health records are, and whether there are alternatives that could be used that would have more utility for us -- as an example, CHOIR, and I gather but I'm not familiar with, the National Academy of Medicine -- to ask for these flexible platforms.

Does anyone want to comment on the use of alternatives to electronic health records?

DR. FARRAR: Michael commented before that the EHR, in all of its forms, including electronic, was designed to be able to bill insurance companies, so we need to keep that in mind in terms of how they're dealt with. We've talked already in this session about the need for collecting pain-specific data, and the CHOIR system was set up to do that.

I think the real issue from the perspective of thinking about how to apply these -- and I don't know how extensively the CHOIR is being used, but I would imagine that it's not used by a very large number of people. As the number increases perhaps,

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as is indicated in the question, it's possible then to conduct studies in that population.

But in harkening back to Bob Kerns' earlier question about how do you include groups that are out in the middle of nowhere or in different patient populations, we need to keep in mind exactly the patient population that's being included in the CHOIR data repository, and it's going to be a subset of the total patient population that we might be interested in.

Michael?

DR. ROWBOTHAM: I don't have experience using the CHOIR system. It's very interesting. With this question, I was thinking about a question earlier in the chat that we haven't gotten to, which is independent practice systems. Those are interesting because they may use an electronic health record that is entirely different than Epic. So the same physician, when they see a patient in the hospital, is on Epic, but when they see them in their clinical practice, it may be something like Allscripts.

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Even though in the San Francisco Bay area we have a harmonization of the medical records, where I can see when a patient's been seen at Kaiser, or one of the Sutter Health hospitals, or any of those things, I can pull up the records, the imaging in the labs, and usually some kind of a clinical summary, but I can't get into the independent practitioners.

So that is an area where more could be done to implement things like CHOIR but, in general, there's even less standardization in independent practices than there are in the large systems where there's a little more forced standardization.

Does anyone have any experience in that area?

DR. FARRAR: I've worked with the CTSA groups since the inception of that program almost 20 years ago. One of their big pushes these days is the harmonization of medical record data, and there's a large push to convert all medical records, hospital and outpatient, to something called OMOP, Observational Medical Outcome

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Partnership. It's a standardized approach to the recording and keeping of medical data.

It's not that we're there yet, but I think that it's very likely that over the next decade or two, we will overcome these problems of not having communication between the various medical record systems, which will facilitate the ability to get at and look for patients across a broad range of practices. So I think it's a big issue now, but I think there are groups that are working on it, and it will become less of an issue as we move forward.

DR. SHERMAN: The next question harkens back to Howard Fields' question about mechanisms and pragmatic trials. This individual asks, "Wouldn't it be true that if we're going to examine heterogeneity of treatment effect in the trial, and this of course is very important for both comparative effectiveness studies and for pragmatic trials, that we would need to take into account the mechanism of action of the treatments, whether neurobiological, or psychosocial, as well as the mechanisms of the patient's pain?"

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DR. BAIR: I'll jump in and just start off here with my two cents. I guess when we're talking about pragmatic trials, and we've talked a lot about input from key stakeholders, patients being one and providers being another very important key stakeholder -- I hope this is not viewed as sacrilegious -- but those key stakeholders generally don't care that much about the mechanisms of action like us as clinical trialists.

I just want to know does this treatment work for me as a patient or does it work when I deliver it to someone. That's less of a concern in a pragmatic trial. A point that Dr. Wasan made yesterday is that, generally, when we're getting towards pragmatic trials, there's already been a degree of evidence in early efficacy trials, where some of the mechanistic issues have already been uncovered. I think that that's more the role of those efficacy studies and the outcomes related to those than a pragmatic trial. So I think it becomes, to me at least, less important.

DR. SHERMAN: Anybody else want to jump in?

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(No response.)

DR. SHERMAN: Dennis, do you want to take the next one?

DR. TURK: Okay. Again, I apologize. We're trying to read through these just to make sure of the order of what we haven't covered and what we have. Let's see. This was directed, again, to John. I think this is John Farrar, not anybody else, not John Markman -- something to bring up later. I think this is from Bob Kerns.

"Thanks for a great talk. Over what period of time are the numbers you're showing for average site recruitment ranging from 3 to 10 per site? Those numbers seem surprisingly low for each site. I'm assuming that industry/FDA trials might recruit over a fairly brief period compared to a CER study. What are your thoughts about this?"

DR. FARRAR: Actually, it comes from Jennifer Haythornthwaite. The numbers for that come directly out of the IMMPACT-ACTTION paper that's just been published by James Walters, which got its data from clinicaltrials.gov in a review of

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a number of trials, and it was limited to a few; I can't remember specifically, but osteoarthritis, back pain, headache, and some other things. It was looking primarily at efficacy trials, and the majority of them were pharmaceutically funded studies.

I think it's an important issue to think about. It's an interesting question as to whether these efficacy trials actually are better recruiting than we are with pragmatic trials. I think the whole point of a pragmatic approach is to try and be able to collect data reasonably quickly in a known population identified by health record or other mechanisms.

It's an interesting question as to how many patients we need to collect per site in order for us to have reasonable confidence that the data we're getting is going to accurately reflect what's being done there. I would argue that at least in pragmatic trials, you would need a lot more patients per site, especially if you're doing a cluster randomization, in order to be able to be

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comfortable that the results are valid.
If you're in fact doing a controlled study where you're blinding it and randomizing by individual, then the number of patients per site can be substantially less. I would argue that what I've quoted here is mostly those kinds of studies and not pragmatic.
DR. ROWBOTHAM: If I could comment on this, the numbers that John gave don't necessarily represent the range. So when it comes to industry-sponsored clinical trials of a new compound, a registration trial, you've got a certain number of sites that don't recruit anybody. So you may open up 50 sites, and you may have 5 or 10 that just come up with zip. Then you'll have another group of sites that maybe get 1 or 2, and then you'll find that you've got other sites that are recruiting more around where the target is for that particular study, 6, 10, something like that.
Conversely, the sponsors, when they come out to the sites, they may only allocate them a limited number. So they may say your contract is for up to

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6 trial participants so that they spread it out, and it's only when you see the failing sites that they maybe open it up to the productive sites and say, well, we limited you to, say, 6 but now you can go up to 12.
When it comes to pragmatic trials, to me that seems like it's a failure if they're not recruiting almost an order of magnitude more subjects into the study than a registration trial because you're really looking at very large data sets, but data sets where there's a lot of noise in them compared to a randomized, placebo-controlled clinical trial because you just don't have anywhere near the control over how the study drug is administered and how everything else is managed that you do in a prospective controlled trial.
DR. FARRAR: No. I agree with that. Just to be clear, these numbers are the average in the trials. The point was that trials range from 3 to 10 on average, and as Michael very rightly says, the range might be anywhere from 2 to 50. But in general, registration trials try and limit the

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number of patients recruited in the individual site. And as he says, and I completely agree, in pragmatic trials, we really are interested in much larger numbers because we have to deal with all the vague reason variability in the data that we're collecting.
DR. SHERMAN: Great. Let's go on to the next question. This is about adaptive designs. "Noting their flexibility that they're pragmatic by nature, do there need to be recommendations related to when a transition of treatment occurs? For example, is it because of safety or tolerability issues versus access, cost, or time, both of which might warrant immediate transition versus a lack of efficacy, which might mean, then, you have to wait a longer period of time to be sure that efficacy had a chance to come to fruition and/or appropriate titration of the treatment prior to transition and the importance of capturing these transition points and their rationale as an outcome?"
DR. FARRAR: Adaptive designs, for better or for worse, is a very broad term. What it started

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out as was adaptive as opposed to a two-group, parallel, randomized-controlled trial. I think the point here is can we make changes to the way in which our trials are being conducted, based on what actually happens in the trials? I think there are some very sophisticated ideas about how to do this brought forward and published by people who are a lot smarter than I am on this topic and certainly would have applicability to both efficacy and pragmatic trials.
I think building in an adaptive process for what we're doing would be a really good idea in the design of trials. One example would be a simple one, which is that you look at all of the results of your trial about halfway through, not from an efficacy perspective but simply to understand the degree of variability since variability is a key feature of how we calculate sample size. If that variability is a lot larger than we had originally thought or proposed, it would suggest that the trial would need to be much larger, and one could extend the sample size in order to accomplish the

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goal of the trial.
So that's a simple adaptive component that could easily be incorporated, and there are other more sophisticated ones that, as I said, others are much better talking about than I am.
DR. BAIR: We have an upcoming adaptive trial that has some features that Dr. Markham recommended, sequential randomization looking at sequences of treatment or combination of treatments. This is going to be across 20 VA sites, involving 2500 veterans with chronic low back pain.
The sequential randomization is breaking up into step 1 treatments and step 2 treatments. Between step 1 and step 2 is looking at efficacy, so do these patients have a 30 percent reduction in their pain interference? We look at efficacy after step 1, and then we'll re-randomize those that don't respond to step 2 treatments, and we also incorporate patient preferences for the three step 2 treatments, which involve chiropractic treatment, yoga, and cognitive behavioral therapy.

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So we've built some adaptive components to the design: patient preferences, sequencing, and combination therapies, and looking at efficacy midway through treatment.
DR. FARRAR: You're talking about adapting the treatment based on the patient response, which I think is a wonderful way to think about how to do this because, in fact, it mimics what happens in clinical practice. That's a very different end of the spectrum of adaptation in clinical trials, but it's a wonderful thought. I'm very excited to hear how it goes.
DR. BAIR: Thank you, John.
DR. ROWBOTHAM: There's one other thing that can be done in adaptive studies, and that is if you have a new treatment that you're rolling out, you may initially have very limited or very restricted access to it by patients, and then you can see how effective it seems to be, and then you can start rolling it out to other groups of patients or deciding that it doesn't work for this group but it might work for another group. So you're doing

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essentially the adaptive design.
If you're doing something like a cluster randomized pragmatic study, you could roll it out in a different sequence, in terms of the eligibility, at one site versus another, and get some comparison data that way. So adaptive designs are very cool, and there are a lot of different ways to work them into a pragmatic trial.
DR. BAIR: I've been impressed with Karen Sherman's work, and I view dosing trials as an adaptation, looking at different dosing of massage interventions, or yoga interventions, or acupuncture as adaptive features to a clinical trial; so very innovative work that I think uses adaptive features.
DR. TURK: I think we're going to have to end this session because we want to make sure there's an opportunity for our break. I apologize to anyone whose questions didn't get brought up, but there will be other opportunity when we have the consensus discussion.
Right now, I want to thank all of the

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participants from the earlier sessions, as well as from the panel, for, really, a very stimulating discussion. I'm hoping that this is going to be very useful as we move forward with the next phase of this meeting, which is in some sense the most critical phase, when we begin to start thinking about important considerations and recommendations both for designs of studies, as well as recommendations for research that needs to be done.
We're going to take a five-minute break now, and when you come back, you can click on the "Consensus Discussion" button to be part of the consensus discussion. In this particular phase, all of the people who are participating in this meeting will have access, and pictures of them will be up there when they speak directly. There's only room for I think 10 or 12 people, so what will happen is the boxes with names go beyond that number, but when you speak, your picture will come up.
So let's take that five-minute break now. When we come back, then you can go and click on the

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"Consensus Discussion" button, and then we will continue the rest of the meeting as we move forward. So thank you all very much.

(Whereupon, a recess was taken.)

Consensus Discussion

DR. DWORKIN: (In progress) -- for clinical research. And thinking about introducing Andrew, I couldn't think of anybody else, with the obvious exception of Howard Fields, who I hope is still on the phone and is equally renowned for preclinical and clinical. So Andrew, thank you for joining us, and for co-chairing this session with David and me.

As an overview, I'm going to start off and say a few things with only a few slides; then we're going to turn over the session to Nat, who has a couple of slides to follow up on the comments he was making yesterday; and then Andrew, David, and I will share the remainder of this session, basically asking people to ask questions and to make comments.

So the housekeeping rules. If you are not one of the people who has been either a presenter,

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or a panelist, or a moderator in the past two days, please turn off your video. What we want to do is only have video of people who have been presenters, panelists, or moderators. That's simply because the only possibility is to show somewhere between 12 and 15 live feeds, so we're going to prioritize the people who've been panelists, moderators, or speakers; so thank you.

Please also be sure to put your computer on mute. You can see there's a mute button at the bottom of the live video thumbnails. Please, please, everybody, if you're not talking, put your computer on mute; so video off for everyone except speakers, moderators, and panelists and everybody on mute.

The way this is going to work is at various points, either David, Andrew, and I will ask you all if there are any questions or maybe call on somebody to answer a question or make a comment. Then of course, unmute yourself and you will be live. Ask your question. We won't see you, but will hear you, and then of course put yourself back

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on mute.

Now, if we show a slide -- and there are going to be a bunch of slides, and we may not get through all of them -- and you have a comment about it -- for example, you really disagree with what's on the slide -- you can say something in the chatbox saying, "I've got a question. Please call on me."

It might help, in addition to identifying yourself, if you say two or three words, no more than two or three words, about your question because it could be things get out of order, and it would help us to kind of figure out who to call on if we had some sense of what your question was about. But it's absolutely fine if you just say, "I'm Joe. I'm Sally. I have a question." But really, it would be best if you could identify yourself because there are a lot of initials, and it's not easy for us to know who all of those people are.

Any of you who were at the NIH Endpoints meeting that was held a couple of weeks ago,

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please, please don't use the chatbox for discussions of issues. Some of you may remember there were extended heated, to some extent tangential, discussions going on during the NIH meeting in the chatbox, and that was a huge distraction, I think, for many people. So let's not do that in the hour and 15 minutes or so we've got left. Let's focus on what's being talked about. But we want to call on you, of course, if you have questions, but then put yourself back on mute.

The first slide, the plan is -- and most everybody on the phone, in the discussion, are familiar with IMMPACT. Ultimately, there is a publication with recommendations, recommended considerations, or considerations. This is one possible outline for that publication that David will be preparing the first draft of. So David is not only responsible for publishing a systematic review but also being the first author and lead preparer of the draft manuscript from this meeting.

So this is one possible outline where the

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manuscript presents considerations, maybe recommendations, for these aspects of pragmatic clinical trials. We've got one slide, sometimes two, for each of these 10 bullets, and we'll see how far we get. But this is one possible outline, and we'll make sure this all gets distributed somehow after today.

So David, if you could advance this to the next slide. David is controlling the slides.

We thought that this was a really interesting slide that Scott Evans presented yesterday. He, of course, didn't title it Scott Evans' Suggestions. We took the liberty of changing the title of the slide and also highlighting two points.

What it seems to me is the two themes of the last two days discussions are highlighted on this slide. One theme is this strain, if you will, between the pragmatic objectives of pragmatic clinical trials and the issue of assay sensitivity. We've talked about that as internal validity versus external validity and generalizability, assay

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sensitivity versus generalizability, et cetera. But as Scott on this slide talks about, you have pragmatic questions, objectives, but he suggests we need to retain rigor. So that seems to be one theme so far of this meeting, assay sensitivity and rigor versus generalizability and external validity.

Another theme -- and we didn't highlight it, but it's here -- is that there are pragmatic objectives of trials, there are also pragmatic designs, and there are pragmatic assessments. So we've gone back and forth talking about pragmatic objectives, pragmatic research designs, and pragmatic assessments, electronic health records, et cetera. That seems to be another theme that's in this slide, though not in the highlighted material, but rather in the faded-out blue material.

So that seems to be two themes that at least some of us heard over the last two days, assay sensitivity versus generalizability and also pragmatic objectives versus pragmatic research

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designs, versus pragmatic assessments.

David, the next slide, please.

We thought this is one way of thinking about that first theme, and as John Farrar emphasized in his presentation, "Assay sensitivity is defined as the ability of a clinical trial --" and one issue is to what extent does this apply to a pragmatic trial -- "to distinguish an effective treatment from a less effective or an ineffective one."

So there may be the question for us -- and this is obviously just provoked discussion -- how can pragmatic trials maximize the generalizability of their results to routine clinical care while preserving assay sensitivity, while preserving their ability to detect effectiveness?

So why don't we just try and see this chatbox thing. Let's be provocative. Does anyone in the group disagree that one theme of this meeting could be described as the second sentence on this slide, and another thing could be there are pragmatic objectives, pragmatic trial designs, and pragmatic assessments: outcome data, baseline,

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clinical and demographic data? Do those seem like sensible reasonable things?

Ian Gilron sent a smiley face, so I assume that Ian is saying he has no dispute with those two themes.

So let's make it easier. If you disagree with anything I've been saying, please -- Ajay Wasan. Terrific, Ajay. Take yourself off mute, Ajay.

DR. WASAN: Okay. Can you hear me ok?

DR. DWORKIN: Yes, great.

DR. WASAN: Okay. Great. I think it's impossible for any study to do everything; that, typically, comparative effectiveness does not concern itself with preserving assay sensitivity because it starts with some assumptions that Matt Bair kind of summarized well in the last panel discussion about if there's some agreed-upon efficacy of the treatments that are to be compared, this is a comparative effectiveness study with a pragmatic focus. Lynn talked about comparative effectiveness studies without a pragmatic focus, I

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think just to couch where my comments are coming from.

Every scientific experiment has to make some assumption, so I think it's asking too much to do that because I think focusing on assay sensitivity actually undermines many of the objectives of pragmatic and comparative effective study in the first place.

DR. DWORKIN: Ajay, I'm not going to answer your question, and Karen has raised the similar question in chat. And I'm not going to call on Karen because in about, I think, 3 to 5 minutes, Nat is going to present two slides on exactly this issue. Then, Ajay, you and Karen can discuss this with Nat, which I look forward to.

So let's set aside the second sentence on this slide because Nat's going to say somewhat more about it, and then we can come back to Ajay's question and Karen's question.

Nat said we should define pragmatic objective. I think the pragmatic objective -- but we haven't defined it, and this is an issue that

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David has raised. I would imagine it's the first part of the second sentence on this slide, that the trial results can be generalized. The conclusions/results of the trials can be generalized to routine clinical care in the community, but let's come back to that also. So that's the second important question that this slide raises.

David, let's move on to the next slide.

Clinical trial objectives. This is not the kind of high-level objective I just mentioned about generalizability to clinical practice. I really would like to hear from Scott, if he's on, about whether as a biostatistician he agrees with what's up here. It seemed to us that at the level of hypothesis testing, that a trial can attempt to show -- test the hypothesis, that treatment that is superior to some control group; placebo, sham, usual care. I agree, and of course I think we all do, that these are very different control groups.

Test whether treatment is superior to what we would consider a control group that isn't really

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including an active treatment; we could look at superiority of treatment A versus treatment B, a much more challenging hypothesis to test, and several people talked about this yesterday. If for no other reason, if you don't show superiority, which is often the case, then you really can't conclude, and it's not legitimate to conclude, that the treatments have comparable benefit.

Then of course noninferiority trials and equivalence trials, equivalence trials are hardly ever done; mostly it's noninferiority. The FDA and others have been saying, really for decades, that if you test the noninferiority of treatment A to treatment B, certainly within pain, neurology, and psychiatry, where you have symptomatic outcomes, you have to include a control group to establish assay sensitivity.

I'm hoping Scott Evans is on the line and could respond to this slide, and also correct us if we were wrong about his previous slide.

Scott?

(No response.)

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DR. DWORKIN: Well, Scott, if you're talking, you're on mute. I actually don't see a bullet with SE, so maybe Scott's not with us.

Does anyone else want to respond?

DR. RICE: It's Andrew here. There's another line of questions that have come up in the chatbox, from Dan Cherkin, Karen Sherman, and people, about whether the term "assay sensitivity" is the appropriate term be using here. Maybe Karen or Dan would like to say a word about that.

DR. CHERKIN: I've been doing research for 25 years on pragmatic trials, and I have never heard anybody use the term "assay sensitivity." So while this term obviously works well for many in this discussion, it seems very foreign and kind of like a laboratory term, which is kind of the antithesis of what might be an appropriate nuance for talking about pragmatic trials.

DR. FARRAR: Bob, if I could jump in.

Dan, so I would ask you, how would you classify a pragmatic trial design that is actually going to be able to answer the question that is

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being asked? Assay sensitivity in clinical trials is used to say that when we conduct the trial, it actually is going to answer the question. So when you design pragmatic trials, you clearly would like it to answer the question.

How do you term that for pragmatic trials?

DR. CHERKIN: We talk about internal and external validity. Those are related to this. It's sort of the scientific rigor of what you're doing that lends credibility. I remember the term David used in his, but basically he said we want both some flexibility because of the realities of the messiness of pragmatic trials, but you also want scientific rigor. So I don't really know what the best alternative would be. I'm just saying that I'm unfamiliar with it.

DR. DWORKIN: Dan, since I was the one who typed the term "assay sensitivity," I'm totally happy replacing that with internal validity. Nat is going to talk more about this, so maybe we should hold off on figuring out what we're talking about. But it does sound like there's a consensus,

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and John I thought put it really well, that we want to believe the trial has the rigor, the quality, and the methodologic features that will allow us to achieve its objectives. In psychiatry, they often use the term "signal detection."

So I think we're all talking about the same thing, but since Nat's going to focus on this in another slide or two, we should hold off and come back to it. It is critically important.

The next slide, David?

This is the placeholder slide to tell me to call on Nat, who will hopefully unmute himself and present a couple of slides, and talk about these issues that we've been talking about for the last few minutes.

It's a pleasure to introduce Nat. If you know him, he has helped with IMMPACT going back to 2001, so Dennis and I owe him a 20-year debt of gratitude. Nat was the founder, CEO, and currently CSO of Analgesic Solutions, now a part of WCG. He's also a director at Tufts Medical School.

Nat, are you with us, and can I turn off my

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microphone and you turn on yours?

DR. KATZ: Can you hear me?

DR. DWORKIN: Yes. Fantastic. Take it away.

DR. KATZ: This wasn't the placeholder slide. This is actually the centerpiece of my presentation just in case any of you haven't had the opportunity to enjoy autumn in New England. This is a picture I took of my backyard yesterday morning, and it's just a great time to be here in New England, so I wanted to share my enjoyment of that with you. I think that's probably my most useful contribution to the meeting, but we can go to the next slide and see if this is useful.

What I tried to do here, this is not a whole presentation on measurement error or assay sensitivity, but I just wanted to illustrate a couple of key points that I think could be relevant to our conversation. First, it's a truth about experimentation that the more heterogeneity you have -- and by heterogeneity, I mean any factor that is not your input into your experiment or your

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output from your experiment. Any additional factors, the more they vary, I would call the heterogeneity, and the more heterogeneity you have in any experiment, including a pragmatic clinical trial, the more measurement error you will have, and the more experimental noise you will have.

I actually use those terms as two different things, but I don't think it's worth belaboring those details right now. The more measurement error you have, and the more experimental noise you have, then the greater degradation you have in the accuracy and reliability of the results of your clinical trial.

Now, assay sensitivity is a term used for one consequence of loss of accuracy and reliability. If you decrease accuracy and reliability, then you lose your ability to discriminate between two things that are different. For example, if you're studying an effective drug, the people on the drug should have a difference in their outcome compared to the people on placebo, and your ability to detect that difference is

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called assay sensitivity, and it depends upon whether your trial as a whole is capable of producing accurate and reliable results. This is just the reality of experimentation. This is why rat scientists use rats in cages rather than chase them around in the yard. There's more variability and experimental conditions.

Even though this may all be self-evident, I figured I would throw in a couple of illustrations on the bottom left. I just pulled a very convenient graph out of a paper published by Neil Singla and colleagues that many of you are probably familiar with, where he looked at the standardized effect size of analgesics that are commonly used in acute pain clinical trials. Almost all of this is non-steroidal anti-inflammatory drugs.

If you look from left to right, the first bar is trials that are done at a single research site. The second bar are trials that are done in 3 to 5 clinical research sites, typically. The third bar are trials that are done in 10 to 30 research sites, typically, and the fourth bar are trials

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done in 20 to 50 sites, respectively. Those happen to be dental pain studies, bunionectomy studies, joint replacement surgery studies, and soft-tissue surgery studies.

What immediately jumps out -- now you might think that this pattern is because somehow nonsteroidal anti-inflammatory drugs work better for dental pain, and they work second best for bunionectomy, and third best for joint replacement surgery, and fourth best for soft-tissue replacement surgery. But the people who do these trials don't think that that's what's going on, and neither do I.

What I think is what's going on, and what those people think is what's going on, is that you simply have greater precision of measurement as you go from right to left -- you lose precision of measurement as you go from left to right because you have less and less control over your experimental methods, and that's why your observed standardized effect size of treatment goes down and down and down.

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So if you were to put a pragmatic clinical trial of the same set of drugs for the same kind of conditions on this graph, where would you get? Now maybe you're talking about a hundred sites where you're doing it in clinical practice centers. There's very little control over the experimental conditions. I don't know where you'd wind up, but I would expect that you would end up with a very small bar indeed or maybe a bar that hovers actually right next to the zero line.

Now, if you don't like that example because you still think that the difference in observed efficacy might be because of the surgical model, you can start to look at some factors that are associated with this loss of experimental control individually. So what I pulled here on the bottom right is a figure from a paper that a few of us published last year, which is simply showing the relationship between the number of sites and opioid clinical trials and the observed standardized effect size of those trials.

As you can see, as you increase the number

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of sites, the standardized effect size shrinks, even though we're talking about more or less the same kind of treatments at more or less the same kinds of doses. People are starting to tease apart some of these factors that impact observed effect sizes of treatment in clinical trials, but the bottom line is that the less control you have over your experimental conditions, the smaller your observed effect size is going to be.

So as we consider doing so-called pragmatic designs, whereby design there's very little -- in fact, I hear -- if I could say it this way -- a lot of bragging about how little control over experimental conditions there are, almost as if it's some kind of merit to have little control over experimental conditions. One needs to consider the potential impact that could have on what it is one is trying to measure.

Now, here I'm focusing on clinical trials for pain intensity, is what we're trying to measure. Obviously, pragmatic designs may have great assay sensitivity for some of the outcomes

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that it's attempting to measure, like, for example, how long patients stay on treatment; or whether people use their treatments; or whether people come for follow-up visits.

There may be certain things that pragmatic trials are trying to measure that they have great assay sensitivity for. Ajay showed wonderful examples of that yesterday when he showed that pragmatic designs in psychiatry are able to separate between two different groups on endpoints, like time to discontinuation for side effects or something like that.

I hope nobody misunderstands me. I'm not in any way suggesting that pragmatic designs don't have sufficient measurement precision to separate groups on outcomes of interest to pragmatic designs. They may very well do so. What I am asking the group to consider is whether pragmatic designs have sufficient measurement precision to differentiate between groups on all possible measures of interest, and I think the answer to that is, no, they don't.

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This is my last slide because, again, I think these issues have already been discussed to some degree, but I want to remind everyone of bullet point number 1.

Oops. Can we go to the next slide, Bob?

I wanted to remind everyone that accuracy of measurement of treatment effects decreases with increasing trial heterogeneity, and I want to just slip this comment in there that this is not overcome by large sample sizes. Sometimes I hear from people, "Well, we don't really care about control and experimental conditions; we'll just add more patients." But that actually doesn't work, and I can get into a detailed discussion about why that is if anybody's interested and share some papers on that topic, too.

So I think if we're going to do what John Farrar asked us to do earlier today, and make sure that our trial methods are adequate to support our trial objectives, then this factor needs to be taken into account.

A second point that I wanted to make is

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about the term "generalizability," which I've lost count how many times I've heard that term thrown around during this meeting. I think, virtually, every speaker used that term at least once. I didn't hear any speaker define that term.

When I do here definitions of generalizability, which normally I have to dig pretty hard for, it's things like it applies to the population that we're interested in. But I've never heard anyone define what that means either, and I've never heard anyone give any definition of the term "generalizability" that I could put a formula to or I could quantify whether it's been achieved or not.

So I hear the term "generalizability" weaponized a lot when it comes to talking about clinical trial design, but I've never heard anyone tell me how I could figure out whether generalizability has been achieved or not.

Generally, when people do attempt to get more specific about what they mean by the term "generalizability," they say things like, "Well, I

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saw your efficacy study done in 63-year-old white people with osteoarthritis of the knee," or whoever, a certain socio-economic status, "but I want to know is that treatment efficacious in black people, or Asian people, or old people, or young people, or people in the north, or people in the south, or whatever it is." "That's fine. That's a question that I can answer."

However, one has to keep in mind, in my opinion, if you have a specific question, that is, what you actually mean by generalizability, like this drug shown to be efficacious in white people, is it also efficacious in black people, it's not necessarily clear that the best way to answer that question, which is what you mean by generalizability, is a trial in 10,000 people in all sorts of clinical practice settings, with no attention, or limited attention, to experimental controls that happens to include 69 people or 180 people who are black, and now you're going to look at those people and see this drug beat placebo. Personally, I don't think you're going to learn

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anything by doing an experiment like that. We can barely figure out how to consistently separate drug from placebo in so-called highly controlled clinical trial designs.

So when I hear the word "generalizability," what I would ask is that the person who used that term define exactly what you mean, and then show me that the clinical trial that you're proposing is the best way to address that study hypothesis. And I think, from time to time, we could all end up agreeing that the best way to answer the question that you proposed under the rubric of generalizability is actually a highly controlled clinical trial and not a so-called pragmatic trial.

So I would ask this group, if we're going to write a paper and we're going to use that word, and we're going to use that word to justify certain clinical trial designs, that ought to be well-thought through. That ought to be well-thought through.

DR. DWORKIN: Nat, I'm going to interrupt because there are questions for you and there are

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questions for me.

Can you wrap up in one minute? Because you're not going to get off the hook just yet.

DR. KATZ: The end.

DR. DWORKIN: Okay. Great

Lynn DeBar, those of you who are watching chat, asked a long question about heterogeneity of treatment effect that I want to answer quickly, and then I want to go back to Nat.

The first person I'm going to call on after I respond to Lynn, or do my best to respond to Lynn, is Smriti, who sent in a question for Nat last night. Then I'm going to ask Dan to say much more about what he said in the chatbox and have Nat respond to it. So that's the plan for the next five minutes.

Lynn, I'm intensely interested in heterogeneity of treatment effect. In fact, I was the one who asked that question about if we're interested in studying the heterogeneity of treatment effect in pragmatic trials, then don't we want to know about the mechanisms of action to

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treatment and the underlying pathophysiologic and psychosocial mechanisms of the patient's pain, in the last section.

So with respect to your question, which I think was about the slide previously, with superiority and noninferiority, blah-blah, objectives, I think that if we're interested in heterogeneity of treatment effect, then we need to make specific predictions about the heterogeneity, and that needs to be built into the trial, ideally, as a primary analysis.

We've written a little bit about that, but to make a long story short, what I would like to propose is that you and I work together to draft two or three paragraphs for this manuscript that David's going to be spearheading on heterogeneity of treatment effect, and that we can write what we both end up thinking is a reasonable proposal, and then include it in the paper, and I hope you say yes.

I want to move on to Smriti's question, which I'll read to you, Nat, and give Dan time to

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prepare for the question he's going to ask you live. The question Smriti sent in last night was, for Nat, "Could some aspects of pragmatic trials be incorporated into a drug development paradigm earlier on? For example, can some aspects be designed as a separate exploratory trial during phase 2 to gain insight so that the combined knowledge from the proof-of-concept explanatory trial, the phase 2 pragmatic trial would help to develop design a more comprehensive phase 3 program?"

So are there things that can be done in phase 2, in a separate phase 2, quote/unquote, "pragmatic trial"? A question for Nat.

DR. KATZ: Well, Smriti has a huge amount of experience in drug development and probably knows more than I do about that question. I'm not sure how to answer that without answering it with a question, which is, what is the hypothesis of the pragmatic design that Smriti is interested in?

DR. DWORKIN: Smriti, it looks like you're on, so can you unmute and answer Nat's question?

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DR. IYENGAR: Yes. Nat, increasingly I think drug development programs are quite conscious of the real-world evidence, so I'm just wondering are there paradigms that drug development programs can consider. While you have to do the traditional trials to understand if your asset has a proof of concept in a regular clinical trial, are there some sort of exploratory trials that can be done in real-world populations that can provide you additional information on how best to design your phase 3 trial?

Are there other aspects that can be incorporated into phase 3 trials that would be useful going forward? It's thinking about it a little differently. I'm just wondering.

DR. KATZ: Well, I think that's a really huge question, and I may not do it justice with a very small answer. But my answer would be, I think it depends upon the pragmatic hypothesis that one is interested in.

For example, because, again, the term "pragmatic" seems so broad and it encompasses so

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many possible questions of interest to clinicians, I think some probably can be answered or explored in the context of a drug development program, but others, it would be hard for me to imagine how to do it, such as is there a difference in efficacy. But in different racial groups, I think a question like that could be rather easily explored in the context of a typical drug development program.

But other questions, like how do different kinds of primary care clinics promote adherence to therapy, or things that really require being in a large group of practice settings with all sorts of challenges that we've heard for two days now in terms of collecting data, to me that feels much more challenging to include within the relatively tight confines of a classical drug development program. But you may know more about it than me, Smriti.

DR. IYENGAR: I was just thinking in terms of having a parallel trial, where you could collect information that can then feed into the design of your phase 3 trial.

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DR. DWORKIN: This is Bob Dworkin. I don't know that people who do pragmatic trials have thought about it, what would be a phase 2 early pragmatic trial that could inform later larger pragmatic trials. Why don't we set that aside now and add it to David's list of possible things to address in the manuscript?

DR. IYENGAR: Sure.

DR. DWORKIN: Both Dan and Karen have expressed concerns in the chatbox, and I'm going to ask Dan to say something -- and this is really about what we've been talking about so far -- and also Karen. The rest of you, so far we don't have a huge number of people raising their hands by nominating themselves in the chatbox. I don't think you need to bother typing so much about what you want to say because so far we're able to call on everybody.

So Dan first, then Karen, and then Nat will respond.

DR. CHERKIN: I guess I'm feeling a little frustrated that we are sort of -- let me back up.

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I think there are fundamental differences in how researchers are trained and the experiences they have. Those that are prepared to do efficacy trials usually of drugs have an expertise in how you do that, and they have their own terminology. Those of us who have done pragmatic trials have different training and personality involved maybe in doing this.

They are very different kinds of trials. Sometimes efficacy trials are called fastidious because they are very neat and clean and controlled. At the other end, the kinds of pragmatic trials are inherently messy. One, the efficacy trials maximize internal validity. What some of us believe at least is that pragmatic trials try to optimize external validity.

Both have their challenges and trade-offs, but I'm feeling that we're getting into sort of the weeds talking about some issues here that are not going to be that conducive to moving on to developing a consensus because I think we're talking kind of past each other. I have no doubt

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that those familiar with efficacy trials know what they're doing and could do it better than I do, but I also think it works the other way. Those of us, while we can maybe learn from people that have done efficacy trials in the model of the gold standard, double-blind, placebo controlled, that does not work in pragmatic trials.

So I'm just calling for maybe a stop and reflection here about the value of some of these discussions. I think more are better at clarifying the differences of these two worlds than in helping us figure out what are the recommendations that will be most useful for promoting high-quality pragmatic trials.

DR. DWORKIN: Karen, do you want to expand on what Dan just said before Nat responds? And maybe I'd like to respond, too, and probably other people do.

(No response.)

DR. DWORKIN: Karen may not be here. So I'll read what Karen said because it looks like we may have lost her. I don't see her initials or a

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video.

Karen said, "I'm concerned that these efficacy trials that Nat describes use people who are not enough like, for example, the standard primary care patients. They don't adhere to rigorous treatment protocols, may take other things, et cetera, many different psychosocial characteristics. So it's not a question of simply doing a slew of trials that are efficacy oriented."

Nat, let me ask Dan a question.

Dan, what is a high-quality pragmatic trial? What are the characteristics of a high-quality pragmatic trial that has the ability to answer the question you ask it to answer; that allows you to test a pragmatic hypothesis? Because I'm obviously one of the people that's a little aligned in the efficacy area.

So when you think about, as a reviewer for journal or for NIH, a high-quality pragmatic trial that will succeed in testing a hypothesis that's pragmatic, what do you look for?

DR. KERNS: By the way, Karen's back.

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DR. FARRAR: Yes, Karen's back.

DR. CHERKIN: I think the first thing you look at is making sure you have a question that answers an important clinical issue that cannot be resolved without some sort of data, incredible data, ideally. Then you get together with a research team that includes a broad range of skills, including statisticians who can tell you what you need to come up with as your primary outcome and what are your secondary outcomes. Then you need to decide what subgroup analyses you're going to do and whether or not you can power on those.

But the success will depend on the design and the execution, given if your question is a good one, appropriate. I think often the biggest threat to success is the execution because of all the problems that speakers have identified and challenges with how things can go awry. It's very complicated to do a pragmatic trial, very different than an efficacy trial, which has complications I'm sure, but they're different.

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Then if you've executed it well, and you've done power analyses that were appropriate, and you meet your recruitment criteria, then the analyses should produce you adequate power to address the questions that you posed. I don't know that this differs from other types of research, except for pragmatic trials, it's really the execution that is the biggest challenge.

DR. DWORKIN: Karen, you're back. Do you want to add something to this before we let Nat respond? I going to also call on Ajay because he's contributing to the same theme. So Karen first, then Ajay, then Nat, and then I'm really looking forward to turning this over to David and Andrew. But first, Karen, and then Ajay, and then Nat.

DR. SHERMAN: Sorry that I was kicked off. I couldn't hear you guys, so I may be a little bit redundant. But for me, for the question for a primary care provider, for example -- and it's not just about drugs; I mostly do non-pharm treatments, but I have to think about everything -- here I am, and a patient comes into my office. I've read that

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drug X works under certain kinds of specialized conditions. I've heard that treatment Y works under specialized conditions. And if you have people who are very gung-ho for physical therapy and they do everything you want them to do, does the treatment work?

But here I am, and I have a patient coming in who has maybe more comorbid conditions, is a little bit suspicious of medical care, and kind of wants to be just taken care of, and all of those other kinds of things. Which of these therapies that are potentially available to me should I employ?

To me, the value of having sort of an unselected population, of course it makes things messier, but on the other hand, I could argue that you have to have such careful calibration for a medication because everything's a cost-benefit analysis, and maybe most of my patients don't actually need your medication to get better because they're not as severe, and you have to test to find out that it's better than placebo and all of those

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other kinds of technical arguments.

So I want to just see what happens, again, with the things that Dan has said and some attention to rigor, but we might fight about is there a minimum degree of internal validity that you need, and then you relax the other, and you focus more on the external validity.

So that's really the question that I'm asking. It's not so much does racial group X do better than racial group Y, but here I am as a primary care provider, and all of these different people and circumstances, they're coming to me, and you cannot do enough efficacy trials to answer the questions that I need for everyday practice. So I think maybe that's enough from me.

DR. DWORKIN: Thank you, Karen.

So we're going to hear from Ajay for a moment, then Ian Gilron, then Nat. Then I'm going to say a couple of words, and then we're going to turn it over to David and Andrew to move what I think is our second slide. We're probably not likely to get through all ten. So Ajay, then, Ian,

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and then Nat.

DR. WASAN: Yes. I think the tension here is that we're talking about CER studies that are efficacy based versus CER studies that are pragmatic based. The CATIE Alzheimer study is an example of a CER that is efficacy based because it had a placebo control.

The STAR-D study is an example of a CER study that's pragmatic based because there was no placebo control, but like many comparative effectiveness studies, it sought to compare at least two treatments that have agreed-upon effectiveness, but it may not be efficacious.

Remember, many people have argued, with good data, that the majority of the effects of antidepressants are placebo, for example, and the thing is, STAR-D's a good example of that CER with a pragmatic focus, that was well designed, that revolutionized the field, and that met its scientific objectives. And it's to Dan's point that it's a fundamentally different approach than an efficacy study, and that's why I'm kind of

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digging my heels in on this assay sensitivity question because I don't think it's a precondition for super high-quality science in the field of CER, and that's already been proven. That's what I would say.

DR. DWORKIN: Ajay, I wish I felt I could respond to you because I'd love to talk to you about the STAR-D study, but I think that's probably tangential.

So Ian, will you enlighten us?

DR. GILRON: No, I don't think I will. I just want to say from previous IMMPACT meetings, we've talked so much about efficacy trials that are tightly controlled, and even within that environment, we've been shocked to see all kinds of challenges and issues with data quality and trial conduct, and different sources of bias that people like Andrew Moore would talk about for a long time.

That's on one hand, but on the other hand, we also recognize the limitations of generalizability because of the way efficacy studies restrict certain populations from the

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trials, et cetera, and there's no question that there's a critical need for real-world studies such as pragmatic and comparative effectiveness studies.

So I think to start off by saying that both are critical to advancing patient care is a great way to start. I think from thinking about Nat's comments, to think about a particular treatment comparison in a pragmatic trial through the same lens that we look at it in an efficacy trial, I think it's not disingenuous, but it's wrong because I believe that in a pragmatic trial, the sources of bias are likely even more substantial due to sometimes poor quality data, important missing data from people who dropped out or won't take therapy, and other sources of variability.

I think in our recommendations, or consensus recommendations, we need to recognize that these are vastly different. Even though you can't blind many nonpharmacological therapies, and we've accepted that but we still want to study them, it doesn't mean that we stop acknowledging the great sources of bias that are associated with that lack

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of blinding. So it's not discrediting it, but on the other hand, pragmatic trials, the way we may have been able to find out the huge problems with opioids weren't, and continue not to be, described in efficacy trials.

So I think the tension here, there's no discrediting over one or the other, but just to be openly cognizant of the limitations of each as we make those recommendations and try not to look at them through the same lens.

DR. FARRAR: And I think --

DR. DWORKIN: Not to look over your comment, I think we need to move on. We're on slide 1.

DR. FARRAR: I understand that, but I think if we don't agree from the start that the two approaches to clinical trials are distinct and different, we're not going to achieve consensus here.

I think there are clearly design issues that have been raised very nicely by Dan, Karen, and Ajay that are simply different, and if we're looking at the way in which pragmatic trials are

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being run and what they're trying to answer, it is completely different in many ways than efficacy trials; not that some of the same principles shouldn't be applied -- and you know this is coming from somebody who spent their entire lives looking at efficacy trials -- but pragmatic trials are answering a different question, and we need to understand that. And if we can't look at this from the perspective of pragmatic trials being different, then we're really in trouble.

DR. RICE: Thank you. I'm going to step in as moderator here because you've only got 30 minutes left. I would suggest that we can agree -- actually, there's more agreement here than we think -- that the first part of the paper really should be about defining what a pragmatic trial is, what its purpose is, what its general methods are, and then only in passing, really, differentiate it from an efficacy trial just to set the scene. Because the main purpose of this document is about pragmatic trials in pain and, therefore, spending a lot of time comparing and taking topics and

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language and things from efficacy trials might not be particularly useful. But what will be useful for our leadership is defining what pragmatic trials are and their language, as Dan, in particular, so eloquently put it.

(Crosstalk.)

DR. KERNS: If I may, I just would emphasize what many of us did emphasize, which is rather than thinking about it as a dichotomy, better to frame it as a continuum. But I think beyond that, what you're saying is exactly right.

DR. DWORKIN: Do we all agree that a pragmatic trial has to be designed in a way that can answer a prespecified question, test the hypothesis; that is has to be designed with the ability to give you a meaningful answer to a question? Because if we all agree on that, then I think much, though not all, of the apparent disagreement disappears.

DR. FARRAR: We all agree with that, but heterogeneity of the treatment effect may not play a role.

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DR. DWORKIN: Yes.
DR. KERNS: But Bob, I have to say it's just interesting even that it comes up. Even the way you just said seemed to imply that some people -- like that's a question about pragmatic trials, can they answer -- empirical questions. I don't think we should go down that road.
DR. DWORKIN: I agree, and I don't want to go down -- fine. I resigned from the PCORI planning committee because I thought the trial being planned was not going to be able to answer any meaningful question, and it was, therefore, unethical. So I don't think there's universal agreement that comparative effectiveness trials, pragmatic trials, need to adhere to a level of rigor that makes it possible to actually answer a question, rather than at the end of the day having an uninformative, inconclusive set of results.
DR. KERNS: Yes, but there are many of us, Bob, that would that get involved in efficacy trials because we don't think they're useful.
DR. DWORKIN: Fair enough.

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DR. RICE: Can we move on? Now that David's put up slide 2, I think that was the big hint about research design.
Does anybody want to have points about this? I think there are particular issues around randomization and blinding, and to what extent we --
DR. FARRAR: So this actually assumes that there needs to be a placebo group. A lot of the trials that are done, if you want to answer the question of whether in a standard primary care physician's office, the writing of a prescription for physical therapy is a good thing to do in all back pain patients, you compare a group that does it with a group that doesn't.
It's not that physical therapy doesn't work. We know physical therapy works in some kinds of back pain. The question we're trying to answer there, to your question, Bob, is does a process of getting primary care physicians to order physical therapy for every back pain patient make a difference in people's lives? It's answering a

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very real question that's very important for primary care physicians, but it doesn't get at the question Howard was asking about whether it's neuropathic or nociceptive. It's not focused on answering that question, but it's a valid question and a real question.
So I would wonder, Andrew, about this. The issue about blinding, obviously if you can blind it's important, but not blinding simply means that you're measuring not only the effect of what you're implementing but the perception of that implementation with the patient, and that's a very real question to be answered.
DR. RICE: I agree, but I think one of the take-homes I took from David's systematic review was that, actually, most of the interventions being tested are impossible to design a placebo group for and actually very, very difficult to blind with a therapist.
DR. FARRAR: Yes, I agree.
DR. HOHENSCHURZ-SCHMIDT: The fact that blinding is on this slide doesn't mean that we

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require that or would put that into the recommendation; that's something to be discussed here. I think distilling the last couple of days together, there was a lot around the sweet spot and answering a question appropriately. And also from the systematic review, we can see that in some instances it might be possible to blind patients and it might be desirable from the research questions point of view, and in many it's not.
So I think under patients, we wouldn't make it a clear recommendation but say it depends. We had different things around study staff, which are probably impossible to blind, but things like assessment, that's probably something where we can agree that that should be blind as much as possible, both outcome sampling as well as analysis.
DR. KERNS: Yes, that's a good point, David.
DR. HOHENSCHURZ-SCHMIDT: Any comments on that? Disagreements?
(No response.)
DR. RICE: I would move on to slide 3 while

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you've got a chance, David.
(Laughter.)
DR. HOHENSCHURZ-SCHMIDT: Okay. Study treatment is actually something we haven't spoken that much about. Any particular points that need to be raised here?
DR. RICE: Well, I think it may have been Karen yesterday who made the rather important point. Often the comparison with goal is to reflect what is done often in primary care, or at least in the general world, and that could be incredibly variable and very difficult -- was the message I took -- to put your finger on with any accuracy, and we may make too many assumptions about those interventions. So I just wanted to see if there is a place to discuss that.
DR. GILRON: Yes. I'm sorry. It's Ian here, and just one comment. For example, with prescribing in a clinical trial where it's a titration schedule that's closely followed by research personnel, compared to real-world practice where a prescription sheet is given to the patient

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and it says start at this dose and increase up towards this dose over a 5-week period, and the patient really just stays at the low dose and never titrates up, just getting data on what the study treatment is I think is a big challenge that at least we should address.
We may or not even have the follow-up data on what dose was actually given in a real-world setting, let alone in an efficacy trial, where depending on how sophisticated the compliance measurement is.
DR. BAIR: I'll just add a point, Andrew. I think it was Bob that made the point about if the comparator is usual care or standard of care, we would recommend that the investigators who write up the results really explain what standard of care -- essentially in primary care, there's not necessarily a standard of care that's universal; it's quite variable, so we'd want that to be described very well and very much in detail.
DR. RICE: Should that even go in the reporting guidelines, do you think?

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DR. BAIR: I think so.
DR. HOHENSCHURZ-SCHMIDT: It is in the reporting guidelines, yes, but rarely complied with, especially when it comes to standard of care as a comparator.
MALE VOICE: Definitely. It's your control group.
DR. FARRAR: And the standard of care is going to be different between different sites, and you really need to account for that when you're using a study. If you don't have very many sites, and you're really in some ways randomizing by the standard of care -- I'm sorry, randomizing by whether the additional care goes into a specific treatment group, unless you understand what the underlying care is in a very clear way, you're at risk for serious bias.
DR. RICE: There are several people on the call who've done a lot of work in pragmatic trials in other areas. Would anybody like to comment on how this question is normally dealt with about defining the standard of care?

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DR. BAIR: I've been asked to provide more details on what standard of care and what usual care is, really describing the comparator and what other co-interventions they are receiving, and showing that it's quite variable. It's nonpharmacologic. It's a variety of pharmacologic treatments. There are several ongoing co-interventions, so we just have to describe that and compare the intervention arm versus that comparator arm.
DR. CHERKIN: I'm not sure that the term "standard of care" is that useful oftentimes because usual care and standard care are usually not at all the same and could be dramatically different. I think in pragmatic trials, while it is true that in each practice the usual care may differ, I think within the context of a trial, you can measure and describe what it was that was being done in the practices.
So I think that's the best you can do, and that data can be used if some interesting differences are noted, for at least exploratory

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analyses, to see if any of that makes any difference in the outcomes.

DR. HOHENSCHURZ-SCHMIDT: I assume a similar thing goes for monitoring patient adherence, as well as treatment fidelity. Interestingly, treatment fidelity, the more you control it, the less the rating on the PRECIS case. I think you might want to do emphasis [indiscernible] to that.

DR. RICE: Bob Kerns, your microphone is on. Did you want to say something, Bob Kerns, or not?

DR. KERNS: Yes. I was going to say -- this came up in the chatbox earlier about the PRECIS domains and reliability scoring. I was involved as a rater, rating, and I think there were 15 non-pharmacologic trials that were identified. It wasn't a systematic review, but just an effort to apply those criteria. We found the most challenging was these domains about fidelity and the issue about treatment fidelity particularly, I think, and also adherence, that they aren't well described.

If there's anything about treatment

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fidelity, it's mostly about treatment delivery as opposed to whether the treatment was actually received. So I think that is a gap in the literature, and the issue of adherence is a very muddy one. Some would look at the descriptions from the lab, paper, and think that the ideal pragmatic trial is not doing anything to enhance adherence or even assess it. It's kind of a wild west kind of approach, and I disagree with that.

So I do think that there is an important area for further discussion in advance around what really this group might think is appropriate in terms of the approach to adherence, both to monitor and whether trying to influence adherence through the intervention is important, and the strategies for measuring adherence. Technically, on the reporting side, those are a couple of areas that I think could benefit from some further consideration, at least as far as I can --

DR. FARRAR: Bob -- I'm sorry. Go ahead, Karen. Never mind.

DR. HOHENSCHURZ-SCHMIDT: Go ahead, Karen, please.

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DR. SHERMAN: For the nonpharmacologic therapies, when we do more pragmatically oriented trials, we do want some degree of fidelity to whatever the agreed-upon treatment, be it, say, yoga, or Tai Chi, or something like that. We're looking for instructors who are good, good enough, but not so good you'd never find them in your community. We allow them to have their own personalities in delivering the treatment that will help people bond with them better, and perhaps practice at home, and that kind of thing.

We haven't actually done treatment enactment or other things like that, but for a progressive kind of treatment like yoga or Tai Chi, where you use certain poses or breathing techniques that are used throughout, and then others are added, you probably could get some kind of a sense from the instructor on how well people seem to be getting it, though we haven't actually formally done that. If you, for example, were able to videotape classes, depending on their size, you might also be

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able to look at how people are doing, so that's a possibility.

But we're quite interested in at least people practicing at home. I kind of think some of this stuff mirrors the real world. In preparation for another trial, I've been doing an online Tai Chi class, and the instructors asked if you have any questions. I said, "I'm having a hard time getting a few things," and she said, "Well, it's a couple of years."

So we're not looking necessarily for perfection; we're looking for good enough that it's going to make a therapeutic benefit. And probably, depending on them, it's as good as it's gonna get for those kinds of trials. For some things, more simple deep breathing or other stuff, probably treatment enactment might be a reasonable strategy.

DR. RICE: Thank you.

Can I just make a comment? Because we only have not that long left. There have been some very useful points made by Dan, and McKenzie, and others in the chat. We are capturing these for the

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manuscript, in particular the issue of the fact that most of these trials, of course, are not done for pharmacological intervention, so we need to be careful not only about taking the language and concepts from efficacy trials, but remembering that, generally, these are not being done for pharmacological interventions, whereas most of us here have spent most of our time looking at drugs. But we are capturing those comments for the writer.

DR. HOHENSCHURZ-SCHMIDT: Okay. I'll just move on, and one comment on that. Also, if they assess pharmacological treatment, sometimes they didn't ask -- or most of the time they didn't ask efficacy questions; they asked questions of real-world implementation.

I don't think we need to discuss placebo or sham control. We've touched on treatment as usual.

Any views on a waiting list? I think, again -- Andrew and I discussed that earlier -- that is a thing that is common in the UK because you do tend to wait in the NHS, but something not overly familiar in the States.

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DR. RICE: Could we just ask if anybody's got a comment? Often in European studies, you see what's called a wait-list control be employed, which are people waiting for often a surgical intervention. Is that a concept on the other side of the pond? We weren't sure if it was or not. I've got one nodding head and one shaking head.

DR. FARRAR: Andrew, it definitely is. It raises the question, though, of the nocebo effect, meaning that people who say, "I haven't had my surgery, and I'm not going to get better until I get my surgery," that gets reflected in what they measure. So I think it's not a bad way to think about it. We certainly use it in things like acupuncture and others, but it does raise that question.

DR. CHERKIN: I agree. I just don't think it's appropriate for pragmatic trials because it introduces an artificial element that can have a nocebo effect.

DR. SHERMAN: The other thing is that pragmatic trials often tend to be a bit longer than

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efficacy studies do, especially primary drug studies, and it might be considered unethical to withhold the treatment for an entire year as opposed to 8 weeks or 12 weeks.

DR. RICE: Some of the way our wait lists are going in the UK, [indiscernible] years, it's your turn.

(Laughter.)

DR. RICE: Ajay's made another point, but should we move on to number 5? Because I suspect that might be one of the ones we need to spend some time discussing a little bit.

DR. HOHENSCHURZ-SCHMIDT: I think we've drilled a lot on getting patients out of electronic health records. I don't think that's something we necessarily need to spend much more time on. We haven't really discussed classic recruitment methods that much.

DR. KERNS: I would say that in our trials, the site of the setting, they are all clinical settings, first of all, as opposed to research settings and advertising. I think in many of the

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trials, there are strategies to optimize identification of patients through proactive recruitment, but it's still embedded in the clinical setting, and the nature of the clinical setting is relevant to the specific question being asked.

In terms of the electronic health record issue, our experience so far is that we've found that there are just great limits to the pain relevant information, pain measures, in the electronic health record, reliably. And thank goodness many of our trials weren't relying on that because in the context of COVID, in particular, the data just were diminished because they weren't being entered. Even pain intensity ratings were no longer being entered reliably because of virtual delivery, and vital signs weren't being taken, and that's the source of the data.

With regard to eligibility criteria, in our collaboratory, there's a great emphasis on -- and this was part of the RFA for all the trials. There was great interest in removing exclusion criteria;

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not removing but minimizing all the extreme cases, and that actually drew the interest of other NIH institutes and offices. So NIAAA and others became joint funders because there were actually patients who were not excluded because of alcohol use, where they're commonly excluded in other trials. So I think there's more focus on exclusion criteria. That has been a big focus.

DR. RICE: Ajay has a couple of questions, and then Nat Katz, please.

DR. WASAN: Oh, I was just putting some comments in the chat. I know we're pressed for time, so it's fine. If everybody looks at my comments about -- that's all.

DR. RICE: Okay. Nat?

DR. KATZ: Yep, the same for me. I just wanted to throw something into the record, but no need to talk about it today.

DR. HOHENSCHURZ-SCHMIDT: The chat is recorded as well, not just the video and the audio from the AV team. I'll send an email.

DR. RICE: We used the word "clinical

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setting," and this is particularly something that Karen made me think about. But the term "clinical setting," we presumably also mean interventions that might not be delivered in a clinical setting, like yoga or whatever. So it's any setting, I presume. Should be emphasize that in the manuscript?

(No response.)

DR. BAIR: You can also say clinical population versus general population.

DR. KERNS: I would say also with regard to that -- this is really to the inclusion criteria. Many of our trials, only a few relied solely on electronic health record data to identify patients. Much more common was electronic health record data to screen for the population from which of these they'd be sampled, and then patient rapport was used for the final inclusion criteria.

DR. RICE: That's very important, Bob.

Can I just raise one other point? I guess it's really important for the trials where we need to generalize. That's an issue that was raised

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yesterday about difficult-to-access populations, whether that's various ethnicities or people who really don't want to engage with health care. We're seeing that in the veterans in the UK. We can access the patients who want to come to the programs but not those who don't.

So how do we access these difficult populations, and should be making a point of that?

DR. FARRAR: Andrew, a quick comment on that, which is when we did our study of acupuncture, we understood that the applicability of whether acupuncture worked or not only applies to people willing to undergo acupuncture. So folks who are too afraid of a needle, to come close to it, aren't going to get benefit from it.

I think there are two ways of thinking about it. One is, for sure, we ought to try and expand the populations to include groups, especially disadvantaged groups with limited access to health care who might well benefit from things if they actually had access. But we also need to accept the fact that there are going to be some folk who

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just are not willing to do yoga, or not willing to do mindfulness, or not willing to do whatever, and that we ultimately are not going to know whether it ultimately would help in that population.

DR. RICE: Thank you.

DR. KERNS: There's a good chance to say I'm hoping that in the future -- and we've already started to talk about this -- that ACTTION will be interested, actually, in what I think is an important effort, public-facing enterprise that tries to build people's fundamental understanding of clinical trials, and pain clinical trials in particular, because I do think that there is an educational issue here that's a barrier to the kind of trials

DR. RICE: Thank you, and a number of people have made good points, which, again, we're capturing.

We only have about three minutes left. Do we want to spend a couple of minutes on concomitant medication? It's a bit pharmacological, and we were trying to get away from some of those

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concepts.
What was the next slide, David?
DR. HOHENSCHURZ-SCHMIDT: I think that was really well covered.
DR. RICE: Oh, outcome domains. Okay. So this is probably the biggest one.
DR. HOHENSCHURZ-SCHMIDT: I like that there are general comments around suitability of the source, and starting with a minimum set of outcome measures, and then thinking about how it affects workflow if you add on to that. That sounds like a very sensible and very general recommendation.
DR. KERNS: Yes, I agree. I think Matt's presentation was great in highlighting his experience, but also a reasonable approach to thinking about selection of outcome measures. I'd emphasize just the point about brevity and removing or trying to minimize respondent burden, and putting the premium on the key outcomes as opposed to secondary, let alone those variables that might help address explanatory questions.
DR. RICE: I think an important point also

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was made yesterday about the ordering of outcome measures, where we tend to put pain intensity measures first, probably erroneously [indiscernible].
We've got one minute to go. This is a really unusual experience for me because as a European, I'm used to being one of the few people left in the room at the end of an IMMPACT meeting because our flights tend to go the next day, and the rest of you have gone off to get your flights. But I'm going to give Bob a chance to wrap up now. But thank you very much. It's been a very enjoyable two days.
DR. DWORKIN: First, I want to thank David and Andrew for taking care of the last hour. I think it's wonderful that we got to the eighth slide.
David, if you could advance to the end. Let's take a look at what's on 9 and 10, and then end up with the final slide.
DR. HOHENSCHURZ-SCHMIDT: That's the final slide.

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Adjournment
DR. DWORKIN: Okay. There's the slide.
I just want to reiterate thanks to everybody, as the slide says, to presenters, moderators, panelists, and everybody else for obviously an incredibly stimulating, thought-provoking, if not exhausting, meeting, and especially to Valerie and Carlos and Jen for making it all happen.
I hope you all have a safe happy weekend. Those of us on the East Coast, enjoy Happy Hour. Those of you who are in the UK, just have a mini Happy Hour before you go to bed. And those of you on the West Coast, clearly you have something to look forward to.
Thanks, everybody. You'll be hearing lots and lots from us in the weeks and months to come, as a manuscript is drafted and as we all get on the same page to agree on its content and hit the submit button.
As you all probably guessed, we almost always submit first to Pain. So thank you all, and

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let us know any thoughts, or recommendations, or advice, or suggestions you have. Andrew and David and I will all be delightedly happy to answer email. Take care, everybody. Stay safe and healthy.
(Whereupon, the meeting was adjourned.)

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