

*ACTION IMPACT XXIV - Pragmatic and Comparative  
Effectiveness Clinical Trials of Pain Treatments*

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*October 22, 2020*

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*A Matter of Record  
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5	INITIATIVE ON METHODS, MEASUREMENT, AND PAIN
6	ASSESSMENT IN CLINICAL TRIALS
7	IMPACT-XXIV
8	
9	Research Design Considerations for
10	Pragmatic and Comparative Effectiveness
11	Clinical Trials of Pain Treatments
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14	Virtual Meeting
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16	Thursday, October 22, 2020
17	12:00 p.m. to 4:30 p.m.
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1	P R O C E E D I N G S	
2	(12:00 p.m.)	
3	Introductions and Meeting Objectives	
4	DR. TURK: Hello. I'm Dennis Turk. I'm the	
5	associate director of ACTTION. Bob Dworkin is the	
6	director of ACTTION, and we are placing this	
7	virtual program on for you as one of the ACTTION	
8	initiatives, and specifically the IMMPACT meeting.	
9	Before I formally welcome you, I'd like to go over	
10	a few details related to housekeeping.	
11	This is the first virtual meeting that we've	
12	been doing, so therefore we're trying to make sure	
13	we accomplish things as efficiently as we can, and	
14	you'll have an opportunity to give feedback on that	
15	at the end of the program.	
16	For general housekeeping, questions can be	
17	submitted throughout the meeting by clicking on the	
18	"Ask a Question" button located in the engagement	
19	panel. After each presentation, five minutes have	
20	been allocated to any questions requesting	
21	clarification of information presented.	
22	All other questions should be addressed	

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1 during the panel discussion. So therefore, if you  
2 have some questions about lack of clarity of  
3 something that was presented, then in fact you  
4 should raise that question at the end of the  
5 presentation or else save more substantive  
6 questions for discussion during the panel  
7 discussion.

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

13 Per the updated publication policy of  
14 ACTTION, anyone desiring to be a co-author of the  
15 manuscript developed, based on the meeting  
16 proceedings, must attend both days of the meeting  
17 for a total of at least 6 hours. Should you  
18 require another copy of the updated policy, contact  
19 Valorie Thompson at the website that's on this  
20 screen.

21 A list of IMMPACT meeting participants and  
22 the 2-day agenda can be found by clicking on either

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1 the "Meeting Participants" or the "Agenda" buttons  
2 within the engagement panel. Please complete the  
3 post-meeting evaluation form that can be found on  
4 the "Feedback Forms" button within the engagement  
5 panel.

6 This is a really important point. We really  
7 want to learn how to do this effectively and  
8 efficiently, how to have these virtual meetings, so  
9 we will make use out of the information you provide  
10 when we start planning for the next virtual meeting  
11 that will be coming up.

12 Now, for the agenda that you're going to be  
13 covering, it starts at 12:00 Eastern Time and  
14 different times depending on what time zone you're  
15 in. You'll get an introduction from me with the  
16 objectives, which is what you're getting right now,  
17 then there will be some discussion for the first  
18 two presentations, discussing definitions and  
19 general considerations for pragmatic and  
20 comparative effectiveness clinical trials, and then  
21 some statistical considerations that one has to  
22 have in mind as they think about these types of

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1 studies.

2 That will be followed up by two  
3 presentations that will be examples of  
4 circumstances, tried and developed, to use  
5 pragmatic trials or comparative effectiveness  
6 trials, and then we'll have a break. After the  
7 break, there will be a systematic review of the  
8 methodological aspects of pragmatic and comparative  
9 effectiveness clinical trials of pain treatments.

10 Now, after those presentations, there will  
11 be panel discussions. As I said earlier, at the  
12 end of any one of those presentations, if you need  
13 clarifying questions, you can ask those at the end  
14 of the presentation using the chat button, but if  
15 you have more substantive questions, please save  
16 them for the panel discussion.

17 On Friday, we're going to begin, again, the  
18 same time, and there will be discussions of issues  
19 related to how you conduct these types of studies;  
20 types of outcomes; the eligibility criteria; using  
21 different sites; rescue treatments; et cetera, in  
22 the same way we talked about previously. Any

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1 clarifying questions can come after those talks.

2 After that, there will be a break and then a  
3 panel discussion. Importantly, following that  
4 panel discussion, there will be a consensus  
5 discussion where specific recommendations can be  
6 made for pragmatic comparative effectiveness trials  
7 of pain treatments; specifically, what can we  
8 recommend to someone who's actually planning to do  
9 one of these studies?

10 We mentioned IMMPACT. Many of you have been  
11 involved with IMMPACT before, but just to clarify  
12 for folks that are new to this, IMMPACT stands for  
13 the Initiative on Methods, Measurement, and Pain  
14 Assessment in Clinical Trials, I-M-M-P-A-C-T. It's  
15 an international consortium of participants from  
16 academic research, governmental agencies, and you  
17 see those listed there, industry, consulting and  
18 research organizations, and consumer advocates.

19 The mission of IMMPACT is to suggest methods  
20 for improving the design, execution, and  
21 implementation of clinical trials of treatments for  
22 pain. IMMPACT does not emphasize outcomes of those

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1 actual studies as far as trying to determine one  
 2 treatment is better or not as well as some other  
 3 treatment, but rather how would you design to  
 4 improve upon the kinds of studies that we're doing  
 5 to get the best benefit of those studies?  
 6 IMMPACT is part of ACTTION, which stands for  
 7 Analgesic, Anesthetic, and Addiction Clinical  
 8 Trials, Translations, Innovations, Opportunities,  
 9 and Networks, or ACTTION. You'll notice we use  
 10 lots of acronyms. The director of ACTTION is an  
 11 expert on developing acronyms, so you have to bear  
 12 with us as we use these.  
 13 But what is ACTTION? ACTTION is a  
 14 public-private partnership with the United States  
 15 Food and Drug Administration. The mission of  
 16 ACTTION is to identify, prioritize, sponsor,  
 17 coordinate, and promote innovative activities with  
 18 a special interest in optimizing clinical trials  
 19 that will expedite the discovery and development of  
 20 improved analgesic, anesthetic, addiction, and  
 21 peripheral neuropathy treatments for the benefits  
 22 of the public health.

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1 Who is IMMPACT? There have been 23 prior  
 2 IMMPACT names. This is the 24th. There have been  
 3 over 200 participants at these meetings. Some have  
 4 been at more than one of those meetings. Academic  
 5 and related participants from multiple countries,  
 6 representing over 125 different academic  
 7 institutions and health systems, have been  
 8 participants.  
 9 By participants, I mean they're engaging in  
 10 the meeting, so not just an audience but they  
 11 actually participate in the meeting; and  
 12 investigators and reviewers from national and  
 13 international government regulatory research  
 14 agencies, including the FDA, NIH, EMA, MHRA, and  
 15 many others. Those individuals actually  
 16 participate in the study and in the discussions  
 17 that are going to be conducted, so they're not just  
 18 passive observers, but they actually are  
 19 participants.  
 20 We have representatives from over 50  
 21 different pharmaceutical and device companies and  
 22 consumer advocacy representatives from seven

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1 different organizations, and I haven't listed them  
 2 all. There have been several individuals from  
 3 different private consulting organizations.  
 4 But most important is you. You are IMMPACT,  
 5 the people who attend these meetings. They're the  
 6 ones who actually contribute to the discussion, the  
 7 consensus, and the development of recommendations  
 8 and considerations for future research.  
 9 What do IMMPACT and ACTTION do? Well, we  
 10 hold consensus meetings in research initiatives.  
 11 We publish those types of systematic statements and  
 12 reviews. We commission actual papers on topics  
 13 that we feel need additional attention. We conduct  
 14 and support scientific studies. We sponsor the  
 15 development of diagnostic classifications. We  
 16 support educational initiatives.  
 17 There have been almost 150 IMMPACT and  
 18 ACTTION articles that have been published; over 600  
 19 different scientific journals, ranging from  
 20 addiction medicine to veterinary medicine and  
 21 women's health since the inception of IMMPACT in  
 22 2003, and it's been cited over 12,000 different

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1 times according to Google Scholar. So we have  
 2 meetings. We develop consensus recommendations or  
 3 considerations. We develop manuscripts and publish  
 4 those papers. They have had a reasonable impact.  
 5 They've been broadly looked at from a whole range  
 6 of different journals, and they've been cited  
 7 fairly widely.  
 8 If you have more interest in knowing about  
 9 ACTTION or IMMPACT, you can go to the website. You  
 10 notice IMMPACT is I-M-M-P-A-C-T, and it's important  
 11 you use the double-M or you'll end up with all  
 12 kinds of unusual places.  
 13 For ACTTION, it's A-C-T-T-I-O-N.org, and you  
 14 can go to that website. There, information will be  
 15 about meetings, about all the past papers that have  
 16 been developed, publications that have appeared,  
 17 who our partners are, and who's been involved in  
 18 those different meetings.  
 19 So what are the objectives of this  
 20 particular meeting? Well, in general, the  
 21 objective is to discuss important considerations  
 22 and provide suggestions regarding the design,

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1 implementation, and evaluation of pragmatic and  
 2 comparative effectiveness clinical trials of pain  
 3 treatments. We want to discuss and consider what  
 4 needs to go into those types of studies and what  
 5 should someone be thinking about if in fact they're  
 6 planning on conducting one of those studies.  
 7 We want to disseminate these considerations,  
 8 observations, suggestions, and research agenda by  
 9 publication in peer-reviewed journals. The only  
 10 way that we can have an impact -- to use a bad pun,  
 11 if I will -- is to get information out there. So  
 12 our goal is to make sure that we get enough  
 13 information developed so that we are able to  
 14 develop a manuscript and publish that manuscript.  
 15 All of you will be asked, if you participate  
 16 in the meeting, if you want to be considered. When  
 17 manuscript drafts are developed, they're  
 18 circulated. You'll have opportunities to comment  
 19 on those. The lead author will integrate that  
 20 information, submit these, and pass them around  
 21 until we come to a final consensus in the  
 22 manuscript.

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1 Important, when we get to that manuscript,  
 2 as you can tell by the number of people that are  
 3 participating in this meeting, that's a lot of  
 4 authors. If in fact everyone doesn't efficiently  
 5 respond, it will take a very long time before we  
 6 can get these manuscripts out. So we encourage  
 7 you, please, if in fact you choose to be an author,  
 8 and you read the draft of the manuscript, and you  
 9 have comments on those, to really provide us with  
 10 that information as quickly as you can, within a  
 11 reasonable time frame of 1 to 2 weeks if at all  
 12 possible.  
 13 So that's what we're going to be doing for  
 14 today, and now we're going to be introducing who  
 15 the moderators will be for morning session.  
 16 I would be remiss if I didn't thank some  
 17 people who really made this meeting possible. This  
 18 is the first virtual meeting that we've had for  
 19 IMMPACT, and we could not have done this without  
 20 the expert assistance we've had from Jana  
 21 Hatton [ph], who is the video production  
 22 person/producer; Carlos Rodriguez, who has been the

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1 technical person; and most of all and important is  
 2 to Valorie Thompson, who has really been the person  
 3 who's been able to pull all of these things  
 4 together into a format that we are actually able to  
 5 use. We really are counting on their support  
 6 throughout, and I hope you'll be there with us. As  
 7 I mentioned, this is our first one.  
 8 What we'd like to do now is to introduce you  
 9 to two moderators for the first session.  
 10 Dr. Robert Edwards -- Rob Edwards is an associate  
 11 professor at Brigham and Women's Hospital and  
 12 Harvard -- and Dr. Daniel Cherkin.  
 13 Dr. Cherkin was a scientific investigator at  
 14 the Kaiser Permanente Health Research Institute.  
 15 Dr. Cherkin is emeritus, but we've been able to  
 16 attract him to come to help us and to provide us  
 17 with his insights, knowledge, and wisdom as we move  
 18 this forward. So let me turn this over to  
 19 Dr. Edwards and Dr. Cherkin.  
 20 DR. EDWARDS: Thanks very much, Dennis, for  
 21 a terrific overview and summary, and thanks very  
 22 much to IMMPACT for organizing this exciting

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1 meeting. I believe my co-moderator, Dr. Cherkin,  
 2 will be introducing the next speaker, which I think  
 3 we can move to now.  
 4 DR. CHERKIN: Thank you, Rob, for stepping  
 5 in there at this lapse there.  
 6 I'm happy to present the first speaker,  
 7 Dr. Lynn DeBar, who is senior investigator at  
 8 Kaiser Permanente Washington Health Research  
 9 Institute in Seattle, and who has a master's degree  
 10 in epidemiology and biostatistics and a doctorate  
 11 in clinical and health psychology. Dr. DeBar has a  
 12 unique experience in research that's pragmatic,  
 13 having worked in the VA for a number of years, and  
 14 for more than the past two decades, within the  
 15 Kaiser system. So I'd like to ask Dr. DeBar to  
 16 kick off the meeting with the first presentation.  
 17 Presentation - Lynn DeBar  
 18 DR. DeBAR: Thanks for that introduction and  
 19 the opportunity to participate in this meeting. I  
 20 wanted to start out just by really thanking both  
 21 IMMPACT and the NIH Health Care Systems  
 22 Collaboratory -- it shouldn't be on the same line

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1 there -- and infinite thanks to Valorie and Carlos  
 2 for their patience in what has been a couple days  
 3 recording ordeal.  
 4       The work I'm going to talk about today  
 5 really reflects work we did as part of the Health  
 6 Care Systems Collaboratory and also some  
 7 PCORI-sponsored work. We have been really lucky to  
 8 have a number of current HEAL initiatives, where  
 9 we've had to employ a lot of these designs and  
 10 really wrestle with some of these issues. VA has  
 11 really pioneered the way for a lot of this, and  
 12 finally I really wanted to thank our fantastic  
 13 research teams and collaborators who really deserve  
 14 a lot of credit in what I'm talking about today.  
 15       To start with some definitions and  
 16 comparisons, there are a variety of ways that  
 17 comparative effectiveness and pragmatic trials have  
 18 been written about, and what I wanted to start with  
 19 is just to recognize where the commonalities are.  
 20 Comparative effectiveness -- actually, both of  
 21 these have been done for many, many years, but in  
 22 more recent years there's been an influx of funding

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1 and really some focused attention that have allowed  
 2 us to make some methodological advances.  
 3       For comparative effectiveness, ARA really  
 4 ushered in a lot of funding and focus on this kind  
 5 of work and the Affordable Care Act. With that,  
 6 the funding of the patients that are at Outcomes  
 7 Research Institute really gave us a leg up in doing  
 8 this work.  
 9       When you look at those Venn diagrams in the  
 10 center, what you can see is comparative  
 11 effectiveness includes randomized clinical trials,  
 12 but it also has a host of really very important  
 13 methodological advances in observational studies,  
 14 which maybe we'll touch on during the meeting.  
 15       The question that's quite vocal and maybe  
 16 somewhat unique to comparative effectiveness  
 17 research is really the tailoring to say what works  
 18 best for whom. Pragmatic trials -- again, things  
 19 that that could be considered pragmatic  
 20 trials -- have been done for a number of years.  
 21 But the illustration off to your upper right,  
 22 really showing that funnel from basic research all

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1 the way to, really, use within the clinical care  
 2 settings, there was a recognition several years  
 3 back that that is a 17-year odyssey, on average,  
 4 from publication to real application of findings.  
 5 So really, the impetus in funding and focus on  
 6 pragmatic trials at the National Institute of  
 7 Health was to try to really accelerate that  
 8 pipeline.  
 9       The availability of big data, and with that  
 10 I would say the adoption, in a widespread way, of  
 11 electronic health records for healthcare delivery  
 12 systems, really allowed a lot of this work to  
 13 happen.  
 14       Part of the hope with pragmatic trials was  
 15 that by having these additional tools, we could do  
 16 bigger, faster, cheaper trials, and really look at  
 17 a variety of factors that we haven't been able to  
 18 in smaller trials. Then finally, implementation  
 19 research on the bottom, both of these approaches  
 20 intersect with implementation research, and I'm  
 21 sure we'll learn about that in the meeting.  
 22       To start with comparative effectiveness

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1 research, the hallmarks of CER are really the  
 2 head-to-head comparison of two or more medical  
 3 treatments or services. Those might be like  
 4 treatments such as illustrated on the left of  
 5 different medications. They may be also treatments  
 6 for the same condition that really have a lot of  
 7 uniqueness to them, so it really covers a variety  
 8 of different situations.  
 9       Importantly, the purpose of this, really, is  
 10 to assist stakeholders' various strengths, so  
 11 consumers, clinicians, purchasers, policymakers, in  
 12 making informed decisions. Then finally, I  
 13 emphasized this earlier, the ability and the focus  
 14 on looking at heterogeneity of treatment effect.  
 15 What works well for whom and how do we tailor  
 16 treatment is really fundamental to CER.  
 17       Pragmatic clinical trials overlap in several  
 18 important ways, but the motivation here is in some  
 19 ways a little bit distinct, and that is motivated  
 20 by relevance and efficiency. These are large  
 21 efficient studies that are designed to be conducted  
 22 in real-world delivery systems. In the circles on

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1 the bottom, you can see some of the hallmark  
2 features.  
3 The study questions and outcomes are shaped  
4 by clinicians, policymakers, and patients of what  
5 are the really critical questions for these folks  
6 in the front lines of care. They're designed,  
7 generally, to be deeply embedded in everyday  
8 clinical practice. They emphasize interventions  
9 that are practical and sustainable in routine  
10 clinical workflow. Data in these really rely on  
11 electronic health records whenever possible; and  
12 finally, a target in the population with greatest  
13 needs, so very broad populations with few  
14 exclusions.  
15 Just quickly, these are by no means  
16 exhaustive but are some of the key parameters that  
17 are considered as we're designing trials and just a  
18 brief comparison of how comparative effectiveness  
19 trials and pragmatic trials really differ in many  
20 important ways from our more conventional  
21 explanatory RCTs.  
22 As you look at the study question,

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1 increasingly, you have stakeholders really at the  
2 table in defining and shaping what the study  
3 question is. In terms of the question answered,  
4 we're really looking in conventional trials at  
5 treatments under more ideal conditions where we can  
6 really maximize internal validity and looking at  
7 what should we believe versus what should we do  
8 with a pragmatic trial, and I would suggest CER is  
9 really the middle of that.  
10 In terms of comparisons, I'd already  
11 mentioned that comparative effectiveness really are  
12 two or more active treatments, whereas often for  
13 pragmatic trials, it's been a real-world  
14 alternative treatment versus usual care, although  
15 it can be head-to-head trials there. But those are  
16 both contrasted with treatment versus no treatment  
17 or versus placebo, more common in conventional  
18 trials.  
19 Data collection, interestingly, for true and  
20 at the end of the continuum pragmatic trials,  
21 relies more on point-of-care clinicians and  
22 electronic health records and registries for

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1 collection of that information, whereas  
2 conventional trials are really outside the care  
3 delivery and more of a hybrid, I would suggest, in  
4 CER.  
5 Outcomes, again really important emphasis on  
6 relevancy to clinicians, patients, decision-makers,  
7 with more of a reliance on EHR and secondary data  
8 in pragmatic trials. Then finally with treatment  
9 adherence, much more rigorous enforcement with  
10 conventional trials, and that really is a continuum  
11 for CER and pragmatic trials.  
12 As I'm talking in the next few minutes, I'm  
13 going to pull along an example of a recent  
14 pragmatic trial we did as part of the NIH Health  
15 Care Systems Collaboratory called PPACT, and I  
16 wanted to say just a couple of words about that so  
17 it's familiar as I refer back to it.  
18 This was a trial that we did in three  
19 regions of Kaiser Permanente: the Pacific  
20 Northwest, in Georgia, and Hawaii. It really was a  
21 trial to work with patients who had a variety of  
22 kinds of chronic pain conditions, and all were

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1 patients on long-term opioid treatment who are  
2 really difficult for the primary care providers to  
3 treat.  
4 What we did is we took what has been used by  
5 many of you and has been looked at for many years  
6 as a multidisciplinary intervention. What was  
7 unique about that was that it was embedded into  
8 primary care and we did it in a very pragmatic way.  
9 So this was a cluster randomized trial, clustered  
10 at the level of the primary care provider. The  
11 intervention I just talked about. The outcomes  
12 were very limited in terms of patient-reported  
13 outcomes and very reliant on the electronic health  
14 record.  
15 In shifting to talk about the fundamental  
16 design issues that we need to grapple with, both  
17 for pragmatic trials and CER, I wanted to run  
18 through some broad overall design issues and then  
19 spend some time on talking about patient-reported  
20 outcomes and also the importance of stakeholders  
21 and the qualitative end of the spectrum.  
22 Any of you that have been involved in

1 pragmatic trials have probably seen this PRECIS  
2 wheel. Essentially, this represents a continuum  
3 between pragmatic and explanatory trials, and these  
4 are scaled from things that if they're right around  
5 the center are due to be quite explanatory, and as  
6 you get further to the outside of that wheel, it is  
7 more pragmatic. These are several important  
8 dimensions of the way trials are designed, and they  
9 allow an evaluation of how pragmatic a trial is.

10 This was a publication that was put out  
11 early in the first round of the NIH Collaboratory  
12 pragmatic trials of which PPACT, that I just  
13 introduced you to, was one of these. The reason  
14 that I'm showing this is just to illustrate that  
15 there is enormous variation in how pragmatic  
16 various elements of design and approach are for  
17 different kinds of trials.

18 You can see PPACT there in the upper center,  
19 and it looks somewhat like a deflated tire. So  
20 we're not way out on the spokes, and I think we'll  
21 talk quite a bit more about this. But I think  
22 there are reasons that sometimes we want to

1 conducting a simple and inexpensive trial.  
2 So there are inevitable external/internal  
3 validity trade-offs, and things like relevance,  
4 feasibility, timeliness are things to consider in  
5 addition to those kind of parameters and dimensions  
6 of the PRECIS wheel. A lot of times these drivers  
7 are really not primarily scientific, but they are  
8 things that you have to do in conjunction with the  
9 delivery system that you're working in.

10 To shift gears and talk about pragmatic  
11 trial designs, some of the common ones, and some of  
12 the benefits and liabilities, particularly early  
13 pragmatic trials often were cluster randomized. I  
14 introduced PPACT and noted that it was a cluster  
15 randomized trial and that we clustered at the level  
16 of the PCP. If you look at that diagram on the  
17 upper right, you can see those bottom squares  
18 denoting patients for example, and that middle rung  
19 would be the primary care providers and that upper  
20 rung, the clinic.

21 If you think about when and why one might  
22 cluster, fundamentally it is the level of the

1 emphasize things like adherence in delivery of  
2 something like a behavioral treatment model,  
3 whereas we can be quite pragmatic in the outcomes  
4 we look at, and analysis, and so forth.

5 LIRE is another study that my colleague  
6 Jerry Jarvik did, looking at inserting findings  
7 from diagnostic images for folks with back pain in  
8 the EHR and feeding that feedback back to primary  
9 care providers. You'll note with that one it's  
10 much more of an inflated cycle, so easier to get  
11 into the extremes.

12 In thinking about how you think about  
13 explanatory and pragmatic features, I'd suggest it  
14 really is a balancing act. I just noted that an  
15 evenly inflated tire may not be possible or the  
16 goal. Sometimes trying to be highly relevant to  
17 decision-makers, whether those are patients trying  
18 to decide on treatment or policymakers, that can  
19 come at the expense of trial efficiencies.

20 For example, patient-reported outcomes might  
21 be very important for patients and the decisions  
22 they make, but those things might be add-ons to

1 intervention that you're doing; are you primarily  
2 touching the patient, in which case you might be  
3 able to do individual randomization. In our case,  
4 in PPACT, we really fed a lot of information back  
5 to the primary care provider, did a lot of training  
6 for how to interact with their patients around  
7 adoption of behavioral skills training, and broader  
8 ways of considering chronic pains.

9 We were really intervening at the primary  
10 care provider level, but the most obvious place  
11 sometimes is to do things at the clinical level if  
12 you're going in and you're really changing practice  
13 at a clinic level.

14 The disadvantage of that, we had started  
15 with the idea of clustering at a clinic level, but  
16 when we looked at clinics across the places I was  
17 showing you, Hawaii, Georgia, the Pacific  
18 Northwest, some of those clinics were small.

19 Hawaii has literally single-room clinics and  
20 some of them were immensely large, and trying to  
21 reach some sort of balance across those clinics was  
22 just too hard to achieve, which is part of the

1 reason we went down to the primary care provider  
2 level. But in doing so, there were some things  
3 that were lost by our ability to really go into a  
4 clinic, and the logistics are much simpler if you  
5 can make changes at a clinic level and really bring  
6 everybody along with you. So there's, again, both  
7 scientific and pragmatic considerations.

8 The other thing to know about clustering is  
9 that the patients, in this case that are clustered  
10 under the primary care provider, are going to share  
11 variants in a way that needs to be accounted for  
12 analytically, so it increases the complexity and  
13 also increases the end.

14 In practice, a lot of times the size of  
15 those clusters can be quite variable. It really  
16 works best when you've got many clusters and maybe  
17 fewer patients in them, rather than to have a few  
18 primary care providers with a lot of patients or a  
19 few very large clinics; so all things I think we'll  
20 touch on.

21 Stepped wedge is another design. I  
22 introduced Jerry Jarvik's LIRE's study, where they

1 contextual change that we've all experienced is  
2 COVID and how that might affect files, so this kind  
3 of design is very vulnerable to those kinds of  
4 things.

5 Finally, I wanted to just introduce a design  
6 that's not as well known but one that if you have  
7 secondary data can have a number of advantages. I  
8 mentioned that what we're trying to do in  
9 comparative effectiveness and pragmatic trials is  
10 to maximize external validity. One of the things  
11 that I think many of us have experienced in pain  
12 trials is that those patients that primary care  
13 providers and others think might most benefit  
14 sometimes are the most reluctant to enroll in  
15 trials.

16 When we looked at our enrollment in  
17 PPACT -- and colleagues in the VA, several of you  
18 who are here, I think all of us sometimes top out  
19 between 10 and 20 percent of eligible patients that  
20 actually enroll. An encouragement or a Zelen  
21 design actually solves for that in some ways. This  
22 is a design where everybody who is eligible -- and

1 inserted the findings from diagnostic imaging to  
2 really educate primary care providers on what those  
3 meant and maybe to discourage inappropriate  
4 referrals for surgery and so forth.

5 When Jerry did that study, he went through  
6 clinics and he added this feature to the electronic  
7 health record in the various healthcare systems and  
8 clinics he was working on, and that was stepped  
9 over time so that by the end of the recruitment  
10 period, all of those clinics had that intervention  
11 alive and going. The advantage of that is that  
12 everybody ultimately gets the intervention, and if  
13 successful, you can really sustain it because it's  
14 already rolled out.

15 The thing to consider -- and I think a  
16 number of colleagues who have done stepped wedge  
17 has found this -- is that if there are any kind of  
18 confounds over that time, it can really wreak havoc  
19 with trying to make sense of it. In Jerry's case,  
20 there were changes in the electronic health record  
21 platforms that needed to be adapted to that really  
22 created some challenge there. An external kind of

1 you need secondary data from the electronic record  
2 to define eligibility -- are automatically enrolled  
3 in the trial and followed over the course, and then  
4 half of those people are randomly selected and  
5 invited to take part in the intervention.

6 In these circumstances, we assume that a  
7 good portion of those people will decline, but we  
8 will continue to follow them with intent-to-treat  
9 analyses. It also gives the option that those  
10 people who might not immediately warm up to  
11 participation but whom you can continue to  
12 approach -- just as we do in clinical care when  
13 people might not be ready to enroll in a particular  
14 intervention -- and you can do that at any point,  
15 say, in a year that you're following those  
16 patients. So it's quite an intriguing design.  
17 It's used increasingly with very stigmatized  
18 conditions like substance-abuse disorders, but we  
19 could also consider it for pain.

20 I'm going to shift and talk about  
21 patient-reported outcomes, really an important  
22 piece of pain-related research, but often things

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1 that aren't baked in, in a regular and frequent  
 2 way, into our clinical workflows in everyday  
 3 clinical care. When we started PPACT -- as I  
 4 mentioned, this was focused on people who are all  
 5 on long-term opioid treatment -- we thought,  
 6 really, we had set things up well because in the  
 7 Kaiser regions that we were working in, in theory,  
 8 those people were all on opioid therapy plans,  
 9 which included the regular administration of the  
 10 briefing inventory.

11 So if you look at that right-hand side, that  
 12 shows all the elements of the opioid treatment  
 13 plans, and I've highlighted or boxed and read that  
 14 that included, or was in theory included, quarterly  
 15 administrations of the briefing inventory.

16 What we found when we started the  
 17 preliminary UG3 year for that trial was, in fact,  
 18 very often those assessments were not happening.  
 19 When we really did some of the formative work with  
 20 our primary care providers, what we discovered is  
 21 that 12 items was way too long to be administering  
 22 in everyday care. That also started with the pain

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1 intensity items, which they said that's really  
 2 giving the wrong message; we really want to be  
 3 focusing on functioning. They did not find this to  
 4 be an easy tool to use with patients.

5 So part of what we did in preparation for  
 6 launching the main trial was to shift the entire  
 7 Kaiser system over to the PEG, which now is used  
 8 much more broadly, so a 3-item, smaller set of the  
 9 BPI. We also used sleep because that was one of  
 10 the functional items that our PCPs cared a lot  
 11 about, and there had been some validation of a  
 12 4-item version of the PEG that included that. But  
 13 we found that much more actionable, and I think as  
 14 we talk about PROs, it's really important to keep  
 15 some of these pragmatics in mind.

16 The other thing that we discovered that  
 17 primary care providers really did not like was the  
 18 idea of doing something that the PROMIS does well,  
 19 where the group of items can be variant. They  
 20 really wanted the same items over time so they  
 21 could look at change and talk about that very  
 22 concretely with the patients.

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1 Then on the bottom, this is just to indicate  
 2 you also have to do this in a context of some kind  
 3 of population management support tools. So the  
 4 Epic reporting workbench does this, and this can  
 5 bring up for clinicians who is due for measurements  
 6 of these kind. But even with those tools, it's  
 7 important to keep in mind that there are going to  
 8 be probably some biases in the information that's  
 9 collected. So patients with more severe disorders  
 10 often come in more frequently. We've got more PROs  
 11 measures in them, and that really needs to be  
 12 [indiscernible].

13 So what did this really look like in PPACT?  
 14 Well, we did rely some on what was collected and we  
 15 did shift the primary tool that was being used to  
 16 the PEG with the sleep item. But we also had to  
 17 augment what was happening in clinical care, and we  
 18 did that by using the patient health records, so  
 19 pushing out through Epic, in a quarterly basis,  
 20 this to patients by secure email. If they didn't  
 21 respond, we used the interactive voice response  
 22 system and recorded the responses that way, and

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1 that meant that only a minority, so roughly a  
 2 quarter of the population, actually needed to be  
 3 reached with a live person. I think that's the  
 4 other thing about these kinds of trials, is we need  
 5 to automate whatever we can so we can spend our  
 6 resources very wisely.

7 So shifting gears now and talking a little  
 8 bit more on the gray side of the aisle and a little  
 9 bit more focused on CER, as you look there on the  
 10 left, those are the fundamental questions PCORI has  
 11 posed as being critical for the clinical trials  
 12 and, frankly, all of the research that they  
 13 support. So it's really based on patients and  
 14 providers being able to make decisions about what  
 15 is best for them under what circumstances.

16 As you can consider those questions, none of  
 17 those questions can really be stated as a null  
 18 hypothesis. We are not looking about is this  
 19 different from not doing anything. It really is a  
 20 comparative question, and those kinds of  
 21 comparative questions of two active interventions  
 22 take a different analytic approach. So I'm hoping

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1 in these two days that we talk more about some of  
 2 the Bayesian approaches that really undergird this,  
 3 undergird things like adapted trials that really  
 4 take into consideration what are the prior things  
 5 that we know that are built into our analytic  
 6 models.  
 7 As I've mentioned, heterogeneity of  
 8 treatment effect is really the quantitative means  
 9 of looking at who does best with what, but I'd also  
 10 suggest that you need to look at that in a  
 11 qualitative way. So as it's noted on the bottom,  
 12 not everything that can be counted counts and not  
 13 everything that counts can be counted.  
 14 So that really leads us to talking about  
 15 stakeholders and their roles in these kinds of  
 16 trials and a couple dimensions to think about with  
 17 this. Your customers in performing these kinds of  
 18 trials are many and varied. I've put in the  
 19 smallest font, funders and other researchers  
 20 because even though that's where we often start and  
 21 we gear how we construct our designs and the hoops  
 22 we go through, it really needs to be designed with

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1 these other stakeholders in mind.  
 2 I would say that, really, this can overlap,  
 3 but there really are two kinds of stakeholders that  
 4 you engage with through these processes. One is  
 5 who uses this evidence and makes decisions? When  
 6 do they make those decisions? How do they make  
 7 those decisions? Those are all important features  
 8 in how you design the trials. Then equally as  
 9 important, when you're conducting these trials,  
 10 what do you need to know? Who do you need to work  
 11 with in order to really be able to do these well  
 12 when they're deeply embedded in clinical workflow?  
 13 The clinical workflow alignment is key. The  
 14 healthcare system partners are often the ones  
 15 delivering the intervention and the team designing  
 16 the study, and this is definitely a team sport to  
 17 be doing this, but they're often the smaller  
 18 circle, as I've shown here.  
 19 The last thing I want to emphasize here is  
 20 the win and why of stakeholder engagement. This is  
 21 really cradle to grave, so to speak. PCORI has  
 22 really brought this home, but really engaging right

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1 from the start, what are the relevant questions of  
 2 high priority? In lighter blue there is that you  
 3 want to really have these folks working with you  
 4 all along the way. Things are often very volatile  
 5 when you're doing these kinds of projects, and you  
 6 need those champions, and you need to problem solve  
 7 in the moment; then finally, to help with some of  
 8 the implementation and really get the findings out  
 9 to the important audiences.  
 10 This is just a note that when one does do  
 11 qualitative work in these kinds of trials, there  
 12 are less conventional tools that can be very  
 13 helpful, and I'm happy to talk more about this in  
 14 discussion. We use things like weekly journaling.  
 15 We did postcards back and forth with our  
 16 stakeholders so that they were really informed as  
 17 we went. So it was really a two-way street. Rapid  
 18 assessment approaches can be extremely helpful.  
 19 These things aren't used in isolation from more  
 20 traditional qualitative methods but are really  
 21 critical to this approach.  
 22 In closing, what I would suggest is what I

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1 hope we're talking about over the course of these  
 2 two days are really the things here in the  
 3 lower-right quadrant, emphasizing external validity  
 4 and probably dealing with more wicked problems,  
 5 very complicated patients, and complicated  
 6 analytics to really untangle this, but I am  
 7 enormously impressed that IMPACT and ACTTION are  
 8 taking this on.  
 9 Things to consider, many of which I touched  
 10 on today, are to really carefully consider design  
 11 and measurement in order to maximize these things;  
 12 generalizability, who you're working with, the  
 13 settings in which you're working in; trying to  
 14 embed this within the everyday clinical workflow;  
 15 and designing for sustainability. Many of these  
 16 things, as I've noted, are questions that are of  
 17 keen interest to our delivery system partners, and  
 18 when that's the case, there's really an underbelly  
 19 that you need to plan for.  
 20 When I talked about PACT, we were doing  
 21 that, really, at the height of the time that people  
 22 were trying to make the pivot from long-term opioid

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1 treatment being the modal kind of treatment, so  
 2 there was all kinds of QI going on at the same  
 3 time. There was all kinds of unpredictable change.  
 4 We really needed to do surveillance to see what was  
 5 happening in usual care.  
 6 I would say this requires partnership in  
 7 what I would call a vertical manner, meaning that  
 8 you need everybody from the C-suite to all of the  
 9 directors in the clinics, to what I think we  
 10 undervalued initially, the medical assistants who  
 11 sometimes were closest to these patients and could  
 12 achieve the most change; so to pay attention and to  
 13 continue to partner along that entire continuum.  
 14 Then finally, I think this is something that  
 15 this group can really move the needle on, trying to  
 16 be brutally realistic about what is needed for  
 17 routine collection of patient-reported outcomes.  
 18 What are the tools that are really going to be  
 19 acceptable and feasible in real-world care and how  
 20 can we get those things used in a regular way that  
 21 would allow us to do things like use Zelen designs  
 22 and rely on EHR data in a way that we have more

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1 hard one to tackle. I think one of the things  
 2 about pragmatic trials and comparative  
 3 effectiveness is it allows us, in the best  
 4 instances, to best mimic the kinds of conditions  
 5 and flows that show up in the everyday clinical  
 6 care.  
 7 I made mention of a Zelen design, an  
 8 encouragement design, in one of the slides, where  
 9 it really takes into consideration everybody who  
 10 has a particular challenge. In that case, it's a  
 11 trial that we're looking at opioid-use disorder and  
 12 concomitant mental health disorders, but it could  
 13 be something we use for pain. I think one of the  
 14 most limiting things that we discovered in our last  
 15 completed trials was that we just didn't have time  
 16 to get folks into the trial who were somewhat  
 17 ambivalent about care at the front end, and I think  
 18 that that's more common than not.  
 19 So if we can think about employing designs  
 20 that really allow for a period of time where people  
 21 may consider being enrolled but it really takes  
 22 some time to get them on board, I think it's a much

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1 confidence?  
 2 So I leave you with just a couple of  
 3 references that are, I think, key for thinking  
 4 about CER work. PCORI has really brought that  
 5 along ways in the years that it's been at the  
 6 table, and increasingly there have been  
 7 partnerships in some of the grand rounds. The  
 8 Health Care Systems Collaboratory has joined with  
 9 the PCORnet, so I would encourage people to look at  
 10 these, and I look forward to the rest of the  
 11 meeting. Thanks so much.  
 12 DR. CHERKIN: Well, thank you, Lynn, for  
 13 that overview of very complex issues facing those  
 14 of us who are trying to advance science through  
 15 these new approaches. We have time for a couple of  
 16 questions now.  
 17 One is a question that says, "In all the  
 18 trials that you have done, which one do you think  
 19 is most beneficial for the patients? Which one  
 20 provides the best way to aid in the treatment of  
 21 pain and function for a person with pain?"  
 22 DR. DeBAR: Boy, that's a big question and a

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1 closer replication of what happens in real-world  
 2 care. I think we haven't talked as much about how  
 3 stigmatizing pain and related conditions can be and  
 4 that it takes some things for people to get over  
 5 the hump of really wanting to participate,  
 6 particularly in the kinds of non-pharmacotherapy,  
 7 self-management types of interventions that many of  
 8 us have championed and are involved in.  
 9 So hopefully that answers that. I hope I  
 10 have more opportunity to talk about those kinds of  
 11 designs. I also didn't have a chance in that short  
 12 segment to talk about adaptive designs, which I  
 13 think really help us to move with the information  
 14 that we're getting from trials. Rather than have  
 15 an extended trial that may by the end be following  
 16 rather than leading what's happening in the field,  
 17 we can make adaptations as we go.  
 18 DR. CHERKIN: Thank you, Lynn. Yes, there  
 19 will be more time for more discussion of this and  
 20 other questions.  
 21 One other maybe simpler question, "You  
 22 pointed out the spectrum between the more

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1 scientifically rigorous classical efficacy trials  
 2 and pragmatic trials at another end of the  
 3 spectrum. Is it appropriate to conduct a pragmatic  
 4 clinical trial that evaluates a treatment that has  
 5 not yet been convincingly found to be efficacious  
 6 in a more rigorous trial?"  
 7 DR. DeBAR: Yes. That's such a good  
 8 question. I hope we talk more about that. I would  
 9 argue that there are some things that can really  
 10 only be done in ways in which they're embedded  
 11 deeply in our delivery system, even if we have  
 12 incomplete knowledge. Again, I'm going to  
 13 reference our current NIMH trial, where we're  
 14 looking at a number of comorbid conditions that  
 15 show up with opioid-use disorder.  
 16 In order to try to do something like that,  
 17 you have to collaborate with delivery systems and  
 18 have a large enough sample, and you've got to be  
 19 doing it in ways -- and I spoke a little bit about  
 20 this -- where you're using the kind of tools that  
 21 are really available in our care delivery system.  
 22 We talk about hybrid designs where there is

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1 effectiveness/implementation, but there are  
 2 instances where I think there are ways, at least,  
 3 in which we're putting various components together  
 4 that we haven't tested well. But if we don't do  
 5 those in the settings in which this is conducted,  
 6 they're hard trials to run. So I think this merits  
 7 a lot more discussion because it's a hard space to  
 8 really be sure you're simultaneously balancing the  
 9 things about external validity and really the rigor  
 10 to be able to interpret what you're doing.  
 11 DR. CHERKIN: Okay. Thank you, Lynn.  
 12 We'll move now to the next speaker,  
 13 Dr. Scott Evans, who is a professor and the  
 14 founding chair of the Department of Biostatistics  
 15 and Bioinformatics at The George Washington  
 16 University. He has an interest in design,  
 17 monitoring, analysis, and reporting and education  
 18 in clinical trials and diagnostic studies. Beyond  
 19 his expertise in biostatistics, he also has become  
 20 very knowledgeable about the study of infectious  
 21 disease.  
 22 Scott?

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1 Presentation - Scott Evans  
 2 DR. EVANS: Let me begin by thanking  
 3 Professor Dworkin and IMPACT for organizing this  
 4 important meeting and for giving me the opportunity  
 5 to be part of it. I'm going to talk to you today  
 6 about pragmatism from a biostatistician  
 7 perspective. The further I go in my career, the  
 8 more I'm able to recognize distinctions between  
 9 research questions that may be subtle on the  
 10 surface but nonetheless importantly different, and  
 11 I think there's lots of room for us to improve on  
 12 finding and answering the most important questions.  
 13 I'm going to begin by telling a quick story.  
 14 Several years ago I had a leak in the roof of my  
 15 house, and it created this water bubble in the side  
 16 of my wall. It was really something I had never  
 17 seen before. In addition to getting a new roof, I  
 18 had to re-paper the wall. I had asked my neighbor  
 19 who'd recently papered a similar size room in his  
 20 house how much paper did you buy, and he replied,  
 21 "Six rolls, six rolls of paper." But upon  
 22 finishing papering of the wall, I'd only used

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1 4 rolls, and I told my neighbor I had 2 rolls left  
 2 and what happened. He said, "Oh that happened to  
 3 you, too."  
 4 Now, this was a lesson that I learned, that  
 5 I actually asked the wrong question. I asked how  
 6 much paper did you buy rather than how much he  
 7 used, so perhaps this was my fault. But this is  
 8 actually a lesson that applies in pragmatic trials,  
 9 that in many of our traditional trials, we answer  
 10 perhaps the wrong question or perhaps an important  
 11 question, but maybe not "the" most important  
 12 question.  
 13 Two things I've learned about traditional  
 14 clinical trials over the years; first of all,  
 15 they're rigorously conducted by experts closely  
 16 adhering to the highest standards of clinical  
 17 trials, but many times they're essentially useless  
 18 for helping clinicians make treatment decisions.  
 19 Perhaps this was said more eloquently by Dave  
 20 DeMets, a well-known statistician, and Rob Califf,  
 21 the former FDA commissioner.  
 22 This was a publication in JAMA 2011. "Most

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1 clinical trials fail to provide the evidence needed  
 2 to inform medical decision-making. However, the  
 3 serious implications of this deficit are largely  
 4 absent from discourse." What they were talking  
 5 about was that trials are not pragmatic enough.  
 6 They're not giving us enough information about the  
 7 effects of interventions as they would be  
 8 experienced in clinical practice; that we're  
 9 answering a slightly distorted question in many of  
 10 our traditional trials.

11 I want to make a few opening remarks about  
 12 real-world evidence and real-world data as they  
 13 correspond to pragmatism. First of all, they might  
 14 be considered to be associated but they are not the  
 15 same. Real-world evidence concerns the data  
 16 source, evidence that we acquire using  
 17 non-traditional -- at least non-traditional for  
 18 clinical trials -- sources like electronic health  
 19 records.

20 Pragmatism is about the question, and one  
 21 does not necessarily imply the other. Studies  
 22 could be very pragmatic without using real-world

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1 data and studies that use real-world data may not  
 2 be very pragmatic either. So if you're interested  
 3 in answering important questions for clinical  
 4 practice, then we should be conducting pragmatic  
 5 studies. To gain the cost and resource  
 6 efficiencies of using existing data, then we should  
 7 consider utilizing real-world data.

8 What might be considered the standard  
 9 efficacy clinical trials, the typical trial setting  
 10 involves control over many different factors, and  
 11 what that does for us is it enhances sensitivity  
 12 for detecting effects. We may get faster answers  
 13 because we're able to see those effects a little  
 14 bit more readily.

15 Some examples of what I mean by this sort of  
 16 control, we have selective enrollment criteria into  
 17 clinical trials. We may use surrogate endpoints  
 18 rather than clinical outcomes. We limit the use of  
 19 concomitant therapies, for example, because we  
 20 think that may confound the outcomes that we  
 21 observe. But utilizing all that control may  
 22 potentially limit the relevancy to clinical

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1 practice of the results that we find.  
 2 On the other hand, if we conduct pragmatic,  
 3 or sometimes called effectiveness, trials, the  
 4 purpose here is to inform decisions about clinical  
 5 practice and policy. One way to think about this  
 6 is we're going to evaluate strategies of  
 7 intervention application for treating patients in  
 8 practice.

9 There are a lot of imperfections in clinical  
 10 practice, but those imperfections are part of the  
 11 game. They're not to be controlled or muted;  
 12 they're part of the question. This is distinct  
 13 from answering questions about biology or  
 14 mechanisms of action, where you might be trying to  
 15 evaluate what sort of effects might an intervention  
 16 have if everybody adhered to therapy and was able  
 17 to tolerate therapy and so forth.

18 The pragmatic trial is trying to evaluate  
 19 how well things work under usual conditions rather  
 20 than under ideal conditions, and the extraneous  
 21 variation, and noise, and perceived imperfections  
 22 that occur in clinical practice are not necessarily

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1 to be controlled, but they're part of the game.  
 2 Let them happen. Let them happen the way they  
 3 happen.

4 Characteristics of pragmatic trials, we  
 5 often have diverse and representative populations  
 6 that enhances generalizability, heterogeneous  
 7 real-world settings. So many of the traditional  
 8 trials we do, we enroll patients from sites who are  
 9 very experienced at trials. They may be very  
 10 select in certain ways, but on the extreme  
 11 pragmatic side you try to do it in everyday care,  
 12 which may be community clinics and so forth.  
 13 Flexible protocols for how interventions are  
 14 utilized, adherence, treatment application and so  
 15 forth, and important patient-centered outcomes  
 16 would be important for pragmatic trials.

17 Here's a contrast between the explanatory or  
 18 efficacy trials versus the pragmatic effectiveness  
 19 trials with respect to a number of different  
 20 characteristics. I'll focus on a couple of these  
 21 characteristics over the next few slides. In the  
 22 explanatory trial, we're looking at efficacy and

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1 can it work under certain conditions. In the  
2 pragmatic trial, it's will it work in practice?  
3 If you look at the setting in which they're  
4 conducted, explanatory trials may be very  
5 well-resourced settings, places that are used to  
6 implementing such interventions. Pragmatic trials  
7 are going to be much more consistent with normal  
8 practice in the real world and variable. Again,  
9 participants may be highly selected in explanatory  
10 trials. We might exclude patients who are unlikely  
11 to comply and that have confounding conditions or  
12 complications.

13 In pragmatic trials, patients are much more  
14 representative. You're trying to get a read on  
15 what happens to patients as they come into  
16 practice. The variation is often minimized in  
17 explanatory trials. We standardize the way we  
18 measure things. We standardize the way we apply  
19 things. But in a pragmatic setting, they're not  
20 necessarily standardized and there's extra noise  
21 and so forth there.

22 I'm going to talk about a few of these

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1 issues. There was a tool, this PRECIS-2 tool, that  
2 looked at a number of different, which might be  
3 considered, dimensions of pragmatism: how the  
4 primary analysis was done; who's selected to get  
5 into the trial in terms of eligibility; how  
6 patients are recruited; what the setting is; and so  
7 forth.

8 There are a number of different dimensions  
9 by which you might categorize or classify a  
10 clinical trial. A trial may be pragmatic in some  
11 respects but not in other respects, and there may  
12 be gradations to how pragmatic they are. This was  
13 a tool to characterize and classify clinical trials  
14 in that way.

15 Some of the most challenging issues for  
16 pragmatic trials in pain, I want to talk about a  
17 couple of issues that I think are perhaps most  
18 challenging for pain trials. First thing is that  
19 pragmatic trials, at least the most extreme  
20 pragmatic trials, would not include blinding  
21 because blinding doesn't occur in clinical  
22 practice. That can be a big issue for pain, and

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1 I'll talk about that.

2 Limited control of concomitant medications  
3 is another big issue that often happens in pain  
4 trials, as we're controlling concomitant therapy,  
5 particularly over-the-counter pain medication; and  
6 flexible application of the intervention and  
7 questions about the quality and completeness, for  
8 example, of real-world data that might be used in  
9 such trials.

10 One concern is a lack of blinding. The most  
11 extreme pragmatic designs avoid blinding and  
12 placebos. They have real-world control groups  
13 without necessarily blinding, and this would avoid  
14 placebo effects, which can be a concern in pain  
15 trials. On the other hand, we know that pain is a  
16 very patient-centered and subjective outcome that  
17 can be affected by knowledge of the treatment.  
18 Knowledge of that treatment can affect adherence.  
19 It could potentially result in treatment cross-over  
20 or drop-out of a study. So that's a particularly  
21 challenging issue in pain trials to be thinking  
22 about.

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1 I thought I might show one example. This  
2 was actually in asthma. This was a four-armed  
3 clinical trial for asthma treatment in which three  
4 of the arms actually were non-active. Albuterol  
5 was the active treatment for asthma, but there was  
6 an albuterol placebo. It was a sham acupuncture  
7 and then there was one treatment group that just  
8 received nothing. So three of these four arms were  
9 actually inactive.

10 Now, when you compared the change in forced  
11 expiratory volume, a common outcome in asthma  
12 trials, what you saw was a big improvement for the  
13 albuterol arm, but the three arms that did not  
14 receive active treatment did less well, and clearly  
15 albuterol was superior to the other three arms with  
16 respect to this change in forced expiratory volume,  
17 an objective measure.

18 But then there was a subjective improvement  
19 that was evaluated by patients, and if you looked  
20 at that particular outcome, the outcomes for  
21 albuterol, the albuterol placebo, and the sham  
22 acupuncture, namely the three arms that thought

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1 they were being treated, were quite similar, but  
 2 the one arm that had no intervention and knew that  
 3 they were not getting any intervention did less  
 4 well.  
 5 So this was basically showing you that  
 6 knowledge of the treatment was affecting this  
 7 particular outcome. The subjective versus  
 8 objective nature of these outcomes kind of played  
 9 into these results. Certainly in pain trials,  
 10 thinking carefully about issues like this would  
 11 certainly be important.  
 12 Other concerns about concomitant medication  
 13 use, pain trials often place strict rules on  
 14 concomitant therapy use such as over-the-counter  
 15 pain medications. The primary reason for this is  
 16 sensitivity to detect effects and that we can try  
 17 to isolate the effect of the treatment in question  
 18 that we're trying to isolate. But pragmatic trials  
 19 place very limited restrictions on concomitant  
 20 medications because in practice, patients are going  
 21 to take aspirin, or ibuprofen, or whatever it might  
 22 be if they're feeling pain. So these are sort of a

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1 dichotomy of an important question to be thinking  
 2 about if pragmatic trials and pain are going to be  
 3 considered.  
 4 What about using real-world data? Well, it  
 5 could be very challenging to use real-world data  
 6 for measuring pain outcomes. We know that  
 7 depending on the type of real-world data, data  
 8 quality and completeness can be an issue. In  
 9 clinical practice, there's not necessarily a  
 10 standardization of measurements and methods for  
 11 measuring outcomes, pain outcomes or other  
 12 outcomes. Some standardization is important in  
 13 this particular area. Even the time of day  
 14 relative to when you measure pain outcomes and so  
 15 forth can be particularly important.  
 16 There is a publication coming out from the  
 17 Clinical Trials Transformation Initiative that was  
 18 evaluating uses of real-world data. They chose,  
 19 actually, to focus on using real-world data for  
 20 specific purposes that may be beneficial but  
 21 particularly low risk. For example, using  
 22 real-world data for planning eligibility criteria

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1 or for enhancing recruitment, maybe you can access  
 2 registry data to know who has a particular chronic  
 3 disease that might have pain.  
 4 That's fairly low risk to try to help  
 5 identify who might enter a trial, but if you're  
 6 going to be using it to measure outcomes on  
 7 patients, that's higher risk. There may be some  
 8 hybrid by which you can use real-world data for  
 9 some purposes, but if you're measuring, say,  
 10 outcomes on patients, you might want to standardize  
 11 and make sure that those types of outcomes are more  
 12 complete and are done in a high-quality fashion.  
 13 Some of the general concerns about pragmatic  
 14 trials is this extraneous variation that is not  
 15 controlled from either limited restrictions on  
 16 entry criteria or the use of concomitant therapies  
 17 may result in a dilution of the treatment effects;  
 18 that if the noise is bigger than the signal, you  
 19 won't be able to see the signal. There's been some  
 20 mixed results about whether that's actually the  
 21 case. Some research suggests that it really may  
 22 not dilute the treatment effect as much as you

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1 think, but that's one of the main concerns, is that  
 2 the noise is bigger than the signal, which may  
 3 create problems in identifying the signal.  
 4 The other thing to be aware of is if we  
 5 conduct trials or try to use real-world data,  
 6 pragmatic trials often have large N, large sample  
 7 sizes. But large numbers don't eliminate biases  
 8 and confounding. They give you more information,  
 9 but they don't eliminate biases and confounding.  
 10 So be wary of that or don't mislead ourselves that  
 11 just because we have a larger sample size, bias and  
 12 confounding are going to go away.  
 13 There are opportunities, I think, in the  
 14 real-world data setting and getting data through  
 15 personal devices. We've done trials in which we  
 16 have been able to collect pain data, for example,  
 17 through prompts in phones and other personalized  
 18 devices, so I do think that's a big opportunity.  
 19 If we could ever really get smart about marrying  
 20 the research enterprise with the clinical practice  
 21 enterprise, and being able to use data and research  
 22 from the clinical practice infrastructure, that

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1 would really be valuable.  
 2 I wanted to make a couple of comments about  
 3 some statistical concerns that are a little bit  
 4 less recognized in my view, and that is that  
 5 typical approaches to analyses, statistical  
 6 analyses, are often not very pragmatic. This has  
 7 really not been recognized in many places, so I'm  
 8 going to show you a couple of examples of what I  
 9 mean.  
 10 Here's a question. We define analysis  
 11 populations in clinical trials and efficacy  
 12 analyses. We use an intention-to-treat population.  
 13 We do a safety analysis in a safety population.  
 14 Those two populations are not the same. At the end  
 15 of the trial, we may try to combine these analyses  
 16 into something we might term a benefit-risk  
 17 analysis, but when you step back to whom does this  
 18 analysis apply, what are we actually estimating?  
 19 Well, in statistics, we estimate a  
 20 parameter, which parameters are characteristic of a  
 21 population, but here we have outcomes being  
 22 assessed in different populations, so there isn't

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1 even clarity about what population we're talking  
 2 about. Then when we start thinking about  
 3 personalized medicine, how do we do personalized  
 4 medicine if we're not even evaluating what's  
 5 happening to the patient? There may be  
 6 correlations between efficacy and safety outcomes,  
 7 and I'm going to show you an example of that.  
 8 Question number 2. Pain is often a symptom  
 9 of an underlying disease and the effectiveness of  
 10 pain management can affect the underlying disease  
 11 outcome. For example, if you were a failure of  
 12 chemotherapy, maybe a downstream result of failure  
 13 to control peripheral neuropathy might be  
 14 associated with that chemotherapy, and in turn the  
 15 change in chemotherapy affects peripheral  
 16 neuropathy outcomes.  
 17 We have this difficult problem of competing  
 18 risks, and circularity, and the fact that pain is a  
 19 symptom of an underlying disease. Yet oftentimes  
 20 we're trying to separate outcomes of the disease  
 21 versus outcomes of treating the symptoms when, in  
 22 fact, they're actually connected and can affect

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1 each other, and that's a very difficult problem.  
 2 Suppose you measure the duration of a  
 3 chemotherapy-associated peripheral neuropathy, and  
 4 you say, well a shorter duration of that peripheral  
 5 neuropathy is better? But the faster the patient  
 6 withdraws from chemo, the shorter the duration, or  
 7 the faster the patient dies, the shorter the  
 8 duration. So the interpretation of one outcome  
 9 really needs context of other clinical outcomes for  
 10 that same patient; yet, we often are analyzing them  
 11 separately. So we have to be careful about that,  
 12 and I'll show you another example of this.  
 13 We've had some great work on estimands,  
 14 meaning clarity about what population parameter you  
 15 really want to estimate, and we finally get people  
 16 to recognize that if we change the analysis  
 17 population, that means we're changing the question  
 18 we're addressing. Here's an example of what I  
 19 mean.  
 20 Suppose we conduct a randomized trial that  
 21 compares two treatments, A and B, and a trial  
 22 participant that is assigned to treatment A

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1 discontinues A and begins a new intervention C.  
 2 The participant then experiences an SAE. It's  
 3 adjudicated as related to C but not to A. So this  
 4 leads to the belief that safety is not an issue for  
 5 A; it's C's fault. So we might continue the trial  
 6 and say, well, I can still do this randomized trial  
 7 of A versus B because it wasn't A that was the  
 8 problem.  
 9 Now suppose 10 additional trial participants  
 10 discontinue A, begin treatment C, and experience  
 11 the SAE. Again, adjudication links the  
 12 relationship to C but not A, but there's no such  
 13 events in arm B. Would you volunteer to be  
 14 randomized into this trial possibly with being  
 15 randomized to treatment A? Well, if you were on  
 16 the data monitoring committee, can you allow  
 17 continued randomization into A?  
 18 So the issue here is that adjudication,  
 19 despite the fact that biologically you might  
 20 attribute this to treatment C, the strategy of  
 21 applying A is a problem because there's nothing  
 22 happening in arm B, and I wouldn't want to be

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1 randomized to treatment A under this case. So this  
 2 is an intention-to-treat issue, that what you're  
 3 interested in from a pragmatic point of view is the  
 4 strategy of its application. This is evaluated in  
 5 a randomized setting. You cannot allow a continued  
 6 randomization into arm A in a case like this, and  
 7 we've talked about this in a recent paper in the  
 8 context of data monitoring committees.

9 Here's another question. Suppose a loved  
 10 one is diagnosed with a serious disease and you  
 11 were selecting the treatment, and you have three  
 12 treatment options, A, B, and C. Let's suppose for  
 13 simplicity that there are two outcomes equally  
 14 important: a treatment success, yes or no, and  
 15 there's a safety event, yes or no.

16 So we have two, an efficacy outcome, a  
 17 safety outcome, and both are binary, and let's  
 18 suppose they're of similar importance. Now,  
 19 luckily enough, there was a randomized trial that  
 20 compared these three treatments, and we'll look at  
 21 those outcomes because that can help inform whether  
 22 we would choose A, B, or C.

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1 There were 100 participants in each of the  
 2 three arms. The treatment success rate was  
 3 50 percent in A, 50 percent in B, and 50 percent in  
 4 C. The safety event rate was 30 percent in A and  
 5 50 percent in B and C. So which treatment do you  
 6 choose? They all have the same success rate. A's  
 7 got the lowest safety event rate. B and C are  
 8 indistinguishable. You can't even tell the  
 9 difference between B and C.

10 So since we're all logical people, we'd  
 11 probably choose treatment A, but instead of taking  
 12 the patients in the trial and analyzing the  
 13 outcomes, which is what we have done to this  
 14 point -- we took the patients in the trial, the  
 15 hundred in each arm, and analyzed the  
 16 outcomes -- what I'd like to do is flip that upside  
 17 down; take the outcomes in the trial and analyze  
 18 what happened to the patients.

19 Now, if you think about that play on words,  
 20 what that means is that there are four possible  
 21 patient outcomes. You either get the treatment  
 22 success, yes or no, with or without the safety

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1 event, yes or no. Our culture has been to use  
 2 these patients to analyze the outcomes, but  
 3 shouldn't we use the outcomes to analyze the  
 4 patients?

5 So here's what I'm going to do. We  
 6 cross-classify and analyze the patients. So it  
 7 turns out that in treatment A, the treatment  
 8 success and the safety event were uncorrelated, so  
 9 there were 35 patients that had the treatment  
 10 success without the safety event. In arm B., the  
 11 treatment success and the safety event were  
 12 positively correlated, so there are zero patients  
 13 that had the treatment success without the safety  
 14 event. In C, they were negatively correlated, so  
 15 there are actually 50 patients who had treatment  
 16 success without the safety event.

17 Now, one or two slides ago, we couldn't tell  
 18 the difference between B and C. If we take the  
 19 outcomes and analyze the patients, we may see some  
 20 things that we're not able to see by  
 21 taking the patients and analyzing the outcomes.

22 Question 5. A negative trial may not mean

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1 that the treatment is good for no one. A positive  
 2 trial doesn't mean that it works for everyone. How  
 3 do we identify the subgroup of patients we want to  
 4 treat? Well, let's return to the example we had.

5 If we had predictive markers for efficacy, then  
 6 we'd identify these people. If we had predictive  
 7 markers for safety, then we'd identify these  
 8 people. But neither of these approaches finds the  
 9 patients that you actually want to treat.

10 So even thinking about this benefit-risk  
 11 type of approach, what you're interested in is  
 12 identifying the patients who have treatment success  
 13 without the safety event, but by looking at one  
 14 outcome at a time, we're unable to find those  
 15 patients. So shouldn't personalized medicine be  
 16 based on analysis of the patient?

17 I call this the clinical trial arithmetic.  
 18 What we do is we compare each outcome and then  
 19 combine how those outcomes compare. But what we  
 20 really should be doing is combining outcomes within  
 21 patient and then comparing how treatment A compares  
 22 with treatment B. That's what's most relevant for

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1 evaluating the effects of treating patients. As my  
 2 father told me many years ago, the order of  
 3 operations is important, and the clinical trial of  
 4 arithmetic has never been quite right.  
 5 There are some evolving methods about how to  
 6 do this. We had written a paper with a colleague,  
 7 Dean Follmann, using outcomes to analyze patients  
 8 rather than the patients to analyze the outcomes,  
 9 and this would be a step towards pragmatism and  
 10 benefit-risk evaluation. We have some methods  
 11 called desirability of outcome ranking that try to  
 12 address things in this way, and the idea is that  
 13 before we analyze hundreds of thousands of  
 14 patients, we really have to figure out how to  
 15 analyze one by combining information within patient  
 16 and evaluating the patient journey through the  
 17 trial, sort of a synthesized analysis of the  
 18 benefits and the harms of the quality of life that  
 19 has been experienced by the patient.  
 20 The way I describe this is there's a map to  
 21 pragmatism as I see it. Where we are today is when  
 22 you think about the number of outcomes we have in

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1 trials, it's fairly high, but we estimate one  
 2 effect for each of those outcomes.  
 3 Where we'd like to be is pragmatism on the  
 4 far right there, where the number of outcomes we  
 5 have is actually reduced and that there's a patient  
 6 outcome, and that patient outcome composes  
 7 individual outcomes on efficacy, and safety, and so  
 8 forth. But then we would estimate, and the path we  
 9 take to get there is we make progress via  
 10 composition of the outcomes, characterizing the  
 11 disease burden for a patient, but then move towards  
 12 personalized medicine by estimating the effect on  
 13 that total disease burden, depending on the  
 14 characteristics of the patient.  
 15 I'm going to show you one quick example of  
 16 this. This is the PROVIDE study. It was a  
 17 prospective, multicenter, observational evaluation  
 18 among adult hospitalized patients with MRSA  
 19 bloodstream infections. The research question was  
 20 what PK dosing target would be optimal for  
 21 treatment outcome. So if you think about dosing,  
 22 well, I want to make sure I get a high enough dose

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1 so that there's efficacy, but if I get too high,  
 2 it's going to be toxic. So it's a benefit-risk  
 3 problem. How do I look at that?  
 4 There were 265 patients in this particular  
 5 study, and we set up what was called a desirability  
 6 of outcome ranking. Treatment success without  
 7 acute kidney injury is the most desirable outcome,  
 8 the patient has a treatment success and avoids  
 9 toxicity. The least desirable outcome is at the  
 10 bottom where the patient dies. But then there are  
 11 gradations of patient response in between in which  
 12 they may be getting treatment success but they may  
 13 have toxicity at various levels.  
 14 In this particular outcome, this  
 15 desirability of outcome ranking had five levels,  
 16 most desirable at the top and least desirable at  
 17 the bottom, and intermediate categories where some  
 18 things go right but not everything goes right.  
 19 What we did is look at the distribution of  
 20 this particular ordinal door outcome by dosing  
 21 levels, and the vertical axis represents the  
 22 quintiles of dosing, the highest dose on the top

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1 and the lowest dose on the bottom, and the  
 2 different colors represent the five DOR categories.  
 3 The bluish on the left is a treatment success  
 4 without acute kidney injury and the purple on the  
 5 far right is mortality.  
 6 Now, as you go from the low doses to the  
 7 high doses, what do you actually see? What do  
 8 patients gain? They don't necessarily gain  
 9 efficacy because this red area is actually  
 10 treatment success but with acute kidney injury, so  
 11 what we're gaining with higher doses is toxicity  
 12 rather than gaining efficacy, and lower doses in  
 13 this particular case may be better.  
 14 So how might this work in pain trials, you  
 15 may have pain trials where there might be an  
 16 outcome, say, with four levels. The most desirable  
 17 at the top is pain control without toxicity and the  
 18 least desirable at the bottom, but there might be a  
 19 few gradations in between. There are a couple of  
 20 different ways in which to  
 21 analyze this particular outcome.  
 22 One method you see on the far right is to

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1 score this like an academic test, and if the  
 2 patient has the most desirable outcome, they get a  
 3 score of 100; the least desirable outcome, they get  
 4 a score of zero. If they're in the intermediate  
 5 categories, they would get partial credit, and then  
 6 you could analyze it sort of as a difference of  
 7 means. There are other methods using ranked-based  
 8 methods.

9 My suggestions, I think it's important to  
 10 address pragmatic questions. I think much of the  
 11 time we're answering the wrong question. We should  
 12 be evaluating strategies of application. I think  
 13 it's a better reflection of the value to society.  
 14 Pragmatic approaches; analysis populations;  
 15 intention to treat; some flexibility in treatment  
 16 application; allowance of concomitant medications;  
 17 analyzing patients rather than outcomes; and using  
 18 real-world data for certain things but not others I  
 19 think can be risky for certain things, but try to  
 20 retain the rigor.

21 I do think that randomization and blinding  
 22 is still important regardless of the fact that the

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1 most pragmatic of studies is avoiding blinding and  
 2 things like that. We've got to be careful about  
 3 using real-world data for addressing endpoints, I  
 4 think, because we need to make sure that we've got  
 5 quality and completeness for outcomes.

6 So I will end there and say, I have no doubt  
 7 you will enthusiastically applaud now because  
 8 you're so relieved that my talk is over. Thank you  
 9 very much.

10 DR. CHERKIN: Okay. Well, thank you,  
 11 Dr. Evans. I'm trying to look over the questions  
 12 here.

13 One question says, "Dr. Evans noted the lack  
 14 of blinding was a concern in pragmatic trials and,  
 15 as he showed in the asthma trial, that albuterol  
 16 was superior to, and sham acupuncture, in terms of  
 17 objective outcomes but was no better in terms of  
 18 subject of outcomes. For asthma, the objective  
 19 outcome may be more clinically important than  
 20 subjective patient reports of improvement.  
 21 However, in the study of treatments for common,  
 22 nonspecific pain problems, could one argue that

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1 subjective outcomes such as increased function,  
 2 quality of life, and less pain may be more  
 3 important or relevant than objective outcomes such  
 4 as improved range of motion?"

5 DR. EVANS: Yes. Thank you for your  
 6 question. I think you're right. I think it's a  
 7 point well taken that many of the outcomes that we  
 8 are interested in have a subjective nature to them,  
 9 and those are certainly important.

10 My point about the blinding, in the most  
 11 pragmatic form of trials, they try to avoid  
 12 blinding because you're trying to mimic what's  
 13 happening in clinical practice as much as you can,  
 14 in regular clinical practice. This is why I talked  
 15 about it. I think it's a difficult area for pain  
 16 trials because blinding in some ways is so  
 17 important in traditional pain trials. So this is  
 18 one area where I think it's a real struggle, and  
 19 real critical talk is going to be needed in pain  
 20 trials. But your point is well taken, and I think  
 21 you have valid points there.

22 I would note that even objective outcomes

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1 are not immune to concerns about a lack of  
 2 blinding. Patients can selectively drop out and so  
 3 forth, and that can still affect that for even  
 4 objective outcomes. But my point was to raise this  
 5 as an important consideration, or one of the main  
 6 or biggest issues for pain trials is thinking about  
 7 the blinding question and wrestling with the pros  
 8 and cons of that.

9 DR. CHERKIN: Okay. Thank you.  
 10 Rob, I've kind of goofed up my screen.  
 11 Could you ask the question that you forwarded to  
 12 me, please?

13 DR. EDWARDS:  
 14 Definitely. That's why they  
 15 have two of us as co-moderators. I'm happy to jump  
 16 in.

17 DR. CHERKIN: Thank you.  
 18 DR. EDWARDS: Scott, a terrific  
 19 presentation. We've got a question that just came  
 20 in from Nat Katz, who also loved your presentation  
 21 and inquired, "Are you drawing a distinction  
 22 between pragmatic questions and pragmatic trials?"

DR. EVANS: Yes. I wanted to make sure that

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1 some of the terminology -- my point was that some  
 2 of the terminology, it's not completely well  
 3 defined and people use it in different ways. What  
 4 I wanted to make sure that we're able to  
 5 distinguish is a lot of people will call pragmatic  
 6 trials those that are using data from  
 7 non-traditional trial sources, and using health  
 8 records data, or other sorts of data from the  
 9 clinical practice infrastructure, but there are a  
 10 lot of studies there that, although they may use  
 11 that data, are not necessarily very pragmatic; and  
 12 there are a fair amount of what you consider to be  
 13 pragmatic trials addressing pragmatic questions  
 14 that may not use much of that data.

15 So I wanted to make sure that we have some  
 16 language and clarity in our own thinking that  
 17 there's a distinction between using data from  
 18 non-traditional sources and potentially from  
 19 clinical practice and addressing what might be  
 20 considered pragmatic questions. So I just wanted  
 21 to make sure there was clarity of thought there.

22 DR. CHERKIN: Okay. Well, thank you, Rob

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1 and Scott. I think, again, like in Dr. DeBar's  
 2 presentation, this is a very complex area.  
 3 Pragmatic trials aren't for the faint of heart, and  
 4 there are a lot of issues to pay attention to. So  
 5 thank you to some of the pioneers in this area, and  
 6 now I'm going to turn it over to Rob to introduce  
 7 the next speaker.

8 DR. EDWARDS: Terrific. Thanks, Scott, and  
 9 thanks very much, Dan.

10 It is a real pleasure to introduce our next  
 11 speaker, who will be Dr. Ajay Wasan. Ajay is a  
 12 psychiatrist and a pain physician, and  
 13 parenthetically an outstanding tennis player as  
 14 well. He's a professor and vice chair for pain  
 15 medicine and the co-director at the Center for  
 16 Innovation in Pain Care at the University of  
 17 Pittsburgh.

18 He and his outstanding research team are  
 19 doing seminal work in areas such as phenotyping of  
 20 patients with acute and chronic pain;  
 21 interventional procedures for pain management;  
 22 pain-related medical informatics; and great work on

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1 pain biomarkers using functional neuroimaging and  
 2 other technologies. I'm very excited to hear his  
 3 talk on lessons learned from psychiatry, the CATIE  
 4 and STAR-D trials. So I'll leave it to Ajay to  
 5 take it away from here.

6 Presentation - Ajay Wasan

7 DR. WASAN: Hello. I'm Ajay Wasan, and I'm  
 8 at the University of Pittsburgh. This over here on  
 9 the right is actually the flagship building at the  
 10 University of Pittsburgh. It's the 44-story tall  
 11 Cathedral of Learning.

12 What I'm going to cover today is a  
 13 discussion of a couple of important trials,  
 14 important comparative effectiveness trials, the  
 15 CATIE trial, which looked at atypical  
 16 antipsychotics in Alzheimer's dementia, and it has  
 17 been very productive and generated over 50 papers,  
 18 and the STAR-D trial, which is even larger and  
 19 perhaps even more important than that and more  
 20 influential, sequential trials of antidepressants  
 21 in major depression.

22 I'm coming at this from the perspective of

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1 what we can learn from these trials, and I think  
 2 what we can learn is this idea of balance, of  
 3 balancing the explanatory and pragmatic components  
 4 of the trial in order to reach the scientific  
 5 objectives and understanding what the trade-offs  
 6 are.

7 This was an editorial I wrote in 2014 on  
 8 this issue, Effectiveness versus Efficacy and  
 9 Explanatory versus Pragmatic. What I argued in  
 10 this editorial is that there's a sweet spot in pain  
 11 medicine research, in the field and in comparative  
 12 effectiveness research, which will yield the most  
 13 scientifically and clinically impactful findings.  
 14 The idea is when you're designing any trial, any  
 15 comparative effectiveness trial, is try to  
 16 understand what is your sweet spot for what you're  
 17 trying to achieve scientifically.

18 This quotation here really summarizes I  
 19 think the upshot of what I'd like us all to take  
 20 away from this talk today, which is, "The optimal  
 21 balance point between the poles of pragmatic and  
 22 explanatory qualities is where these approaches

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1 mutually strengthen each other to create the most  
 2 robust framework for a clinical trial design."  
 3 Dr. Lynn DeBar may have already shown this  
 4 in her talk, and I apologize for the redundancy,  
 5 but one very important tool that's out there for  
 6 helping to balance the pragmatic versus the  
 7 explanatory is the PRECIS-2 tool. There was a  
 8 PRECIS-1 version. That was very successful, and  
 9 it's been validated and refined into PRECIS-2. A  
 10 nice description of this appears in the BMJ in  
 11 2015.  
 12 This was a very comprehensive process to  
 13 arrive at this tool. Eighty international  
 14 trialists, clinicians, and policymakers contributed  
 15 to this. What you have are nine different domains  
 16 over here that represent different aspects of a  
 17 clinical trial, and you can design each of these  
 18 domains from the most pragmatic, which is the outer  
 19 ring, so to speak, of 5, graded a 5, versus the  
 20 least pragmatic and more explanatory, which is a 1.  
 21 You can get a sense in each of these key  
 22 areas where does your trial lie on that balance

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1 point between explanatory and pragmatic. It's very  
 2 valuable for matching design decisions for how the  
 3 results of a trial are intended to be used.  
 4 Looking at all of this, this is from my own  
 5 impressions in the literature and my own  
 6 impressions of these trials of CATIE and STAR-D.  
 7 What I've summarized here are some key issues, I  
 8 think, in comparative effectiveness trial design  
 9 that really cut across multiples of these domains.  
 10 For instance, it's particularly important  
 11 that any interventions that are tested are tested  
 12 in routine clinical delivery settings when  
 13 possible. That really speaks to generalizability,  
 14 which is I think very important, but with attention  
 15 to minimizing the known confounders. That is, of  
 16 course, the best approach to causal hypotheses.  
 17 It's this issue of what is the magnitude of  
 18 the unknown confounders when you're doing a study  
 19 in a more routine clinical delivery setting, and  
 20 that's what actually stymies and vexes a lot of the  
 21 clinical trialists and the evidence-based medicine  
 22 scientists. It's that tension and that conflict

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1 that's there, and that is I think a key balance  
 2 point.  
 3 Other key balance points are the inclusion  
 4 criteria. Do you choose broad or specific? It's  
 5 important to consider. Duration of tracking the  
 6 intervention; are you just looking for a signal of  
 7 the effectiveness? So maybe you only tracked an  
 8 intervention for two months or are you actually  
 9 looking for durability, and you want to know what  
 10 the results are at one year? So important things  
 11 to keep in mind. Also, what's the specific dose of  
 12 the intervention? Do you have one dose for all  
 13 subjects or is there a range of dosing that's  
 14 allowed for all subjects? Of course that  
 15 introduces confounders as well that you need to be  
 16 aware of.  
 17 Then randomization and lots of issues over  
 18 how you randomize, when to randomize, and where to  
 19 randomize. Do you include crossover randomization  
 20 or not? All these of course have implications for  
 21 explanatory versus pragmatic trial design.  
 22 Outcomes assessment, this is important, too. Do

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1 you have very rigorous outcomes assessments for a  
 2 very specific set of outcomes that you're looking  
 3 for or are you looking more at global health  
 4 outcomes and if generalizability, for instance, is  
 5 the key goal that you want? So again, things that  
 6 need to be balanced. Data analysis, lots of issues  
 7 there, for instance, doing intention-to-treat  
 8 analysis versus only analyzing those who completed  
 9 treatment.  
 10 I'll talk a little bit about the CATIE  
 11 trial. It stands for Clinical Antipsychotic Trials  
 12 of Intervention Effectiveness. There were several  
 13 CATIE trials. There was one for chronic  
 14 schizophrenia as well, and I won't really go into  
 15 that. That trial design was similar, but there was  
 16 no placebo arm. It was only a comparative  
 17 effectiveness trial of five different  
 18 antipsychotics, and the upshot found that  
 19 olanzapine was superior.  
 20 What I'm going to talk about more is the  
 21 CATIE Alzheimer's trial, which looked at  
 22 olanzapine, quetiapine, and risperidone in low

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1 doses -- those are all atypical antipsychotics --  
 2 or placebo, in 450 subjects. It was double-blinded  
 3 and randomized. They did provide 2 doses for each  
 4 drug, low and high medication doses, so you might  
 5 start someone on low and then gradually go up. The  
 6 high dose was not like schizophrenia high. It was  
 7 quite low actually because, really, just small  
 8 doses of atypical antipsychotics are used in this  
 9 patient population.

10 They had two primary outcomes, and this is  
 11 very important. It's an important decision they  
 12 made, and it's unique, and it certainly gets at  
 13 this issue of the purpose of the trial that you may  
 14 actually need to create some unique outcomes. The  
 15 outcome they had is time from initiation treatment  
 16 to discontinuation of any treatment. The idea is  
 17 that if a treatment was effective, it would be  
 18 continued. So if it would help control the  
 19 agitation and psychosis, it would be effective and  
 20 it would be continued, but if the treatment was not  
 21 effective or if there were significant side effects  
 22 like extrapyramidal symptoms, dizziness, confusion,

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1 et cetera, then the treatment would be stopped.  
 2 So the time to treatment initiation is  
 3 really a proxy for treatment failure. That's a  
 4 primary outcome. The minimal improvement benchmark  
 5 on the clinical Global Impression of Change scale  
 6 at 12 weeks, that was the second primary outcome.  
 7 This is the paper published in the New England  
 8 Journal, and they had two primary hypotheses that  
 9 were tested.

10 I think it's important to appreciate these.  
 11 One is the three atypical antipsychotic treatment  
 12 groups taken together will be superior to the  
 13 placebo group in terms of all-cause treatment  
 14 discontinuation, and number two, the three  
 15 antipsychotic treatment groups will be equivalent  
 16 to each other with respect to response at 12 weeks  
 17 regardless of subsequent randomizations.

18 So what they did in this study is first they  
 19 used fairly rigorous enrollment criteria. Each  
 20 patient had to have a DSM diagnosis for Alzheimer's  
 21 and deficits on a mini mental status exam. That's  
 22 a fairly rigorous approach, but they used a fairly

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1 pragmatic approach for some of the specific  
 2 symptoms that are indications for using  
 3 antipsychotics.

4 Psychosis, aggression, and agitation  
 5 symptoms were determined by the judgment of the  
 6 treating physician and the patients had to have  
 7 those for 4 weeks. The prescribing reflected  
 8 clinical practice, and if a subject was not  
 9 responsive to medication, that medicine could be  
 10 discontinued in 2 weeks, and then the subject could  
 11 move to phase 2.

12 This is an outline of the design. We're  
 13 going to focus on phase 1 here, which is each of  
 14 these 4 arms, placebo versus the 3 antipsychotics.  
 15 Then say for instance, in 2 weeks if someone failed  
 16 the first antipsychotic, they could be randomized  
 17 to one of these other arms, which is the  
 18 randomization to either of the two antipsychotics  
 19 they didn't have or citalopram. That's an SSRI.  
 20 That's fairly well tolerated in the elderly. Then  
 21 those who got placebo would be randomized actually  
 22 into the 4 arms, including citalopram, so without

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1 placebo.

2 One thing to think about is this is a fairly  
 3 sophisticated adapter trial design, and  
 4 historically we have not had very many adapter  
 5 trials in our field of pain, and that's something  
 6 for us to think about. If we designed a big  
 7 adapter trial, we're sort of pushing the envelope.  
 8 Is our field really ready for that? Is the science  
 9 there to support it? So again, things to think  
 10 about.

11 This is a summary of the main outcomes, and  
 12 it's very interesting here. Over here on the left,  
 13 this is the time to discontinuation. It's a  
 14 Kaplan-Meier curve, and this is discontinuation for  
 15 any reason, so lack of effectiveness or for too  
 16 many side effects. You can see that the drop-off  
 17 rates, they all essentially are the same. There's  
 18 no significant difference between them. But if you  
 19 split it up into discontinuations related to lack  
 20 of effectiveness -- that's here -- there was a  
 21 clear separation between all three of the  
 22 antipsychotics and placebo, which is this orange

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1 line at the bottom, and it really appears here that  
 2 olanzapine and quetiapine are performing better  
 3 than risperidone.  
 4 Then if you look at the discontinuation for  
 5 the reason of adverse effects, you see the opposite  
 6 Kaplan-Meier curve. Of course you'd expect those  
 7 on placebo that have the least side effects and  
 8 that gets discontinued least often, while the other  
 9 3 antipsychotics get discontinued more. In this  
 10 case, olanzapine was discontinued at the greatest  
 11 rate with the quetiapine and risperidone somewhere  
 12 in the middle.  
 13 When you look at this second outcome, the  
 14 Global Clinical Impression of Change, these are  
 15 some of the comparisons, similar; and there was a  
 16 trend towards the antipsychotics producing more  
 17 impression of change, more global improvement than  
 18 the placebo, but that was not significant.  
 19 So some key lessons here that come out of  
 20 this. Looking at a combined primary outcome of  
 21 efficacy plus adverse effects is very pragmatic.  
 22 It may be something very useful to consider for a

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1 pain trial, but it would be important to  
 2 distinguish between the effectiveness outcomes and  
 3 the adverse effects outcomes.  
 4 Another thing is would the assay sensitivity  
 5 of this trial be improved if the primary outcomes  
 6 were continuous in some fashion? It's kind of hard  
 7 to do for what the aims were of this study but  
 8 something to think about for pain trials.  
 9 Also, when you're looking at effectiveness  
 10 studies, it seems that re-randomizing treatment  
 11 failures is important, and that's an adaptive  
 12 component. That's a version of a smart design, and  
 13 some of the other speakers might be speaking in  
 14 more detail about what this is. A smart design is  
 15 a fairly sophisticated adapter trial approach.  
 16 When I'm talking about re-randomizing treatment  
 17 failures, really it's just step one in a smart  
 18 design.  
 19 We'll move on to STAR-D. That stands for  
 20 Sequence Treatment Alternatives to Relieve  
 21 Depression. It's a much more complicated study, so  
 22 what I'm going to present really is a general

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1 overview about what I think is more important about  
 2 this study. It was designed to assess the  
 3 effectiveness of treatments in generalizable  
 4 samples and ensure that the delivery of the  
 5 treatments was adequate at the same time.  
 6 The study tried to look at the symptomatic  
 7 outcomes for outpatients with nonpsychotic major  
 8 depressive disorder who treated initially with  
 9 citalopram. That was step 1. That was phase 1 in  
 10 the trial. The question fundamentally of the trial  
 11 is what you do next if citalopram fails. So if  
 12 1 SSR fails, what do you do next?  
 13 Having phase 1 being citalopram only,  
 14 establish treatment remitters versus non-remitters.  
 15 That was the key. Remitters means that almost all  
 16 the symptoms of depression go away. They're trying  
 17 to identify the treatment-resistant subgroup, and  
 18 just to note, that's a little bit different than  
 19 treatment-resistant depression because technically  
 20 that's defined as failing two antidepressants, not  
 21 one.  
 22 What they did in level 1, they gave an

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1 adequate dose of citalopram for an adequate  
 2 treatment trial to look at this efficacy, and this  
 3 was done in routine clinical settings in outpatient  
 4 psychiatry practices and primary care. The primary  
 5 outcome was remission and depression symptoms, and  
 6 that's also a unique primary outcome. That's  
 7 almost the absence of depression symptoms versus  
 8 response.  
 9 Typically in antidepressant trials, you  
 10 define response as being a 50 percent improvement  
 11 in symptoms since that is very clinically  
 12 meaningful, but they looked at remission here. To  
 13 give you some sense of what difference that might  
 14 include, in randomized trials of antidepressants,  
 15 typically you'd have a 20 to 30 percent remission  
 16 rate and a 35 to 45 response rate.  
 17 So it's something for an adapter trial to  
 18 consider, which is what really should be the  
 19 primary pain outcome? Should we think about things  
 20 a little bit differently in adapter trials, in  
 21 these comparative effectiveness trials, versus a  
 22 classic randomized-controlled trial for pain

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1 outcome?

2 Some of the key features, STAR-D had

3 4,000 patients. It was very broad entry criteria,

4 nonpsychotic major depression diagnosed by DSM

5 checklist and also having high symptom scores on

6 the HAM-D, which is the Hamilton Depression Symptom

7 Rating Scale. It's been noted in some editorials

8 that actually many of the patients in STAR-D would

9 not have qualified for FDA phase 3 antidepressant

10 trials, so this gets at the increased

11 generalizability that I mentioned before.

12 The dosing was flexible but rigorous.

13 Citalopram actually had a pretty high dose range.

14 We actually don't use 60 milligrams anymore because

15 of some cardiac issues that can occur. The patient

16 could be increased every 2 to 4 weeks. The

17 treatments were unblinded. They were prescribed by

18 a psychiatrist or a primary care physician. It was

19 measurement-based care, so the decisions by the

20 treating physician for whether to increase the dose

21 or determine that the patient was a treatment

22 remitter or non-remitter were used by symptom

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1 checklists.

2 There was some degree of patient choice for

3 which treatments they could receive. Patients, if

4 they got randomized, for instance, to a cognitive

5 therapy arm, they can choose to reject that and go

6 into a medication arm. This is particularly

7 important. I think it's an important lesson that

8 we really should include patient choice as an arm.

9 It's revolutionary, but it's important, and there's

10 a precedent for doing this. In the STAR-D trials,

11 I think patient choice is crucial particularly when

12 you're thinking about multimodal pain trials and

13 how to optimize multimodal care and do comparative

14 effectiveness around those issues, so I would keep

15 that in mind.

16 They had 12 to 14 weeks per treatment, per

17 treatment level, and I will show on the next slide

18 what I mean by that and when you follow up. One

19 consequence of the patient choice was that those

20 who were randomized to cognitive therapy, only a

21 much smaller percentage chose to stay in that

22 arm -- no offense to all the psychologists here who

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1 are listening -- so they could not actually compare

2 the cognitive therapy to the other medications.

3 This is a summary of the study flow.

4 Initial treatment, as I mentioned, is citalopram,

5 then patients could be switched to a couple

6 different antidepressants, bupropion cognitive

7 therapy as I mentioned; sertraline; venlafaxine; or

8 they could have an augmentation strategy, which

9 means that you add something to the citalopram.

10 Even if the citalopram is not working, you could

11 add something to it, so bupropion, buspirone, or

12 cognitive therapy.

13 Then level 3 is if they failed those, then

14 they can be switched to mirtazepine or

15 nortriptyline, or again they could have something

16 augmented. So you could have something added to

17 the other drugs they're on. It could be lithium or

18 it could be a thyroid hormone. Number 4 was

19 actually switching to tranylcypromine, which is

20 Parnate, which is an MAOI, an older antidepressant

21 that has more significant side effects and dietary

22 considerations, or mirtazepine combined with

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1 venlafaxine.

2 These are some of the main studies that are

3 published in the New England Journal of Medicine.

4 Over here are the outcomes of the switch to the

5 different antidepressants. Basically, it didn't

6 matter what you switched to, there was a consistent

7 rate of increased remission. And that's really the

8 wrong word, meaning that it's better to say that

9 more subjects responded.

10 So those who had not responded to citalopram

11 got switched, and then there was a meaningful

12 percentage of people who remitted when a different

13 antidepressant was used, but it didn't matter which

14 antidepressant was used; and similar outcomes with

15 augmentation. For the augmentation, augmentation

16 worked, but it didn't matter if you had buspirone

17 or sustained-release bupropion, both of those

18 increased the number of remitters.

19 Some important study takeaways -- and I'll

20 be finishing up; only a couple slides left --

21 level 1 citalopram achieved 33 percent, who on that

22 in phase 1 achieved remission. Some of the

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1 important takeaways were, for all the levels, if  
 2 there's a partial benefit at 6 weeks, it's  
 3 important to raise the dose, and you would  
 4 definitely get more treatment remitters then.  
 5 The outcomes of switching to a different  
 6 antidepressant or augmentation were no different  
 7 between the treatments, and with this process of  
 8 persistent and vigorous treatments, most patients  
 9 actually entered remission. These are the numbers  
 10 of how it works out. If you go through all the  
 11 steps, up to 67 percent of all subjects total  
 12 actually entered remissions, assuming that they  
 13 stayed in treatment.  
 14 So paying attention to attrition and the  
 15 different phases in relapse is particularly  
 16 important, and the remission rates did drop off per  
 17 stage. So by the time you got to the fourth stage,  
 18 of those who had already been treatment resistant  
 19 to all these other treatments, only 15 percent did  
 20 respond with remission. But that's important  
 21 because some of these patients have significant  
 22 symptoms like suicidality, and if you can decrease

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1 and eliminate that symptom, that's very, very  
 2 important and meaningful.  
 3 Seven weeks was the average time needed to  
 4 achieve remission, and interestingly, it's  
 5 important to know in a multiphase study that all  
 6 the treatments can be compared to each other. It's  
 7 hard to explain, but due to different  
 8 considerations in the trial, it turned out that the  
 9 augmentation arm could not be compared to the  
 10 antidepressant med switching arm. So it's just  
 11 something to be aware of that in multiphase trials,  
 12 they were able to compare.  
 13 Over here on the left is just to give you a  
 14 sense of the number of subjects in each of the  
 15 different cells. You can see it's fairly  
 16 complicated how the randomization goes. You look  
 17 here at the bottom, by the time you get to this  
 18 level 3 switching and level 4, essentially there's  
 19 just not enough patients that you can even analyze,  
 20 so keep that in mind.  
 21 Over here is just a graph of the attrition  
 22 rates and relapse rates. I would say it's an

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1 important lesson for our pain studies that we want  
 2 to think about pain flares. How do we model pain  
 3 flares in the studies? How do we anticipate them?  
 4 Do we think of pain flares during the period of  
 5 follow-up and treatment to be outcomes or are they  
 6 confounders? They're both, obviously. What do we  
 7 do with those is particularly important, and the  
 8 STAR-D trial has shown that.  
 9 There has also been a number of downstream  
 10 reanalyses of the STAR-D data. Most recently, for  
 11 instance, there's some predictive modeling using  
 12 machine learning techniques to understand who  
 13 responds and doesn't respond. For many of these  
 14 studies and for many of the editorials that have  
 15 been written, these are some of the key takeaways  
 16 that popped out to me, that it would be important  
 17 to understand the characteristics of early  
 18 responders.  
 19 Several of these characteristics had already  
 20 been identified in STAR-D, such as higher physical  
 21 health ratings of baseline and lower anxiety at  
 22 baseline. Certainly for pain trials, we want to

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1 think about how do we identify early responders,  
 2 and do we actually consider re-randomizing at 2 two  
 3 weeks if there is no response? That's something  
 4 that would also be fairly novel, but it can also be  
 5 scientifically important.  
 6 Other things in terms of generalizability,  
 7 thinking about where the treatments are  
 8 administered, different clinical sites like  
 9 psychiatry versus primary care in this study. Is  
 10 the treatment delivered the same? Does that  
 11 introduce any kind of unmeasured confounders due to  
 12 treatment at clinical sites? So that's another key  
 13 design element.  
 14 Thank you. Thank you for listening. I've  
 15 been very lucky, and I've been blessed with some  
 16 terrific colleagues, including Dr. Edwards, who's  
 17 part of this meeting today. Over here is actually  
 18 a snapshot of some graffiti on a sidewalk in  
 19 Pittsburgh. That's I think a nice message for all  
 20 of us. This is actually a picture from the inside  
 21 of the Cathedral of Learning. So thank you very  
 22 much and have a great rest of the meeting.

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1 DR. EDWARDS: Thank you very much, Ajay.  
2 That was a terrific presentation. I think we'd all  
3 agree that those complex interesting trials  
4 probably have a lot of important lessons that we  
5 all could take when we're planning future adaptive  
6 and pragmatic studies.  
7 I think we just have time for one question  
8 or two. There's one that came in. The question  
9 is, "How should we weigh patient preferences and  
10 patient choice versus the use of randomization to  
11 ensure a particular study question is answered?  
12 For example, in the STAR-D trial, would you prefer  
13 giving patients the choice of augmentation versus  
14 starting a new antidepressant and discovering that  
15 the majority choose augmentation, or would you  
16 prefer to randomize and finally answer the question  
17 of which, if either, produces better outcomes?"  
18 DR. WASAN: Well, I think that in a nutshell  
19 is the tension between the explanatory and the  
20 pragmatic. If you have more pragmatic bend and you  
21 want to understand not just what's effective but  
22 also what's acceptable to the patients and try to

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1 get some insight into what they prefer, randomizing  
2 the choice and understanding why patients choose  
3 what they choose would be important, but that would  
4 dilute your ability to really sort out the,  
5 quote/unquote, "efficacy" aspects of each of the  
6 treatments.  
7 But that dilution, if you have an adaptive  
8 trial in which, say, treatment failures get  
9 randomized to something else, that dilution effect  
10 of patient choice I think becomes less and less  
11 important there. So again, this is about  
12 translation -- it's more generalizability.  
13 Translation might be the wrong word, but that's  
14 what I would think about it.  
15 DR. EDWARDS: Absolutely.  
16 One more question for you, Ajay, comes in  
17 from John Farrar, I believe. "Terrific talk." And  
18 he wonders, "Given that it's unlikely that any pain  
19 treatment works in everyone, is there any way to  
20 build in consideration of subgroups that might have  
21 a better response and a way of finding them in  
22 large pragmatic trials?"

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1 DR. WASAN: Yes. That's a great question.  
2 One way to do it, if you're thinking about a large  
3 pragmatic trial, one of your objectives might be to  
4 find which treatments work for targeted subgroups.  
5 That gets at it. For instance, you may do a trial  
6 in which you do some like phenotyping, and then the  
7 patients are randomized based on their phenotype to  
8 one of many options.  
9 Let's say you're doing a back pain trial,  
10 and the patients who have back pain, plus  
11 widespread pain, or back pain plus depression,  
12 naturally you would think they could do better on  
13 duloxetine versus other treatments because that  
14 might be a preferred phenotype just looking at the  
15 data. So you might selectively randomize them more  
16 to the duloxetine versus the other. That might get  
17 at that issue of how do you use phenotyping in  
18 order to get at the most pragmatic question, which  
19 is which subgroups are going to do the best with  
20 which treatments?  
21 Another example is say you have epidural  
22 steroid injection, you might selectively randomize

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1 people to epidurals if they had back pain plus  
2 radicular pain because that's the situation where  
3 epidurals tend to work the best. So I think there  
4 are some ways to do it, but no one's really done  
5 that before, and it's a big opportunity to advance  
6 the field that way.  
7 DR. EDWARDS: Terrific. Thanks, Ajay.  
8 I'm going to squeeze in one more question,  
9 maybe a brief one. This one comes in from Penney  
10 Cowan, and she wonders, "With increasing treatment  
11 effectiveness creating reduced pain and increased  
12 function, would not that also lend itself to  
13 increases in pain flares as patients in the trials  
14 become more active?"  
15 DR. WASAN: Yes, yes. Thanks, Penney;  
16 always great to hear from you, and that's another  
17 thing I think that's underappreciated. Oftentimes,  
18 when we're just looking at pain outcomes, we see  
19 pain doesn't change, but that's because people  
20 self-titrate. They start doing more and they're  
21 more active, so they reach the steady-state level  
22 that they made. So a 7 out of 10 may be good for

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1 that person, and they can do a lot more, and it  
 2 shows in their function.  
 3 My point on the pain flares is that I think,  
 4 in general, we need to pay more attention to that,  
 5 like your question alludes to. We need to  
 6 understand that better and understand the impact of  
 7 the pain flares and how we model the pain flares  
 8 analysis. Do we treat the pain flares during the  
 9 trial? What's this interplay between the change in  
 10 pain and change in function? I think that's all  
 11 really important to think about ahead of time.  
 12 DR. EDWARDS: Great. Thanks very much,  
 13 Ajay. Thanks for a terrific talk. Thanks very  
 14 much to our question submitters as well.  
 15 I think we'll now move on to the next  
 16 speaker on our list. It's really a great pleasure  
 17 to introduce Dr. Bob Kerns, who will be our next  
 18 speaker. He's one of the world's preeminent pain  
 19 psychologists. And not only has Bob himself had a  
 20 tremendous influence on the field, he's also  
 21 trained an almost unbelievable number of today's  
 22 leaders in biopsychosocial pain research.

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1 Bob is a professor of psychiatry, neurology,  
 2 and psychology at Yale School of Medicine. He's a  
 3 co-director of the NIH, DoD, and VA Pain Management  
 4 Collaboratory Coordinating Center, which brings  
 5 together a double-digit number of exciting, mostly  
 6 multisite trials of nonpharmacologic pain  
 7 treatments in VA, DoD, and other healthcare  
 8 systems. Bob and his group at Yale have published  
 9 hundreds of high-impact papers, covering areas such  
 10 as comprehensive pain care for veterans,  
 11 nonpharmacologic pain management, predictors of  
 12 outcomes of pain treatment, and personalized or  
 13 precision pain medicine.  
 14 So it will be a great pleasure to hear from  
 15 Bob, who will be talking to us about lessons  
 16 learned From the NIH, DoD, and VA Pain Management  
 17 Collaboratory.  
 18 Presentation - Robert Kerns  
 19 DR. KERNS: Hello, everyone. My name is Bob  
 20 Kerns. I'm speaking to you from New Haven,  
 21 Connecticut at Yale University. I'm virtually here  
 22 with my colleague Cynthia Brandt and Peter Peduzzi.

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1 The three of us are multiple PIs or program  
 2 directors for the United States National Institutes  
 3 of Health, Department of Defense, Department of  
 4 Veterans Affairs Pain Management Collaboratory  
 5 Coordinating Center.  
 6 The focus of my presentation today is to  
 7 inform you about this important tri-government  
 8 agency partnership, focusing on the conduct of  
 9 pragmatic clinical trials of nonpharmacologic  
 10 approaches to management of pain and co-occurring  
 11 conditions. Our collaboratory is informed by the  
 12 gap between evidence and practice.  
 13 There's growing evidence to support the  
 14 integrated, coordinated multimodal and  
 15 interdisciplinary model of pain care that provides  
 16 for patient activation and pain self-management,  
 17 and in particular, the evidence supporting the  
 18 efficacy, if not the effectiveness, of  
 19 nonpharmacologic approaches and integrative models  
 20 of care. However, as you all are aware, there's  
 21 limited uptake of these approaches in routine care  
 22 in the United States and there are significant

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1 barriers to timely and equitable access to these  
 2 approaches.  
 3 The veteran and military health systems  
 4 supported by the Department of Defense and  
 5 Department of Veterans Affairs are ideally  
 6 positioned to address this gap for many reasons,  
 7 including the fact that they are large, integrated  
 8 healthcare systems. They are conceptually  
 9 described as learning healthcare systems that  
 10 support clinical research integrated into clinical  
 11 care settings. They have experience with large,  
 12 multisite clinical trials, and very importantly in  
 13 the context of pragmatic trials, they have  
 14 integrated electronic health records that provide  
 15 data that can be used in the context of the conduct  
 16 of these trials.  
 17 The Collaboratory in fact involves an  
 18 approximately \$81 million investment over six years  
 19 of funding. The Collaboratory is currently in the  
 20 beginning of the fourth year of funding for some  
 21 projects or a third year of funding for some  
 22 others. You see here the long list of supporting

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1 NIH institutes and centers and programs, as well as  
 2 two branches of the Department of Defense Medicine  
 3 Research Program, as well as the VA Health Services  
 4 Research and Development Service.  
 5 The objective of our collaboratory is the  
 6 conduct of pragmatic clinical trials to evaluate  
 7 whether nonpharmacologic approaches for management  
 8 of pain and multimorbidities are effective when  
 9 they are delivered in these healthcare agencies.  
 10 Why pragmatic studies? To promote the  
 11 generalizability of the results and protect rigor  
 12 and answer questions that inform VHA, the Veterans  
 13 Health Administration, and the Defense Health  
 14 Administration about what services to make  
 15 available to patients with pain throughout their  
 16 systems. It's also important to note that although  
 17 there's a focus on the VA and DoD, we hope that the  
 18 results will inform other healthcare systems about  
 19 nonpharmacologic approaches and integrative models  
 20 of care for pain management.  
 21 The nonpharmacologic approaches that we're  
 22 focused on really are a large number that were

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1 relatively recently identified by a VA-sponsored  
 2 health services research and development  
 3 state-of-the-art conference on nonpharmacologic  
 4 approaches to chronic musculoskeletal pain. You  
 5 see here a list of some but not all of the  
 6 approaches that were found to have support through  
 7 evidence synthesis reviews and evidence synthesis  
 8 maps of these approaches.  
 9 Some of our trials also specifically focus  
 10 on integrated models of care. Of course, many of  
 11 you are aware of the VA and Department of Defense  
 12 stepped care model that was put in place in policy  
 13 in VA over a decade ago, as well as a more recent  
 14 and importantly quite innovative and  
 15 forward-thinking model of care called the Whole  
 16 Health Program or All Health Initiative that is  
 17 designed to empower patients in taking direct  
 18 responsibility for their health, promoting  
 19 activities, and to reduce health-damaging  
 20 behaviors.  
 21 Pragmatic clinical trials in our  
 22 collaboratory, of which there are 11, were all

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1 funded by either the NIH, DoD, or VA as cooperative  
 2 agreements supporting their trials and involved a  
 3 two-year pilot or demonstration phase, followed by  
 4 a four-year implementation phase. All of the  
 5 trials have now successfully transitioned to the  
 6 implementation phase and almost all are actually  
 7 involved in recruiting for their trials at this  
 8 present time.  
 9 Here is a list of the 11 pragmatic trials.  
 10 In this slide, you can see the titles of the  
 11 pragmatic trials, the principal investigators, and  
 12 the funding source, either NIH, VA, or DoD. I'll  
 13 just make a few comments about the breadth of this  
 14 program. There are trials like the first one  
 15 listed by Fritz and Rhon that examine the  
 16 stepped-care model for low back pain management in  
 17 the military health system.  
 18 Another one that focuses on a model of care  
 19 is the Taylor-Zeliadt trial, in the middle of the  
 20 slide, that focuses on the complementary and  
 21 integrative health approaches and uptake of these  
 22 approaches in the context of the Whole Health

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1 Initiative. Similarly, the Seal and Becker trial,  
 2 in the bottom left of the slide, is focused on this  
 3 approach as well.  
 4 Others of the projects are studying more  
 5 specific nonpharmacologic approaches like Alicia  
 6 Heapy's project in the middle of the left column,  
 7 focusing on an innovative, interactive voice  
 8 response approach for delivering a CBT-like,  
 9 self-management program virtually, via the phone,  
 10 and using IVR that's asynchronous. In fact, it  
 11 doesn't involve any therapy direct therapist  
 12 contact. The project by Brian Ilfeld, in the  
 13 bottom of the middle column, is focused on  
 14 ultrasound-guided percutaneous peripheral nerve  
 15 stimulation in the perioperative setting.  
 16 The focus of our trials, pragmatic clinical  
 17 trials, has been highly informed by the Pragmatic  
 18 Explanatory Continuum Indicator Summary, or the  
 19 PRECIS-2, Domains, which are listed here on this  
 20 slide. They focus on eligibility with an emphasis  
 21 on minimal exclusion criteria to promote  
 22 generalization and the principle of justice, if you

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1 will, to encourage inclusion of people who might be  
 2 potential targets or appropriate participants in  
 3 the trials and in receipt of these interventions if  
 4 they prove to be effective.  
 5 Recruitment all occurs in the context of  
 6 routine clinical care. The settings are all in  
 7 clinical care settings, primary care physical  
 8 therapy settings or surgery settings, and so forth.  
 9 Quite importantly I think for the focus here, as an  
 10 effort to promote pragmatic trials as opposed to  
 11 more explanatory trials, the trials all focus on  
 12 patient-centered outcomes: pain; pain reduction;  
 13 ability to function in daily life; quality of life;  
 14 medication usage/reduction; and discontinuation,  
 15 and all measures, from qualitative and other  
 16 research, that have evidence supporting their  
 17 importance in the eyes of people with pain.  
 18 Here's a slide with a specific example of  
 19 the Chiropractic Care for Veterans Trial of Goertz  
 20 and Long and the PRECIS-2 diagram. You'll see in  
 21 this trial, the trial is highly pragmatic,  
 22 relatively speaking, on the continuum from

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1 explanatory in the middle of the circle to  
 2 pragmatic on the outer edges of the circle, with a  
 3 specific focus on pragmatic outcomes that are  
 4 important to patients, and maybe a little less  
 5 pragmatic in terms of their recruitment and  
 6 follow-up approaches. They've embedded other  
 7 strategies to enhance what could be done in the  
 8 context of approaching patients in the clinical  
 9 care setting either for recruitment or for  
 10 follow-up.  
 11 The Collaboratory is supported by a  
 12 coordinating center that's based here at Yale.  
 13 I've already emphasized that there are three  
 14 program directors. Our coordinating center  
 15 supports the conduct of the pragmatic clinical  
 16 trials. We've been involved in their further  
 17 refinement, initiation, and efforts to help them  
 18 implement their trials. We support a large  
 19 steering committee that is comprised of all the  
 20 members of the coordinating center, the principal  
 21 investigators, the sponsors, and other important  
 22 entities such as a separate stakeholder advisory

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1 board and a patient resource group.  
 2 Our collaboratory coordinating center  
 3 supports work groups, which I'll show you on the  
 4 next slide, where teams come together led by  
 5 co-chairs, faculty-level persons with expertise in  
 6 particular areas of the work groups, and are  
 7 supported by program managers and supported by the  
 8 coordinating center that are populated actually by  
 9 either the PIs or their representatives. Finally,  
 10 our efforts are to disseminate best research  
 11 practices informed by our collaboratory efforts  
 12 within the Veterans Health Administration, Defense  
 13 Health Administration, and more broadly, in the  
 14 academic and scholarly scientific literature.  
 15 Here's a list of the work groups:  
 16 biostatistics and study design; phenotypes and  
 17 outcomes; electronic health record; data sharing;  
 18 ethical and regulatory issues; stakeholder  
 19 engagement; and implementation science. I've  
 20 already told you about the organization of these  
 21 groups, and ultimately the groups are designed to  
 22 guide, support, and facilitate further refinement

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1 and development of the pragmatic trials and to  
 2 disseminate generalizable knowledge.  
 3 We've had much success and progress in the  
 4 last several years as we've begun this  
 5 collaboratory. All projects, as I've mentioned,  
 6 have transitioned to the implementation phase. All  
 7 the projects agreed to use the PEG3 as an outcome  
 8 measure, not necessarily a primary measure but as a  
 9 secondary measure to promote data harmonization and  
 10 sharing across trials, with the potential for the  
 11 whole to be greater than the sum of the parts.  
 12 We all agreed on a common definition of  
 13 opioid use as either an outcome or as a covariate,  
 14 drawing on data from the electronic health records  
 15 in the VA or DoD systems. We've agreed to use the  
 16 AUDIT-C or the PHQ-2 for phenotyping alcohol use  
 17 and depressive symptom severity, respectively.  
 18 We've added additional inclusion criteria and  
 19 phenotyping harmonization as appropriate to  
 20 individual trials or small clusters of trials.  
 21 We've agreed on a common definition of  
 22 high-impact chronic pain to identify a particular

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1 subpopulation of interest, and we've developed  
 2 standardized approaches to measuring self-reported  
 3 use of nonpharmacologic and complementary  
 4 integrative health approaches, which is an  
 5 important outcome in several of the trials and may  
 6 be relevant in further phenotyping of the samples  
 7 in the other trials.

8 We right off the bat address site overlap in  
 9 our trials. Literally, these trials cover over  
 10 70 sites across the country with over 50 VA-based  
 11 facilities being involved as sites for the trials,  
 12 a large number of DoD sites, and a small number of  
 13 non-VA/non-DoD sites in some of the trials as well.

14 Right off the bat, we realized that many of the  
 15 trials had overlapping sites in terms of  
 16 recruitment, so we worked hard to minimize that  
 17 overlap, to minimize competition for subjects, and  
 18 to minimize possible contamination across trials.

19 We had a large push at the beginning around  
 20 biostatistics advice, and there was a lot of group  
 21 discussion as well as project-specific  
 22 consultation. There were specific white papers

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1 developed to address missing data and other  
 2 important biostatistical and study design issues up  
 3 front. We worked in the ethics and regulatory  
 4 group to overcome many challenges related to  
 5 multiple IRBs and ethical challenges in the conduct  
 6 of these trials and promoted shared learning and  
 7 identification of best practices. A specific  
 8 outcome, and great group that's been involved that  
 9 was formed, focuses on the issue of justice and  
 10 health equity, and a manuscript has emerged from  
 11 this really rich discussion that will be submitted  
 12 soon.

13 We've addressed issues of stakeholder  
 14 engagement across the continuum from veterans and  
 15 service members and their dependents, to senior  
 16 policy leaders in the VA and DoD, and even outside  
 17 our organizations. These groups have focused on  
 18 shared learning and best practices. The discussion  
 19 was informed by a lot of qualitative data from  
 20 several of the trials that were collected in the  
 21 pilot phase.

22 There's a manuscript that's in press in an

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1 upcoming special issue of Pain Medicine, a  
 2 supplement that actually will highlight the  
 3 Collaboratory and includes a protocol paper, so to  
 4 speak, of each of the 11 trials, complemented by  
 5 several other papers, including this one on  
 6 stakeholder engagement.

7 We've tried to promote the active support of  
 8 leaders at the military treatment facilities and VA  
 9 facilities through letters from the Collaboratory  
 10 Coordinating Center to those individuals, and we've  
 11 built a patient resource group and external board  
 12 that's actually chaired by retired Lieutenant  
 13 General Eric Schoomaker, a former army surgeon  
 14 general who's a great cheerleader for this project.

15 Data sharing, we've been approved and we  
 16 hope to be contributing data to the HEAL  
 17 repository, and we've done a lot of work building  
 18 out our website. We're quite proud of this, and I  
 19 hope many of you will take a look at the website  
 20 that's listed here. Furthermore, we've developed  
 21 and written responses related to the COVID-19  
 22 pandemic on the PMC website and coordinated and

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1 supported unified measures to account for COVID-19  
 2 impact across the 11 trials, and a paper on this  
 3 was published in Translational Behavioral Medicine.

4 We've also crafted written and video  
 5 responses that address the Black Lives Matter  
 6 movement and disparities in pain care, leveraging  
 7 the PMC pragmatic clinical trial PI expertise,  
 8 particularly Diana Burgess from the University of  
 9 Minnesota and the Minneapolis VA Health Care  
 10 System. We've addressed many other issues in the  
 11 context of COVID-19, and you see them listed here.

12 I think most importantly, we've built a  
 13 supportive community that's come together at a time  
 14 of great challenge and stress, but a great  
 15 opportunity for learning, especially in the context  
 16 of this collaboratory and as parts of the VA and  
 17 DoD as learning healthcare systems. We've  
 18 coordinated efforts to identify significant changes  
 19 to the protocols themselves, particularly  
 20 addressing issues of sampling and recruitment  
 21 plans, but also changes in the way assessments were  
 22 to be carried out and the interventions themselves,

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1 some of which have shifted from in person to  
 2 virtual delivery.  
 3       There's a manuscript on this, addressing  
 4 many of these issues that are currently under  
 5 review. We've developed additional survey  
 6 questions for participants in the trials regarding  
 7 the impact of COVID, and we hope to be able to use  
 8 these data for further phenotyping in our studies.  
 9       We've collaborated with our forerunner, the  
 10 NIH Health Systems Research Collaboratory, to share  
 11 in solutions and best practices and develop  
 12 recommendations that go far beyond our  
 13 collaboratory or their projects, including, by the  
 14 way, the PRISM, NIH HEAL Initiative PRISM trials  
 15 that are supported by that collaboratory. We have  
 16 been involved in encouraging our PIs to be in  
 17 active communication with their sponsoring agencies  
 18 as well as the relevant IRBs and DSMBs.  
 19       I'll close with just a few testimonials.  
 20 You can read them here on the slide. The bottom  
 21 line is they all really emphasize the value of  
 22 participation in this collaboratory and the

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1 opportunities for building, trusting, and sharing  
 2 relationships and camaraderie to support each other  
 3 as well as the success of the individual trials.  
 4       With that, I want to thank everybody for  
 5 your interest and participation. Please check out  
 6 our collaboratory and follow us on Twitter. I'd  
 7 also point to the upcoming issue of the Pain  
 8 Medicine supplement, so stay tuned for that.  
 9 That's due to be published in December or January,  
 10 and also an existing paper that was published last  
 11 year in the Journal of Pain Medicine that describes  
 12 our collaboratory in more detail than I had time  
 13 today. Thank you.  
 14       DR. EDWARDS: Thanks very much, Bob. That  
 15 was a wonderful talk, and it is a really exciting  
 16 collaboratory network that you've set up.  
 17       I just want to announce to the group that we  
 18 are running a little bit behind, so we will be  
 19 shortening the break. It will be just a 5-minute  
 20 break, so hopefully those of you on the West  
 21 Coast who are counting on eating lunch can eat very  
 22 quickly.

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1       We do have just a couple of minutes, Bob,  
 2 and I have a couple of questions that came in, so  
 3 I'll read the first one here. "The PMC appears to  
 4 have harmonized on a number of phenotype and  
 5 secondary outcome variables. Do all the 11 trials  
 6 also use the same primary outcome; and if not, was  
 7 that considered?"  
 8       DR. KERNS: Thanks, Rob. And by the way, I  
 9 can't go without thanking you for that overly  
 10 generous, maybe from my point of view, a little  
 11 comical introduction, so thank you.  
 12       In fact, no. There was a lot of discussion  
 13 right up front. All of the trials of course were  
 14 independently peer-reviewed and have DSMBs that are  
 15 also engaged in helping make determinations about  
 16 the design of the trials and such issues as primary  
 17 outcome measures. None of them changed, I think,  
 18 their primary outcomes as a function of whence they  
 19 were involved in the Collaboratory through the  
 20 shared discussions.  
 21       What we were able to do, though, was to  
 22 harmonize around the use of the PEG3. I think

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1 maybe one or two of the trials had already proposed  
 2 to use that as a primary outcome or they used the  
 3 Pain Inventory as a primary outcome or secondary  
 4 outcome from which the PEG can be derived. The  
 5 simple answer is no. Yes, that was considered, but  
 6 there were many reasons that that wasn't feasible.  
 7       DR. EDWARDS: Great. Thanks very much, Bob.  
 8       A final brief question, I think, before the  
 9 break, "Given that all of the collaboratory trials  
 10 seem to have progressed to the implementation  
 11 phase, could you comment on what you'd say are the  
 12 one or two most important lessons that were learned  
 13 from the planning phases of these trials?"  
 14       DR. KERNS: Sure. I think several of the  
 15 projects actually had plans for qualitative work  
 16 that involved key stakeholders/patients, but also  
 17 clinicians in the trenches, which they were going  
 18 to rely on to actually deliver the interventions,  
 19 recruit subjects, et cetera, and other policy  
 20 makers.  
 21       I think it was through that pilot work that  
 22 actually several projects made important changes to

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1 accommodate the interests of those key  
 2 stakeholders, and of course that continues to be  
 3 important moving forward, as projects actually have  
 4 needed to adjust their protocols, their recruitment  
 5 plans and assessments, and even the interventions  
 6 themselves in the context of COVID and the rapid  
 7 closing of in-person care and the shift to virtual  
 8 care, and now the gradual reopening in some parts  
 9 of the country of that care.

10 So I would say that the workaround  
 11 stakeholder engagement and their input was  
 12 critically important for many of the trials, and  
 13 I'd highlight that as a key part of what we did.

14 DR. EDWARDS: Terrific. With apologies to  
 15 those watching the clock, I'm going to have to  
 16 squeeze in one more brief question. Another of the  
 17 world's preeminent pain psychologist trained by Bob  
 18 Kerns as it happens, Jennifer Haythornthwaite  
 19 wonders, "Since these trials require massive  
 20 collaborations, could you comment on the key  
 21 processes that you and your team used to build the  
 22 level of engagement and investment that you've

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1 achieved?"

2 DR. KERNS: Yes. I think we got great  
 3 advice from the Health Systems Research  
 4 Collaboratory leaders and work group chairs right  
 5 off the bat, which was the issue of trust was  
 6 emphasized over and over and over again. I think  
 7 that even in the context of a pilot phase, there  
 8 was some inherent competition so to speak. They  
 9 all were striving to be successful, and their  
 10 priorities or incentives were about their own  
 11 particular trials. So we had to work pretty hard,  
 12 I'd say over the first couple of years, to build  
 13 this sense of community and sharing, and trust in  
 14 that context loomed large.

15 So I think it was through the work groups,  
 16 and that people started to get to know each other  
 17 and started to feel more comfortable sharing their  
 18 warts, their problems. At some point, we were able  
 19 to actually integrate a plan where every month in  
 20 our monthly steering committee calls, either three  
 21 or four projects, PIs, provide updates to the whole  
 22 community. We added a quote, "barrier scorecard"

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1 where people had to lay out where they thought some  
 2 of the key challenges for their trials were, with  
 3 an emphasis on what they were trying to do to  
 4 address them.

5 I think that focus on helping people share  
 6 best practices and lessons learned in a kind of  
 7 prideful way, albeit with acknowledging the  
 8 problems in the background, I think really was a  
 9 good strategy to help build that sense of  
 10 community.

11 There's lots more I could say about that,  
 12 and some of the quotes I think on the last slide  
 13 speak to that. But I'm glad you picked up on that,  
 14 Jennifer, because I do think it's not an easy thing  
 15 with a large community to build that sense of  
 16 camaraderie, and I think we've been successful in  
 17 doing that, and I'm happy to talk about that later  
 18 in more detail.

19 DR. EDWARDS: Thanks very much, Bob;  
 20 important lessons for all of us.

21 Thanks so much to the speakers so far, to  
 22 the panel, and to those of you in the audience. I

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1 think we will now have time for a 5-minute break  
 2 before we come back with our final speaker, and  
 3 then time for discussion. Thanks all.

4 (Whereupon, a recess was taken.)

5 DR. EDWARDS: Welcome back, everyone. I  
 6 hope everyone managed to get a short break in.

7 After extensive research, I've concluded  
 8 that I now have the pleasure of introducing our  
 9 only speaker who has an 18-letter-long last name,  
 10 so we'll hope this goes well.

11 David Hohenschurz-Schmidt is an osteopath  
 12 and a neuroscientist, which is a really neat  
 13 combination of backgrounds. He's a doctoral  
 14 researcher at Imperial College in London, in the  
 15 UK. He and his group are doing exciting work on  
 16 the autonomic nervous system and pain, among other  
 17 areas, and probably like the rest of you, I'm  
 18 excited to hear his talk about pragmatic trials of  
 19 pain therapies, a systematic review of methods.

20 Take it away. Thanks, David.

21 Presentation - David Hohenschurz-Schmidt

22 DR. HOHENSCHURZ-SCHMIDT: Hello, everyone,

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1 and thank you to the previous speakers for their  
 2 presentations so far. I'll be presenting to you  
 3 the results of a systematic review of trial  
 4 methodology, which was commissioned by IMMPACT in  
 5 order to inform this meeting. I've got no  
 6 financial interest to declare, apart from the fact  
 7 that I received an honorarium from IMMPACT for this  
 8 work, and I'm funded by the Alan and Sheila Diamond  
 9 Trust for my PhD work, which this falls part of.

10 So rather than speaking of pragmatic trials,  
 11 I like the formulation of taking a pragmatic  
 12 attitude to trial design because that tells us that  
 13 there's not either a very explanatory RCT or  
 14 pragmatic trials, but rather a continuum of how  
 15 easily translatable trial results are into  
 16 real-world decision-making.

17 Looking at trials where authors said that  
 18 they had adopted such pragmatic attitude to trial  
 19 design, we asked how common those self-declared  
 20 pragmatic trials are in the pain field, which  
 21 interventions and patient populations they  
 22 examined, and what the methods employed are, both

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1 in terms of general trial design and those relevant  
 2 to generalizability into real-world  
 3 decision-making. Ultimately, the aim of this work  
 4 was to inform the present meeting with a clear and  
 5 systematically sourced picture of what is currently  
 6 going on in this field.

7 Based on 57 studies that met our eligibility  
 8 criteria, all published within the last couple of  
 9 years, we can say that pragmatic trials in pain not  
 10 only study pharmacological therapies, but a wide  
 11 range of complex pain interventions and management  
 12 programs, including cognitive behavioral  
 13 approaches, physical and manual therapy, and  
 14 surgery.

15 They're usually designed as comparative  
 16 effectiveness trials, but the size and center  
 17 number varies, averaging at around 300  
 18 participants. We also identified a range of areas  
 19 where reporting, especially the reporting which  
 20 would be relevant to judge generalizability, was  
 21 deficient, as well as some areas where design and  
 22 conduct of pragmatic trials was apparently more

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1 difficult to achieve than in others. For example,  
 2 patient recruitment, pragmatic outcome assessment,  
 3 or follow-ups were often less akin to what you  
 4 would expect in clinical practice.

5 Before going into those results in more  
 6 detail, I'd like to make you familiar with the  
 7 methodology employed for our systematic review. We  
 8 followed a preregistered protocol. We really  
 9 wanted to capture what is going on in this field  
 10 across the spectrum of pain therapies. To achieve  
 11 this, we conducted a systematic review, meaning  
 12 that we went to great lengths to capture all  
 13 relevant studies.

14 Our comprehensive search strategy was  
 15 applied to seven databases and the search was  
 16 designed to capture any RCT on patients reporting  
 17 clinical pain irrespective of the pain diagnosis or  
 18 the therapy under investigation. The only  
 19 requirements we had was that some primary outcome  
 20 measure relevant to the treatment or management of  
 21 people in pain was to be affected, and the trial  
 22 had to be declared by the authors to be either

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1 pragmatic, practical, or part of comparative  
 2 effectiveness research. That already shows you one  
 3 of our limitations up front. We had to rely on  
 4 author self-report.

5 We also looked at the last couple of years  
 6 only because we wanted to get a picture of the  
 7 current practice, not a historical development. We  
 8 also excluded smaller and feasibility trials, as we  
 9 were interested in the challenges of running  
 10 full-scale clinical trials.

11 Screening and data extraction was then done  
 12 in duplicate, and importantly we weren't interested  
 13 in outcome data, but in trial methodology only, so  
 14 we didn't extract outcome data. Our data  
 15 extraction focused on a number of fields: key  
 16 aspects of trial design, pragmatic trial design,  
 17 and conduct and analysis.

18 We also assessed how trialists handled the  
 19 tension between internal and external validity by  
 20 looking at methods deemed to affect internal  
 21 validity, such as randomization procedures,  
 22 allocation concealment, and blinding of

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1 participants. Thirdly, we also looked at the  
 2 introduction and discussion section to see how  
 3 authors justified and contextualized both the  
 4 choice of their trial methods, as well as the  
 5 results that they obtained.

6 As part of the data extraction process, we  
 7 rated each trial on what's called the PRECIS  
 8 instrument that has originally been developed to  
 9 influence or to facilitate the design of pragmatic  
 10 trials but has also been used retrospectively to  
 11 assess how pragmatic a trial is across nine  
 12 prespecified domains.

13 As you can see here, each of those domains  
 14 is rated on a scale from 1 to 5, where 1 signifies  
 15 a very highly controlled explanatory approach and 5  
 16 signifies that this method was very similar to what  
 17 you would see in normal, everyday practice. The  
 18 PRECIS instrument has been shown in this  
 19 retrospective rating to have good inter-rater  
 20 reliability and is reasonably well able to  
 21 distinguish an explanatory and pragmatic trial.

22 As you can see here, the domains range from

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1 how patients were selected and recruited, to how  
 2 similar the setting and the internal organization  
 3 of the setting and the treatment delivery, to  
 4 clinical practice, all the way to the choice of  
 5 outcome measures, the extent of follow-up  
 6 assessments, and then the primary analysis. We go  
 7 into that in much more detail later when we talk  
 8 about the results.

9 Data synthesis, then, was mainly  
 10 descriptive, talking about what we found. We also  
 11 assessed if certain trial methods were more  
 12 prevalent under certain circumstances. Like I  
 13 said, no formal risk of bias assessment was  
 14 conducted because we weren't interested in outcome  
 15 data, but we did have a look at baseline age data,  
 16 assessing if there had been a potential problem  
 17 with randomization and checking if there was  
 18 heterogeneity between groups in this feature.

19 The only deviation from our preregistered  
 20 protocol was the addition of two subgroup analyses.  
 21 Here, we investigated whether those PRECIS ratings  
 22 differed between pharmacological and

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1 nonpharmacological trials, as well as between  
 2 chronic and acute pain interventions. We screened  
 3 around 770 articles and ended up including  
 4 57 trials. We may have excluded trials which were  
 5 pragmatic but too small or not declared as  
 6 pragmatic by the authors.

7 Before we look at the individual methods, it  
 8 may be worth looking at the objectives of those  
 9 trials. What I did for this was to look at the  
 10 aims and objectives statement in each trial report  
 11 and just feed that into a simple word cloud  
 12 algorithm, so the larger the word, the more  
 13 frequently used the word was. Unsurprisingly here,  
 14 the most commonly used words were around concepts  
 15 of comparing pain interventions with usual care or  
 16 to assess as comparative or real-world  
 17 effectiveness.

18 I'll now be describing the sample and some  
 19 general trial methods before we then discuss  
 20 aspects that are more relevant to the pragmatic  
 21 trial design itself. Amongst those 57 trials, we  
 22 had 21 percent looking at pharmacological therapies

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1 and then a big bunch of studies, as well, looking  
 2 at cognitive behavioral approaches, surgery,  
 3 acupuncture, manual therapy, and a few more exotic  
 4 therapy interventions.

5 In terms of the diagnosis, as you would  
 6 expect, the bulk of trials examined musculoskeletal  
 7 pain, 9 percent looked at pain after medical  
 8 interventions, and 5 percent at neuropathic pain  
 9 and headaches. Just one more point here,  
 10 interestingly, only one study looked at a diffuse  
 11 chronic pain condition, in this instance  
 12 fibromyalgia.

13 We looked at the duration of the pain. In  
 14 half the trials, chronic pain was studied, but it  
 15 wasn't possible to even get an idea of how long  
 16 patients were suffering from pain in about  
 17 28 percent of the trials. So that's our first  
 18 instance of poor reporting, and then we had  
 19 something else. I'm going to go through this  
 20 presentation. The median number of participants  
 21 was 234 at the point of randomization, with the  
 22 largest trial recruiting 1,700 participants. We

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1 kept the sample size at a minimum of  
2 40 participants per arm.  
3 Almost half the trials -- you can see that  
4 on this slide -- were conducted in primary care  
5 settings, but we also had around 30 percent each in  
6 secondary and in highly specialized tertiary care.  
7 Nine percent of the trials took place in community  
8 settings, which included patients' homes. As you  
9 can see from this slide here, most trials,  
10 79 percent, took place across multiple centers with  
11 a median of 5, but a huge range from 2 to  
12 100 clinical trial centers.  
13 Interestingly, only two reports assessed  
14 differences between trial centers, and these  
15 authors also discussed how those differences may  
16 have impacted trial outcomes. I'd argue that's  
17 something important when you have a multicenter  
18 trial, especially if you have a hundred different  
19 settings or even five very different trials, that  
20 that should be considered.  
21 Lastly, most trials were funded exclusively  
22 from public sources, three-quarters of all trials.

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1 Only 12 percent were fully industry funded. As an  
2 interim summary from this section, it was  
3 interesting to see that, for example, drug trials  
4 were much less common than what you'd expect in the  
5 pain field in general, plus also that we had so few  
6 industry-funded pragmatic trials.  
7 We're now going to talk about the general  
8 trial methods employed starting with the choice of  
9 the comparator. Like I said, most were comparative  
10 effectiveness trials with around half the studies  
11 choosing another active specific intervention as  
12 their comparator. We also had placebo-controlled  
13 trials. Nine percent were placebo controlled.  
14 That's interesting because there's currently debate  
15 in the field of pragmatic trials of whether you can  
16 call a placebo-controlled trial pragmatic given  
17 that in the real clinical environment you wouldn't  
18 have placebo interventions, so they do exist.  
19 Blinding was not always reported, but where  
20 it was, authors reported that patients were blinded  
21 to group allocation in about a quarter of all  
22 studies, providers only in 7 percent, and assessor

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1 blinding was commonly done in the vast majority of  
2 trials. Looking at randomization, we can see that  
3 half of the trials were individually randomized  
4 with half of those using some kind of blocking  
5 mechanism. Stratification by site was the most  
6 commonly employed stratification method, and in  
7 10 percent of the trials, the unit of randomization  
8 was something other than patients, normally  
9 treatment centers or providers, but also towns in  
10 one instance.  
11 Ninety percent of the trials were designed  
12 as superiority trials, and even though you cannot  
13 claim equivalence or comparable effectiveness in a  
14 superiority trial that fails to show a significant  
15 difference between groups, 9 out of 24 unsuccessful  
16 superiority trials did put some inappropriate spin  
17 on their results by claiming equivalence or  
18 comparative effectiveness. We had four studies  
19 designed as noninferiority trials, and despite  
20 current FDA recommendations, none of those  
21 noninferiority trials included a placebo-controlled  
22 group. Out of 15 trials with multiple declared

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1 primary outcome measures, only 9 addressed the  
2 issue of multiplicity in their analysis.  
3 We're now going to look in more detail at  
4 the individual ratings on this PRECIS tool. The  
5 overall rating was 3.8 across all domains, and  
6 looking at a sample of self-declared cardiovascular  
7 trials, which was recently reviewed, we had a very  
8 similar average rating. That's beyond the scope of  
9 this presentation, but going into the individual  
10 domains, there was quite a difference in which  
11 domain was higher and lower range. As a reminder  
12 here, scores closer to 1 are towards the  
13 explanatory end and closer to 5 are towards the  
14 pragmatic end of this spectrum.  
15 We're now going to have a look at the  
16 individual domains, starting with patient  
17 eligibility, which asked to what extent the  
18 participants in the trial were similar to those who  
19 would receive the intervention if it was part of  
20 usual care. As part of this, we also looked at  
21 reporting guidelines, mainly the standard CONSORT  
22 recommendation but also 2008 CONSORT extension for

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1 pragmatic trials. Only 68 percent of the studies  
 2 reported their eligibility criteria as explicitly  
 3 framed to show the degree to which they included  
 4 typical participants or, where applicable,  
 5 providers, or hospitals.

6 The main reason for low ratings in this  
 7 domain was the exclusion of common comorbidities.  
 8 That was the case in about a quarter of all studies  
 9 and, similarly, common medications were a reason  
 10 for non-eligibility in 7 studies. Eligibility  
 11 criteria for providers, such as the minimum amount  
 12 of years in practice, were confirmed in 6 trials,  
 13 but that was very rarely reported; so not reported  
 14 in three-quarters of all trials, similarly for  
 15 criteria for trial settings. Authors very rarely  
 16 justified how they chose who would deliver the  
 17 intervention and where the trial would be  
 18 conducted.

19 The question of recruitment asked how much  
 20 extra effort is made to recruit participants over  
 21 and above what would be seen in usual care. This  
 22 was the lowest average rating across all nine

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1 domains. What would be considered pragmatic is  
 2 convenient sampling, where you just include  
 3 patients who walk through the door anyway.  
 4 Instead, we can really see here that recruitment  
 5 was a challenge in trials, and pragmatic trials in  
 6 particular.

7 Despite the fact that 58 percent employed  
 8 some kind of targeted recruitment strategy, such as  
 9 identification through records or targeted efforts,  
 10 despite that fact, 27 percent of all trials missed  
 11 their recruitment target. The PRECIS domain of  
 12 setting asked how different the setting of the  
 13 trial and usual care settings are, and organization  
 14 means how more elaborate the organization and the  
 15 care delivery was compared to what you would see in  
 16 usual care.

17 Again, there's a CONSORT extension item  
 18 which asks the authors to report key aspects of the  
 19 setting, which determine the trial results. If  
 20 that had been done, that would really enable the  
 21 reader much more to generalize how the results from  
 22 this trial apply to their particular setting.

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1 However, compliance with this item, this reporting  
 2 item, was very low with only 37 percent of all  
 3 trials complying. Similarly, a discussion of  
 4 possible differences in other settings, where  
 5 clinical traditions have served as organizations  
 6 and staffing and resources varies from those of the  
 7 trial, only happened in a third of all studies.

8 Aspects of the intervention delivery were  
 9 standardized in 61 percent of the studies, and out  
 10 of those, 31 percent employed some kind of fidelity  
 11 monitoring. On the other hand, the extent to which  
 12 participants had to adhere to the treatment regimen  
 13 was very flexible, generally, also demonstrated by  
 14 the fact that post-randomization exclusion criteria  
 15 such as minimum compliance or lack of adverse  
 16 events was only present in 9 percent of the  
 17 studies.

18 This PRECIS domain, a follow-up is concerned  
 19 with the frequency and duration of follow-up  
 20 appointments, as well as the intensity of the  
 21 clinical assessments compared to usual care. Based  
 22 on this, we had an average rating of 3.2, again

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1 relatively low, meaning that follow-up was often  
 2 more elaborate than what would be expected in  
 3 normal practice.

4 I'd also like to use this opportunity to  
 5 talk about trial duration. The average, longest  
 6 point of follow-up was one year, but that ranged  
 7 from just a few hours in a trial of acute  
 8 myocardial infarction to 10 years in a trial  
 9 comparing partial and complete knee replacements.  
 10 The average attrition of such follow, the average  
 11 attrition was 15 percent.

12 In pragmatic trials, the choice of outcomes  
 13 should reflect what matters to the patient, and  
 14 that means choosing direct symptom reports or  
 15 function-related measures over lab tests and  
 16 surrogate markers. In our sample of analgesia  
 17 trials, those were mainly patient-reported outcomes  
 18 relatively well established potentially, and not  
 19 least, thanks to the efforts of IMMPACT. Objective  
 20 outcome measures were mainly used, as secondary  
 21 outcomes were employed in about half the studies.  
 22 One thing I'd like to add is that amongst those

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1 outcome measures, not a single trial assessed or  
2 even discussed risk-benefit analyses to any extent.  
3 The primary analysis, the highest rating  
4 here, according to the PRECIS definition, would be  
5 given for the employment of a true  
6 intention-to-treat principle. That was reported in  
7 84 percent of all trials. However, despite this  
8 fact, 21 percent did actually exclude participants  
9 who did not provide follow-up data or had missing  
10 outcome data. So there's a distinction here  
11 between what they called intention to treat and  
12 what they actually did.  
13 We're briefly going to look at a selected  
14 set of reporting items, so they're all CONSORT  
15 items. Like I said before, the general CONSORT  
16 recommendations were complied with relatively well,  
17 however the CONSORT extension for pragmatic trials,  
18 reporting with that was relatively poor, which is a  
19 shame when you think about the fact that pragmatic  
20 trials are designed to inform clinical practice in  
21 a very generalizable way, and as a trial author,  
22 you're really in a position to put the reader into

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1 your shoes and tell them what the trial setting  
2 looked like, what was done, and how that might be  
3 applicable to other settings.  
4 We look at individual domains here. First  
5 of all, the contextualization of the trial amongst  
6 other available treatments and justifying why  
7 you're doing this trial was only done in a little  
8 bit more than half the trials. Similarly, the  
9 choice of outcome measures and follow-up procedures  
10 was only justified in half the trials. That may be  
11 due to the fact that outcome measures are  
12 relatively well established in the pain field.  
13 How and if resources were altered in order  
14 to conduct the trial was only reported in half the  
15 studies, and looking at the last two columns here,  
16 very low, somewhere between 34 and 37 percent  
17 reporting compliance with a description of the  
18 setting features, which may have determined the  
19 trial results, and only 32 percent did actually  
20 contextualize the trial findings outside of this  
21 trial setting.  
22 In our correlation analyses, we did not find

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1 any association between average PRECIS ratings and  
2 funding source, the number of trials centers, or  
3 the type of therapy or pain descriptor. Similarly,  
4 the participant blinding status was not associated  
5 with PRECIS ratings, funding source, trial size, or  
6 the analysis method. Large trials did, however,  
7 have less attrition.  
8 When we looked at our sample, it was obvious  
9 that a couple of subgroup analyses were required,  
10 so we compared drug and non-drug studies and didn't  
11 find any difference in average pragmatism ratings.  
12 But looking at the individual domains, we saw that  
13 drug trials had less protocol flexibility, which  
14 probably doesn't come as a surprise that drugs  
15 weren't prescribed in a less flexible way.  
16 Comparing acute and chronic pain trials, as  
17 a little caveat here, in both of those instances,  
18 the number in those categories differs quite a bit.  
19 We had more chronic pain trials and we had more  
20 nonpharmacological trials that were needed. By  
21 comparing acute and chronic pain trials, we had,  
22 overall, higher pragmatism ratings in acute pain

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1 trials, and looking at individual domains, we saw  
2 that much more recruitment efforts had to be made  
3 in chronic pain trials, which potentially drove  
4 this correlation.  
5 By way of the summary, I'd just like to  
6 point out a few less than a few more surprising  
7 findings here. Based on our systematic review, we  
8 can say that pragmatic trials in pain research  
9 exist and that they are relatively pragmatic when  
10 you compare them to a different field. We can say  
11 that they comply well with general reporting  
12 guidelines, and we've seen musculoskeletal pain and  
13 non-drug interventions dominate. Potentially  
14 related to that effect, we only had very few trials  
15 that were industry funded.  
16 Some of the challenges we saw are likely  
17 similar to normal traditional randomized-controlled  
18 trials, including recruitment and retention.  
19 However and importantly in this field, issues with  
20 that may interfere with pragmatic aims of  
21 generalizability. Also, generalizability, or  
22 rather the reader's ability to judge

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1 generalizability, may be frustrated by  
 2 inappropriate reporting.  
 3 A few points that we may pick up on, or may  
 4 wish to pick up on, in discussion, first of all, we  
 5 may want to decide if and where we need more  
 6 pragmatic trials. That could be in pharmacological  
 7 research, so it could be that we want to value  
 8 real-world effectiveness over safety and early  
 9 efficacy evidence maybe in certain pain conditions,  
 10 such as headaches, neuropathic pain, fibromyalgia,  
 11 which were underrepresented in our sample.  
 12 We may wish to think about promoting the  
 13 features and the domains seen in the PRECIS domain  
 14 and include that into recommendations. I think  
 15 something where the PRECIS tool falls short is its  
 16 lack of focus on the choice of analysis methods.  
 17 Like I said, you get a high rating for  
 18 intention-to-treat analysis. I'd argue that  
 19 there's other information relevant to real-world  
 20 decision-making such as cost effectiveness and  
 21 risk-benefit considerations.  
 22 Also, something that would make a huge

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1 difference to the field would be more deliberate  
 2 reporting of pragmatic trial methods and the  
 3 contextualization of the trial and its findings,  
 4 basically in line with existing CONSORT extension.  
 5 I also think, though, that it should be made  
 6 explicit where concessions had to be made in terms  
 7 of less pragmatism in trial design due to  
 8 feasibility reasons, how this was compensated for,  
 9 or how this may have affected the generalizability  
 10 of outcomes.  
 11 Based on that, I'm looking forward to the  
 12 discussion now, and I'd like to say a very, very  
 13 big thank you to my supervisors, Professor Andrew  
 14 Rice from Imperial College, as well as Professor  
 15 Bob Dworkin, who's put me in the position to be  
 16 able to produce this work and present it here.  
 17 Thank you for that. I'd also like to highlight the  
 18 contribution of Dr. Annie Bethea Kleykamp, who took  
 19 me by the hand from the protocol development all  
 20 the way to the analysis, as well as thank you to  
 21 everyone who helped with the protocol design, data  
 22 extraction, and analysis. Thank you.

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1 DR. EDWARDS: Great. Thanks so much, David.  
 2 That was a stimulating and intriguing summary and  
 3 review of some of the recent findings in the field.  
 4 It was a nice way to end a terrific series of  
 5 talks. I have a couple of questions for you that  
 6 have come in, and then after that, we'll move to a  
 7 full panel discussion.  
 8 The first question is, "It sounds like in  
 9 your set of 57 recent studies that you reviewed,  
 10 larger trials actually had less attrition." This  
 11 person seemed surprised by that. "Any idea what  
 12 might have contributed to that effect?"  
 13 DR. HOHENSCHURZ-SCHMIDT: No, that's really  
 14 a correlation that we found, which we haven't  
 15 looked into in more detail afterwards. It may be  
 16 to do with larger trials simply putting more effort  
 17 into general trial design, and retention is one of  
 18 the issues which we thought wasn't addressed in  
 19 many of the trials. Maybe larger or more elaborate  
 20 trials paid more attention to that.  
 21 DR. EDWARDS: Excellent. Thank you. I've  
 22 got one more question that's come in. Let me see

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1 if I can find it. Yes.  
 2 "In your excellent talk, you listed trial  
 3 methods in your review of pragmatic trials. It  
 4 looks like about 10 percent of them used placebo or  
 5 sham comparators, as you nicely noted during the  
 6 talk. Should we really consider those to be in the  
 7 category of pragmatic trials?"  
 8 DR. HOHENSCHURZ-SCHMIDT: Well, yes. I  
 9 think there's debate around that at the moment like  
 10 I highlighted. I think your opinion papers this  
 11 summer and coming up and also being responded to by  
 12 the authors from the PRECIS tool, they argued that,  
 13 yes, you can still gain information there, which is  
 14 relevant to clinical decision-making over and above  
 15 efficacy. But that's one of the issues, I think,  
 16 we need to discuss in the group as well.  
 17 DR. EDWARDS: Excellent. It's almost like  
 18 we planned it. That is a perfect lead-in. Thanks  
 19 to the short break we took, we're now only a few  
 20 minutes behind, which is great, and we can move to  
 21 the full panel discussion. I'll let my  
 22 co-moderator, Dr. Cherkin, introduce some of the

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1 first questions for the panel, and we'll look  
 2 forward to hearing the responses.  
 3 Panel Discussion  
 4 DR. CHERKIN: Well, thank you, Rob.  
 5 I'd like to start off with a broad question  
 6 for the panelists.  
 7 "Do you believe that pragmatic clinical  
 8 trials represent a paradigm shift from the  
 9 double-blind, placebo-controlled mostly drug trials  
 10 that have been considered the gold standard for  
 11 research in previous decades? If so, what do you  
 12 believe needs to be done to change how researchers,  
 13 funders, and the general public understand the  
 14 value of pragmatic trials for improving care?"  
 15 I am not actually being able to view  
 16 anybody's -- I guess the plan here is that if you  
 17 want to answer it, you just speak up.  
 18 DR. KERNS: I'll start by just saying what's  
 19 intuitive to me, which is, no, I don't think it's a  
 20 paradigm shift. I think that there will be  
 21 continued need to think about advanced trial  
 22 designs that are more explanatory in nature and to

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1 foundation, obviously, for efficacy trials can help  
 2 us to be able to design trials and have some sense  
 3 of -- I mean, mechanism remains important for what  
 4 and how you're formulating your questions, but  
 5 there are also really important things like usual  
 6 care and measuring that along the way.  
 7 That becomes, in some ways, really the  
 8 important benchmark in these trials rather than  
 9 placebo. That's very important when you're looking  
 10 at mechanisms and you're trying to ferret that out.  
 11 But, in fact, many of the questions that we're  
 12 asking are things in which real-world care is  
 13 moving quite quickly, and the benchmarks we need in  
 14 order to understand the signal of what we're doing  
 15 against what's happening in these environments is  
 16 quite different.  
 17 I know, Dan, your role here is as a  
 18 moderator, but you have also, I think, written  
 19 quite provocatively about maybe the benefits of  
 20 looking at placebo as part of the interventions  
 21 themselves. I don't know whether we'll get to that  
 22 kind of discussion, but I think it could be

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1 promote the explanatory trials, just as maybe we  
 2 further emphasize a focus on the pragmatic end of  
 3 the continuum and encourage funders and  
 4 investigators to think about the key questions that  
 5 they want to ask of the trial and design their  
 6 studies to best address that, that question.  
 7 So I don't think it's either one or the  
 8 other or replacing an old paradigm with a new one.  
 9 DR. CHERKIN: Any other panelists have a  
 10 comment on that?  
 11 DR. HOHENSCHURZ-SCHMIDT: Maybe talking  
 12 about funding, as you've seen from the review,  
 13 there's very little industry funding going into  
 14 this. Do other panel members think promoting that  
 15 over simple efficacy signals and safety signals, is  
 16 that something that needs to happen?  
 17 DR. EDWARDS: Anyone?  
 18 DR. DeBAR: I was going to comment to follow  
 19 up on Bob's answer, but I can also maybe speak to  
 20 David's for a moment. I completely agree that it's  
 21 not an either/or but it's certainly a bold plan for  
 22 efficacy and pragmatic trials. In fact, the

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1 important.  
 2 DR. CHERKIN: Great. Thank you, Lynn.  
 3 Rob, do you want to take the next question?  
 4 DR. EDWARDS: Definitely. We had one come  
 5 in from Ian Gilron for the full panel, maybe  
 6 starting with Scott Evans if that's okay. So Ian  
 7 wonders, "What does the evidence show about the  
 8 handling and impact of missing data on the validity  
 9 and meaningfulness of results from real-world  
 10 trials? Which are likely expected to have more  
 11 missing data than do more controlled trials."  
 12 Scott, if you don't mind starting, that  
 13 would be great, and then anyone can jump in.  
 14 DR. EVANS: I think it's a great question  
 15 and, of course, one of the potential concerns with  
 16 relying on non-traditional data sources. I think  
 17 it's going to be very trial-specific, and  
 18 outcomes-specific, and so forth, but if you get a  
 19 high prevalence of missing data, significant  
 20 prevalence -- and it doesn't have to be that high  
 21 to be impactful in terms of threatening the  
 22 integrity of your study and the integrity of your

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1 results -- we're going to run into issues.  
 2 I did have one or two slides where I  
 3 mentioned a project from CTTI, the Clinical Trials  
 4 Transformation Initiative, in which they were  
 5 studying real-world data and its uses. One of the  
 6 things that came out early in that project was we  
 7 started critically thinking about when and how can  
 8 you use, say, electronic health records or claims  
 9 data for trials.  
 10 One clarification that became evident was,  
 11 well, the devil's in the details. How are you  
 12 going to use that data, and is it low risk or high  
 13 risk for either missingness or incompleteness? If  
 14 it is -- for example, if it's an endpoint for a  
 15 trial -- then that's a major issue. So that  
 16 particular group moved from, although it's a very  
 17 important thing to be thinking about, can we  
 18 actually use these types of data for measurement of  
 19 patient outcomes?  
 20 Maybe there's a hybrid approach, where  
 21 there's certain data that is perhaps either more  
 22 reliable that might be lower risk, and that can be

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1 used for other purposes. But for things like  
 2 endpoints, you can't take too big a risk. You've  
 3 got to get the results on patients if you're going  
 4 to be doing trials, and that often needs more  
 5 formal assessment. But maybe we can use the data  
 6 for other purposes, whether it's for eligibility  
 7 and recruitment or even during the conduct of the  
 8 trial for other things.  
 9 So I do think it's a major issue. I think  
 10 the prevalence is going to depend on what you're  
 11 measuring and where we're looking for the data, but  
 12 it is a front-and-center concern.  
 13 DR. EDWARDS: Excellent. Thanks, Scott.  
 14 Any other panel members that would like to  
 15 add anything about the handling of missing data in  
 16 pragmatic trials?  
 17 DR. KERNS: I would just say even now in the  
 18 context of a collaboratory and in the context of  
 19 COVID, where trials are relying on electronic  
 20 health record data, the data that are missing  
 21 aren't necessarily missing at random and that there  
 22 are potentially some aspects of the missingness

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1 that can be understood or explained and others that  
 2 can't. It gets very complicated.  
 3 By the way, it changes over the course of  
 4 the trial, which adds an additional complexity. A  
 5 couple of our trials started before the COVID  
 6 lockdown, and now there are issues about how data  
 7 has re-emerged in the electronic health record as  
 8 in-person or other care starts to re-emerge and how  
 9 that period will be addressed analytically in the  
 10 approach.  
 11 DR. EDWARDS: Excellent. Go ahead, Lynn.  
 12 DR. DeBAR: I would just add a couple of  
 13 things. I think this is a really important topic,  
 14 and I talked very briefly in my talk about what we  
 15 did to augment the collection of PROs for pain to  
 16 what was happening in the [indiscernible] system.  
 17 I think we could do that systematically and really  
 18 do it strongly. We may end up with enough data  
 19 without the kind of reactivity when we rely on  
 20 point-of-service, collect data, and that it could  
 21 be really useful.  
 22 What I mean when I say that is if somebody's

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1 coming in and they're getting a BPI or a PEG when  
 2 they're coming in with a pain flare, and that data  
 3 is what we're looking at in an outcome study, we're  
 4 going to get a real different density in that data  
 5 with people who have very complicated, severe  
 6 conditions and folks who may be experiencing some  
 7 improvements.  
 8 On the other hand, if we can push out those  
 9 assessments -- and we have lots of tools to do that  
 10 for the personal health record and those kinds of  
 11 devices, IVR -- and we collect it more routinely,  
 12 and we know what's happening to people in their  
 13 day-to-day lives -- I think there's much more data.  
 14 I don't think it has some of the limitations.  
 15 I don't know that we'll ever be able to do  
 16 the heterogeneity of treatment effect analyses and  
 17 have the samples that are needed to do that  
 18 robustly if we don't somehow partner with our  
 19 colleagues in the clinical front line to be sure  
 20 that what's used there are psychometrically  
 21 validated tools and that they're delivered in such  
 22 a way that we at least minimize some of these

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1 compounds.

2 I don't think it replaces some of the more

3 rigorous sort of research caliber measurements that

4 we do, but maybe we do that with a subset, and we

5 really create crosswalks and understand what we can

6 determine with those PROs. But I hate to have us

7 say there's research grade and there's clinical

8 grade, and we really shy away from what we can do

9 in the delivery system, because I think if we don't

10 do that, then we're always going to end up with

11 this divide between what's happening in clinical

12 practice and what we're doing in research.

13 DR. EDWARDS: Thanks very much, Lynn.

14 If it's okay, we'll go on to the next

15 question. One just came in from Matt Bair

16 specifically for Ajay Wasan.

17 "Ajay, in your excellent presentation, the

18 concept of treatment-resistant depression was

19 raised. Is there a similar concept in pain, so

20 treatment-resistant pain, and could that be a

21 potential moderator of treatment effects in our

22 pain clinical trials?"

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1 DR. WASAN: That's a great question. I have

2 not seen that concept, but we've talked about this

3 in many IMMPACT meetings, like isn't the patient

4 phenotyped who doesn't get better with anything?

5 Isn't that a phenotype that somehow we should

6 attempt to model and capture? Hard to say because

7 by the time we see patients in the studies, it's

8 hard to know all the different treatments they've

9 had, between physical therapy and different meds.

10 Of course, defining treatment-resistant

11 depression, it's a pretty narrow definition with

12 antidepressants, but there's also a similar piece

13 in depression because it's not as if medication is

14 the only treatment that they've sought also. I

15 mean, there are a lot of other nonpharmacological

16 treatments for depression which might be equally as

17 effective; so not just seeing a psychotherapist,

18 but even spiritual treatment, if you have someone

19 who goes to church a lot.

20 So there is a similar issue in major

21 depression, but we don't really have that concept

22 for chronic pain, but it's something we definitely

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1 need to think about.

2 DR. CHERKIN: Okay. I'll ask the next

3 question.

4 "Dr. Evans had suggested in his presentation

5 trying to retain the rigor of conventional

6 randomized trials as much as possible in pragmatic

7 trials, including blinding. I want to know from

8 the panelists to what extent is blinding possible

9 or desirable in pragmatic clinical trials of

10 nonpharmacologic treatments for pain?"

11 DR. WASAN: Well, I'll answer that. I

12 think, again, it's a balance issue. Of course it's

13 very hard to blind both sides, provider and

14 patient, with nonpharmacologic, but you can blind

15 the assessor or you can also blind pieces of it.

16 We're starting a trial now where we have some

17 treatments for pain, and then one of the goals is

18 to try to wean opioids, and the doctor weaning the

19 opioids is shielded from knowing what treatment arm

20 the patients were randomized to. I think a term

21 that gets thrown around is shielding where you can,

22 understanding that it's maybe a little bit of a

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1 leaky shield and it's not the same as blinding, but

2 there's some value, I think, to shielding when you

3 can do it.

4 DR. CHERKIN: So beyond trying to blind the

5 outcomes assessor to treatments, to what extent is

6 it really possible to blind the patients receiving

7 the treatment or the clinician providing the

8 treatments and the assistant?

9 DR. WASAN: Well, I think that's also in the

10 spirit of pragmatic trials. I think that is

11 another reason why in the collaboratory that

12 Dr. Kerns is leading, it's focused on

13 nonpharmacologic treatments. Nonpharmacologic

14 treatments, for many of those reasons, are really

15 much more suited to perhaps being tested in

16 pragmatic trials. I don't know if maybe that's one

17 of the rationales that, Bob, you guys were thinking

18 when you came up with this. That would be my

19 reaction.

20 DR. CHERKIN: Bob?

21 DR. KERNS: Well, I didn't come up with the

22 RFA for the collaboratory. But, yes, you saw in

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1 one of my slides that this was really informed by a  
 2 particular awareness of the gap between the  
 3 evidence for multiple nonpharmacologic approaches  
 4 and even growing evidence of the effectiveness of  
 5 certain models of care, in integrated models of  
 6 care, and the actual uptake, even in integrated  
 7 systems like the VHA and DHA.  
 8 So in that context, again, it's about the  
 9 question that's being asked. In this case, there  
 10 was a particularly strong interest in trying to  
 11 address that gap, and to do that, it seemed like  
 12 trials that were more pragmatic, as opposed to  
 13 explanatory on that continuum, made sense because  
 14 it really was trying to address largely an  
 15 organizational and patient care delivery question.  
 16 Whether it's about nonpharmacologic  
 17 approaches versus pharmacologic approaches or other  
 18 interventions, I would say maybe I'm not so sure  
 19 that that's the case. I think there are key  
 20 questions about the effectiveness of pain  
 21 medications that can be better addressed in a  
 22 pragmatic context as well. Even though it's

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1 nonpharmacologic, one of the trials by Brian Ilfeld  
 2 that focuses on percutaneous stimulation,  
 3 peripheral nerve stimulation in the perioperative  
 4 setting, there's some evidence of the efficacy of  
 5 that approach, but it certainly is reasonable even  
 6 there.  
 7 So you could think about that as being  
 8 appropriate for an efficacy trial. Does it work?  
 9 But it seems entirely appropriate to think about it  
 10 in the context of a pragmatic design as well, which  
 11 is the case here.  
 12 DR. EDWARDS: A quick follow-up to that  
 13 excellent discussion about blinding, this one's  
 14 from Jennifer Haythornthwaite. "What about  
 15 electronic assessments done privately or at home as  
 16 an alternative to blinded assessments?"  
 17 Any comment from the panelists on that?  
 18 DR. WASAN: Yes. I definitely should have  
 19 mentioned that because that's really become the  
 20 standard now. That's an important point. Many of  
 21 us use REDCap and other methods to send the PROs  
 22 directly to the patient. That particularly also

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1 helps that issue.  
 2 DR. HOHENSCHURZ-SCHMIDT: Just on that note  
 3 of blinding, it's definitely an issue in  
 4 nonpharmacological trials. But when we looked at  
 5 our sample, there were certain questions where  
 6 maybe blinding was not that important. One, for  
 7 example, was a chiropractor trial, where the  
 8 question was, is it more beneficial to have  
 9 patients in when they have pain or is maintenance  
 10 care more appropriate? I think you could argue  
 11 that that's something which doesn't necessarily  
 12 need to be blinded.  
 13 On another note -- and I hope I captured that  
 14 correctly -- my colleague, Dr. Jan Vollert, as  
 15 well, has just published a paper. Part of the  
 16 assumption that we talk about here is that  
 17 subjective outcomes are more susceptible to placebo  
 18 effects. That seems to be pretty accepted but is  
 19 not necessarily always well founded. So his recent  
 20 paper, for example, showed similar placebo response  
 21 in rheumatoid arthritis trials in both lab markers  
 22 and subjective outcomes. That's something to take

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1 into consideration, I think.  
 2 DR. EDWARDS: Excellent. Thanks, David.  
 3 We have several good questions from John  
 4 Farrar about phenotyping and subgroups. I'll just  
 5 read one of them here.  
 6 "Given the variability in pain phenotype and  
 7 response, do you think that pragmatic trials might  
 8 focus on testing pain treatment processes rather  
 9 than individual treatments?" So process consisting  
 10 of what treatments to start with, how to progress  
 11 through treatments, what order to use  
 12 multidisciplinary approaches in, et cetera. I  
 13 imagine Lynn and Bob and other members of the panel  
 14 might have some comment to make about that.  
 15 DR. KERNS: I'll start. Yes, I think  
 16 absolutely. Key questions for primary care  
 17 providers in the VA are exactly those that John is  
 18 highlighting: what do I do first; next; the best  
 19 combination in the context of the field to push for  
 20 multimodal care? And these are all unanswered  
 21 questions.  
 22 As I pointed out, or tried to point out,

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1 several of the trials actually are, I think,  
 2 studying more processes or models of care. Some  
 3 are asking in that context very pragmatic questions  
 4 like the chiropractic trial, which is essentially  
 5 examining dose of care. I think one of the trials  
 6 uses a SMART design, where it is sequential testing  
 7 of approaches contingent on response to the  
 8 beginning level of the trial.  
 9 So I do think that some of these really key  
 10 questions that at least clinicians and providers  
 11 are asking the research community really are  
 12 addressed within the context of a pragmatic trial  
 13 and focus more on these processes, or steps, or the  
 14 other aspects I just highlighted.  
 15 DR. CHERKIN: Okay. I'll ask the next  
 16 question.  
 17 "The presentations did not make much mention  
 18 of measuring cost or cost effectiveness of  
 19 pragmatic trials. Is this not important  
 20 information to have for those who would be  
 21 considering adopting an intervention that was found  
 22 successful in the initial pragmatic trials for

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1 application in their own setting?"  
 2 DR. KERNS: Several of our trials in  
 3 collaboratory do include a budget impact analysis  
 4 rather than a more complete cost effectiveness  
 5 analysis. Those were secondary aims and our  
 6 tertiary aims, and are being addressed in a few of  
 7 the trials. I agree that the opportunity to  
 8 examine cost, money, in the context of these kinds  
 9 of trials, is a great opportunity and oftentimes  
 10 missed in the design of trials.  
 11 Of course, there's added cost to doing that.  
 12 The standards in the field have matured, and it's  
 13 not just a simple add-on. To do it well, there's a  
 14 need to make a serious investment in the ability of  
 15 the trial to really do that well. I think, again,  
 16 maybe the VA and DoD systems as integrated  
 17 healthcare systems are particularly tailored, but  
 18 even there, increasingly of course, in the last  
 19 decade, in the national push in the VA to paying  
 20 for care in the community to improve access, this  
 21 makes even that all the more challenging. So I  
 22 think that's a tough nut to crack but something

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1 very important.  
 2 DR. CHERKIN: Any other either disagreements  
 3 or additions to what Bob said?  
 4 DR. WASAN: Yes, I can add something there.  
 5 I've been part of a couple of large comparative  
 6 effectiveness trials funded by PCORI, and as many  
 7 of us know, PCORI has this language that says you  
 8 cannot officially do cost effectiveness analysis.  
 9 That was part of, I think, how the Obama  
 10 administration was able to get PCORI funded; it  
 11 satisfied congressional demands.  
 12 So it's difficult to overtly do that,  
 13 actually, in some of these large PCORI grants,  
 14 which have been, in the civilian medicine world,  
 15 one of the only funding agencies for these kind of  
 16 studies in the past five years.  
 17 Then secondly, even if you are trying to do  
 18 cost effectiveness analysis, it's very hard to get  
 19 the data you need. For actual true, healthcare  
 20 costs, you really can only get that from the  
 21 insurance company directly. Even where I am,  
 22 there's a partially integrated healthcare delivery

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1 system, and even then, from our own insurance  
 2 companies, it's very hard to get the actual true  
 3 cost of care. So those become major barriers even  
 4 though all of us agree this is important to get.  
 5 DR. CHERKIN: Lynn, do you have any comments  
 6 from the perspective of Kaiser?  
 7 DR. DeBAR: Yes. I think -- and Bob spoke  
 8 to this a little bit -- as opposed to where Ajay is  
 9 finding some advantages to being systems like  
 10 Kaiser or VA where we have more integrated care  
 11 delivery and we can do these kinds of things more  
 12 seamlessly, I think the other place -- and we do  
 13 cost analyses, really, in all the more pragmatic  
 14 trials that we do.  
 15 I think the methodology around cost analysis  
 16 may also inform some of these discussions, and  
 17 maybe we can come back to it because the  
 18 variability in cost is really quite, quite  
 19 pronounced. Ethically, you wouldn't be able to do  
 20 a trial large enough to really power cost analyses,  
 21 so there are ways in which you look at the relative  
 22 benefit for the cost, and you can model those

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1 things and really think about who your customer is;  
 2 in this case, a lot of times the operational  
 3 leaders.  
 4 I had talked about the various trade-offs,  
 5 some of them quite subjective. I think that cost  
 6 effectiveness analyses really works in a realm  
 7 where they're straddling what's important for  
 8 policy and how you come at this with the best tools  
 9 available. So maybe we'll have chance for further  
 10 discussions, so thanks for the question.  
 11 DR. KERNS: Dan, if I might build on this  
 12 topic, I appreciate the focus on budget and money,  
 13 but I place that in the broader context of  
 14 implementation. Studies focused -- or integrating,  
 15 or hybrid designs that integrate implementation  
 16 methods, that ultimately can benefit the field and  
 17 stakeholders, if there are positive results and  
 18 products from the trials, the VA is interested, of  
 19 course, in promoting their uptake.  
 20 So if there's an embeddedness of efforts to  
 21 address a broader array of implementation,  
 22 barriers, opportunities, and facilitators in the

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1 context of these trials, I think that's important.  
 2 In the context of the collaboratory, it wasn't part  
 3 of the original design to have an implementation  
 4 science work group, but that was actually added  
 5 after the fact, and I think it was a very important  
 6 and insightful addition to the Collaboratory, and  
 7 one that I think will benefit or heighten the  
 8 impact of the trials moving forward.  
 9 DR. CHERKIN: Thanks, Bob.  
 10 Rob?  
 11 DR. EDWARDS: Thanks, everyone. Incoming  
 12 question from Bob Dworkin.  
 13 "For Bob Kerns and others on the panel, in  
 14 the Collaboratory and in other trials that aren't  
 15 blinded, are standard methods built into the  
 16 studies to reduce patient expectations as much as  
 17 possible; for example, in the way the consent forms  
 18 and study staff present the study to patients?"  
 19 DR. KERNS: I don't know that I would say  
 20 that's true across the trials, but I think some  
 21 trials more than others have attended to that  
 22 issue, actually quite explicitly. It's not that

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1 what they're getting is hidden, but I think there  
 2 is an effort to make sure that people are aware  
 3 that -- I guess all the trials at some level have  
 4 existing evidence of efficacy, if not  
 5 effectiveness, so there is more an issue of people  
 6 in the trials are likely to be informed in the  
 7 consent form that there's no particular benefit to  
 8 them personally for participating in the trials  
 9 because these services are potentially already  
 10 available through routine clinical care.  
 11 So that's maybe different in some of our  
 12 trials and in other trials, but maybe actually  
 13 consistent with the notion of a pragmatic trial  
 14 being on the far end of the continuum from  
 15 explanatory trials to pragmatic trials, where the  
 16 intervention studies already have some evidence of  
 17 efficacy, if not even effectiveness.  
 18 DR. DeBAR: I would just add a different  
 19 variant to that. I've mentioned that, at least  
 20 initially, a lot of pragmatic trials were cluster  
 21 randomized trials. If you do a cluster randomized  
 22 trial, your question should be one that really

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1 addresses that cluster.  
 2 Say, for example -- and this may go back to  
 3 multimodal and the way that things are rolled  
 4 out -- that what you're really doing is you're  
 5 going into a setting and you're shifting things at  
 6 a, let's say, clinic level about how care is  
 7 organized. If you do that, there are many  
 8 instances in which you may not consent individual  
 9 patients. Because it's being done at that level,  
 10 these are -- and this kind of gets to some of the  
 11 safety things that were discussed. Many of the  
 12 components of pragmatic trials are things that have  
 13 been well, well tested and that have pretty  
 14 favorable safety findings, so those are not things  
 15 you're looking at as much.  
 16 But if you're randomizing at a clinic level  
 17 and you can measure things without needing to go to  
 18 the individual patient -- so for example, you're  
 19 looking at some of the implementation outcomes,  
 20 adherence to treatment for example -- those could  
 21 be trials where you step around that quite  
 22 dramatically. So in thinking about the full

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1 spectrum of trial designs and questions, I think  
2 there are instances where that doesn't have to be a  
3 liability.  
4 DR. EDWARDS: Excellent. Thank you.  
5 Bob, while we're still on the subject of  
6 this question, a follow-up inquiry related to data  
7 harmonization in the Collaboratory. Someone asks,  
8 "Is data sharing across these 11 trials being  
9 discussed or might there be creation of a pain  
10 registry for that collaboratory?"  
11 DR. KERNS: Right. So this is a great  
12 opportunity to go back and revisit the question I  
13 answered earlier about harmonization on the primary  
14 endpoints. In fact, I should have mentioned that  
15 several trials are already proposed when they  
16 submitted their application, proposed using the  
17 BPI, for example, or the numerical rating scale  
18 pain intensity measure. So even without any  
19 discussion within the collaboratory community,  
20 there are subgroups of trials that are harmonized  
21 just by chance, I guess, a coincidence on some of  
22 those measures.

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1 Because by virtue of our implementation  
2 science work group, which was added -- it was  
3 actually added through an administrative supplement  
4 that was funded very early on from the HEAL  
5 Initiative, and by virtue of that, we are part of  
6 the HEAL collaboratory, broadly speaking. As I  
7 mentioned in one of the slides, just briefly, we  
8 have been invited to contribute, for the trials,  
9 data into the HEAL data repository, and their  
10 consent forms accommodate to that when they had a  
11 consent form.  
12 So there will be opportunities not only to  
13 potentially aggregate data across our trials but  
14 potentially across other trials in the  
15 Collaboratory. I think particularly relevant may  
16 be some of the PRISM trials, but there are others  
17 as well. So I think there are great opportunities  
18 for that.  
19 Of course, there are major issues around  
20 data sharing, partly, I would say because we're  
21 talking about two big government agencies and  
22 sharing data with another one, and a wide range of

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1 issues about data safety, security protections, and  
2 so forth. So I think it's a great concept, but  
3 we'll have to see how that all shakes out.  
4 The bottom line is the Collaboratory  
5 Coordinating Center, I should also be clear, is not  
6 a data coordinating center. We actually aren't  
7 involved or exempt from human subjects research.  
8 So we're really supporting individual trials and  
9 the PIs, rather than being in the position to  
10 create ourselves some data registry or data  
11 management system.  
12 So I think, just to be clear, that's the  
13 state we're in right now. I think there are  
14 opportunities to summarize for some of the projects  
15 to partner with other of the projects that are  
16 trying to address similar enough questions with the  
17 same or similar kinds of outcomes and to actually  
18 share data in aggregate, but we'll have to see  
19 downstream how that goes.  
20 DR. CHERKIN: Thank you, Bob.  
21 The next question is directed at Dr. Evans,  
22 asking him to comment more about the, quote,

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1 "desirability of outcome ranking," unquote. "Is  
2 this desirability from whose perspective: patient  
3 provider or researcher?"  
4 DR. EVANS: Yes, this is a good question,  
5 and it can be constructed from either a caregiver  
6 perspective or a patient perspective. The purpose  
7 of that particular approach, what we call the DOR,  
8 desirability of outcome ranking, was for some of  
9 the reasons that I had outlined. We could be  
10 missing the boat on certain treatment effects by  
11 analyzing each outcome separately in its own bucket  
12 and then trying to somehow combine those  
13 outcome-specific effects in some way. There can be  
14 associations and correlations between these  
15 outcomes that may affect your interpretation of a  
16 different outcome.  
17 So the turn on words that I had used was  
18 what we typically do in trials, is we take the  
19 patients in the trial, the trial participants, and  
20 we analyze their outcomes, but you can gain insight  
21 to things if you flip that around and take the  
22 outcomes in the trial and analyze what happens to

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1 the patients. If you're thinking about pragmatic  
 2 questions, that's a natural fit when you're  
 3 thinking about pragmatic questions.  
 4 So we had come up with this notion about  
 5 desirability of outcome ranking. The first time we  
 6 had done this, it was created by research  
 7 clinicians who were knowledgeable in a particular  
 8 disease area to do that, but of course, the next  
 9 natural question that came, "Are there ways in  
 10 which you can bring in the patient perspective?"  
 11 There are ways in which you can do that. So yes,  
 12 you can do that. It's perhaps a little beyond  
 13 being able to describe here, but you can certainly  
 14 look at it from a patient perspective.  
 15 DR. CHERKIN: Okay. Well, thank you, Scott.  
 16 Rob?  
 17 DR. EDWARDS: Excellent. We have a  
 18 question. I'm going to preface this one by saying  
 19 that I know that the IMMPACT group is planning a  
 20 future IMMPACT meeting focused on patient  
 21 engagement in clinical trials that will bring  
 22 together advocates, experts, and engagement of

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1 other stakeholders in order to make some probably  
 2 much-needed recommendations about how to involve  
 3 individuals with pain and other advocates in the  
 4 design of these trials.  
 5 So with that in mind, here's the question  
 6 for Ajay Wasan and the rest of the panel. "Have  
 7 people with pain ever taken part in the development  
 8 and designs of clinical trials? This could be a  
 9 way to address the expectation of care and the  
 10 outcomes of what is important to people with pain."  
 11 This question comes from Penney Cowan. Thanks,  
 12 Penney.  
 13 DR. WASAN: Yes. Definitely, especially in  
 14 the PCORI trials, that's a big part of it. In  
 15 fact, PCORI requires, and to their credit at PCORI  
 16 I think it's really changed how we design clinical  
 17 trials by including patients. From the very  
 18 beginning when you do your letter of intent, you  
 19 actually need to describe how you're engaging  
 20 patients themselves in the design of the trial.  
 21 That's also spilled over to NIH trials. Rob  
 22 Edwards and I are part of -- it's part of the HEAL

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1 Initiative -- something called BACPAC, which is a  
 2 whole consortium and a series of multiple trials  
 3 for back pain. In that consortium, too, most of  
 4 the trials have a patient representative -- at  
 5 least if not one, at times several -- to do exactly  
 6 what you suggested. So it is becoming more and  
 7 more frequent, and even expected in some cases.  
 8 DR. KERNs: I mentioned that many of our  
 9 investigators, PIs, get investigators in the VA  
 10 Health Care System, and many, maybe all of them  
 11 actually as I think about it, are in VA health  
 12 services research and development-sponsored centers  
 13 of innovation, like ours at VA Connecticut called  
 14 the PRIME Center.  
 15 These centers all now have patient  
 16 engagement committees. There are some patient  
 17 groups. I think for the most part, the PIs of the  
 18 projects who came from those settings, which they  
 19 are probably half of the trials at least, I think  
 20 all had engaged the groups of patients even in  
 21 identifying the key questions to be pitched in  
 22 response to the RFA, and then certainly have

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1 continued to involve them.  
 2 I mentioned that during the pilot  
 3 implementation or pilot demonstration phase, I  
 4 think several of the projects actually had an  
 5 explicit subproject or pilot that involved engaging  
 6 patients, even after the project was funded and the  
 7 study is designed, but in the context of further  
 8 refining their approach, engaged patients in  
 9 helping them make some of those decisions.  
 10 I also would be remiss if I didn't  
 11 reemphasize what I mentioned briefly in my  
 12 presentation, which was that we have a separate  
 13 collaboratory coordinating center-sponsored patient  
 14 resource group of very distinguished -- we would  
 15 all be impressed with the credentials of this  
 16 group, some of whom are academics, but many are  
 17 patient advocates or involved in other patient  
 18 entities -- veteran service organizations and so  
 19 forth -- that serve as resources for the  
 20 collaboratory and the trials in particular.  
 21 So I think it is a growing interest, as Ajay  
 22 has already mentioned, at PCORI, but even in NIH,

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1 and certainly in VA, it's just a standard now in  
 2 terms of at least health services, if not broader  
 3 clinical and rehabilitation research.  
 4 DR. CHERKIN: Thank you, Bob.  
 5 The next question is, "The presenters have  
 6 described numerous challenges in conducting  
 7 high-quality pragmatic clinical trials, even with  
 8 the substantial financial and technical support  
 9 that has been provided in the context of the pain  
 10 management collaboratory. These challenges include  
 11 not only the usual ones of doing a rigorous study  
 12 but also the complexity of stakeholders, the  
 13 importance of relationships and trust, and all of  
 14 that to get all the pieces to work together so that  
 15 the trial has a chance of producing credible  
 16 results.  
 17 "So even if these trials are successful,  
 18 it's not clear that the same interventions will be  
 19 successful even when implemented in other settings,  
 20 not just because of the setting being different in  
 21 terms of affecting directly the outcomes, but just  
 22 the processes of doing such complex interventions

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1 to improve care. So given these challenges, what  
 2 do you see as the potential for pragmatic clinical  
 3 trials to have a major impact on health care in the  
 4 future?" It's sort of a reality test.  
 5 DR. WASAN: I can start off a little bit. I  
 6 appreciate that concern. I just want to remind  
 7 everyone that one of the reasons there's more  
 8 interest in pragmatic trials or comparative  
 9 effectiveness research with a large pragmatic  
 10 component is because of the problems of purely  
 11 explanatory trials and RCTS and their difficulty in  
 12 actually changing pain care and having their  
 13 findings translate to actual clinical care; so to  
 14 keep that in mind.  
 15 I don't know this literature very well, but  
 16 the majority of the pragmatic trials in this  
 17 country have really been in primary care you would  
 18 think. So you'd get to ask yourself which seems to  
 19 have been more effective or more influential in  
 20 changing care or improving care? Was it the  
 21 pragmatic trial or the RCT? And someone who has a  
 22 primary care background might be able to comment on

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1 that. This is where, actually, if we all had live  
 2 mics, Matt Bair could speak about this since he's a  
 3 primary care physician as well.  
 4 So that's what I would kind of throw back  
 5 is, yes, they're messy and they're complicated,  
 6 pragmatic trials, but clinical care is messy and  
 7 complicated, and there actually may be more  
 8 relevance of a pragmatic trial, but we don't really  
 9 know.  
 10 DR. CHERKIN: Thank you. I agree with what  
 11 you said, but I think this question is, really,  
 12 just addressing the issue of implementation in  
 13 other settings of the interventions that have been  
 14 found in an initial pragmatic trial to be  
 15 effective. There are so many issues in successful  
 16 implementation that have to do with trust,  
 17 et cetera, and not just with the particular  
 18 intervention. So that's where this was coming  
 19 from.  
 20 DR. WASAN: No, no. I agree. It's a  
 21 generalizability issue. For instance, I'm part of  
 22 a large pragmatic trial that took an intervention

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1 proven in a pragmatic trial to be effective of  
 2 physical therapy intervention in the UK and do  
 3 something very similar, a stratified type of care  
 4 for physical therapy based on psychosocial risk  
 5 factors in the United States and much different  
 6 outcomes. So yes, there's a generalizability  
 7 question. That's how I would agree with you there.  
 8 DR. DeBAR: Dan, I would just add -- and  
 9 maybe I'm not addressing this fully either. But I  
 10 think that one of the things that we've learned in  
 11 these is that you really -- I think I referred to  
 12 it as vertical integration. You're going to move  
 13 care whether you're doing QI initiatives or you're  
 14 doing pragmatic trials, but it's really important  
 15 that the sponsorship be from the highest level down  
 16 to the level of medical assistance, people that are  
 17 assisting in day-to-day care.  
 18 I think those are part of the lessons  
 19 learned about how do we do this work and how do we  
 20 sustain it. Those are going to be built into the  
 21 very fabric of the trials. I think that delivery  
 22 systems are chaotic, things are always shifting, so

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1 those lessons learned I would argue could be  
 2 generalizable in and of themselves.  
 3 The other thing I was going to add to what  
 4 was said earlier, which may not be making the mark,  
 5 is that one of the advantages of doing trials in  
 6 multiple healthcare systems is that you've got an  
 7 invariant core, and then you often have some  
 8 different tailoring, really, about how those things  
 9 are implemented, which I would argue helps to  
 10 increase potentially generalizability, and you can  
 11 figure out what are the things that you really need  
 12 to hold with some rigor.  
 13 I think we all had these PRECIS-2 designs  
 14 where we said you can be way out on the  
 15 [indiscernible] or you can be in a little bit  
 16 closer. Some of those, when they're aspects of the  
 17 intervention itself, may be things we want to  
 18 insist on. So anyway, I do think that those  
 19 questions can be answered in part with some of the  
 20 design features of our trials.  
 21 DR. CHERKIN: Thank you, Lynn.  
 22 DR. KERNS: I'll just mention and remphasize

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1 stakeholder, stakeholder, stakeholder, stakeholder  
 2 engagement. The bottom line of our collaboratory  
 3 in the promise of success is because there's  
 4 organizational commitment, embracing of these  
 5 trials, and shared funding of the trials. So there  
 6 already is an organizational investment in this  
 7 kind of research because there is a view, I think  
 8 an overarching view, that the VA in this case or  
 9 the DoD should be providing evidence-based care,  
 10 and that's part of the mission explicitly in these  
 11 organizations, and buy-in is I think important.  
 12 I don't want to minimize for a minute the  
 13 complexities and challenges because, of course,  
 14 even in a VA system, it's a large, integrated  
 15 healthcare system, but it's comprised of literally  
 16 closer to 2,000 points of access and care. There's  
 17 a saying in the VA, "If you've seen one VA, you've  
 18 seen one VA." There also is optimism about some  
 19 level of uptake and implementation of positive  
 20 findings and results, but generalizing that to the  
 21 most rural and least academically oriented settings  
 22 that are under-resourced and so forth, there are

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1 still great challenges to all of this.  
 2 DR. CHERKIN: Thanks, Bob.  
 3 DR. HOHENSCHURZ-SCHMIDT: I'll just add to  
 4 that. We're talking about generalizability a lot  
 5 when we talk about it from the design perspective.  
 6 I think what came out from our review, and if you  
 7 think about the end users of the evidence, where  
 8 they get the evidence from, that's usually  
 9 scientific papers. They don't have access to a  
 10 research conference, then can talk to the trial  
 11 designers.  
 12 So if you improve reporting, I think you'd  
 13 have a huge impact on the uptake. If you're  
 14 private cap, a manual therapist or something, and  
 15 you're asking yourself a question about dosage, or  
 16 spinal manipulation, or something, but you can't  
 17 really judge how the trial was designed, how they  
 18 implemented the intervention, what the patients  
 19 wear [indiscernible] -- simple things, sometimes I  
 20 think the journal of guidelines of word limits are  
 21 actually in the way of appropriate reporting. But  
 22 I think at least some kind of online supplement,

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1 where things are described in much more detail than  
 2 what you usually get out of a scientific paper,  
 3 that's something which would have a big, big  
 4 impact.  
 5 DR. CHERKIN: Thanks, David.  
 6 Rob?  
 7 DR. EDWARDS: Thanks, everyone.  
 8 David, I think this next question will also  
 9 start with you, although everyone should feel free  
 10 to chime in. This is from Bob Dworkin as well.  
 11 He notes, "A pragmatic trial could be  
 12 designed, for example, to test whether yoga is  
 13 superior to acupuncture in chronic low back pain.  
 14 But as David noted in his talk, the nonsignificant  
 15 primary analysis cannot be interpreted to mean that  
 16 the treatments are comparable. So wouldn't it be  
 17 more informative to test noninferiority with a  
 18 usual care group in order to ensure assay  
 19 sensitivity, rather than test those two treatments  
 20 head to head?"  
 21 DR. HOHENSCHURZ-SCHMIDT: What I can comment  
 22 on is that that's not a common approach even though

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1 it's recommended, yes. You have assay sensitivity,  
 2 and are you sure that your comparator does what  
 3 it's supposed to do is something that needs  
 4 addressing. Also, I think including a usual care  
 5 group adds another layer of information, which is a  
 6 pragmatic approach.  
 7 DR. CHERKIN: Okay. Anybody else?  
 8 (No response.)  
 9 DR. CHERKIN: Here is a question, "Thoughts  
 10 on the trial design of stratified equipoise  
 11 stratum, which is the largest set of different  
 12 treatments he or she is willing to be randomized  
 13 over, then randomize the patient to their equipoise  
 14 stratum, and then all-causal inferences about  
 15 pairwise comparisons compared to the efficacy would  
 16 be based within equipoise stratum randomized  
 17 contrast."  
 18 If I understand this correctly, this is kind  
 19 of related to expectations or preferences and  
 20 controlling for that. I am not sure. Anybody want  
 21 to take that one?  
 22 DR. KERNS: I'll just say I don't think

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1 that -- as I understand the question -- any of our  
 2 trials have taken into account patient expectancies  
 3 or, as you put it, what they're willing to do other  
 4 than they wouldn't consent to the trial if they  
 5 know they're being randomized, and they don't want  
 6 one or the other treatment. But I do think that  
 7 issues about this makes sense to me, and it's an  
 8 important consideration, and one that's often only  
 9 tacitly considered in the design of trials and  
 10 recruitment approaches, but bears greater  
 11 attention.  
 12 DR. CHERKIN: Okay.  
 13 DR. EDWARDS: Excellent. Thank you. I'll  
 14 jump in if that's okay, Dan. I have another  
 15 question here. This one I believe is from Ewan  
 16 McNicol, who is a pharmacist here in the Boston  
 17 area treating chronic pain patients. This one's  
 18 for Scott Evans, particularly.  
 19 "Scott, in your slides on subgroup analysis,  
 20 you assign equal weight to efficacy and safety.  
 21 What happens when those two are not equal; for  
 22 example, pain relief and constipation versus pain

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1 relief and respiratory depression? Similarly, what  
 2 if the side effect occurs on the continuum; for  
 3 example, mild versus debilitating nausea?"  
 4 DR. EVANS: Those are good points. You can  
 5 prioritize and weigh different outcomes in  
 6 different ways. There are even ways to do that on  
 7 a personalized level. We've had examples of that.  
 8 I think my broader point about subgroups was that  
 9 the way we typically identify subgroups of patients  
 10 is based on either efficacy and a single variable,  
 11 a pain outcome for example, or avoidance of a  
 12 particular safety problem, but neither one of those  
 13 actually identifies the subgroup of patients you  
 14 really want to treat. The patients you really want  
 15 to treat are those who experience the efficacy and  
 16 avoid the safety problem; that is a benefit-risk  
 17 problem, so thinking about our subgroup evaluations  
 18 to identify those patients from a benefit-risk  
 19 point of view rather than a predictive marker for  
 20 efficacy or a predictive marker to avoid a safety  
 21 problem.  
 22 But you are right. Clearly different

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1 outcomes are of different importance; point number  
 2 one, that their level of importance could certainly  
 3 be interpreted at a patient level. But there are  
 4 methods in place that we're working on, and we  
 5 continue to work on, that try to recognize that.  
 6 On the one hand, you can do an analysis that  
 7 does a transparent, prespecified analysis for a  
 8 particular weighting system or value system in the  
 9 way you weight or value different outcomes but  
 10 could also show you an analysis where either  
 11 individual patients or clinicians could say, "Well,  
 12 I have a different perspective," and this outcome  
 13 is more important for me than some other outcome.  
 14 How would treatments compare under that scenario?  
 15 You can show how two treatments contrast as you  
 16 vary your value system, so we have some ideas about  
 17 how to do that. Thank you.  
 18 DR. CHERKIN: Rob, shall I ask the next  
 19 question?  
 20 DR. EDWARDS: Yep. All yours. Go for it,  
 21 Dan. Thanks.  
 22 DR. CHERKIN: This questioner says, "I

1 commend Dr. DeBar on being able to embed  
 2 pain-specific PROs in the electronic health record  
 3 with her pragmatic trial. How was she able to do  
 4 this? Was there a clinical moment to do this?"  
 5 DR. DeBAR: Thank you for the question. I  
 6 think in some ways we were kind of at the right  
 7 place at the right time. That trial I was  
 8 referring to was limited to patients with chronic  
 9 pain who were on long-term opioid treatment. And  
 10 at the time, the Kaiser settings in which we are  
 11 working required that their patients be on an  
 12 opioid therapy plan, and that required a certain  
 13 frequency of assessment.  
 14 At the time that we entered the field and we  
 15 were doing the preliminary work in the first UD3  
 16 year, they were using the Brief Pain Inventory, and  
 17 it was interesting because I think many of us,  
 18 particularly those of us who are psychologists,  
 19 think of that as a really brief measure, but for  
 20 primary care providers, that was unduly long in the  
 21 clinical setting.  
 22 When we did some of the formative work, one

1 these questions about functioning.  
 2 So I think what it shows is there's a real  
 3 interplay to what clinicians may be able to really  
 4 use in the field what's meaningful to patients and  
 5 what we might be able to promote. The other tools  
 6 that we had were that we weren't trying to do all  
 7 of that in a face-to-face encounter, so we really  
 8 took advantage of what we could push out and have  
 9 people do remotely online. As I'd noted earlier,  
 10 the use of interactive voice response was a means  
 11 of collecting that because it just would have been  
 12 to resource-intensive to try to get frequent  
 13 measurements had we not been able to use those  
 14 [indiscernible] technologies. Thanks for the  
 15 question.  
 16 DR. EDWARDS: Thanks very much, Lynn.  
 17 The next question, it looks like is for the  
 18 full panel, comes from Nat Katz, who wonders, "What  
 19 is the evidence that pragmatic trials of treatments  
 20 for pain have sufficient assay sensitivity to  
 21 detect analgesic effects compared to a control  
 22 group?"

1 of the early things we found was that they said,  
 2 "Well, we only asked you the first four questions  
 3 to get credit," credit so that they were monitoring  
 4 their patients, and those were the questions that  
 5 were related to pain intensity.  
 6 What they were able to recognize is that  
 7 when they were just asking the questions around  
 8 pain intensity, the ensuing conversation with  
 9 patients was about how can you reduce my pain. You  
 10 asked me these questions; you must be able to  
 11 reduce it, where we were really starting to promote  
 12 that functionality and functional impairment was  
 13 maybe where we needed to put an emphasis.  
 14 So what we were able to do was to work with  
 15 Kaiser nationally and make what was embedded into  
 16 Epic, the PEG. The three items, the version of the  
 17 briefing inventory, we actually included a fourth  
 18 because sleep impairment was really important to  
 19 our PCTs, and that was a tool they were really  
 20 enthusiastic about using because they said we  
 21 concretely know how to talk to our patients when we  
 22 ask four questions, and we can talk to them about

1 DR. WASAN: I can start out with that. We  
 2 all know and love Nat Katz, and we know when Nat  
 3 asks a question, he generally has an answer himself  
 4 in mind. In the interest of being provocative, I  
 5 would counter -- I know a lot of people on this  
 6 webinar might be a little shock by that, but that's  
 7 not necessarily the point of a pragmatic trial. I  
 8 think a pragmatic starts with treatments that have  
 9 already demonstrated efficacy and already have  
 10 demonstrated assay sensitivity, and then says how  
 11 do you compare them to each other in a more  
 12 real-world clinical context?  
 13 So I think it's a bit much to expect  
 14 pragmatic trials to meet their objectives and also  
 15 demonstrate all of these explanatory components.  
 16 We have to assume some stuff is proven for that  
 17 treatment. We have to assume something and then go  
 18 forward and plan. So that would be my counter to  
 19 that.  
 20 DR. EDWARDS: That's an extremely effective  
 21 counter, Ajay. Other thoughts from the panelists?  
 22 (No response.)

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1 DR. EDWARDS: If not, I have another  
 2 question here, if that's okay with Dan, if he  
 3 doesn't mind if I jump in with the next one. Also  
 4 for the full panel, "Are there some conditions that  
 5 lend themselves to pragmatic trials more than  
 6 others? For example, is it easier to do a  
 7 pragmatic trial in patients with musculoskeletal  
 8 low back pain or knee osteoarthritis pain than in  
 9 patients with a neuropathic pain condition?"  
 10 DR. KERNS: I'm not sure why that would be.  
 11 In fact, maybe I'm missing the point. Our trials,  
 12 at least in our collaboratory and the ones I think  
 13 that David found in the literature, were, for the  
 14 most part, relatively large trials that were  
 15 multisite in nature. Actually, I think there's  
 16 reasonable expectation -- all the studies are  
 17 powered to detect the facts. It's not intuitive to  
 18 me why that would make a difference.  
 19 DR. EDWARDS: Fair enough. I've got one  
 20 more question, and then, Dan, I can flip it back to  
 21 you. I'm going to try to combine two questions  
 22 into one. It's a question from Jennifer

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1 Haythornthwaite. "Do you think the incentives for  
 2 patients to enroll in effectiveness trials are  
 3 different than the incentives for efficacy trials,  
 4 and how might this affect recruitment and  
 5 retention?" I'm going to combo that, because they  
 6 both mention incentives, with a question about how  
 7 cost might influence patient choice, and in  
 8 pragmatic studies do patients or should patients  
 9 pay as they usually do for treatments?  
 10 Any comments from the panel on patient  
 11 incentives and cost to patients in pragmatic  
 12 trials?  
 13 DR. WASAN: Well, we do know in pragmatic  
 14 trials, cost is a big issue because many times the  
 15 trial doesn't pay for the treatment. It assumes  
 16 that insurance would pay for that treatment or  
 17 charges it to insurance. So in the civilian world  
 18 that becomes a real problem because of co-pays, and  
 19 access, and prior authorizations. So that's also a  
 20 confounder to a pragmatic trial and something that  
 21 needs to be taken into account, so that is a big  
 22 factor.

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1 For instance, if we know that certain  
 2 co-pays for things like physical therapy, that the  
 3 majority of patients who have a significant co-pay,  
 4 a pragmatic trial might pay for that co-pay, which  
 5 some can argue, well, that's not too pragmatic.  
 6 But on the other hand, if patients can't get the  
 7 treatment of interest, then you have a failed trial  
 8 to begin with. No matter whatever you're trying to  
 9 test, they have to at least get the treatment  
 10 you're interested in testing.  
 11 So cost and preference make a big  
 12 difference. Also, the preference part is important  
 13 because this gets to this issue where I've  
 14 advocated for patient choice as an arm,  
 15 particularly in comparative effectiveness and  
 16 pragmatic studies, because these are all the  
 17 factors that are crucial. It wraps in the aspect  
 18 of expectations. Patient choice wraps in the  
 19 aspect of cost and why patients choose, and that  
 20 drives, I think, a lot of the pragmatic outcomes.  
 21 So there are some unique concerns. I think  
 22 it's a very good point, that you need to think

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1 about those two issues, the cost and the  
 2 preference, because it is different for explanatory  
 3 versus pragmatic trials.  
 4 DR. CHERKIN: Okay. I wanted to give the  
 5 panelists a chance to ask questions of one another  
 6 if they had any. Are there questions you've been  
 7 keen on asking but didn't feel that it would be  
 8 appropriate, since you're all on the panel, to ask  
 9 one another?  
 10 DR. KERNS: I put one in the chatbox earlier  
 11 for Lynn --  
 12 DR. CHERKIN: Go ahead.  
 13 DR. KERNS: -- and thought that she might be  
 14 able to address it. I'm sorry there's noise in the  
 15 background. I'll be quick.  
 16 In the current national discourse around  
 17 race, and racism, and broader issues of equity, and  
 18 then bringing that to bear on pragmatic clinical  
 19 trials, and embedded in clinical settings where  
 20 there are known disparities in care, access to  
 21 care, and how care is delivered et cetera, even, by  
 22 the way, in the VA, what are the risks to pragmatic

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1 trials?  
 2 Maybe the same as other trials, where those  
 3 same differences and disparities related to  
 4 underrepresented or disadvantaged groups are being  
 5 carried into the trials themselves. Is this  
 6 important to consider, and are there strategies  
 7 that you can think about?  
 8 I guess this is for you, from your  
 9 experience, but really for anybody on the panel, or  
 10 the audience even, to think about are there  
 11 strategies to try to address that without  
 12 undermining the pragmatic-ness, if you will, of the  
 13 trial?  
 14 DR. DeBAR: You don't ask easy questions,  
 15 Bob. I think this is a great question. I will  
 16 also say that this has been an active conversation  
 17 in the HEAL multidisciplinary working group this  
 18 year, where there's really a recognition that  
 19 sometimes because there are so many logistic  
 20 barriers and challenges, we're not always doing  
 21 these trials in the clinical populations and the  
 22 settings where we really most need that.

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1 I don't think I have a perfect answer to  
 2 this by any means. I had mentioned earlier that I  
 3 think if we can have trials that really build in,  
 4 as part of the design, some of the things that many  
 5 of us have experienced as huge barriers in the work  
 6 we're doing, we might be part of the way there.  
 7 One of those things that occurs to me is that we  
 8 are really poor at engaging patients up front  
 9 sometimes, particularly for various  
 10 non-pharmacotherapy treatments where there's a lot  
 11 more that we're asking from patients as well.  
 12 So can we build things where part of what  
 13 we're testing are those engagement strategies where  
 14 we allow a much longer lead in, and we look at how  
 15 long it takes to encourage -- and I talked about  
 16 encouragement designs -- people to engage in a  
 17 trial. This is a real challenge, but I think we  
 18 really need to be assured that our clinical staff  
 19 involved are representing a diversity of  
 20 communities and really bring those sensibilities to  
 21 the table.  
 22 Penney Cowan had brought up in one of the

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1 earlier questions about stakeholder engagement, and  
 2 I think we're getting better at this. PCORI has  
 3 certainly pushed us a long ways along this  
 4 spectrum, but to be really clear about what are the  
 5 true barriers involved in treatment, what's  
 6 acceptable to people, and to do a much better job  
 7 of really addressing those things up front.  
 8 With COVID by necessity, we're pushing a lot  
 9 of things into telehealth, and there are some  
 10 wonderful things about that; but to really be  
 11 thinking carefully about what are the additional  
 12 barriers that that has for people because access to  
 13 those kinds of modalities are not uniform, and  
 14 there are some really interesting community studies  
 15 that are trying to figure out how do you get phones  
 16 to people that have much more transient life  
 17 circumstances.  
 18 I feel like my answer's all over the place,  
 19 but to the extent we can build it into our design  
 20 and to the extent that we're really engaging  
 21 stakeholders from a range of communities up front,  
 22 and all the way through as well -- because we're

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1 never going to solve all those things, and we need  
 2 to adapt as we go. But we have a lot of  
 3 opportunity and a lot of challenges to do that  
 4 work.  
 5 DR. KERNS: I'll just say that I brought  
 6 this to the attention of, for example -- just to  
 7 raise the question, to what extent across for  
 8 people that do have their finger on the pulse of  
 9 clinical trials and published clinical trials, like  
 10 David, I might ask David, are commonly  
 11 underrepresented groups well represented in their  
 12 pain clinical trials? And I think the answer is  
 13 not, that we have the same problems in our trials  
 14 overall as is true in the healthcare system.  
 15 I do feel passionate about this issue. As  
 16 I'm kind of near the end of my career, this is one  
 17 that I'm very interested in the public discourse  
 18 about this. By the way, it's not just race, it's  
 19 gender, rurality, poverty, and as an older person,  
 20 older persons, and I do think it's really an  
 21 important challenge for all of us. It's not unique  
 22 to pragmatic trials, but it did come up in our

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1 discourse because we're embedding them in clinical  
 2 trials where these disparities exist, and doing  
 3 nothing doesn't seem to be the right solution.  
 4 DR. HOHENSCHURZ-SCHMIDT: I think it's great  
 5 that you're bringing it up, and I'd just like to  
 6 add on to that. There are actually a few of those  
 7 trials. We had one in the inner city area looking  
 8 at less well-served populations. We had a few  
 9 elderly trials, and we had a few rural trials,  
 10 which I think comes down to the issue that  
 11 pragmatic trials ask pragmatic questions, and those  
 12 are real issues on the ground. So it's great that  
 13 you're bringing it up.  
 14 DR. EDWARDS: Excellent. Thank you, and  
 15 thanks particularly to Nat Katz for the stimulating  
 16 and critical question he asked before about assay  
 17 sensitivity. We've now gotten several additional  
 18 follow-up questions that have come in. I'm going  
 19 to read two that essentially ask a similar question  
 20 in slightly different ways.  
 21 "Given Ajay's counter to Nat, do you think  
 22 it would be possible to design a clinical study for

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1 a drug in development that can both meet regulatory  
 2 requirements for approval and provide pragmatic  
 3 data to clinicians?"  
 4 Similarly -- and this one comes from Bob  
 5 Dworkin -- "There are no existing pain treatments  
 6 that have shown consistent efficacy in clinical  
 7 trials, so a pragmatic trial that doesn't include  
 8 some kind of control group, whether usual care or  
 9 placebo, to demonstrate assay sensitivity would  
 10 seem to have very limited value because it's likely  
 11 the results will be inconclusive or uninformative,  
 12 unless one treatment's shown to be superior to  
 13 another, which is not very likely."  
 14 So to sum it up and put my own twist on it,  
 15 should we be designing at least 3-arm trials for  
 16 these pragmatic studies, which have active  
 17 treatment comparator, active treatment, and then a  
 18 controlled placebo or usual care kind of arm in  
 19 order to preserve the test of assay sensitivity?  
 20 I'm happy to hear from the whole panel on this one.  
 21 We've got somewhere around 7 or 8 minutes left if  
 22 you'd like.

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1 DR. KERNS: Running out of steam.  
 2 (Laughter.)  
 3 DR. KERNS: Obviously, break wasn't long  
 4 enough.  
 5 DR. EDWARDS: Fair enough. We'll try to  
 6 keep longer breaks for the session tomorrow, and I  
 7 think Nat Katz wins the prize for being able to ask  
 8 questions that are maximally stumping but really  
 9 fascinating and critically important I think to  
 10 consider.  
 11 Well, I'll follow that up. I'm going to put  
 12 Ajay on the spot specifically because he's a  
 13 psychiatrist and I'm a psychologist, so we have an  
 14 ongoing rivalry. So any chance I get to poke him a  
 15 little, I'm going to take, even in a public forum  
 16 like this one.  
 17 Ajay, if you're designing your next  
 18 pragmatic trial, say, comparing psychologically  
 19 oriented physical therapy to some other  
 20 nonpharmacologic treatment for chronic low back  
 21 pain, are you going to include a usual care or a  
 22 placebo-controlled sort of group because you're

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1 worried about being able to demonstrate assay  
 2 sensitivity of those treatments under study?  
 3 DR. WASAN: Well, I think usual care with a  
 4 placebo, each one of those offers different things.  
 5 We think about usual care as also a natural history  
 6 control for what might end up regression to the  
 7 mean, and placebo, actually I think of it really as  
 8 an active comparator. I think that neuroscience is  
 9 strong enough that when you give someone a placebo,  
 10 you're activating enough endogenous analgesia  
 11 responses that it's not inert. It actually is an  
 12 active comparator, and with usual care, you're  
 13 still getting some treatment also.  
 14 So even these things we call controls are  
 15 pretty messy. I think there's so much scientific  
 16 importance to understand which treatments seem to  
 17 get patients better that just doing a head-to-head  
 18 comparison of two treatments that are  
 19 presumed -- I'll use "presumed" -- to be  
 20 efficacious is very reasonable to do without the  
 21 assay sensitivity because demonstrating this,  
 22 quote, "assay sensitivity" is a very messy

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1 situation in itself and rified with all kinds of  
 2 confounders because none of our comparators are as  
 3 clean as we would like.  
 4 So that's what I would say. But please,  
 5 someone on the panel help me out with a better  
 6 answer.  
 7 DR. KERNS: Well, I'll just say also, I  
 8 think usual care isn't usual care, isn't usual  
 9 care, and in a system like the VA, usual care is  
 10 changing over time. Even that term needs to be  
 11 better defined, as many of our projects are trying  
 12 to do in our collaboratory as a whole.  
 13 Actually, we're convening one of our annual,  
 14 this time virtual, steering committee meetings in  
 15 just a couple weeks, and one of the topics is  
 16 exactly this: can we better define usual care or  
 17 standard of care in the context of these trials and  
 18 apply some standard or encourage at least  
 19 collection of data, or monitoring, somehow to  
 20 better understand the evolving landscape of usual  
 21 care in the context of the single pragmatic trial?  
 22 Maybe that's a little off base, but it's not

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1 just a simple matter of assay sensitivity I don't  
 2 think.  
 3 DR. DeBAR: I would just agree with both  
 4 Ajay and Bob on this. One of the trials that we're  
 5 conducting and just getting underway right now  
 6 seemed to me really straightforward when we  
 7 proposed it. It's comparing two telehealth arms of  
 8 CBT-based treatments, learning from our patients  
 9 that if we were really going to get at folks in  
 10 rural and medically underserved areas, we had to  
 11 make those kinds of modalities available. And  
 12 we've got a usual care arm as well because we know  
 13 how much things fluctuate over time.  
 14 What we didn't anticipate was that COVID  
 15 would come along, billing restrictions would lift,  
 16 the ubiquity now of telehealth modalities, and all  
 17 kinds of things out there promoting themselves as  
 18 CBT online and telephonic treatment is part of the  
 19 landscape. So I think it is really critical that  
 20 we have that usual care arm. I think even with all  
 21 the noise and pragmatic trials, we still have the  
 22 opportunity, I think, to look at interventions

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1 where we build in much more treatment integrity  
 2 than is commonplace in a lot of healthcare systems.  
 3 So I'm optimistic that when we look at this,  
 4 even though I think there will be all kinds of  
 5 reports of people getting various bits and pieces  
 6 of what on the surface looks like common therapies,  
 7 we'll be able to see signal through noise. But  
 8 that's an example, I think, of the migration, if  
 9 you will, of services over time in a way that we  
 10 really want to take into account in these kinds of  
 11 trials.  
 12 Adjournment  
 13 DR. EDWARDS: Thanks very much, Lynn. That  
 14 was an awfully nice summary.  
 15 I think we're down to the last minute or two  
 16 before our hard stop. I think at this point we can  
 17 thank IMPACT very much for organizing this  
 18 meeting. Thanks a million to Dan Cherkin,  
 19 co-moderator for this session, and thanks, of  
 20 course, to all of our panelists who provided  
 21 extremely good input and wonderful talks. Thanks  
 22 especially to David for his gracious understanding

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1 of my pronunciation of his last name. But in  
 2 addition to that, thanks to all the panelists.  
 3 I'm happy to give anyone who wants it the  
 4 final word, and then I think we can wrap up for the  
 5 afternoon.  
 6 (No response.)  
 7 DR. EDWARDS: Terrific.  
 8 Jen and Valorie, I think we might be all  
 9 wrapped up.  
 10 (Whereupon, the meeting was adjourned.)  
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