

*ACTION - IMPACT XX - Assessment of Pain Outcomes
Clinical Trials of Chronic Pelvic Pain and IBS*

July 13, 2017

*A Matter of Record
(301) 890-4188*

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1 presentation, I really want to give you some
2 housekeeping details so you'll be familiar with
3 these, and this is things to keep in mind.
4 First of all, even before we get there, note
5 the microphones in front of you. They are quite
6 sensitive. They are voice activated. You don't
7 have to push any buttons to turn them on or turn
8 them off. When you speak, please give your name
9 because this is being recorded, so be careful how
10 you whisper to your next-door neighbors and what
11 you say about people because we're going to know
12 who you are.
13 Those minutes of the transcript will be made
14 available on the ACTTION website, so anybody who's
15 interested, who was unable to attend the meeting
16 will have access to those. I'll also say that, of
17 these speakers, we will ask them, with their
18 permission if they're willing, to make their slides
19 available to us also for us to put up on the
20 ACTTION website.
21 What we've noticed in the past is some
22 people like me stick in a cartoon or two that are

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1 copyrighted, so they don't want those on there, so
2 they may delete those. But it will all depend on
3 whether there's any proprietary information that
4 people have. But the idea is to make this as
5 transparent and as available to everybody since
6 there are approximately 44 people at this meeting
7 and there are many more people who are interested
8 in this topic.
9 So let's just go to the housekeeping. Make
10 sure you sign in on the registration. And you'll
11 have to do that on both days, and sign in and sign
12 out so that we know that you're here. Cell phones,
13 put them on silent, please. There's nothing more
14 distracting. Those of you who are speakers and
15 many of you who are going to be speakers know that,
16 when a cell phone goes off, put it on vibrate or
17 turn it off totally.
18 I mentioned about the microphones. They're
19 voice activated. Say your name first. The way the
20 microphones are set up is that if a lot of people
21 want to ask questions, once five lights are on, it
22 will not let anybody else get in. Then, when

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1 someone is done speaking, then they'll be able to
2 get back on.
3 So it's a maximum of five at a time, but as
4 the lights go off, then you can come back on. But
5 if you notice there are 5 and you're trying to
6 speak and nothing's happening, that's because
7 they're set up. They're activated that way.
8 The restrooms are out this door to the left,
9 to the right. Go left half a corridor or quarter
10 of a corridor and then to the right on down there.
11 Other things, lunch is going to be served in the
12 Vista Terrace room, which means you have to use the
13 other elevators versus these to go to it.
14 For those that were here last night for
15 dinner, it's the same room, I believe, that we had
16 dinner in last night. It's on the mezzanine level
17 in case you don't know, so when you go to the other
18 elevators, go to the mezzanine level, the Vista
19 room. There will be a sign there for you to see
20 it.
21 So you know that check-out on Friday is
22 going to be at noon, so please make sure that one

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1 of the coffee breaks and one of the opportunities
2 that you have, that you check out on time so that
3 you can get out of here. However, let me caution
4 you that, although check-out time is at 12:00, we
5 won't leave this meeting. We're going to lock the
6 doors. You can't leave until we have developed a
7 consensus about some recommendations that we can
8 make to improve the field.
9 So although you're going to be checked out
10 of your room, you can't leave the hotel, you can't
11 leave this room until we have a consensus of what
12 those recommendations are going to be, at least in
13 a draft format. So therefore, don't try and escape
14 and don't think you can get out early if we finish
15 things, because we haven't finished them until we
16 say we've finished.
17 Taxis can be ordered for the airport and the
18 people at the front desk, Valorie, who is sitting
19 in the back there with the blonde hair, and Andrea,
20 who's outside right now, they can help you if
21 there's any problems with that, help you with
22 shared taxis. Any assistance, they are the people

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1 who can really help you when it comes to logistics.
2 If you haven't met Valorie, she's sitting
3 there right in the back. She has the blonde hair.
4 They both have blonde hair, so Andrea and Valorie
5 both have blonde hair.
6 These meetings, as far as the organization
7 and the logistics, couldn't happen without Valorie
8 and her group putting things together. So we thank
9 Valorie and Andrea for all the work that they do.
10 They are extremely helpful. Any questions you have
11 for those that have not already been involved, they
12 can help you out on many things you want.
13 So that's it as far as the logistics. Make
14 sure you say your name even though you think people
15 may know who you are, because the person's who's
16 transcribing, sitting in the back doesn't know who
17 you are, and she can't always see your name tags.
18 If you don't have a name plate in front of
19 you, by the way, you should make sure you have one
20 so that people can see who you are. That's it for
21 the housekeeping.
22 Why are you here? What is this? Well, I

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1 mentioned to you that this was the IMMPACT meeting.
2 It is the 20th. And what you're here for, in case
3 you're not sure why you're here, this is what the
4 meeting is about, Recommendations for the
5 Assessment of Pain Outcome and Clinical Trials of
6 Chronic Pelvic Pain and Irritable Bowel Syndrome.
7 If you are not here for this meeting, now is
8 the time to leave. Okay? So make sure you're in
9 the right place and everybody knows that's what the
10 meeting is about.
11 Now, you've heard some acronyms. So what is
12 IMMPACT? Now, for some of those people who have
13 been here before, they've seen some of this. But
14 what IMMPACT is not; this is what they're not.
15 They're not the International Micronutrient
16 Nutrition Prevention and Control Program. If
17 you're here for that meeting, it's down the hall.
18 They're not the Interactive Mass Model
19 Proximity and Collision Testing Organization.
20 You're not here for that.
21 We're not the Immigrant Public Action
22 Coalition of Trenton, New Jersey, although Governor

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1 Christie has pushed that we should be part of that.
2 We're not the International Maine Maritime
3 Potato Action Team, although Shannon does come from
4 Maine, so she's also promoting that, the
5 organization.
6 We're not the Infrastructure Management
7 Mapping planning Coordination Tool. All these are
8 IMMPACTs. But that's not what we are.
9 We're not the double impact taekwondo,
10 although it sometimes feel that way, and you're
11 going to notice that we do tend to focus and do
12 things like that to get people to work on these
13 things.
14 So that's what we're not, although that
15 picture of Bob Dworkin at the bottom there, in case
16 you don't know him, he's sitting over there, he
17 does have a way of getting people to cooperate and
18 work together. So whenever we see any debates,
19 discussions, disagreements, we bring up Bob, and he
20 will take care of you, take care of all issues.
21 He'll resolve those.
22 To note, there's a coveted award, IMMPACT.

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1 It's a nice acronym. The Dworkin Award, he
2 actually got the award, the initial award, for the
3 most tortured IMMPACT acronym. And this award went
4 to the 1916-1917 recipient for the In-Hospital
5 Mortality for Pulmonary Embolism Using Claims Data,
6 IMPECD [ph].
7 If you have someone you'd like to nominate
8 for next year's award, we'd be more than happy to
9 put them on the list, or if you'd like to come up
10 with your own acronym, feel free to do that.
11 So what is IMMPACT? We know what it's not.
12 It's the Initiative on Methods, Measurement, and
13 Pain Assessment in Clinical Trials, I-M-M-P-A-C-T.
14 The logo is on the left, and that's important
15 because if you want to find out more about IMMPACT
16 ever, and if you go to Google, make sure you put
17 I-M-M, because if you put I-M, you're going to see
18 impact, the normal spelling. You're going to find
19 out all kinds of unusual interesting things that
20 will entertain you, but not who we are. So that's
21 what the organization is.
22 It's an international consortium of

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1 participants from academic research, governmental
2 agencies, the U.S. FDA, U.S. NIH, U.S. VA. We have
3 representatives from the EMA periodically,
4 industry, consulting and research organizations,
5 and consumer advocates.
6 So that's who we are. It's an invited
7 meeting. We try to bring people to represent all
8 the different disciplines that are relevant to
9 specific topics. We try to make sure that we
10 involve the appropriate regulatory people from the
11 right divisions or the right organizations when
12 possible. We thank them all, those that are here,
13 and many more tend to drift in late because of
14 traffic in the Washington, D.C. area, but we
15 welcome them and appreciate their support.
16 The mission of IMMPACT is to suggest -- and
17 that's suggest. We have no ability to dictate, to
18 require, to make mandatory. We can only suggest
19 methods for improving the design, execution,
20 interpretation of clinical trials for pain.
21 So that's what we're trying to do. The idea
22 is not to promote any products or any biases of our

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1 own type, but just to improve the quality of how
2 studies are done to in fact get to the point where
3 we in fact can try to improve the quality research,
4 expedite the research, improve the speed with which
5 new treatments come along. So that's who IMMPACT
6 is.
7 IMMPACT is part of ACTTION. Remember, I
8 told you about acronyms; so here's another one for
9 you. It's the Analgesic, Anesthetic, and Addiction
10 Clinical Trials, Translations, Innovations,
11 Opportunities, and Networks, ACTTION,
12 A-C-T-T-I-O-N. You'll notice there's a theme here,
13 double letters, to try to make sure that you can
14 find us because if you go to Google and type in
15 A-C-T-I-O-N, you will have a hard time finding who
16 we are.
17 What does ACTTION do? And it's ACTTION.org.
18 And for those that are not familiar with it, go to
19 our website to be able to find out as much as you
20 could want to know about us. But ACTTION is a
21 public-private partnership with the United States
22 Food and Drug Administration. We appreciate

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1 working, cooperating collaboratively, and the
2 support from the FDA.
3 The mission of ACTTION, little bit broader
4 than just what we saw for IMMPACT, is to identify,
5 prioritize, sponsor, coordinate, and promote
6 innovative activities with a special interest in
7 optimizing clinical trials -- you'll see where
8 IMMPACT fit within this -- with a special interest
9 in optimizing clinical trials that will expedite
10 the discovery, development, and improved analgesic,
11 anesthetic, addiction, and peripheral neuropathy
12 treatments for the benefit of the public health.
13 That's what ACTTION is. IMMPACT is one program,
14 one initiative within the broader ACTTION
15 initiative.
16 Who is IMMPACT? Who is involved with these
17 things? I've sort of alluded to this already, but
18 so far, over the 20 different meetings that we've
19 had, we've had 200 participants, some of whom have
20 been to multiple meetings, so over times.
21 We've had people from academic and related
22 participants from 12 different countries, four

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1 different countries here at this particular
2 meeting, countries as far away as Australia,
3 Belgium, Canada, Denmark, Finland, France. You
4 could read those for yourself.
5 So we have people from lots of
6 representation, although, predominantly, the people
7 in the room, because of the ease of getting here
8 and cost, are from North America. But we do have
9 people -- and thanks to Ralf Baron and to Katy -- I
10 can't see where -- she's hiding in the back -- that
11 came over from the U.K. Thank you both.
12 There are representatives from 90 different
13 academic institutions, whether they're university
14 based or hospital based, they're all academic and
15 they all have scholarly interests, so we have tried
16 to arrange for lots of them to be here.
17 As we've mentioned, we have participants
18 from different governmental agencies, including the
19 Department of Defense, the Drug Enforcement Agency,
20 EMA, FDA, National Institute of Health, SAMHSA, and
21 the VA. And we thank the VA for being here, for
22 your help. Thank you for supporting us.

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1 These are people who are all involved in
2 understanding these different things that we're
3 doing.
4 We've had support for different meetings,
5 different numbers, different organizations,
6 different companies for from over 46 different
7 pharmaceutical companies since the beginning, and
8 in the future, we may also be having support from
9 device manufacturers.
10 We have consumer advocacy representatives.
11 We've had five different organizations here. Chris
12 Veasley, thank you for being here, trying to keep
13 us all not forgetting who the end user is going to
14 be, which is the person that we're developing these
15 treatments for.
16 We could easily get lost up in the
17 methodology, data, and analytic approaches, and the
18 outcome measures, but we have to remember that
19 these are all geared toward an end user. So we try
20 to have people represent those individuals here as
21 well. We have several private consulting
22 organizations who have representatives who attend

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1 here, who are interested in analgesic trials.
2 From the FDA -- and I'm not going to read
3 these off to you, but we've had some different
4 divisions from CDER and also from the Center for
5 Device and Radiological Health, the Office of the
6 Commissioner, all of whom have been at different
7 meetings. And obviously, depending upon the topic,
8 different people would be at different meetings,
9 and not everybody's going to be at the exact same
10 meeting.
11 From NIH, we see lots of different
12 institutes. I'm not going to read them for you,
13 but we've had representations from a lot of the
14 different NIH institutes. We've also had from the
15 Rocky Mountain Poison Control. We've had
16 representatives from the EMA, as I mentioned. And
17 we're happy to have someone from the Critical Path
18 Institutes, Stephen Coons, who's in the back, who's
19 at this particular meeting.
20 The idea is we want to involve -- the
21 message I'm trying to give you is we try to involve
22 the relevant people as much as possible to help us

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1 get to our objective, which is to improve the kinds
2 of studies that we do to get to help people who
3 have various chronic pain problems. For ACTTION,
4 it's more than just pain. It's also anesthetics,
5 and peripheral neuropathy, and addiction.
6 What do we do? Well, since 2001, I told
7 you, we've had 20 different meetings. You're not
8 going to read these now, but just to give you a
9 flavor, those that want to know this, you can go to
10 the IMMPACT or the ACTTION websites, IMMPACT.org or
11 ACTTION.org, to see what's going on at these
12 different meetings.
13 We attempt to put up all slides when they're
14 available from the different meetings, the
15 presenters. You'll notice that we have presenters,
16 if you look at the program, and then we have lots
17 of discussions. The intent is more important
18 things in my opinion goes on during the
19 discussions, not only the formal discussions and
20 the panels, but also over coffee, and over dinner,
21 and over lunch. So we intentionally build in lots
22 of those things.

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1 But these are the first 14 different
2 meetings of some of the topics. If you want to
3 know more about them, you can see them. The slides
4 when possible are always put up on the website.
5 Every one of these meetings, almost up to
6 the last one so far, we have produced manuscripts
7 that get published describing the consensus and
8 recommendations.
9 Remember, we can't require. We can't
10 mandate. All we can say is, based on these groups
11 of individuals who all contributed to the
12 discussion, these were the best recommendations we
13 could come up with as you're thinking about either
14 designing your clinical trial, the outcomes you may
15 be using, the kinds of data analytic strategies you
16 may be using, and how you go about involving
17 patients.
18 We've got a lot of different topics that are
19 coming up. The meeting that you're at today,
20 obviously, is this specific one.
21 Notice by the way that one of our meetings
22 was co-organized with OMERACT, for those of you

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1 that are familiar with OMERACT. And that was an
2 assessment of physical function because the people
3 in the rheumatology world were equally interested
4 and dedicated to working in this area, so they
5 co-collaborated with us on this.
6 We've had one meeting on pediatric pain, so
7 there was one of those consensus meetings.
8 Predominantly, we've been with adults, but we did
9 have that one meeting. And you'll also note when
10 you go and see the manuscripts, we have multiple
11 authors.
12 Everybody who's at the meeting is invited to
13 be an author. They can decide, yes or no, they
14 want to sign on. To date, other than some people
15 from regulatory agencies who have not been able to
16 for different types and purposes, all the
17 academics, all the other people who have attended
18 have all been authors on these people.
19 So what you'll notice is the manuscripts,
20 when you see them, often have 40 authors on those
21 things. So congratulations. Depending upon the
22 alphabetical order, you could be high up. I'm

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1 changing my name to Aaron Aardvark, and I expect I
2 will be the first author on all these papers. And
3 poor Sanz and Bardow [ph] is not going to be able
4 to do this so well. He'll be the last, so it'll be
5 okay, but those in the middle understand that.
6 The way that manuscripts get developed is
7 based on our discussions, based on the information
8 we get, based on our ability to look over these
9 slides. We develop a draft manuscript. The draft
10 is circulated to all of you to look at, to comment
11 on. It's a draft.
12 We then will revise and deal with it.
13 Depending upon the nature of it, we come around
14 another time. You'll see it again. At that point,
15 you can say, "Hey, I'm not interested in staying on
16 this as an author. I disagree." We hope that
17 won't happen, but it could happen.
18 So you're not committing yourself to be an
19 author until you say, "Yes. In fact, I'm willing
20 to be an author on that particular manuscript."
21 And when people are unable to or choose not to want
22 to be an author, we do acknowledge that they were

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1 present at the meeting, just in fairness for people
2 to know who they were.
3 All the agenda, all the speakers, everything
4 from this meeting will be on the website. So if
5 anybody who wants to know was my friend Joe at that
6 meeting I couldn't attend, they can find out about
7 that.
8 So that's what's going to be going on. What
9 do we do, as I mentioned, we publish lots of
10 manuscripts, consensus statements, methodology
11 reviews, commission papers on certain topics.
12 We've conducted scientific studies or we've
13 sponsored conducting those studies.
14 We've developed diagnostic classifications.
15 We're in the process right now of -- we developed
16 an initial classification template taxonomy, and
17 now we have working groups on different diagnostic
18 areas in which they're developing those.
19 Ursula is where, right in the front. Ursula
20 is the co-chair of the working group that's
21 developing the diagnostic classification for many
22 of the conditions that we're going to be talking

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1 about at this particular meeting.
2 The idea is we have a template that
3 describes what needs to be considered, and then
4 when you get to the specific diagnostic, or medical
5 areas, or problem areas, then the experts in those
6 working groups -- and I believe we have nine of
7 those different working groups. They're going to
8 be encouraged to develop guidelines for the
9 taxonomy for two to three prevalent conditions that
10 we know that we're not going to cover every one of
11 these.
12 The idea is we're hoping that other groups
13 will say, well, you didn't have our condition, or
14 we think that will be useful. They can ask to be
15 involved. And to the extent that they'll follow
16 the template that we set up, any group that has a
17 specific diagnostic area that's not one recovered
18 can try to develop as long as they follow the
19 template. Those are all published, so you can see
20 these.
21 Everything is transparent. I am trying to
22 make that point to you, that everything we talk

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1 about is going to be available through the
2 transcript, which is available. Slides for as much
3 as possible will be on the website.
4 The manuscripts that will come out of these
5 meetings will all be, to the extent possible, as
6 clear as possible, what we talked about. The
7 debates, the discussions, the difficulties, that
8 will all be there. So that's sort of what we do.
9 We also are developing educational
10 initiatives. The North American Pain School, some
11 of you may be familiar with that, which is jointly
12 done with groups in Canada. They invite young
13 investigators. You have to apply to come to this.
14 I believe they let in 30 people each year with the
15 idea being that they get a fast-track course, a
16 full week of being housed in a resort in Canada, in
17 which they spend all the time doing nothing but
18 giving lectures and discussions about pain from
19 basic physiology, anatomy to clinical
20 decision-making, to epidemiology, to policy.
21 The idea is you bring a representative.
22 They had their first meeting last year. It was

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1 quite successful. I was able to attend that.
2 ACTTION has decided to be a co-sponsor, support
3 them with this particular initiative. We're hoping
4 it will continue. ACTTION has committed to
5 continuing to support this for as long as we can.
6 If any of you are interested, they have a
7 fascinating website with all the details about the
8 meeting, the presentations, who was there. They
9 had a whole range of things, and it was really a
10 fun meeting.
11 So if any of you have students who are
12 interested in any way, shape, or form in the area
13 of pain, they should consider looking into this and
14 possibly applying for it.
15 It's for North America. There's an
16 equivalent one in Europe. And I don't remember
17 what the official name of that one is called, but
18 this was modeled after that one just to make it
19 easier for people in North America to get to. So
20 that's the other thing that we are doing.
21 IMMPACT and ACTTION, we've published, as I
22 mentioned, over 100 plus papers. It's been cited

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1 over 6,000 times, published in 100 different
2 journals with diversity from addiction medicine to
3 women's health. The women's health, we've been in
4 those journals.
5 My favorite veterinary medicine, they
6 actually have been citing some of our guideline
7 recommendations for doing trials. I don't think,
8 for the patient-reported outcome measures, they've
9 been so interested. I don't know. John Farrar's
10 not here. Actually, he was involved with one of
11 these, and he will be here later.
12 So that's sort of what we are. The website,
13 just so you see what it looks like, you'll notice
14 along the bottom there, if you see, who is on the
15 steering committee, meetings, what was going on,
16 publications. We developed a measure called the
17 SFMPQ2 with Ronald Melzack, which is an expansion
18 and development of the McGill Pain Questionnaire, a
19 short form that many of you may be familiar with,
20 who has been sponsoring the meetings.
21 So everything is transparent, everything you
22 want to see for IMMPACT. There will be an ACTTION

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1 one. In addition to all this, there will be all
2 the other things about what goes on with ACTTION.
3 So that's who we are. What are the
4 objections for this meeting? You hopefully have
5 picked it up quite well. It's to discuss, debate,
6 haggle important considerations, to provide
7 suggestions regarding outcomes for clinical trials
8 to improve the quality of chronic pain and IBS.
9 The idea is, can we improve the quality of
10 studies, can we improve the consensus, some
11 agreements about what the outcomes might be to
12 foster systematic reviews, to foster meta-analysis,
13 to foster younger people coming on and developing
14 research, to provide information to regulatory
15 agencies, which don't have to -- there's nothing
16 binding. That's all we do is just give
17 information. They can take that.
18 For those of you that might be from those
19 agencies, hopefully this information will be useful
20 to you. The same is true for the VA, and NIH, and
21 the Office of Women's Health at NIH. And these are
22 things that we hope will be useful and important to

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1 you. But this is what we're going to do.
2 To disseminate these considerations and
3 observations, suggestions, and research, nothing
4 will stop or die at this meeting. Even if we
5 totally disagree, we'll write it up as if there was
6 disagreement and not consistency. But we want to
7 put the information out there.
8 So we will try to disseminate these
9 considerations, what went on in our debates, the
10 pros and cons, the advantages and disadvantages,
11 suggestions for a research agenda; that is if we
12 identify areas for which we can't make any
13 recommendations because at this point, we're
14 missing sufficient information, what might those
15 studies be? And then we try to get this published
16 in peer-reviewed journals, usually the relevant
17 journals, depending upon the nature of the topic.
18 We've had a lot of them in Pain, in the Journal of
19 Pain, and Osteoarthritis and Cartilage. We've had
20 them in some anesthesiology journals.
21 So we've tried to get them placed -- dental
22 journals. We've tried to have them placed in the

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1 appropriate journals. So that will be discussed by
2 this group, at least the steering committee and
3 Ursula and Nick Verne. He's still involved with
4 this I assume, who couldn't be here. So they will
5 help us make some decisions. You'll have input
6 where that might be. So that's what we're going to
7 do.
8 Now, in order to do this, we need to do some
9 herding, and you're going to not like being herded,
10 but we have to try to gear -- we've got to get to
11 that end. We've got a day and two-thirds, or
12 longer, if you choose to make us do that, to try to
13 bring this about.
14 So we have to do a little bit of herding,
15 and you will feel like you're being herded. But
16 what we've learned over there is there are some
17 gentle arts. And this, by the way, for Shannon and
18 Jen, who are going to be doing a lot of the
19 yeoman's work on this, IMMPACT participants have to
20 be herded. And what we've learned is -- I had
21 black hair when I got started. So this is what we
22 learned over years. Participants don't like to be

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1 herded. In fact, you can rarely herd IMMPACT
2 participants, but that doesn't stop us from trying.
3 So we'll keep working at it, and they'll keep
4 working at it.
5 Participants prefer to herd themselves, but
6 aren't very good at it. So you guys think you can
7 do things, but sometimes you need a little
8 guidance. Participants understand that they
9 sometimes need to be herded, however, that doesn't
10 make them any easier to herd. So even though you
11 might see a value, you don't want to do this.
12 Harsh herding usually has negative
13 consequences, so we've learned that. So we have to
14 find the gentle art of doing this, and this is sort
15 of how you do it. We find that there's a way to
16 pull people together. This is for the rugby people
17 who like to see those kinds of slides. And the
18 idea is for us to work together to discuss, to
19 debate, to look for commonalities, to look for
20 agreements, to look for the areas that may be
21 inconsistent, to find a way to try to improve the
22 quality of the research, to improve and expand new

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1 and better treatments or improvements on the
2 treatments that are available, that help the end
3 user, which is the provider to the person who has
4 that particular condition.
5 So that's what this is all about. I'm going
6 to turn this meeting over. I don't know if you
7 have any questions, quick questions, about either
8 housekeeping or anything I've said about what we're
9 going to do to you and how we're going to herd you.
10 This is your chance to do it. If not, I'm going to
11 introduce the people who are heavily involved.
12 Bob, you want to make a comment?
13 DR. DWORKIN: Yes. Bob Dworkin. As some of
14 you may know, at noon today, there's going to be a
15 webinar where the National Academy of Medicine
16 panel that was asked by the FDA to prepare a report
17 on how to deal with the opioid epidemic crisis.
18 We'll be having a webinar at noon today
19 where they roll out the National Academy of
20 Medicine response to the FDA's request. That's
21 from noon to 1:00. So Valorie has been lovely
22 enough to arrange that we'll have in this room,

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1 starting at noon, that webinar for any of you who
2 want to see what the NAM is going to suggest to
3 FDA.
4 We'll also be serving lunch upon the
5 mezzanine, and maybe we'll be able to end a little
6 bit before noon so people can run upstairs, grab
7 some lunch, and then come down if you're interested
8 in hearing what the National Academy of Medicine
9 has to say.
10 DR. TURK: Thanks, Bob.
11 Valorie, anything else that we didn't cover?
12 MS. THOMPSON: Not a thing.
13 DR. TURK: Anything from the media people,
14 from the audio/visual? Anything that we didn't
15 cover? They've got their thumbs up.
16 Any questions before we get this or before
17 we start?
18 (No response.)
19 DR. TURK: What we've done is, ACTTION has a
20 director sitting over there, Dr. Dworkin, and has
21 an associate director, me, and has assistant
22 directors, and two of them are here today, Shannon

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1 Smith from the University of Rochester and Jennifer
2 Gewandter also from the University of Rochester.
3 Most of you should know who they are. If
4 you don't, you will get to know them because they
5 can herd. They are good at doing this, and we're
6 counting on them to do this. So I want to turn the
7 meeting over to them, and they'll give a little bit
8 more information and then get started.
9 So Shannon, you're going to be the starter.
10 For any of the speakers, there is a pointer, a
11 laser pointer, and just push the green button to go
12 forward on the slides, and that's all you got to
13 do. And the people in the audio/visuals will take
14 care of everything else.
15 DR. SMITH: Thanks, Dennis. So I am Shannon
16 Smith. As Dennis mentioned, on behalf of Jen
17 Gewandter, Bob Dworkin, Dennis Turk, and myself, I
18 want to again welcome you all and thank deeply the
19 steering committee who has helped us plan this
20 meeting, as well as Valorie, Andrea, and their
21 team. They've been really instrumental in getting
22 this meeting together. So thank you to all of

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1 them.
2 I just want to announce first, before we
3 start the meeting, that for all the speakers, we're
4 going to be giving you a little sign that says when
5 you have 4 minutes left and then a sign that tells
6 you when your time is up because we have a very
7 tight-packed schedule, and we're already behind
8 schedule. So we're going to do our best to try to
9 stay on schedule as much as we can.
10 The first two moderators I'd like to
11 introduce are Tony Lembo, who's at Harvard
12 University, at the medical school as well as Beth
13 Israel Deaconess Medical Center, and Ursula
14 Wesselmann, who's a professor at the University of
15 Alabama in Birmingham.
16 So the two of them will be moderating this
17 first section, so I'm going to hand it over to them
18 now. Thank you.
19 DR. WESSELMAN: Yes. I want to thank the
20 organizers for putting this topic actually together
21 for IMMPACT. And we were saying yesterday evening
22 at the dinner how productive it is for all of us

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1 who work in the field of pelvic pain, IBS, and
2 other visceral pain syndromes to actually have a
3 forum to get together because we are all in very
4 different subspecialties.
5 We will have four speakers this morning. We
6 will have a coffee break after the first two
7 speakers. And then, if you look in the program,
8 you will see that we have very much time actually
9 for the discussion. It's an hour and 40 minutes,
10 so what I encourage you to do is to please make
11 note of your questions. We will discuss mainly at
12 the end of the lectures unless there is any burning
13 question that needs to be addressed right away.
14 So we have a lot of time for discussion, so
15 please think about the questions we would like to
16 discuss as you hear the four speakers.
17 It's a pleasure to introduce the first
18 speaker, Henry Lai, who is a urologist at
19 Washington University in St. Louis. He will talk
20 on interstitial cystitis, overview and assessment
21 of pain outcomes, and implications for inclusion
22 criteria.

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1 Presentation – Henry Lai
2 DR. LAI: Good morning, all. I'm going to
3 spend the next 20 minutes talking about
4 interstitial cystitis and bladder pain syndrome. A
5 lot of what I'm talking about is controversial
6 about a case definition. What is IC/BPS, and what
7 are the current outcome assessments that we have,
8 and what are new ways to move forward?
9 So what really is interstitial cystitis? I
10 always like to start the PowerPoint with this
11 description because it kind of captures what the
12 patients are really facing. So I will read it out
13 to you
14 We have all met at one time or another
15 patients who suffer chronically from their bladder,
16 and we meet someone who has suffered chronically,
17 periodically, and constantly have to urinate or
18 often go at all moments of the day and night, and
19 it hurts every time they urinate. It's very
20 miserable. It's very distressful. It affects
21 their physical health and their mental health.
22 It is a miserable condition to have. I

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1 mean, I can only imagine what life is like if you
2 have to go to the bathroom every 30 minutes
3 throughout the day. You can't sleep. You can't
4 rest. It disrupts your work schedule. It hurts
5 all the time. It affects your sexual life,
6 physical health, mental health, and it's not going
7 away. It's like you have a perpetual urinary tract
8 infection, but you don't. It is a miserable
9 condition to have.
10 But what is the contemporary case definition
11 of interstitial cystitis and IC/BPS? Now, this is
12 the definition that has been endorsed by the AUA,
13 which has more than 22,000 members in the United
14 States and across the world, as well as SUFU, which
15 stands for the Society of URODYNAMICS, Female
16 Pelvic Medicine and Urogenital Reconstruction,
17 which is a subspecialty, a specialized organization
18 to look at pelvic conditions.
19 So this is the definition endorsed and being
20 used to define IC/BPS. The patient needs to have
21 pain, pressure, discomfort perceived to be related
22 to the bladder. They have to have low urinary

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1 tract symptoms such as frequency, urgency,
2 nocturia, in the absence of infections and other
3 identifiable causes such as cancer, et cetera.
4 Now, this case definition is actually very
5 similar to what is being adopted by the Europeans,
6 by the EAU and ESSIC, and this is very similar.
7 BPS is a condition where patients would have
8 chronic pelvic pain, pressure, discomfort related
9 to the bladder and at least one urinary symptom.
10 And you have to rule out other confusable diseases.
11 So if you look at the commonalities between
12 the contemporary case definitions across both sides
13 of the Atlantic, you realize it is a chronic
14 condition. It's characterized by pain, pressure,
15 and discomfort in the bladder or the pelvic area.
16 It has to be associated with urinary tract symptoms
17 such as frequency, urgency, and nocturia.
18 It is based on the report of pain and
19 urinary symptoms by the patient. As you know,
20 there's no pathognomonic pathology, imaging
21 finding, and perhaps with the exception for a
22 smoker or a patient with Hunner's lesion, there is

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1 no pathognomonic cystoscopic finding.
2 There are no biomarkers that we use commonly
3 in clinical practice. It is essentially, like a
4 lot of the other pain syndromes, a clinical
5 syndrome. It is consistent of a heterogeneous
6 population. So I wanted to lay out the background
7 right here.
8 Our contemporary definition is actually
9 quite a departure from the NIDDK criteria for
10 IC/BPS research. That was developed more than
11 30 years ago. The reason I wanted to bring this up
12 is because this IC/BPS research definition from the
13 NIDDK is still commonly used by regulatory agents
14 and in clinical trials. So I want to give you a
15 perspective of what it was.
16 In 1987, the NIDDK established a committee
17 to streamline the research for IC/BPS. And in
18 1988, the year after, they emphasized cystoscopic
19 finding. The context of this definition is, at the
20 time, there was really no research definition of
21 interstitial cystitis. So it was meant to be a
22 starting point where the NIH can enroll patients

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1 and study the conditions. So they have to lay out
2 some inclusion/exclusion criteria and kind of
3 define what the condition is.
4 It was thought at the time that IC/BPS is a
5 bladder disease rather than a pain syndrome. It is
6 based on expert opinion and expert consensus, but
7 the intention at the time is to have a research
8 definition -- I want to emphasize a research
9 definition, not a clinical definition -- to enroll
10 relatively uniform populations so you can study
11 them and to have some kind of objective criteria to
12 enroll them into the clinical study. That's the
13 context.
14 To have interstitial cystitis according to
15 this definition, the patient needs to have pain.
16 They need to have urinary urgency. But much more
17 importantly, they have to have some kind of
18 objective cystoscopic finding in the bladder.
19 When you look inside a bladder, you have to
20 either see Hunner's lesion or you have to see
21 glomerulation, which is a submucosal hemorrhage
22 inside the bladder. Now, there are other criteria

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1 such as your dynamics criteria, how long you have
2 to have the pain, and you have to rule out other
3 things like infection. But the gist of this is
4 that you need to have pain, urgency, and a certain
5 cystoscopic finding.
6 Now, this is for a good intention, but
7 unfortunately, this research definition becomes a
8 clinical case definition where people use it to
9 diagnose IC/BPS. So clinicians start to use this
10 definition to define or diagnose IC/BPS.
11 Sometimes, unfortunately, they will do a cystoscopy
12 on the patients and find that while there's no
13 Hunner's lesion in the bladder and there's no
14 glomerulations in your bladder, therefore, you
15 don't have IC/BPS, and therefore, I don't really
16 know how to treat you.
17 I still see that these days, and I think
18 this is very unfortunate that the research
19 definition becomes the clinical criteria for
20 clinical care.
21 It's also somewhat unfortunate that this
22 becomes the de facto definition of what IC/BPS is

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1 from a regulatory perspective, enrollment in
2 clinical trial, clinical trial design, and drug
3 approval.
4 The real problem with this research
5 definition is that Hunner's lesion is very
6 uncommon. It's only seen in about 10 percent of
7 the patients. Glomerulation, that you are required
8 to have, is really nonspecific in this condition.
9 And the majority of the patients that fit the
10 contemporary definition of IC/BPS are actually not
11 covered by this definition.
12 So I have to admit that patients with
13 Hunner's lesion in the bladder is a different group
14 of patients. They are what we call the classic
15 interstitial cystitis patients. So they have focal
16 visible distinct area of information in the bladder
17 that you can see on cystoscopy. So it's almost a
18 sunburst pattern that you can see in the focal area
19 inside the bladder with radiating vessels to the
20 side, and sometimes they bleed when you
21 hydro-distend them.
22 You can see this in office cystoscopy. You

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1 can see this with hydrodistension. Sometimes, it
2 will resemble carcinoma in situ of the bladder that
3 tempts you to do a biopsy, but you will see chronic
4 information on the biopsy specimen.
5 So Hunner's lesion, I think, is a distinct
6 group, in a different group among the population.
7 Patients with Hunner's lesion are typically treated
8 differently from the rest of the IC/BPS patients.
9 In general, you have good response.
10 The AUA guideline will say that you need to
11 try to identify Hunner's lesion. If you see them,
12 you could treat them with fulguration or injection
13 of cannula, which is triamcinolone, into the
14 bladder.
15 The data are limited because they are small
16 series, single-center series, but a lot of them
17 suggested you get a pretty reasonable response if
18 you do either a cannula injection or fulguration
19 into the bladder. It last probably about a year or
20 two, so we need repeated treatment.
21 The problem is that most of the IC/BPS
22 patients that we see these days actually don't have

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1 Hunner's lesion, perhaps up to 10 percent. The
2 other 90 percent of the people have normal
3 cystoscopy, and they are the difficult ones to
4 treat. So what do you do with them?
5 Glomerulation is another definition that you
6 need to have, another criteria you need to have in
7 the NIDDK definition of interstitial cystitis.
8 There has been a long overdue systematic review,
9 but this paper basically said that glomerulation is
10 not specific, is almost irrelevant to IC/BPS. The
11 conclusion from the systematic review is that there
12 is no convincing evidence in the review literature
13 from the last few decades that glomerulation should
14 be included in the diagnosis of phenotyping of
15 IC/BPS.
16 I think they sum it really well. We should
17 not be looking for glomerulations to define the
18 conditions. The real problem is that the NIDDK
19 criteria that are still in use actually miss the
20 majority of patients that will fit the contemporary
21 case definition of the disease.
22 This is a paper from the Journal of Urology

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1 that summarizes it really well. So it says at the
2 bottom, "Strict application of NIDDK criteria will
3 have misdiagnosed more than 60 percent of the
4 patients with the conditions" because it is just
5 too restrictive to be used by conditions for
6 diagnosis of the condition.
7 So it is good as a research definition to
8 enroll a homogeneous group of patients for
9 research, but it will miss a lot of people that
10 actually have the clinical condition. It may not
11 be good for the clinical diagnosis.
12 So I try to summarize some of the problems
13 with the criteria because it really doesn't address
14 a large unmet need of patients and society. There
15 are a lot of patients who have IC/BPS who do not
16 fit the criteria. So if we use that criteria for
17 regulatory reasons, for clinical trial, and drug
18 development, it is doing almost a disservice to
19 patients and society overall.
20 We are really restricting to a very narrow
21 minority of subgroup of patients. But the reality
22 is that it is a heterogeneous patient population,

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1 just like any other pain syndrome. It is a
2 clinical syndrome, and we really desperately need
3 novel treatment. And I will allude to that later,
4 the fact that we don't have objective biomarkers,
5 imaging, cystoscopic finding, et cetera. It
6 doesn't mean that the patient needs to suffer and
7 stay with the old way of doing things.
8 Now, this is a very nice paper that actually
9 compares the people who fit the NIDDK criteria
10 versus the ones who don't fulfill the NIDDK
11 criteria. This study basically enrolled patients
12 that fit the contemporary case definition of IC/BPS
13 and do a cystoscopy on a subset of the patients,
14 and identify ones that fit the NIDDK criteria and
15 the ones who do not. And they look at different
16 things in this comparison.
17 So if you compare the patients who fit the
18 criteria versus the ones who don't fit the old
19 NIDDK criteria, there's really no difference in
20 urinary biomarkers among the ones that they have
21 looked at, where they did the bladder biopsies of
22 those two groups of patients. There's really no

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1 difference in bladder biopsy features. They look
2 at a number of biomarkers and really didn't see
3 much.
4 They look at the symptoms, the clinical
5 presentation of those two groups of patients. It
6 looks like, other than an increase in urinary
7 frequency, nocturia, and decreased bladder
8 capacity, and the NIDDK group, there really isn't a
9 lot of difference in the other clinical
10 presentations, either.
11 Now, the clinical reality is that the IC/BPS
12 population is heterogeneous if you do cystoscopy on
13 them. I think I alluded earlier that only about
14 10 percent of the patients have Hunner's lesion.
15 Not a lot of patients have glomerulation, and it's
16 really not specific to the conditions. In a
17 majority of the patients, the bladder actually
18 looks fine.
19 So in this study, they define the patient
20 population into three different groups, mild
21 symptoms, moderate symptoms, and severe symptoms,
22 and they look at cystoscopic finding. I mean, it's

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1 really all over the place. It's only a minority of
2 the patients, in this case about 10 percent, that
3 have Hunner's lesion inside the bladder, but you've
4 got varying cystoscopic finding in the clinical
5 populations.
6 Now, there has also been histologic studies
7 done. Patients are enrolled based on the clinical
8 criteria, and they look in multiple ways in the
9 bladder, biopsies, and see what other differences.
10 They have actually done some innovative clustering
11 algorithms to divide the patients into three
12 groups.
13 The majority of the patients actually have a
14 normal bladder. The bladder histology is
15 completely normal. There is only a very small
16 number of people that have a loss of urothelium
17 with edema, and inflammation, and glomerulation, and
18 mast cells in the bladder. There's a middle group
19 of about 8 percent that lost to urothelium, but
20 without a lot of growth evidence of inflammation in
21 the bladder.
22 So the clinical reality is that the

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1 population is heterogeneous when you biopsy them.
2 That leads to the recognition that it is a syndrome
3 with a heterogeneous population. And the ESSIC,
4 the European guideline, even suggests that we
5 should further classify and phenotype the patients
6 based on what we see on cystoscopy and based on
7 what we see on the bladder biopsy because they are
8 actually different groups of patients if you try to
9 classify them a little further.
10 So the criticism on the NIDDK criteria is
11 not only from this side of the Atlantic Ocean.
12 Even the EAU guideline set the diagnostic criteria
13 described by the NIDDK almost 30 years ago and was
14 formulated for research purposes only and is
15 inappropriate for clinical care, clinical trial,
16 et cetera.
17 So IC/BPS is a very difficult syndrome, just
18 like other visceral chronic pain syndromes. It's
19 very difficult to treat because it is a
20 heterogeneous population. There isn't a lot of
21 objective biomarkers that we could put our hands
22 on and we have really very poor understanding of

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1 the etiology, what's causing the conditions.
2 Some would argue that there are deficient
3 urothelium in the bladder that allows the urine to
4 be exposed to the bladder and cause other issues in
5 the bladder. Others will argue it's a neurologic
6 condition involving central sensitization,
7 peripheral sensitization, et cetera.
8 The current treatment is the linear
9 algorithm. You do first-line treatment, second-
10 line treatment, third-line treatment, fourth-line
11 treatment. But what we really need to do is to
12 move towards individualized treatment or IC/BPS.
13 We need to define a phenotype and pathophysiology
14 of the conditions, and then map the phenotype and
15 pathophysiologies to specific treatment so that we
16 can improve the clinical outcome. For example, if
17 there is peripheral dysfunction in our patient, you
18 may want to consider myofascial physical therapy.
19 So to move forward in IC/BPS, we need to
20 define a clinical population. We need to recognize
21 it's a heterogeneous population. We don't want to
22 be very restrictive, but in fact, we need to

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1 recruit patients and phenotype them in the clinical
2 trials. And Dr. Clemens tomorrow will talk about
3 what we find on the MAPP in terms of understanding
4 the pathophysiology of the symptoms.
5 We also need to have better tools to assess
6 clinical outcome. This is traditional, ubiquitous,
7 and it's almost standard clinical tool to assess
8 clinical outcome. It's called the IC Symptom Index
9 and IC Problem Index.
10 Essentially, it's a composite score that
11 combines bladder pain, urinary frequency, urgency,
12 and nocturia symptoms of patients. But there have
13 been some recent psychometric studies that show
14 that you should not be combining the outcome with a
15 composite score that combines both pain and urinary
16 symptoms.
17 So the MAPP developed a new score that
18 separates out the pain symptoms from the urinary
19 symptoms, and they should be measured differently,
20 so there's a psychometric study.
21 As part of the MAPP, we follow patients over
22 the course of a year, and then we were able to

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1 identify different subgroups of patients. There
2 are some patients whose pain gets better over time,
3 some that are stable, and some are worsened. And
4 there are people that improve the urinary symptoms
5 over time, some are stable, some are worsened, and
6 the two groups are not exactly the same.
7 We have done some studies as part of the
8 MAPP that Quentin will probably talk about more
9 tomorrow that the longitudinal outcome over a year
10 was somewhat different between the people who have
11 improvement in their pain symptoms and improvement
12 in urinary symptoms.
13 There are certain predictors of patients
14 whose urinary symptoms get worse over the course of
15 a year, and there are certain predictors of
16 patients whose pain gets worse over the course of a
17 year. They do overlap somewhat, but they are not
18 identical.
19 I think it's better to measure pain and
20 urinary symptoms separately because, as we know
21 from both the MAPP study and clinical care of
22 patients, some of the urinary symptoms can improve

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1 with certain treatments such as neuromodulation in
2 a stem [ph]. And the pain component may or may not
3 improve, so they track differently.
4 There are other potential outcome measures
5 we could look at. For example, we've been looking
6 at flares, which is very common the patients. The
7 urinary pain frequency, urgency, gets worse with
8 flares. Longer flares are associated with worse
9 pain and urinary frequency.
10 We have been doing focus groups to capture
11 aspects of flare that are important to patients.
12 Perhaps this is something we might want to consider
13 as a potential outcome in future clinical trials
14 because it does impact patients' overall health.
15 There are also potential biomarkers that we
16 could look at. We have to submit we currently
17 don't have validated biomarkers for IC/BPS. It
18 would be ideal if we could have some diagnostic
19 markers to identify the patient population and also
20 measure the outcome. But the fact that we don't
21 have it doesn't mean the patient needs to suffer
22 for the next 30 years.

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1 So I would say just move on, have better
2 clinical case definitions of IC/BPS, and consider
3 looking at some novel outcome measure for the
4 condition. Thank you for your time.
5 (Applause.)
6 DR. LEMBO: Thank you, Henry. That was
7 great.
8 We're going to hold questions, as we said,
9 until after all the speakers. Our next speaker is
10 Michel Pontari. He's professor and vice-chair of
11 the Department of Urology at Temple University and
12 the Lewis Katz School of Medicine. And his talk is
13 going to be on prostatitis. Thank you, Mike.
14 Presentation – Michel Pontari
15 DR. PONTARI: I want to thank you for
16 inviting me to this very interesting meeting. This
17 is the NIDDK classification of prostatitis. This
18 was adopted after a consensus conference in 1995
19 and published in 1999. Type 1 is acute bacterial
20 prostatitis. These are people who actually have an
21 infection, a tender prostate, come into the
22 hospital with a fever, and dysuria, and get IV

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1 antibiotics.
2 Type 2 is chronic bacterial prostatitis,
3 actually relatively uncommon. People who actually
4 have a bacterial infection in the prostate, they
5 get treated with antibiotics in between episodes.
6 They are asymptomatic, and don't have pain.
7 Type 3 is the most common, about 90 to
8 95 percent of patients, which is what we're going
9 to deal with today. Chronic pelvic pain syndrome
10 has been called the "headache in the pelvis." It
11 was arbitrarily divided into 3A and 3B with
12 inflammation in either seminal plasma, express
13 prosthetic secretions, or post-prosthetic massage
14 urine, and 3B is no inflammation. So far, there
15 have not been many clinically or any clinically
16 significant differences between these.
17 Type 4 is asymptomatic inflammatory
18 prostatitis. These are people who have no
19 symptoms, but on biopsy or for some reason have a
20 post-EPS, and will have inflammation but without
21 pain.
22 So type 3 combines a prior diagnosis of

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1 chronic non-bacterial prostatitis and prosthetic
2 prostatodynia. There was a classification from '78
3 from George Drach and raised this question of
4 significance of inflammation. There is no
5 correlation between inflammation and symptoms, and
6 the term "chronic pelvic pain syndrome" is used
7 instead of prostatitis because it recognizes that
8 pain may not be from the prostate.

9 The term "prostatitis" is a horrible term
10 because it implies that there is inflammation or
11 something with the prostate. These guys have
12 pelvic pain that may not be coming from the
13 prostate, which is important.

14 What we use is the NIH definition, and the
15 key symptom in prostatitis is pain. What separates
16 what we call prostatitis from BPH is pain. Guys
17 come in with frequency, urgency, "Doc, I get up at
18 night." We call that BPH. They come in, "Doc, I
19 get up at night and I got this pain." We call that
20 prostatitis.

21 The NIH definition is genital, urinary, or
22 pelvic pain for at least three months with or

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1 without voiding symptoms in the absence of
2 uropathogenic bacteria, in the absence of other
3 causes of pain such as malignancy.

4 So in terms of epidemiology, the UDA study
5 found that there was about 1800 visits per 100,000
6 population. We did a study with the International
7 Consultation of Male LUTS. Over 24 studies of
8 prevalence was 7.1 with a median of 6.7. It's
9 higher in Africa than North America, and the
10 incidence is about 3.3 per 1,000 men or about
11 267,000 cases a year in the U.S.

12 So to help study this, the NIH formed the
13 CPCRN, the Chronic Prostatitis Collaborative
14 Research Network, in 1997, and there were six sites
15 across America. We enrolled 488 men with chronic
16 prostatitis over a four-year-period. The mean age
17 is 42, so these are young guys who have this
18 condition. And the range was 4 percent with less
19 than 25 and 13 percent were greater than 55. I
20 have patients with this condition between the age
21 of 16 and 88 all over the map. It isn't just one
22 age that gets this.

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1 In this, we study symptoms, bacterial
2 studies, symptom scores, and we did three clinical
3 trials. So for a symptom assessment, we developed
4 the NIH CPSI, the chronic prostatitis symptom
5 index, which is a validated, self-administered
6 index. We compared symptoms to patients with BPH
7 and asymptomatic controls and came up with three
8 sections.

9 What happened in the development was there
10 was a review of prior literature with an inventory
11 of symptoms. There were several studies prior to
12 this, de la Rosette in '93, George Brabalis back in
13 '90, and a large study by Rich Alexander using an
14 internet survey that catalog some of the symptoms
15 that these patients had. And this was the basis
16 for going to focus groups of 6 to 8 patients from 4
17 sites and talking about their pain symptoms,
18 urinary symptoms, quality of life, physical
19 functioning, a lot of the impact domains.

20 There was an initial draft of 55 questions
21 covering pain, urinary symptoms, sexual symptoms,
22 quality of life, and economic impact. There was

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1 cognitive testing, and then there was a revised
2 draft with 5 centers. We sat down with 2 patients,
3 said, "Do you understand this?" and trimmed down
4 the 21 items.

5 Then with this, we also gave them the AUA
6 Symptom Score. This is the standard assessment of
7 symptoms in urology for lower urinary tract
8 symptoms. Nocturia, frequency, urgency,
9 essentially 7 different categories that we use, and
10 4 demographic questions.

11 The control groups were men with BPH and
12 asymptomatic controls, so there was not
13 surprisingly a difference in pain. The men with
14 BPH had less than 10 percent pelvic pain. I think
15 that in and of itself is actually interesting
16 because men who come in just BPH, if we don't ask
17 them, we're not going to get that they have pain.
18 So 10 percent of guys we thought, oh, you just have
19 BPH actually had pain and much lower than the other
20 controls.

21 The top four pain locations became items 1A
22 and D in the index, so the penis, testicles,

<p style="text-align: right;">Page 61</p> <p>1 bladder, and the perineum. The frequency of pain 2 became item 3. The intensity was a 10-point scale, 3 which is item 4. And we added ejaculatory pain. 4 If there's one symptom that seems to be almost 5 pathognomonic of men who we think have prostatitis, 6 it's post-ejaculatory pain. 7 For urinary symptoms, these men had a lot 8 more dysuria than everybody else, so that became 9 question 2. The AUA Symptom Index was high in both 10 the prostatitis and the BPH patients and almost 11 equivalent. So what was done was that 2 symptoms 12 seemed to recreate the entire AUA Symptom Score. 13 That was obstructive, voiding symptoms, and 14 frequency, and these together became 5 and 6. So 15 these weren't selected for any reason other than 16 they recreated the rest of the symptom score. 17 For quality of life, there were 8 questions 18 over 2 domains, psychological distress and physical 19 limitations. And these all seemed to perform 20 equally well, so we picked two of them, put them on 21 the score, and then the overall quality-of-life 22 item became number 9.</p>	<p style="text-align: right;">Page 63</p> <p>1 symptoms were only responsive in those who had 2 marked improvement, and there was a small response 3 in any scale for those who became worse. 4 So if you get worse, the NIH CPSI is not 5 going to reflect that very well. If you get 6 better, the pain and quality of life is going to be 7 a lot more responsive than the urinary symptoms. 8 What they found here, too, is that in 9 between sections of the GRA, in between categories 10 was 4 points. So 4 points seems to be the smallest 11 perceptible change, but the ROC curves indicated 12 that 6 points was a better choice for who has a 13 clinically significant response. 14 A slightly different study was done by 15 Turner out in Washington, looking at primary and 16 secondary care, not tertiary care sites. They 17 compared the NIH CPSI to a grade A chronic pain 18 scale. Pain and quality of life were markedly 19 associated with this scale and urinary symptoms had 20 a low correlation. 21 So again, the pain and quality of life were 22 responsive to change; urinary scale is not, similar</p>
<p style="text-align: right;">Page 62</p> <p>1 So this is the score. It's 9 questions, 2 43 points. There is the pain subscale, which is 1 3 to 4. There is urinary, 5 and 6, and the quality 4 of life is at the end. It's asymmetric. How this 5 is scored, you can have a maximum of one on some, 6 you have 10 on the others. 7 There was a study that Quentin did on 8 rescoring this on a 0 to 100 scale, and it didn't 9 seem to make any difference. So the max score is 10 43 and anything above 15, we would consider 11 significant symptoms. 12 So how responsive is this? Kaye Probert 13 looked at patients enrolled in our first clinical 14 study, and this was responsiveness to change over 15 time in 174 men in our first CPCR study, looking 16 at a total and 3 subscores versus the global 17 response assessment. This GRA had seven items, 3 18 on the other side, and of no change. 19 So patients who improved in total pain and 20 quality of life were highly responsive, and then as 21 you went from slight improvement to marked 22 improvement, it became more responsive. Urine</p>	<p style="text-align: right;">Page 64</p> <p>1 to what we had seen in Probert's study. And the 2 recommendation was you can use the NIH CPSI, but 3 add another validated pain measure to it. 4 So how did this respond in our trials? We 5 did three trials. The first one was 6 weeks of 6 either ciprofloxacin, 500 twice a day or 7 Tamsulosin. And this was a 2-by-2 block, so you 8 either got placebo and placebo, cipro and placebo, 9 Tamsulosin plus placebo, or both drugs. 10 Essentially, it was a negative study, so the 11 NIH CPSI, there's no difference between 12 cipro/no cipro, tamsulosin/no tamsulosin for the 13 total or any of the subscores. 14 We did a second study, a 12-week study 15 looking at Alfuzosin, which is an alpha blocker, in 16 men who were alpha-blocker naïve and symptoms less 17 than 2 years. We thought, wow, this is the group 18 it's going to work in. And what's interesting is 19 that -- and it got published in the New England 20 Journal I think because we got the exact same 21 response for both groups, which is pretty hard to 22 do, but 49.3 response.</p>

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1 (Laughter.)
2 DR. PONTARI: Incredible.
3 So the endpoint was a 4-point reduction in
4 the NIH CPSI, which is the smallest perceptible
5 change. Absolutely no change, absolutely no
6 difference to assess, so no difference in total, no
7 difference in the subscores.
8 We came close in the third one. We did a
9 trial of pregabalin. It was a dose escalation from
10 150 to 600. We had found from people in this room
11 that 450 was good for fibromyalgia, so we went up
12 to 600 over 2 weeks at each dose.
13 The primary outcome was a 6-point drop. We
14 were pretty confident we were going to have a
15 significant improvement. For the primary outcome,
16 we got 0.7, very close, but not quite. But the
17 secondary outcomes all significantly improved.
18 Now, one caveat is the secondary outcomes
19 are only in people who completed the trial. For
20 the GRA, it was people who -- if you are a non-
21 responder, if you dropped out, you were a
22 non-responder. So we have to take it with a grain

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1 of salt. These were only in people who completed
2 the trial. But it was significant for total score,
3 all the subscores, so that any other outcomes in
4 McGill was significant. So if you improve, it
5 seems to go with that.
6 Quentin did an adaptation, where they
7 added -- this is for the male; there's a female
8 also -- 2C and 2D, which is pain or discomfort with
9 bladder filling or pain or discomfort relieved by
10 voiding. And with this scale, called the GUPI,
11 which is what we use now, and the MAPP, the RSC
12 curves had 7 points for this versus 6 defines a
13 responder and 4 point again is the minimum
14 perceptible change. So this is what we use in the
15 MAPP.
16 So Henry's study was interesting from the
17 standpoint of the men. This is in the MAPP. They
18 asked patients, "Do you have pain with bladder
19 filling and/or relieved by bladder emptying, and do
20 you have urgency, or do you have none of these?"
21 What we talk about in the MAPP are people
22 who have bladder pain, painful urgency, or none,

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1 and what's interesting is, as you can see the,
2 75 percent of the men had bladder symptoms. So
3 these are men who would be, by prior criteria,
4 characterized as interstitial cystitis, and this
5 was a really interesting phenomenon for us.
6 Going back, I looked at all the old studies.
7 I'm not sure if we didn't ask. It didn't come up.
8 We sat with men in focus groups for the NIH CPSI,
9 and this didn't come up. This was not one of the
10 symptoms that we found. But it turns out that if
11 you ask these questions specifically, 75 percent of
12 the men have this.
13 Going from both to either to
14 neither -- sorry, from neither to either to both,
15 you see an increase in severe pain, frequency,
16 urgency, symptom burden, depression, worsened
17 quality of life, including IBS. So if you go more
18 towards men with bladder symptoms, they have an
19 increased incidence of IBS, up to about 30 percent.
20 This was the study that Henry had mentioned,
21 Jamie Griffith's study. They did look at factor
22 analysis. I think the first line I'd like to put

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1 in here, "Questionnaires differ in their
2 assumptions about how symptoms cluster together."
3 We always thought pain in urinary symptoms have to
4 be from the same thing. Well, maybe they're not.
5 So looking at this, two factors came out,
6 pain and urinary symptoms. Pain also correlated
7 with depression, whereas urinary does not. So
8 their conclusion was the total score is they
9 combine pain and urinary symptoms into one score,
10 limited for clinical and research purposes.
11 In terms of the impact domain of emotion,
12 just as in other things such as the vulvodynia
13 paper that we got, catastrophizing the men with
14 prostatitis is important. It's associated with
15 greater disability, depression, urinary symptoms,
16 and greater pain. And in this study by Dean Tripp,
17 helplessness was the strongest predictor of pain,
18 even after controlling for depression and urinary
19 symptoms.
20 Now, in terms of entrance criteria, there
21 has been nothing like the uproar over IC for
22 prostatitis. So there was a consensus conference,

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1 a very small one, here in Washington in 1998. It
2 was international because we had people from
3 overseas. And at that point, there was a consensus
4 that was developed for adoption following the
5 criteria for clinical studies in prostatitis. It
6 used the NIH definition, the 1995 NIH
7 classification scheme, the eligibility criteria
8 that we came up with for the CPCRN, and the NIH
9 CPSI.

10 So the first three I think would still
11 stand. I think the CPSI we have to look at as an
12 outcome measure because I don't think it would work
13 as a total. This is what we came up with for the
14 CPCRN. Used the NIH criteria, do you have pain for
15 greater than 3 months, and the inclusion criteria
16 would be sort of common-sense things.

17 It's a diagnosis of exclusion. If you have
18 pain from prostate cancer, we don't want you here.
19 If you had BCG, we don't want you. We even
20 excluded unilateral orchialgia. So patients who
21 only had pain in the testes were not included in
22 these trials; structured neurologic disease, and

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1 prior prostate surgery.

2 So as far as the MAPP entrance criteria,
3 there was a CPCRN and now we're in to the MAPP era,
4 pretty similar. We had a little bit of difference
5 in terms of the length of disease in terms of IC
6 and the prostatitis, so we kept the old prostatitis
7 one, 18 years old, again, non-zero score, so
8 they're really pretty similar.

9 As far as inclusion criteria, the only thing
10 I could see with the MAPP that's different than
11 CPCRN was a history of non-dermatologic cancer.
12 There were some deferral criteria that I think are
13 useful in terms of if you're going to do a trial.
14 These are the deferral criteria we used for the
15 CPCRN.

16 So if you had an infection at that point, we
17 didn't exclude you. We said, "Come back in
18 3 months and see if it's gone." So you couldn't
19 have an active infection within 3 months, a recent
20 STD. If you'd undergone a prostate biopsy in
21 3 months, you can come back and see if your
22 symptoms have persisted, acute or chronic

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1 epididymitis from the last 3 months, and/or genital
2 herpes in the last 12 months.

3 So with prostatitis, the main symptom we're
4 talking about is pain. It's what distinguishes it
5 from BPH. And 75 percent of men with prostatitis
6 or chronic pelvic pain syndrome also have bladder
7 pain.

8 So the implications are first for
9 treatments, because you can use bladder medications
10 for these, but also, these men may have to be
11 included in whatever interstitial cystitis is. So
12 what the bladder symptoms are, having these guys in
13 one silo may not be completely appropriate.

14 Pain and urinary symptoms may not respond
15 together. Using a combined score is probably not a
16 good idea. The NIH CPSI and GUPI total scores are
17 likely not useful in clinical trials, and so far,
18 we have had minimal controversy in the entrance
19 criteria for chronic pelvic pain syndrome. Thank
20 you.

21 (Applause.)
22 DR. LEMBO: Thank you, Michel.

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1 So we're going to take a break now. It's
2 supposed to be a 20-minute break. Maybe we could
3 make it a little bit shorter so we'll catch up a
4 little bit on time. We have an hour and 40 minutes
5 for discussion, so we should be able to catch up
6 then. So why don't we reconvene in about
7 15 minutes? Thank you.

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

10 DR. WESSELMAN: We want to continue with two
11 more topics, vulvodynia and IBS. And as I said
12 before, we will have a discussion right after that.
13 And we want to keep on time so that we can finish
14 just before 12:00 so that we can look at the
15 webinar that is scheduled for 12:00. And lunch
16 apparently is right here on this level, so it will
17 be easy to eat and watch the webinar.

18 It's my pleasure to introduce Andrea Rapkin,
19 who is a professor of OB/GYN at UCLA, and the topic
20 of her lecture is vulvodynia, overview and
21 assessment of pain outcomes and implications for
22 inclusion criteria.

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1 Presentation – Andrea Rapkin
2 DR. RAPKIN: Thank you, and thank for the
3 opportunity to speak this morning. How is the
4 volume level? Okay.
5 The most recent nomenclature for vulvodynia
6 is now called the 2015 classification. This does
7 not differ substantially from previous
8 classifications, but I will point out where it
9 does. There hasn't been quite as much dissension
10 about this nomenclature as there has been with
11 prostatitis and bladder pain syndrome.
12 This particular series of definitions was
13 developed through a consensus with most of the
14 groups that are involved with the research of
15 vulvodynia, the International Society for the Study
16 of Vulvovaginal Disorders, the IPPS, International
17 Pelvic Pain Society, and the International Society
18 for the Study of Women's Sexual Health.
19 This is a pain-based classification system,
20 and as with other disorders, there are two main
21 classes of vulvar pain. We're not interested in
22 specifically vulvar pain caused by a specific

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1 disorder. But vulvar pain is an idiopathic pain
2 disorder of at least 3 months duration. So the
3 previous classification system included pain of
4 6 months duration. This is moved down to 3 months
5 duration.
6 Again, being a pain-based system, we are
7 defined only on the basis of location triggers,
8 temporal pattern, and onset. The specific visual
9 or sensual characteristics of the syndrome are not
10 included here, so we have location, localized. The
11 most common localized area is to the vestibule, and
12 I'll show you a picture of that for those who are
13 not familiar with the vestibule in a moment. The
14 other area of localized vulvar pain is the
15 clitoris, but this is much less common.
16 The pain can be generalized to the entire
17 vulvar region. This seems to be again less common.
18 Probably only about a 10th to a 20th of the
19 patients may have some generalized pain as well,
20 and this would be considered a mixed picture.
21 Those with only generalized pain in my
22 experience tend to be much older and tend to be

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1 confused with patients with either pudendal
2 neuralgia or with a referred hyperalgesia from,
3 say, a bladder pain syndrome or other pelvic pain
4 disorders.
5 Now, the trigger is important, but the
6 trigger may be provoked, or spontaneous, or both.
7 And in this situation, we're primarily talking now
8 about the vestibulodynia. The reason for using on
9 vestibulodynia is, one, it's the most prevalent
10 type of vulvodynia and, two, it is the most well-
11 studied type of vulvodynia. So going forth, I'm
12 going to be focusing on provoked vestibulodynia or
13 PVD.
14 How is the pain provoked? Most typically
15 with sexual contact, vulvovaginal penetration, but
16 also with tampon use, and in many women with
17 sitting or with tight clothing, there is pain in
18 the genital area.
19 We also have the mixed pattern, whereby
20 there's pain that is provoked and spontaneous.
21 These patients are part of a spectrum and tend to
22 have more severe pain. The spontaneous pain alone

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1 without provoked symptoms is very rare. Temporal
2 pattern, it's unlike other pain conditions. The
3 pain wouldn't be constant if it's provoked,
4 however, it's generally intermittent.
5 The onset, however, is interesting, and we
6 wish we had more information about this aspect. So
7 when we talk about someone with PVD1 or primary
8 vestibulodynia, we're talking about an individual
9 who says, as long as they remember having genital
10 contact, they've had pain.
11 Well, that usually doesn't go back into
12 childhood. We don't have any real good prospective
13 studies. So the "as long as I can remember" often
14 goes back to, well, the first time I tried tampons,
15 or the first time I was trying to touch the area,
16 or I was with a sexual partner.
17 Acquired, however, is an individual who has
18 had a period of comfortable or pleasurable genital
19 contact followed by onset of pain. And often, it's
20 a very acute onset of pain. Women may say that it
21 suddenly started with a particular episode of
22 intercourse that was uncomfortable, or that they

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1 thought they had a bladder infection or a yeast
2 infection, and in fact may go in and be treated
3 multiple times for these infections, only to find
4 that it's not actually an infection.
5 Now, the new classification system includes
6 potential factors associated with vulvodynia. I
7 think these are very important because this may in
8 the future be part of the phenotyping or
9 subgrouping of patients, but right now there isn't
10 data to suggest that this would be the case. So we
11 have individuals who commonly would have
12 musculoskeletal factors.
13 Now, the sensitivity of the vestibule and
14 the sensitivity of the pelvic-floor muscles are
15 correlated, but not well correlated, so there are
16 different factors that may predict each. But it
17 has been demonstrated that many women with PVD do
18 have muscle overactivity, do have increase in
19 muscle tone, decreased relaxation, and alterations
20 even on ultrasound of the bulk of the muscles.
21 Neurologic mechanisms are being evaluated
22 more recently with imaging studies, but there is

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1 some changes in peripheral neuroproliferation, plus
2 or minus mast cells, et cetera; and of course,
3 psychosocial as with any chronic pain condition.
4 But what isn't evaluated I think as well in other
5 chronic pelvic pain conditions, and it is our area
6 to really focus on, is sexual functioning because
7 that's the primary area that's impacted with PVD.
8 So likely not one disorder, it may be a
9 constellation of disorders, but I think this is the
10 case with many of the conditions we're talking
11 about. Pathophysiology is unknown. There are many
12 different studies, many different theories.
13 There's information on neuroproliferation,
14 and this comes from not only biopsies, but the fact
15 that many women with provoked vestibulodynia are
16 treated by vestibulectomy. So yes, in the
17 beginning of treatment for IC, there were some
18 individuals who had cystectomy no longer done, but
19 vestibulectomies are still performed.
20 There are still many studies evaluated the
21 histopathology. It cannot be diagnostic in a
22 specific patient, but there have been some changes

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1 with free nerve endings, with staining for nerve
2 growth factors, substance P with mast cells, plus
3 or minus to granulation.
4 We're looking at CNS processing, as are many
5 other individuals, but as of yet, you cannot get an
6 MRI and predict what diagnosis and what treatment
7 outcome, functional or otherwise, the muscular,
8 myofascial problems.
9 Now, the issue with hormones, we're going to
10 exclude individuals who were clearly estrogen
11 deficient; so if an individual is post-menopausal
12 with genital urinary syndrome of menopause or if an
13 individual has lactational amenorrhea. But someone
14 who's been on long-term low-dose hormonal
15 contraceptives that are known to lower estrogen
16 levels, the question is what's going on in these
17 patients, do they have a different picture, should
18 they be a subcategory?
19 Of course, comorbidities; about 50 percent
20 of patients with PVD have comorbidities, and the
21 more comorbidities, the worse the symptoms.
22 Genetic polymorphisms have been identified, but are

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1 as yet not useful for treatment.
2 Lots of psychological factors, and in
3 particular, as I said, sexuality has been looked at
4 quite a bit. Unfortunately, either we don't think
5 as an initiating factor, but certainly as a result,
6 lower desire, arousal, satisfaction, orgasm, more
7 negative attitudes on the part of patient and
8 partner. So partner responses are often very
9 important in these studies, and I'll get to that
10 soon.
11 Here is the vestibule. So the vestibule is
12 that area of the vulva outside the hymeneal ring
13 and will include the posterior hymeneal remnants as
14 well. And the vestibule stops where the vulvar
15 tissue begins to look like epithelialized skin as
16 opposed to mucus membrane.
17 The vestibule itself in the past has been
18 shown to have areas of erythema, and in fact, in
19 Friedrich's criteria, erythema was one of the
20 characteristics, but it's now not considered to be
21 necessary. This accounted for initially why the
22 condition was called vulvar vestibulitis.

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1 As with prostatitis, which we've just heard,
2 it is no longer considered to be an itis. And the
3 areas of erythema are there, but they may be
4 vasodilatation from neurogenic inflammation, for
5 example.
6 Some of the prevalence studies are done with
7 questionnaire, with phone survey, and it is unclear
8 how well they correlate with actual findings on
9 examination, but there is some correlation to be
10 sure. About 8 percent of women have this provoked
11 vestibulodynia.
12 So the recommendations for outcome measures
13 for clinical trials is one of the manuscripts that
14 was developed by Ursula and her colleagues, other
15 individuals who are not here today, Caroline
16 Pukall, Sophie Bergeron, Candace Brown, Gloria
17 Bachmann.
18 You have a copy of this, and much of what
19 I'm going to say going forth reflects or includes
20 some of these aspects because I think it was really
21 very well done, looking at recommendations for
22 outcome measures. And obviously, the purpose is

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1 similar to the purpose for this entire meeting, to
2 provide consistent measures, facilitate comparisons
3 across studies, and improve outcome measures for
4 multiple dimensions, in particular the very
5 important measures of interpersonal relations,
6 sexuality, and et cetera.
7 So in this particular manuscript and in the
8 studies developing from that, the IMMPACT framework
9 was used, but the sexuality measures were added.
10 And again, there was a focus on PVD.
11 The recommendations were that the
12 psychometric properties be foremost, that there be
13 evidence that these particular measures that are
14 used are valid and reliable wherever possible, that
15 the issues relate to practical application.
16 So we've seen a couple of survey
17 questionnaires that are quite short, but once
18 you're evaluating different dimensions, including
19 sexual functioning, partner response, affect,
20 et cetera, you can have quite a large bulk of
21 questionnaires that are given to patients for
22 assessment.

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1 It would be important that these measures
2 had been used in prior clinical trials of PVD so we
3 can see how they perform. And with vulvodynia, it
4 would be nice to have some specific measures, just
5 like with the GUPI or GUPTI [ph] -- I don't
6 remember what you're calling it now -- there were
7 questions that were added for female having to do
8 with pain at the opening of the vagina and the
9 vulva area. There are very specific measures for
10 vulvodynia, and I'll get to some of those in a
11 moment.
12 So some of the core measures to consider
13 again are the fact of how do we define inclusion
14 criteria. This hasn't been quite as difficult for
15 PVD because we do have a location; we have pain
16 localized to the vulvar vestibule or mixed. The
17 pain should be provoked or mixed.
18 In terms of onset, we are still evaluating
19 PVD1 or PVD2, but it is not clear how important
20 these items will be. Note that, as part of the
21 2015 criteria, exam is no longer part of that, but
22 all of the individuals currently who are doing any

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1 research in vulvodynia outcomes are including
2 examination findings. Also, the level of pain
3 required to fulfill diagnostic criteria hasn't
4 specifically been established, but generally is
5 accepted as about 3 out of 10 or greater on a VRS
6 scale.
7 So if we're looking at pain with gentle
8 contact of the vulvar vestibule, this was initially
9 taken from the Friedrich's criteria. So as I said,
10 it may not be part of the 2015 nomenclature, but it
11 is part of what is important researchers feel for
12 entrance criteria, for inclusion criteria.
13 The pain level with the cotton swab hasn't
14 really been standardized. So do you brush the
15 cotton along the vestibule? Another approach
16 that's been more or less standardized is to place
17 the cotton swab at a perpendicular angle and to
18 depress to a third of the head of the cotton swab.
19 It's not included in trials, but in my
20 experience, it does matter to some degree how you
21 place the cotton swab, and again, the threshold for
22 inclusion.

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1 But what about this vulvar sensitivity
2 testing? How useful is it really? Unfortunately,
3 the patient sensitivity on exam and their reports
4 of clinical improvement of pain with intercourse
5 don't really correlate that well.
6 Now, in my patients, we do the sensitivity
7 testing with every visit, and I have found that
8 there is some correlation, but we tend to find the
9 sensitivity with a Q-tip lagging behind or being
10 more problematic, even when they're starting to
11 have improvement with pain with intercourse. And
12 we know that sexuality is very complicated,
13 obviously.
14 Again, self-report and objective pain
15 ratings may not be correlated with sexual function
16 parameters or satisfaction, again reflecting the
17 complexities here, and the fact, as I'll get to, of
18 the pelvic-floor involvement.
19 Cotton swab tests can have some false
20 positives, so individuals with no complaints of
21 pain with intercourse may have discomfort when
22 their vestibule is prodded with a dry cotton swab,

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1 moistened as well.
2 So what about this vulvar sensitivity? It
3 is increased when you have individuals who have a
4 younger age of the first onset of vulvar pain,
5 provoked vulvar pain. And it is more correlated
6 when you have the provoked pain, obviously, and
7 also correlated with pain after intercourse.
8 It is not associated with comorbidities, so
9 the more comorbidities doesn't necessarily increase
10 vulvar sensitivity with cotton swab. There aren't
11 really significant changes or differences with PVD1
12 or PVD2, meaning primary or secondary, or if an
13 individual has spontaneous pain.
14 Luckily, for those who have had trouble with
15 their algometers when they use them in a research
16 setting, the cotton swab test does correlate well
17 with algometer findings.
18 Now, just what would the exclusion criteria
19 be? Well, infectious, inflammatory, neoplastic.
20 Neurologic is a little confusing, again, with how
21 you make a diagnosis of pudendal neuralgia, for
22 example. But we would exclude obvious neurologic

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1 trauma, iatrogenic, and the hormonal deficiencies.
2 And I've already mentioned some of the
3 controversies in that area of the hormonal
4 contraceptives.
5 So these are the frequently studied
6 parameters, the pain intensity and vulvar
7 vestibular sensitivity, 1 versus 2, comorbidities,
8 anxiety, and depression. Clearly, further
9 phenotyping is important.
10 My goodness, I'm talking. Let's skip over
11 this.
12 The tampon test may reflect more than
13 intercourse pain, the situation of pain in the
14 vestibule. And this is because many women are
15 avoiding sexual contact, it's so painful. So the
16 tampon test was developed by David Foster and has
17 been validated. And this is placement and
18 withdrawal of a tampon and then determining what the
19 pain is.
20 It's reliable, tested 3 weeks in a row, good
21 validity, and better adherence than asking a woman
22 to have intercourse when they have pain. They may

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1 not even have a partner at this time.
2 Pain intensity has been looked at by both
3 the NRS and the VRS. The problem with pain
4 intensity scales is that we can't use pain in the
5 last 24 hours. We really need to think about "pain
6 the last time you attempted vulvovaginal
7 penetration" or pain during non-sexual contact
8 activities. You can also switch from pain in the
9 preceding month, where they may not have even tried
10 contact, to pain during last 4 penetration
11 attempts.
12 I'm going to mention a few times, if I have
13 any time left, the VPAQ, which is a recently
14 validated vulvar pain assessment questionnaire that
15 has two pain intensity domains and has been able to
16 cover many of these domains.
17 Also important would be aspects related to
18 the sensory descriptors of pain. Certainly the
19 Short-Form McGill and then the VPAQ, which I have a
20 copy of if anyone is interested, has a pain
21 descriptor's subscale. So it would be recommended
22 to include the VPAQ with the Short-Form McGill.

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1 Temporal pattern, as I mentioned, is less
2 important because pain tends to be provoked. I'm
3 going to skip over the data on PVD1 and 2. There
4 are some inconsistencies here.
5 What about physical functioning? Yes, the
6 SF-36 is helpful. It has not been used in many PVD
7 trials because the pain is provoked, as I said, and
8 can be avoided by avoiding genital contact.
9 However, because of the comorbidities, it's
10 important to look at health-related quality of life
11 and also to look at specific-to-PVD physical
12 functioning. So the VPAQ has a life interference
13 subscale, and there's a quality-of-life scale from
14 the VQOLS that could be added.
15 Another core outcome is looking at
16 sexuality, Female Sexual Function Inventory. The
17 problem with this inventory is that it asks for
18 your different questions in the last 4 weeks. For
19 women who are no longer sexually active, this is a
20 problem. There is in the VPAQ now a self-
21 penetration interference subscale for self-contact,
22 and this can be useful. So consider as a secondary

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1 measure the PROMIS scale minus the ejaculation
2 questions.
3 Sexual satisfaction, distress, and
4 interference should be included as secondary
5 outcome measure, and you can find these in VPAQ,
6 and there are other measures that can be used.
7 In terms of emotional functioning,
8 vulvodynia is associated with depression, anxiety,
9 however, they're not clinically significant levels.
10 They're different than controls, but obviously
11 should be measured along with catastrophizing ways
12 of coping as well.
13 So in the literature of vulvodynia, the
14 BD-II has been used quite a bit for this anxiety
15 because trait anxiety doesn't change at all with
16 treatment. The state of the STAI could be used.
17 PVD emotional response questionnaires that
18 are specific would be important, and again, you can
19 look at the VPAQ or the PASS-20. The PASS-20 is
20 interesting because it's important that fear of
21 intercourse pain be assessed, and that can be
22 assessed with anxiety related to sexual activity.

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1 Of course, for any treatment trial, you
2 wanted to look at global improvement and treatment
3 satisfaction. And these should be adapted to women
4 with vulvodynia, and PGIC has been adapted to women
5 with vulvodynia.
6 Let's skip over to -- supplemental measures,
7 domains that are relevant would be the social role
8 functioning, in addition, relationship adjustment,
9 and documenting comorbidities. Of the impacts,
10 core and supplemental domains, the ones that are
11 particularly relevant, 4 vulvodynia studies include
12 interpersonal functioning, coping, and social role
13 functioning.
14 These are more important than the other
15 supplemental domains. Of course, the core domains
16 of pain, physical, and emotional functioning,
17 improvement symptoms and disposition are very
18 important.
19 So in sum, there is no single validated PVD
20 questionnaire for all measures. I've tried to go
21 into measures that should be considered core and
22 supplementary. The vulvar pain assessment

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1 questionnaire captures most of these core and
2 supplemental domains, and some measures from PROMIS
3 should be added for secondary. And that's about
4 it. Thank you.
5 (Applause.)
6 DR. LEMBO: Thank you, Andrea.
7 We're going to move on and talk about
8 irritable bowel syndrome. We're really fortunate
9 to have Bill Chey, who's a professor of medicine
10 from the University of Chicago, who's going to talk
11 to us about it. Thank you.
12 Presentation – William Chey
13 DR. CHEY: Thanks so much for the invitation
14 to the organizers of the meeting and to Tony for
15 inclusion in this meeting. I'm going to talk to
16 you about IBS. I've really focused on issues
17 around measuring pain, as I thought that's what I
18 was supposed to do. So if I left stuff out that
19 was supposed to be included, I apologize.
20 Let's start with a general overview of IBS.
21 I think everybody in the room has some familiarity
22 with this, but there are certainly some nuances

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1 that bear mention that have tremendous overlap with
2 all the other things, all the other topics that
3 have been discussed already this morning.
4 So this, like many of the other conditions
5 already discussed, is a symptom-based diagnosis.
6 There is no biomarker that we can utilize to
7 identify patients with IBS at the current time.
8 It's a very prevalent problem. It affects anywhere
9 from between 7 to 15 percent of the general
10 population in the United States.
11 It has a remarkable impact on quality of
12 life. Particularly, severely affected patients
13 have dramatic impairments in quality of life as
14 well as work productivity, and it really should
15 come as no surprise that this is a very expensive
16 disorder, billions of dollars on an annual basis in
17 direct and indirect costs.
18 We currently utilize the Rome IV criteria to
19 diagnose IBS, particularly for clinical research
20 studies. Now, there are some differences, and you
21 can see the Rome IV criteria on the slide. There
22 are some importance differences between Rome IV

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1 versus Rome III. Rome IV was just released in May
2 of 2016. Rome III was the standard for many years
3 before that.
4 If you look at this slide, it says recurrent
5 abdominal pain, one day per week, associated with
6 two or more of the following, related to
7 defecation, onset associated with change in stool
8 frequency, or onset associated with change in stool
9 form.
10 Just so you know this about the differences
11 between Rome III and Rome IV, remember that Rome
12 III included abdominal pain and discomfort.
13 Rome IV is focusing really solely on abdominal
14 pain.
15 Now, let me just say that I'm going to China
16 in two months to discuss the unhappiness in the Far
17 East with that decision. So this has created some
18 controversy, although there is lots of qualitative
19 research to suggest that patients draw a clear
20 distinction between pain and discomfort, and that
21 in some parts of the world -- not Asia, but other
22 parts of the world -- they actually had difficulty

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1 describing or identifying with the word
2 "discomfort."
3 The other thing is that we raised the
4 threshold for the diagnosis, so one day per week.
5 It used to be 3 days per month. That will
6 obviously have some effect on the overall
7 prevalence of the condition.
8 Then the last changes to mention is related
9 to defecation. Recall that Rome III said "relieved
10 by defecation." And the reason we made that change
11 is because, again, in epidemiological research, it
12 became clear that there's a small subset of
13 patients with IBS who have exacerbation of their
14 pain with defecation.
15 So the majority get relief of their pain
16 with defecation, but a smaller proportion get
17 actual worsening of their pain with defecation.
18 Remember that IBS can be or is diverse from
19 a clinical phenotype standpoint. There are
20 patients with constipation, patients with diarrhea,
21 and patients with a mixture of both constipation
22 and diarrhea.

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1 Also remember that, from the standpoint of
2 the Rome criteria, we distinguish between these
3 different IBS subgroups on the basis of stool
4 consistency, not stool frequency, although from a
5 regulatory standpoint, as we'll talk about in a
6 moment, for the constipation subgroup, we focus on
7 stool frequency as opposed to stool consistency.
8 Now, there are multiple symptoms that are
9 reported by patients with IBS, not just the ones
10 that are included in the definition created by
11 Rome. So if you look at this particular graphic
12 from the UCLA group, you'll actually see that
13 patients commonly endorse complaints around gas and
14 bloating, for example, in addition to problems with
15 pain and altered defecation.
16 You might ask -- and this question comes up
17 a lot -- well why isn't, for example, gas and
18 bloating part of the Rome definition for dividing
19 patients with IBS? And the reason for that is
20 while somewhere in the neighborhood of 80 to
21 85 percent of patients with IBS endorse those
22 complaints, it turns out that those complaints are

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1 also extremely common in virtually every other
2 functional GI diagnosis as well as the healthy
3 population.
4 So while it's a common complaint in patients
5 with IBS, it unfortunately offers little
6 discriminative value from healthy volunteers as
7 well as patients with other functional GI
8 disorders.
9 In terms of what symptoms are the most
10 bothersome, actually, I think a theme that comes
11 out over and over again as you talk to patients
12 with IBS is the unpredictability of their symptoms.
13 It's the inability to be able to know what symptoms
14 they're going to experience and when they're going
15 to experience them. And that creates a lot of
16 secondary situational anxiety that I think
17 amplifies their symptoms as well as drives their
18 illness experience.
19 But you can see that, outside of that, the
20 next most bothersome symptom is abdominal pain
21 followed by distension and urgency, actually, which
22 is interesting.

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1 Now, there are a number of challenges.
2 These challenges are really the same as has been
3 described with many of the other disorders that
4 have already been discussed this morning, issues
5 around overlap.
6 One thing that's important to mention in
7 patients with IBS is that somewhere in the
8 neighborhood of 30 to 50 percent of IBS, patients
9 have at least 1 other functional GI diagnosis. So
10 in addition to IBS, they'll have functional
11 dyspepsia. They'll have functional heartburn.
12 They'll have proctalgia, so a variety of other GI
13 symptoms.
14 But in addition to that, as has already been
15 mentioned, a variety of other non-GI-related
16 conditions, which I think gives us insight into the
17 pathophysiology of at least a subset of these
18 individuals. I firmly believe that patients who
19 have multiple overlapping pain disorders have more
20 of a top-down disease as opposed to a bottom-up
21 driven disease. And that, at some point down the
22 road if that's validated, may well have treatment

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1 implications in regards to the selection of, for
2 example, pain modulators.
3 The pathophysiology of IBS is diverse. So
4 there is an interaction between a variety of host
5 factors, luminal factors, and environmental
6 factors. I think that the building blocks that
7 we've talked about for many years, important to the
8 pathogenesis of IBS, abnormalities and motility,
9 visceral sensation, brain-gut interactions, are
10 still operative. But I think as time goes on,
11 we're increasingly becoming aware that these
12 factors are really influenced by issues like, for
13 example, permeability, immune activation, genetics.
14 Biosalts, interestingly, as sort of going
15 back to the future, have been knocking around for a
16 long, long time. But it's increasingly clear, for
17 example, that we've been missing patients with
18 bioacid malabsorption who present as otherwise
19 being diagnosed with IBS.
20 Psychological, psychosocial factors as the
21 last speaker mentioned, very important. And food,
22 I think again is increasingly becoming recognized

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1 as one of the main drivers for symptoms in patients
2 with IBS. In fact, I think that the two main
3 environmental stimuli for IBS symptoms are
4 psychosocial stressors as well as food.
5 In fact, realize that somewhere between two-
6 thirds and three-quarters of IBS patients associate
7 a symptom onset or worsening with eating a meal.
8 And I'm emphasizing this because, to me, it's so
9 interesting that from a research standpoint and
10 also from a therapy standpoint, we have focused a
11 lot on many of these other factors, and our
12 therapies are really largely predicated upon
13 pharmaceuticals, but we have very little evidence
14 in the way of how diet therapies may benefit
15 patients with IBS.
16 So we're going to focus the rest of the talk
17 on the issue at hand, which is measurement of
18 abdominal pain and a couple comments about
19 abdominal pain in patients with IBS.
20 So we have already talked about the fact
21 that this is a symptom-based diagnosis. It's
22 heterogeneous, both phenotypically as well as

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1 pathophysiologically. And along that same line,
2 pain is also multi-dimensional. And again, as has
3 already been discussed by the speakers that
4 preceded me, there are a variety of different
5 issues that play into pain, and there are a variety
6 of different issues that we can measure in regards
7 to pain.
8 We'll talk about where we are at the current
9 time, but I think that for this group, regardless
10 of what discipline we're talking about, right now,
11 we're really focused almost exclusively on pain
12 intensity. But I think we'd all agree that for any
13 of us that actually take care of patients, there
14 are a variety of different issues around pain that
15 involve factors other than intensity that are
16 equally important to the patient.
17 So understanding the impact of different
18 pain dimensions is important certainly to guide PRO
19 development for future clinical trials, as we're
20 discussing today, and define inclusion criteria,
21 which I assume will also be discussed later in this
22 meeting.

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1 Now, a couple other things to consider about
2 pain in IBS is that, right now, we lump all
3 patients with abdominal pain and altered bowel
4 habits together as suffering with IBS. Now, I've
5 already emphasized to you that these patients are
6 remarkably heterogeneous from a clinical phenotype
7 standpoint: diarrhea, constipation, and a mixture
8 of both.
9 Now, we lump all those patients under the
10 rubric of IBS, but realize that the characteristics
11 of pain of not just the bowel habits, but also
12 abdominal pain are different amongst these
13 different subgroups. This is something that we've
14 only very recently started to learn.
15 This is work from Brennan Spiegel's group at
16 UCLA -- he was kind enough to share a number of
17 these slides with me -- that shows that there are
18 differences, for example, in the mean frequency of
19 pain attacks amongst patients with different
20 subgroups of IBS. So patients with IBSD have more
21 frequent pain attacks than patients with IBSC or
22 IBSM.

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1 The proportion of pain attacks, which
2 interfere with work or daily activities is also
3 different. And this is interesting because the
4 IBSD patients have more frequent pain attacks, but
5 the impactfulness of the abdominal pain is greater
6 amongst IBSC patients. In fact, I'll show you data
7 from our own group that we just presented at DDW
8 this past year that shows the exact same thing.
9 Now, behavior is during pain attacks, so
10 taking medications roughly -- or between the
11 groups. But look at "goes to bed." Patients with
12 IBSC actually behave very differently than patients
13 with other subgroups of IBS in that regard.
14 And patients will tell you this in clinic.
15 The way that they frequently will respond when
16 they're in a painful flare is they go to bed and
17 try to go to sleep. And defecation on the other
18 hand is a much more common endpoint for patients
19 with IBSD and IBSM, IBSD in particular.
20 Now, this is the data that I told you about
21 that we just recently presented at our national
22 meeting last year. We haven't published this in

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1 full manuscript form yet. But it's an interesting
2 study that was conducted in 71,000 U.S. citizens
3 using a digital app-based platform that we've
4 created at UCLA Cedars and University of Michigan
5 called My GI Health.
6 This is an app-based platform that utilizes
7 the PROMIS questionnaires to be able to determine
8 the frequency and severity of all GI symptoms. So
9 all 8 of the most commonly reported GI symptoms for
10 which a patient might see a gastroenterologist are
11 assessed as part of this platform using computer-
12 adaptive technology so that the patient only
13 answers questions about the symptoms that they're
14 experiencing.
15 Anyway, utilizing this, we were able to
16 identify a large number of patients with IBS, and
17 we were also able to stratify between the different
18 subgroups of IBS on the basis of a whole variety of
19 different types of symptoms, including abdominal
20 pain.
21 It's interesting that, of patients with
22 IBSC, they had significantly greater PROMIS scores

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1 for abdominal pain. So their overall PROMIS scale
2 scores for abdominal pain were really quite
3 dramatically higher than the other subgroups or
4 than IBSD in particular. So it's interesting that,
5 again, the frequency in that one study was a bit
6 more in IBSD, but the overall burden seems to be
7 greater for IBSC. Similarly, you can see small
8 differences for abdominal pain severity, which
9 trended towards but didn't reach statistical
10 significance.

11 But bothersomeness was significantly greater
12 in the IBSC group as well -- in our study, we
13 actually had a small increase in frequency, which
14 you can see is really a very small difference.

15 At the current time, the standard to measure
16 pain in patients with IBS is an 11-point numeric
17 rating scale. And this has gone through a lot of
18 iterations over the last several decades. I've
19 been involved in virtually every drug development
20 program as has Tony. Tony and I have been
21 developed literally in virtually every drug
22 development program for IBS that's occurred over

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1 the last 20 years. And I can tell you that, the
2 way this has evolved, the pain has always been
3 assessed utilizing either Likert scales or NRS.

4 Initially, the very early trials with
5 alosetron, for example, used a 5-point Likert
6 scale. But over time, we've recognized that the
7 sensitivity of a 5-point Likert scale is probably
8 not great enough to really distinguish between the
9 relatively small differences that can occur in the
10 treatments offered for patients, a heterogeneous
11 population like IBS.

12 So the current standard is an 11-point
13 numeric rating scale, and that's been evaluated now
14 by several different groups and validated, and
15 we'll talk about that. So the currently utilized
16 numeric rating scale assesses pain over the last
17 24 hours. The PRO guidance is, you need a weekly
18 average of worse pain to be greater than 3 to
19 qualify for clinical trials. And that is the
20 current standard that's utilized or that is
21 recommended by FDA.

22 This NRS does work. It's been validated

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1 against a variety of different clinical anchors.
2 And it turns out that in a number of different
3 studies now, an MCID of around 2 or a difference of
4 around 30 percent in reduction of pain score is
5 clinically meaningful. And that's actually been
6 validated against, again, whole variety of
7 different factors, including IBS Symptom Severity
8 Scale, the Functional Bowel Disease Severity Index,
9 IBS QOL, EQ5D, which is an assessment of quality of
10 life as well as presenteeism in a variety of
11 individual IBS symptoms.

12 So lessons learned about pain in IBS, pain
13 and discomfort are different. This is actually
14 work again from the UCLA group, but has also been
15 validated by other groups. And that is that
16 patients really just make a distinction between
17 abdominal pain versus abdominal discomfort.
18 Somewhere around 80 to 85 patients really draw that
19 distinction, which tells you that a smaller
20 proportion actually considers them to be more on a
21 continuum and to be the same, really be part of the
22 same spectrum of the same disorder.

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1 IBS pain is multi-faceted. Some pain
2 dimensions drive illness experience more than
3 others. Probably the one that drives it the most
4 is severity, but frequency and bothersomeness are
5 also extremely important in terms of what drives
6 the patient to go see the physician and what also
7 causes them to experience disability, both in
8 regards to their home life and work.

9 Patients with more intense, frequent,
10 constant, and unpredictable pain have higher
11 illness, impairments, and again that word,
12 "unpredictability," I think is a really important
13 thing that's really difficult to measure. But
14 again, if you talk to patients, patients will tell
15 you that one of their biggest concerns is not
16 knowing when they're going to have a problem.

17 The multidimensionality of pain should be
18 borne in mind as we develop conceptual frameworks
19 for PROs. So I think, unlike some of the other
20 conditions that have been discussed so far, the FDA
21 has actually released regulatory guidance for
22 trials being conducted in patients with IBS.

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1 A couple of themes that come out of the pre-
2 reading documents that were sent to all of you,
3 what I think are important to emphasize is, for
4 many years, the standard in IBS trials was to
5 actually use a global assessment primary endpoint,
6 so Subjects Global Assessment, SGA, adequate
7 relief, or satisfactory relief, so a single
8 question item that assessed global IBS symptoms.
9 We're actually very comfortable with that in
10 the IBS investigative community for many years.
11 FDA has problems with a global endpoint for a
12 variety of different reasons, I think many of them
13 quite valid. So they've recommended that a single
14 general item asking patients to rate overall change
15 in IBS symptoms as a primary endpoint to support an
16 efficacy claim is not recommended. So that's
17 pretty much out for us in IBS trials.
18 What they've recommended instead is a
19 primary endpoint that encompasses the main symptoms
20 of IBS, so really consistent with the Rome
21 criteria, abdominal pain and abnormalities in bowel
22 habits.

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1 For drugs that are developed to treat a
2 single IBS system -- and we're starting to see more
3 of these, for example, drugs specifically targeting
4 pain, for example. Specific symptoms or signs
5 should be the primary endpoint, but the other
6 symptoms of IBS should be assessed, not necessarily
7 to determine if there's efficacy, if none is
8 expected, but to make sure that you don't
9 exacerbate any of the other key symptoms of IBS.
10 So what is the actual regulatory guidance
11 right now for the different subgroups of IBS, for
12 IBSC? And the pain response definition is going to
13 be durable across all of the different IBS
14 subgroups, so for pain severity, weekly average of
15 worse pain in the past 24 hours, a score of greater
16 than or equal to 3 on a 11-point numeric rating
17 scale is what's currently used to identify patients
18 who are eligible for an IBSC trial.
19 As I mentioned earlier, for IBSC, stool
20 frequency is currently the bowel-related symptom
21 that's focused on, so fewer than 3 complete
22 spontaneous bowel movements per week is also a

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1 recommended entry criteria for IBSC trials on the
2 basis of FDA guidance.
3 Now, in terms of responder definitions, a
4 decrease in weekly average of worse abdominal pain
5 in the past 24 hours, of greater than or equal to
6 30 percent, and that's based upon that validation
7 data that I alluded to earlier in this discussion;
8 and also, an increase of at least one complete
9 spontaneous bowel movement per week from baseline
10 in terms of stool frequency.
11 Actually it's interesting. I think the FDA
12 very rightfully identified a number of concerns
13 about global endpoints, and they recommended
14 interim guidance in terms that I've just laid out
15 for you. The interesting thing was there was very
16 little validation data of the recommended interim
17 endpoints.
18 What's I think very gratifying is that
19 there's been publication recently of some work.
20 It's post hoc work, and we have to accept all the
21 limitations of that, that actually validates the
22 endpoints selected by FDA.

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1 This is actually data from a post hoc
2 analysis that was published on the heels of the
3 linaclotide phase 3 clinical trial program.
4 Remember, linaclotide is a guanylate cyclase C
5 agonist that's FDA approved for the treatment of
6 patients with IBSC as well as chronic idiopathic
7 constipation.
8 What they identified using clinical anchors,
9 so patient-reported complaint questionnaires, which
10 assess symptom-specific patient rating of change as
11 well as degree of relief of IBS symptoms, is that a
12 threshold of 30 percent was very consistent with
13 their post hoc analysis from those clinical anchor
14 data.
15 In addition, they also validated that the
16 increase in complete spontaneous bowel movements of
17 1 per week was also consistent with the degree of
18 change identified by patients who felt better
19 following drug therapy.
20 So for IBSC, we actually have at least some
21 post hoc data that validates the thresholds that
22 have been recommended by FDA for responders in

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1 patients who are entered into large randomized
2 control trials.
3 This is also an interesting analysis that
4 was part of this paper, and this looked at varying
5 the number of weeks needed to meet the FDA
6 responder endpoint. Remember that -- I didn't
7 mention this, but I should have -- right now that
8 the regulatory standard is at least 6 of 12 weeks
9 of response to be defined as a responder.
10 It turns out that the overall accuracy
11 offered by changing the threshold turns out to be
12 greatest right at that 6-week cutoff point. You
13 can see that as you start to demand a greater
14 number of weeks, of course your specificity goes
15 up, but your sensitivity drops quite precipitously.
16 Also, varying the percentage of improvement, that
17 is the weekly average in abdominal pain score, you
18 can also see how that affects the results as well.
19 For IBS, it's the same regulatory
20 recommendation in regards to abdominal pain, that
21 is a 30 percent -- or first in terms of just
22 enrollment criteria, a weekly average of worse pain

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1 in the past 24 hours of at least 3 on an 11-point
2 NRS.
3 Here, though, for stool, for the
4 bowel-related complaints, it's not stool frequency.
5 And this is an interesting story, which is that
6 when the FDA initially came out with their interim
7 guidance on this particular topic, they actually
8 wanted a stool frequency endpoint for diarrhea.
9 Actually, the functional GI community pushed
10 back really hard on the FDA, including producing
11 evidence to show that in patients with diarrhea-
12 related complaints, stool frequency is oftentimes
13 not a good surrogate assessment for complaints of
14 diarrhea, clinical complaints of diarrhea. So I
15 think it was gratifying for everybody involved that
16 they were willing to revise the criteria and base
17 it more on stool consistency.
18 You can see that patients to be included in
19 trial should have at least 2 days of Bristol Stool
20 Form scale score of 6 or 7, which is loose or
21 watery stool.
22 To be a responder, the same definition in

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1 terms of improvement in overall pain score saw a
2 reduction from worse abdominal pain in the last
3 24 hours at baseline of at least 30 percent. And
4 then here, we see a responder definition that's
5 really based on improvements in stool consistency,
6 so a 50 percent reduction in a number of days with
7 the bowel movements that is type 6 or 7 using the
8 Bristol Stool Form Scale.
9 So to summarize, IBS is a symptom-based
10 disorder without a reliable biomarker at the
11 current time. It's a multi-symptom disorder, and
12 it's heterogeneous both from the phenotypic
13 standpoint as well as the pathophysiological
14 standpoint.
15 Symptoms are largely measured using patient-
16 reported outcomes because that's all we really have
17 to measure at the current time. Pain measurement
18 in IBS focuses right now on severity, but I hope
19 that I've shown you and open your minds to the
20 thought that we may want to think about other
21 aspects of pain other than only severity or
22 intensity.

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1 A 30 percent reduction in abdominal pain
2 severity has been determined to be clinically
3 meaningful and is the current regulatory standard
4 as recommended by FDA.
5 The last thing that I have on the summary
6 slide that I think is also important to think
7 about, and it ties into the comments that I made
8 earlier, is that we may need to think differently
9 about how to measure pain and what aspects are
10 important to pain based upon IBS subgroup.
11 So in other words, frequency, intensity,
12 bothersomeness, unpredictability are all traits
13 that may differ between patients with IBS and
14 IBS-C, for example. So thank you very much.
15 (Applause.)
16 Q&A and Panel Discussion
17 DR. LEMBO: At this time, we're going to
18 take questions and have a discussion. We'd like to
19 invite the panelists to come back up to the table.
20 And this is supposed to be a discussion, so if
21 anybody has questions, why don't we go ahead and
22 raise your hand. We'll take them individually, and

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1 please state your name, of course.
2 DR. KATZ: Daniel Katz from Boston. So my
3 question is the following. It seems like we've
4 chopped up the body into all these different parts,
5 and if your functional disorder happens to be in
6 your colon, then you get managed by one group of
7 specialists, and if it's in your bladder, you're
8 going to get managed by a different group of
9 specialists. And if it's in your vagina, you get
10 managed by a different group of specialists.
11 The outcome measures that we've heard about
12 all relate to, well, should it be 2 bowel movements
13 or 3, or 2 urinations or 3, or all of these very
14 kind of organ-specific numbers.
15 But when I listen to each one of the
16 speakers, it seems to me that there's a common
17 message, which is that there's an underlying
18 proclivity that certain people have towards being
19 sensitive to pain or other stimuli. And if that
20 happens to show up in your bladder, well, then
21 whatever passes through your bladder is going to
22 cause or evoke symptoms; if it happens to be air

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1 passing through, if it happens to be a tampon
2 passing through it. But the commonality is that
3 whatever gets in touch with that organ will provoke
4 whatever -- evoke -- the stimuli are.
5 So it seems to me that a relevant question
6 is, what is that underlying proclivity towards
7 being sensitive to pain, and how do we identify
8 when that is present? How do we diagnose that?
9 And could that be a treatment target? Certainly it
10 is for tricyclic antidepressants and other things,
11 and does that have any implications for how we
12 measure outcome of clinical trials in these
13 disorders?
14 Are we losing something by just focusing on
15 the superficial manifestation of whatever the end
16 organ is that's bearing the brunt of it, especially
17 since most of these patients, as I've heard, have
18 symptoms referable to multiple different end
19 organs.
20 DR. WESSELMAN: We should probably go
21 through each speaker because we have four different
22 pain syndromes, which are all -- yes. This is a

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1 really key point, and I was thinking about it,
2 exactly about what you mentioned when some of you
3 presented data on each individual pain syndrome,
4 because the drugs that actually had some efficacy
5 aren't the general pain drugs that we also use for
6 neuropathic pain.
7 So the question is really, as we are trying
8 to identify certain endpoints for a given
9 manifestation of visceral pain, are we going the
10 right way, because this research has actually been
11 going on both in basic science research as well as
12 in clinical translational research for the last
13 20 years, but we have not really identified any
14 pharmacological targets that have proven to be very
15 valuable.
16 So we might actually want to step back and
17 think about these overlapping visceral pain
18 conditions to see if we address them from kind of
19 above rather than trying to pinpoint a certain
20 symptom that we want to have as a primary endpoint.
21 DR. CHEY: I think it is an excellent point.
22 I think there is an investigative way to think

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1 about this and a clinical way to think about this.
2 The clinical way to think about this is moving
3 towards multi-disciplinary care models because
4 there is a lot of commonality between these
5 different conditions.
6 I think that, increasingly, there is
7 evidence to suggest that a team-based integrative
8 approach that embraces not just the GI symptoms,
9 but for example, we have a -- Quentin knows about
10 this -- called the Michigan Bowel Control program,
11 where we have collaborative effort between the
12 urogynecologist, colorectal surgeons, physical
13 therapists, gastroenterologists, behavioral
14 therapist, dietitians. We all see patients
15 together, and I guarantee you our outcomes are
16 significantly better than the patients that are
17 seen individually by just GI, or urogynecology, or
18 colorectal surgery.
19 So from a clinical standpoint, I think that
20 we're moving towards more of those holistic care
21 models.
22 From an investigative standpoint, I still

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1 think, though, that the peripheral symptoms are
2 important triggers, even for patients who have a
3 central sensitization, a central abnormality in
4 pain processing or perception. So we're moving
5 those peripheral symptoms, which are oftentimes
6 important triggers for that sensitivity. It still
7 makes a lot of patients better.

8 I think that one of the reasons why the
9 therapeutic gain in the clinical trials is so
10 marginal is related to exactly the points you
11 raise, which is that some patients are more
12 top-down, some patients are more bottom-up. And
13 then there's a whole bunch of patients where it's a
14 combination of both. I think that,
15 mechanistically, we cap out at a relatively low
16 rate with a lot of the drugs that are targeting one
17 specific mechanism.

18 DR. LAI: From the perspective of IC, I
19 think you realize that it is a heterogeneous group
20 of populations. There are those that are more of a
21 top-down picture with systemic manifestation and
22 with chronic overlapping pain syndrome of IBS,

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1 fibromyalgia, vulvodynia, et cetera. But there is
2 also a subgroup within the IC/BPS which is very
3 bladder-centric.

4 We've shown pictures of people having
5 Hunner's lesion inside the bladder, and they do get
6 better just injecting cannula or fulguration
7 locally in the bladder. So if it's a stomach
8 effect, you wouldn't expect these patients to get
9 better with very localized treatment.

10 If they are bladder-centric patients with
11 Hunner's lesion in the bladder with pelvic-floor
12 discomfort, they get better with pelvic-floor
13 physical therapy. But they are these top-down
14 people, too. So there's a top-down, bottom-up, and
15 there is overlap because there is interaction
16 between the peripheral end organ to the brain and
17 central sensitization.

18 As you alluded to, I think IBS literature is
19 clear on that, is that sometimes you tune down the
20 peripheral trigger, and your central sensitization
21 or systemic manifestation do get better.

22 So I think one of the challenges here is to

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1 define the phenotypes, who is top-down, who is
2 bottom-up. And they both need to be included in
3 the clinical trials, but you need to phenotype
4 them, identify them almost a priori, rather than
5 doing it afterwards, because any single drug that
6 targets a single receptor or mechanism, if you just
7 mix in the entire group, and analyze it as an
8 entire group without some a priori power
9 calculation about the different phenotypes, it is
10 very likely going to wash out the effects in
11 clinical trials.

12 I think this is one of the reasons why a lot
13 of IC clinical trials fail because we think it's a
14 single entity, but it is really not.

15 DR. RAPKIN: I think by looking at provoked
16 vestibulodynia, we've already narrowed the focus
17 quite a bit. Our patients with generalized
18 vulvodynia in fact behave a little bit more like
19 some of the chronic visceral pain disorders.

20 With provoked vestibulodynia, unlike
21 emptying the bowel or emptying the bladder, you can
22 avoid contact with the vestibule. And in addition,

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1 the contact is generally of a sexual nature, which
2 as we know is very involved.

3 So this is a little more specific to the PVD
4 population. Otherwise, I agree with everything
5 everyone has said. And again, our most important
6 treatment outcomes do include multi-disciplinary
7 approaches, particularly addressing cognitive,
8 behavioral, and pelvic-floor physical therapy.

9 DR. PONTARI: So there is data with chronic
10 pelvic pain syndrome that there is up-regulation or
11 there's evidence of central sensitization, both
12 efferent and afferent from University of
13 Washington. I agree. It's hard to avoid some of
14 the triggers. You're not going to not have sex or
15 urinate, so it's harder to avoid those.

16 One thing we're trying to do with the MAPP
17 and education with the urologist is first to
18 realize that people have other syndromes. I mean,
19 people walk in with just prostate, but it's like,
20 you have to ask about the bowel, rheumatologic
21 stuff. So part of it is training people with all
22 those other -- and then making appropriate

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1 referrals, and trying to get the rest of the person
2 treated as well.
3 DR. LEMBO: I think I echo what everybody
4 says. Clinically, we do look for patients, try to
5 identify patients with the other chronic pain
6 syndromes. As gastroenterologists, we focus on the
7 bowel, but we do treat those patients differently,
8 because we do feel that it does take a multi-
9 disciplinary approach.
10 We've found that, through some research
11 work, those patients with -- actually, we call it,
12 extraintestinal because we're GI focused --
13 extraintestinal manifestations tend to have much
14 more anxiety and depression. And oftentimes, at
15 least in some modeling, it seems like the anxiety
16 and depression is driving a lot of the
17 extraintestinal symptoms. So we try to treat those
18 as aggressively as we can. And I think everybody
19 it sounds like is doing the same thing, looking at
20 the top-down or bottom-up approach.
21 So we tend to use a lot more of the
22 centrally active drugs, but I think it's a great

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1 point.
2 DR. KATZ: So I guess, for Bob and for
3 Dennis, who are managing this meeting, I guess the
4 question is, if we end up in this meeting without
5 proposing some kind of measure for this central
6 sensitization that is common across all these
7 syndromes as a way of classifying the patients when
8 they come into the study and as a way of measuring
9 their outcome, have we really done our job here if
10 we just focus on what's happening in the end organ?
11 DR. PONTARI: How do you measure central
12 sensitization?
13 DR. BRUEHL: This is Steve Bruehl. I'm just
14 going to ask a related question to that. So what I
15 hear from I think every single panelist is that
16 every one of the conditions discussed is
17 heterogeneous. There appear to be subtypes. It
18 seems like everybody agrees there are certain
19 subtypes that are top-down and implying some type
20 of central sensitization.
21 For us, the only effective way to measure
22 central sensitization in the laboratory is temporal

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1 summation protocols. And I'm not sure clinically
2 whether that is practical to do that, but I know,
3 under the right conditions, they're reasonably
4 reliable; intraclass correlation about 0.7 or so,
5 which is not spectacular, but it's adequate.
6 I'm wondering whether, as a clinical
7 assessment, if anyone has ever attempted to do that
8 routinely and looked at what effect that might
9 have. Now, I just would mention as an aside, we've
10 been doing this, been working with an urologic
11 surgeon who's interested in overactive bladder
12 syndrome, which by definition is not pain. We're
13 actually seeing central sensitization elevated in
14 that group compared to controls as well.
15 I just wanted to throw that out there as an
16 assessment methodology. I'm just curious to see
17 what people's experiences are with that.
18 DR. PONTARI: I think Pat Fitzgerald did
19 that in IC. Quentin, you can correct me if not.
20 I'm sure that that happens in some patients with
21 interstitial cystitis, that you see that summation
22 effect. That's the only study that I know. You

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1 may know some others.
2 DR. CLEMENS: I think the NIH right now has
3 convened a group to try to examine this I guess
4 from the clinical standpoint, and the concept is to
5 develop a standard review of systems. So one way
6 to do it is something like there's a CMSI, which I
7 think was Complex Multi-System Inventory that was
8 developed at University of Michigan.
9 I think that's being used as a template
10 where each of the various groups is providing input
11 to that and adjusting it, but the concept would be
12 in a clinical trial or potentially from a clinical
13 standpoint you administer that and can capture in
14 an IBS patient, for instance, a standardized
15 assessment of bladder symptoms or vulvodynia
16 symptoms, et cetera, and use that from a clinical
17 standpoint, and also use it, let's say, in a
18 clinical trial to maybe look for a signal; hey,
19 this drug worked well for my condition and it looks
20 like their IBS symptoms got better.
21 So that's one potential way as long as it's
22 short enough to potentially be used for clinical

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1 purposes to be a surrogate for central
2 sensitization based on the presence of widespread
3 symptoms.
4 We're doing that in the MAPP. The other
5 thing that we're doing is a body map, which may be
6 even a simpler, more clinically useful way where
7 patients can just put a check mark on where it
8 hurts. And we're examining constructs related to
9 number of sites versus pain severity of those sites
10 and seeing -- in the MAPP, we're doing
11 this -- whether pain severity is an important thing
12 to measure or just number of sites.
13 But those are a couple different ways where
14 it might be measured clinically and adaptable to
15 clinical care and also of course for research.
16 DR. PONTARI: And Steve Hart's doing the
17 pain sensitivity test, too --
18 DR. CLEMENS: The sensory testing.
19 DR. PONTARI: -- the thumb crusher, where
20 you're trying to see where you are on the pain
21 sensitivity scale, too.
22 DR. LAI: I think it would be useful if you

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1 could use some kind of QST, quantitative sensory
2 testing. It could be something complicated or
3 something as simple as a pin prick to look for a
4 temporal summation as a surrogate measure, central
5 sensitization.
6 I think it would be useful to investigate,
7 to see if what you see in QST might predict a
8 certain response to certain centralized systemic
9 treatment. I just don't think there's any data for
10 IC or CP at this point to guide treatment. I don't
11 think it's even looked at as a possibility.
12 The other thing, like Quentin mentioned,
13 there's a body map. People who check a lot of pain
14 sites throughout the body, that could be a
15 surrogate measure of increased sensitivity and
16 perhaps would correlate with what you see on
17 quantitative sensory testing.
18 So that could be even a potentially more
19 practical approach to identify these people with a
20 top-down syndrome.
21 DR. WESSELMAN: Next is Bob.
22 DR. DWORKIN: So if I were to do a

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1 pregabalin trial, I might predict that temporal
2 summation would improve versus placebo, and I would
3 predict that pain would improve versus placebo.
4 But would you guys predict that -- and then this is
5 the top-down question -- that pregabalin would
6 improve the urinary or defecation symptoms?
7 DR. CHEY: Not necessarily, and therein lies
8 the problem. I will say I think FDA was wise to
9 provide some guidance for drugs aimed at single
10 items, because there are clearly situations -- pain
11 is probably the one that's most obvious -- where
12 there will be drugs that largely target pain, and
13 you just want to make sure that they don't make the
14 other symptoms worse.
15 But no. I think that, mechanistically,
16 there are lots of examples you could come up with
17 where you might only affect diarrhea, constipation,
18 or abdominal pain.
19 DR. LAI: Doesn't the CP trial show that it
20 improves urinary symptoms?
21 DR. PONTARI: Right. So again, the
22 secondary outcomes are only people complaining, but

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1 it did show that. And I would say, in some people,
2 I would expect it. And the question is, is pain
3 and urinary coming from the same thing? That's the
4 question. If the urinary symptoms are coming from
5 pain, which I think they are in some people, I
6 would expect it to improve urinary symptoms in some
7 people.
8 DR. DWORKIN: Urinary pain or frequency?
9 Frequency?
10 DR. PONTARI: Right. When we say urinary,
11 we mean frequency and urgent -- well, then there's
12 painful urgency. So pain, period, urinary symptoms
13 as a separate thing, I would expect, yes, in some
14 people.
15 DR. LAI: At least with interstitial
16 cystitis, a lot of urinary habits that you're
17 seeing is driven by pain. The reason they go to
18 the bathroom every 30 minutes is because when the
19 bladder fills up and the visceral organ gets
20 distended by the urine, they start feeling pain.
21 So they're going to the bathroom every
22 30 minutes, every hour, to relieve the bladder, to

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1 decrease pain. So if you can improve the pain,
2 this could be a secondary thing that you could see
3 in terms of improving the frequency or urgency.
4 That also drives to the point perhaps you
5 need to look at them separately. Using the
6 composite score is fine, but if you track them
7 separately, you may see a stronger signal of what
8 is actually happening here.
9 DR. WESSELMAN: Next is Andrew.
10 DR. RICE: Thank you. Coming from a
11 neuropathic pain background, I get a slight
12 hypertensive crisis every time I hear the word
13 "central sensitization." It seems to me it's
14 something that came from observations made by
15 Clifford Woolf and others about a very short-lived
16 phenomenon that occurs in experimental rodents for
17 few tens of seconds and both in the musculoskeletal
18 area and I'm hearing in this area. It almost crept
19 in as a kind of diagnosis, and then people start to
20 infer mechanisms, and therefore probably drug
21 targets from it.
22 Certainly, in the neuropathic pain

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1 community, there's been a lot of kickback against
2 that. One of the most aggressive arguers about it
3 has been Pierre Hanson [ph]. And I kind of go
4 along with his approach, but I don't necessarily
5 take it to the extreme he does.
6 To define it on the basis of altered
7 sensitivity is not adequate because that can easily
8 be a primary sensitization. And any form of
9 sensory profiling -- and maybe Ralph has a
10 different view -- can't really define central
11 sensitization and certainly can't start to describe
12 neurologic mechanisms to that pain.
13 So if one thing that comes out of this for
14 your community is some agreement on what you mean
15 by central sensitization, and how you should
16 measure it, and what is reasonable to imply from
17 it, and what is not reasonable, as stated, to imply
18 from it to me would be a valuable thing. But it's
19 a term we hear bandied around a lot, particularly
20 in the therapies community, without sometimes
21 people thinking exactly what they mean by it.
22 I don't know if I'm being unreasonable or

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1 not, but that's my view.
2 DR. WESSELMAN: Has anybody a comment
3 directly to that? Yes? Go ahead.
4 DR. BARON: Perhaps I should comment on this
5 because you addressed me personally.
6 (Laughter.)
7 DR. BARON: I'm a strong believer that there
8 are some, but very few, measures in QST, in
9 quantitative sensory testing, which clearly are
10 indicative of a problem we call central
11 sensitization, whatever this is. And there are
12 some items which we assess and measure in our
13 testing protocol, which are clearly only present in
14 patients with an insensitivity. And I think if you
15 reduce your assessment tools to these few parts of
16 the protocol, I think you have an idea about
17 central sensitization.
18 DR. RICE: Are you confident that those
19 tools differentiate between peripheral
20 sensitization?
21 DR. BARON: Yes.
22 DR. RICE: You're talking about --

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1 DR. BARON: If I'm talking about pinprick
2 hyperalgesia and dynamic allodynia, for example,
3 you can measure these abnormalities in a remote
4 area, even in a patient with visceral pain. For
5 example, in head zones, you can find signs of, yes,
6 desensitization. So it really is indicative of a
7 central process, not a peripheral process.
8 DR. RICE: Would it be useful, therefore, to
9 define appropriate sensory tests for this group?
10 DR. BARON: What shall I say? Yes.
11 (Laughter.)
12 DR. RICE: They don't have flat skin that we
13 have the luxury of in most of our conditions. They
14 have difficult-to-access areas of the body.
15 DR. BARON: Well, but I'm talking about
16 remote areas like head zones, where you have remote
17 pain -- any groups. I think even Cathy is doing
18 some QST in these areas.
19 DR. RICE: I still think it'd be useful to
20 define what central sensitization is in this
21 context.
22 DR. BARON: Right.

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1 DR. RICE: It'd be a big progress.
2 DR. WESSELMAN: Sharon was first.
3 DR. HERTZ: I was just interested in hearing
4 a little bit about some of the genetic phenotyping
5 in the vulvodynia. This work that's being done, is
6 there any cross-talk for the different syndromes in
7 terms of that type of work and any common findings?
8 DR. RAPKIN: I think that just the
9 beginning, most of the large ongoing studies now
10 have been collecting material for genetic study.
11 But the current polymorphisms are usually
12 hypothesis driven. So for example, in some of
13 David Foster's work, what he's looked at, are
14 alterations in the way inflammation related to
15 candida infection has been looked at.
16 In these studies having to do with oral
17 contraceptives, there are alterations in genes
18 relating to the androgen receptor. So I think
19 unfortunately right now, they're hypothesis driven.
20 But looking overall at gene-wide association
21 studies, not a lot yet.
22 DR. PONTARI: So in MAPP, we have a genetics

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1 group, and we started out and identified a bunch of
2 candidate, SNPs, whatever it was. And then Dan
3 Clauw went to the folks who are collaborating with
4 the University of Michigan and said, "Well, if you
5 have less than 100,000, we're not going to do it,"
6 because we really don't have the numbers needed to
7 do that, and that's where we are.
8 A lot of little studies have identified a
9 lot of interesting things, but we don't have enough
10 patients to do a meaningful study at this point.
11 DR. WESSELMAN: Roger?
12 DR. WIEDERHORN: I have a question for
13 Dr. Pontari and for Dr. Lai, and that is that
14 Dr. Lai identified classical IC pain as
15 bladder-centric, which to me means visceral.
16 Painful bladder and for various gradations of
17 chronic prostatitis, is there any somatic
18 component? Is there any way to distinguish
19 visceral versus somatic in either of these two
20 conditions?
21 DR. LAI: I think that's really one of the
22 things that the MAPP study wanted to look at,

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1 because there's a realization that it could be a
2 visceral disorder in some people and the
3 realization that there could be systemic
4 manifestation in some patients. I think we need to
5 distinguish those two groups. I'm not sure you
6 would want to call them two different disease
7 conditions.
8 I mean, if you're going to say, well, all
9 the risks are going to be called interstitial
10 cystitis and study that way, and all the systems
11 and potential overlapping conditions, it's all
12 going to be called BPS --
13 DR. WIEDERHORN: Right. No, I agree.
14 DR. LAI: -- I'm not sure is the right path.
15 DR. WIEDERHORN: Yes. But is there a
16 component of each in some of these patients, or is
17 one all -- like for IC with a Hunner's ulcer, maybe
18 it's more likely to be visceral, less likely to be
19 somatic.
20 DR. LAI: I think at least I'm aware of two
21 papers where they compare patients with Hunner's
22 lesion versus one without Hunner's lesion, and they

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1 looked at different things. I think there are some
2 slight differences in the urinary frequency, how
3 often they go to the bathroom, and nocturia, how
4 often they go to the bathroom at night.
5 There are some demographics differences in
6 terms of men versus women. Men are more likely
7 going to have Hunner's, for example. And the ones
8 with Hunner's lesion tend to be older, probably at
9 least a decade older. We're actually doing the
10 same study, hopefully have a third paper in this
11 area.
12 We also look at systemic syndrome because
13 that really is the question. Do people with
14 Hunner's lesion have systemic manifestation? Do
15 they have somatic symptoms? And I think the answer
16 is yes.
17 We see, at least in the population that
18 we're studying, and we haven't published, is the
19 people with Hunner's lesion do have irritable bowel
20 syndrome, but less likely, statistically less
21 likely.
22 So you could make an argument they are

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1 statistically or maybe clinically less likely to
2 have systemic manifestation among the ones with the
3 visceral syndrome, but again, it's not going to be
4 a clear-cut line. You don't. It's not
5 zero percent.
6 DR. WIEDERHORN: But I was thinking mainly
7 of a pelvic-floor disorder as opposed to a prostate
8 disorder or bladder disorder manifesting pain, and
9 is there any way of differentiating that or no?
10 DR. PONTARI: I didn't used to believe in
11 pelvic-floor dysfunction, but now I do because
12 people get better with therapy. And if somebody
13 can help us with diagnosis, that would be great.
14 It's hard. I mean, you can go in, you can palpate,
15 and things like that.
16 Clearly, there are people who respond very,
17 very well to pelvic-floor physical therapy. People
18 will come in who we think -- pain with ejaculation,
19 you think, all right, you're contracting the
20 muscles, and this is probably pelvic floor. And
21 pelvic-floor spasm can give you pain at the tip of
22 the penis characteristically, so the answer is yes.

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1 I think what's hard is an objective measure
2 of that, which someone knows more -- I'm sure
3 happens in other syndromes, too, I would imagine
4 with IBS and probably vulvodynia.
5 So do vulvodynia patients get better with
6 pelvic-floor PT?
7 DR. RAPKIN: Yes, certainly quite a large
8 number do. It's one of the most effective
9 modalities. But the actual measurement of the
10 algia -- we have a vulvalgesiometer that I know
11 Frank Tu is also using.
12 Ours has not functioned in the last 6
13 months, and the individual who created it can't
14 seem to fix it. We have the issue that you have to
15 have some sort of a pressure sensor covered by a
16 glove and go and transduce through a computer
17 system. It's not like using a von Frey hair or
18 something like that.
19 DR. LEMBO: It's interesting that in the GI
20 world, we've used pelvic-floor therapy for
21 constipation. And there are lots of studies
22 showing that if you do sphincter retraining, with

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1 or without manometric or balloon expulsion,
2 documentation, patients tend to do pretty well with
3 it. And it's increasingly recognized in IBS.
4 Bill, I don't know if you knew of any data
5 with pain associated with it. We know that the
6 defecatory part tends to get better, but I'm not
7 sure about pain.
8 DR. CHEY: Yes. We published a paper on
9 this, actually, and there are actually two papers
10 now that show the exact same thing. And that is
11 that patients with constipation-related symptoms
12 who undergo anorectal manometry or defecography and
13 have evidence of outlet obstruction constipation,
14 who then undergo physical therapy and biofeedback
15 training, for many years, as Tony alluded to, we've
16 accepted that those patients' constipation symptoms
17 get better. But it's really interesting that the
18 abdominal pain and bloating get better in a subset
19 of the IBS patients.
20 So if you look at, for example, scores using
21 the PAC-SYM, which is a validated instrument in
22 assessing constipation that looks at bowel

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1 symptoms, rectal symptoms, and abdominal symptoms,
2 PAC-SYM scores for all three domains actually get
3 better with physical therapy and biofeedback
4 training.
5 I think of it this way. I look at it this
6 way, which is that, again, I think we have a
7 tendency to want to oversimplify things, so we
8 think of it as just top-down or just bottom-up, and
9 it's not. Most of the patients have both, and the
10 peripheral problem is an important trigger for the
11 visceral hypersensitivity, if you will.
12 DR. LAI: Just to respond to Rog, there are
13 some IC patients who have pelvic-floor tenderness,
14 and I think in fact probably 70, 80 percent of the
15 people do. There are some IC patients who do not
16 have pelvic-floor tenderness, and there are
17 patients with pelvic-floor tenderness without any
18 bladder symptoms.
19 So I think as part of the clinical
20 assessment and moving forward for clinical trial,
21 we need to assess the pelvic floor in patients with
22 interstitial cystitis. In fact, if you took the

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1 interstitial cystitis clinical trial and look at it
2 globally, the one trial that will show positive
3 results in a randomized controlled trial is to take
4 the IC patients, identify those that have
5 pelvic-floor tenderness, and subject them to
6 physical therapy of the pelvic floor.
7 That particular group of patients have
8 positive results in a randomized controlled trial.
9 So that shows you the power of phenotyping, and
10 narrowing your subgroup of patients, and targeting
11 to the potential cause because if you just mix in
12 everybody else, I think that would be a negative
13 trial.
14 DR. BUTTERFIELD: Noam Butterfield of
15 Vancouver, Canada. This is also a question for
16 Dr. Pontari and Dr. Lai. We hear a lot about the
17 heterogeneity and CPPS and IC/BPS, but also the
18 overlap between the diseases.
19 So if either of you are a PI, and you have
20 two different studies, and one's an IC/BPS study
21 and one's a CPPS study in males, which study would
22 you put your males into?

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1 DR. PONTARI: That's why we came up with the
2 term UCPPS, in all seriousness, because the NIH had
3 the ICDB, interstitial cystitis database. There's
4 a CPCRN. We had one guy at Temple who was in both.
5 It's all symptom based.
6 DR. LAI: I think the majority of the males
7 will qualify for both criteria. If they're somehow
8 arbitrary, there are two different entry criteria.
9 DR. PONTARI: Right.
10 DR. BUTTERFIELD: What are the
11 differentiating criteria that -- if you were
12 designing your own protocol, would you say we can't
13 have two separate protocols because it's the same
14 disease? Because clearly, they currently have
15 different nomenclature and they still have slight
16 differences. But what would you define as those
17 key characteristics that would differentiate
18 between the two?
19 DR. PONTARI: The entrance criteria for MAPP
20 is men and women. I'm trying to think of the MAPP
21 criteria we showed.
22 DR. CLEMENS: I think there are some men

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1 who -- I think the answer I might give is the
2 presence of significant bladder symptoms if you're
3 trying to differentiate between a male with IC
4 versus classic CPPS.
5 There are some men who have chronic perineal
6 pain. They have no urinary symptoms at all. They
7 just hurt down there in the perineum. They would
8 probably not meet criteria for IC. They wouldn't.
9 And the traditional thought has been that most of
10 the men with chronic pain have minimal urinary
11 symptoms. And what we're finding in the MAPP study
12 is that the rate of these urinary symptoms is more
13 than we thought.
14 What we're not getting at necessarily with
15 the analysis is that I think a fair number of these
16 men actually have perineal pain and ejaculatory
17 pain as what's driving the care seeking, and their
18 urinary symptoms of, oh, by the way, but not
19 necessarily something that would cause them to see
20 the doc.
21 So you could look more closely at that, and
22 really I think it's the severity and bothersomeness

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1 of the urinary frequency and potential bladder pain
2 that would discriminate there.
3 DR. LAI: A distinguishing feature would be
4 like Quentin said, do they have urinary frequency
5 and urgency out of the ordinary? Does the pain
6 that they're describing get worse when the bladder
7 fills up, and does it get at least temporarily
8 relieved when the bladder empties?
9 So those are potentially the distinguishing
10 criteria. I don't think the pain criteria really
11 sets you apart.
12 DR. PONTARI: No. The question is whether
13 you want the frequency or not. There are IC trials
14 now where you get men and women. It's the same
15 thing. And you're asking for pelvic pain. You're
16 not asking for actual prostatitis, inflammation,
17 BPH stuff. That's a different thing. It's just
18 whether you want to look at urinary symptoms or
19 not.
20 I don't even know if we know the clinical
21 significance right now of the guys with the bladder
22 pain versus not because we just found it like a

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1 couple years ago. We weren't looking for it for
2 20 years. So we're not even sure -- actually,
3 there were women, too.
4 Twelve percent of women in the MAPP, in your
5 study, didn't have bladder symptoms. These are
6 people we might think have urethral syndrome,
7 whatever it is. We think these are pelvic floor.
8 So 25 percent of men and 12 percent of women have
9 no bladder symptoms on the MAPP, but they have
10 pelvic pain.
11 DR. CLEMENS: I have a question for Bill. I
12 was interested that new Rome criteria get rid of
13 discomfort. So for IC patients, no matter how much
14 we try, sometimes we can't get them to say they
15 have pain. It's pressure or discomfort. There is
16 something causing them to urinate every half an
17 hour.
18 So I guess from the standpoint of -- I don't
19 know; we talked about hurting at the beginning.
20 We've moved in the opposite direction in the IC
21 world, where we very much encourage the inclusion
22 of discomfort as part of their criteria. This goes

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1 along with the concept that we have identified pain
2 and urinary symptoms as kind of separate constructs
3 that track differently.
4 So what tends to be concerning sometimes is
5 when there's a drug study or any intervention that
6 requires a pain level of a certain amount for IC,
7 you're excluding quite a number of patients who are
8 extremely bothered by what's called non-painful
9 urinary frequency. And I think what we're moving
10 to is the concept of dual outcomes and trying to
11 stratify based on those types of symptoms so that
12 discomfort is allowed, pain not necessarily as long
13 as they have severe.
14 So I guess to comment about the question,
15 what about a person, do they exist, who defecate
16 all the time but don't have pain, and they don't
17 have any other types of symptoms? I mean, I would
18 think that would be IBS, and yet, by the Rome
19 criteria, they don't meet those criteria. So do
20 they exist or how do you handle them?
21 DR. CHEY: This is a totally fair question.
22 And I think the answer is just realize that Rome

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1 really has created criteria for disorders mouth to
2 anus. So in other words, there's a diagnosis,
3 functional diarrhea or functional constipation,
4 where patients can have only constipation or
5 diarrhea and not have pain criteria that would
6 satisfy the diagnostic criteria for IBS.
7 I actually agree with you a hundred percent.
8 In all of our trials, we always measure discomfort
9 as well, but we measure them separately, so we
10 measure pain and discomfort separately. On the
11 basis of the criteria, we do have a minimum
12 threshold for abdominal pain. It's not just to
13 fulfill the definition for IBS. It's a practical
14 issue around being able to measure change.
15 Obviously, if a person has a mean worse pain
16 score of 1 or 2, it's going to be really hard to
17 measure a statistically significant change with an
18 intervention. So what we've figured out over time
19 is that that minimum standard, if you really want
20 to do an assessment for pain, is probably that
21 level of that threshold of 3.
22 DR. WESSELMAN: Does anybody have a specific

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1 comment to this question still, or are these new
2 items to be -- yes?
3 DR. EDWARDS: Yes, if you don't mind if I
4 follow up on that. Rob Edwards from Brigham and
5 Women's. It strikes me there's an interesting
6 potential disconnect between the pain we think
7 these patients experience and how we measure it.
8 So it sounds like we're talking about largely
9 intermittent and provoked pain for these folks.
10 The Rome criteria for IBS indicate that I
11 think you only need to have pain related to
12 defecation one day a week or more; correct? With
13 vulvodynia, certainly there are ways that people
14 can avoid provoking pain in the vestibular and
15 vulvar regions. With prostatitis, presumably
16 people can reduce ejaculatory events if they've got
17 major post-ejaculatory pain.
18 So a lot of our pain assessments do things
19 like what you see up there on the screen and look
20 at the worst abdominal pain in the past 24 hours.
21 So that seems like it would work for some
22 conditions like fibromyalgia, which is one of the

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1 things that I study. But for people with IBS or
2 vulvodynia, who are only having intermittent pain
3 episodes and maybe only a couple of times a week,
4 which is all it takes to meet the criteria for
5 these conditions, is this a problem that we're
6 measuring pain in this way; in other words, that
7 we're measuring intermittent pain with questions
8 about average pain in the last 24 hours, when
9 potentially, patients haven't had any of those
10 pain-provoking events?
11 DR. CHEY: Yes, it's definitely an inherent
12 problem, the conditions like IBS. And probably
13 interstitial cystitis, I imagine, is the exact same
14 way. I don't know of a better way to do it.
15 That's the problem. I take all of your comments.
16 I think you're spot-on in all of your comments.
17 But unfortunately, I'm not sure there is another
18 way that I'm aware of to really do it. People have
19 toyed around with things like, for example, pain on
20 only the days that you have pain, for example.
21 Like for example, the bowel-related criteria
22 is interesting. One thing I didn't mention to you

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1 is it's greater than 25 percent with diarrhea or
2 constipation of IBSC or IBSD, but Rome IV went to
3 only for when you're having abnormal bowel habits.
4 It used to be that you had to have 25 percent
5 overall.
6 So in a way, we kind of addressed that a
7 little bit when we most recently revised the
8 criteria. But I totally take your point. I'm not
9 sure that I know of a better way to do it, though.
10 DR. DWORKIN: If I'm understanding
11 correctly, a patient who had 2 days in the past
12 week where their worst abdominal pain was 7,
13 they're not going to meet your criteria because
14 their weekly average is 2. And yet they've had 2
15 really bad days.
16 DR. CHEY: That's right.
17 DR. DWORKIN: So the answer perhaps is what
18 you said, that you only take the average of the
19 days when they had pain, and you don't include in
20 the denominator the days where they were pain-free.
21 DR. CHEY: You can definitely do that. You
22 can definitely do the post hoc analysis. For

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1 example, we routinely will do that. We'll look at
2 that. And the good news is, the drugs that work
3 for that overall pain measure, the way we currently
4 do it, are also responding. You know what I'm
5 saying?
6 But to your point, there are definitely some
7 patients that don't make it into the trial because
8 they don't meet the threshold. And I think it's
9 largely a pragmatic issue about just being able to,
10 again, measure a change. But I take your point.
11 And the thing is, you can definitely do a post hoc
12 analysis to look at that very point.
13 DR. DWORKIN: You could if you entered that
14 patient in the trial. The patient who had two 7s
15 and 5 0s, you could show change because your
16 treatment could in fact take those 2 days of 7 pain
17 and, after 8 weeks of treatment, he can now
18 have -- he or she -- 3s.
19 DR. CHEY: Good point. It's an interesting
20 proposition. I don't think that we have really
21 discussed that specifically, but I think it's a
22 point that's worth discussing.

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1 DR. WESSELMAN: Is there a comment to this
2 question?
3 DR. LEMBO: Ursula, can I comment? I need
4 to take this a little further. So this leads to
5 the question that we're only measuring, as you
6 indicated in your talk, intensity. In this case,
7 the FDA has said the worst abdominal pain, which is
8 kind of an interesting change that occurred for us
9 because prior studies just measured abdominal pain,
10 said rate your abdominal pain.
11 When the FDA required us to switch to worst
12 abdominal pain, we were actually in the middle of
13 the linaclotide trials going from phase 2b to
14 phase 3.
15 Now, remember there was a lot at stake for
16 the company by switching that one word, and we were
17 quite nervous about it because we had no idea how
18 people would respond. We had never asked. And it
19 turned out that the responses were almost
20 identical. So it means that most patients just
21 used the word -- interpreted their pain as being
22 the worst pain. That's the way we read it.

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1 But the question you brought up earlier,
2 Bill, is we're only measuring intensity. We're not
3 doing frequency, duration. There are all these
4 other components, bothersomeness, that we don't
5 include and should we include.
6 I'll just say one other thing, which is
7 that, for years, we did bothersomeness. We did
8 intensity and bothersomeness, two big components,
9 and we found that patients actually responded
10 identically, at least the IBS patients. And we
11 actually tried to move the questions apart in
12 different parts of the questionnaire, and it didn't
13 seem to matter, so we dropped it a while back.
14 Do you have comments? Should we add these
15 to our --
16 DR. CHEY: I think bothersomeness is
17 definitely more of a global kind of assessment, but
18 I do really wonder about this issue about, for
19 example, frequency, in addition to intensity. And
20 in a way, since you have the diary data and you
21 know whether somebody reported zero, you do have
22 that in a way. It's just not formally assessed

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1 because the way we're doing it now is worst
2 abdominal pain.
3 So somebody might have 4 really intense
4 episodes of pain in a day, but you're only going to
5 capture that one parameter, one aspect of the pain;
6 so actually, reading more about this and thinking
7 about this in the lead up to this meeting, and
8 feeling more and more like we would actually
9 benefit from a little bit more of a deeper dive in
10 regards to measuring pain and understanding how our
11 drugs affect pain, different aspects of pain.
12 DR. LAI: Do you think the frequency or the
13 intensity of what you call the IBS attack or maybe
14 in IC what we would call flares, would that be a
15 potentially meaningful outcome to look at, how
16 often you have the attacks and how intense is an
17 attack compared to your baseline?
18 DR. CHEY: Yes, I think it might be. I
19 think that's an interesting hypothesis that remains
20 to be tested. The other thing that we've learned
21 from our recent work is this difference between
22 subgroups. I mean, patients' experience of pain is

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1 really different in the IBSC versus the IBSD group,
2 for example, and that's something I think we're
3 just really starting to understand.
4 The D patients have pain around their bowel
5 movements. So they get pain; they have to go to
6 the bathroom. That's typically what happens. The
7 C patients have this pain all the time. They feel
8 uncomfortable, full all the time.
9 So it's very different. It's not universal,
10 but from a pattern recognition standpoint, their
11 experiences are really quite different.
12 DR. TURK: The frequency included in that
13 definition, essentially, your second bullet is in
14 fact a frequency measure, so you have both
15 intensity and a frequency.
16 DR. CHEY: But that's for stool as opposed
17 to pain, yes.
18 DR. TURK: Right. But you are looking at
19 the frequency of the symptoms that are related to
20 the condition.
21 DR. CHEY: Well, the frequency of bowel
22 movements, yes.

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1 DR. PONTARI: Is there any IBS equivalent to
2 where you have different locations pain? Are there
3 different locations like low quadrant left, you
4 know, rectal things? Do you guys have that?
5 DR. CHEY: Yes. So there's been a whole
6 bunch of studies looking at that. And the common
7 theme from the studies is that the largest
8 proportion of IBS patients have pain in the left
9 lower quadrant, but that's probably only about
10 half. And then the other half have pain all over
11 the place, like upper abdomen, lower abdomen.
12 You'll notice in the Rome criteria, it does
13 not distinguish on the basis of location. What's
14 interesting is if you look at the qualitative work
15 by Brennan and Lin Chang's group at UCLA, it's
16 interesting, though, that patients have these
17 attributions like left lower quadrant pain, they
18 say I have colon pain, or upper abdominal pain,
19 they say I have stomach pain or esophagus pain.
20 So it's interesting. The patients attribute
21 the location of the pain to some anatomical
22 attribution, which of course may be completely

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1 wrong, but that's how they think about it.
2 DR. WESSELMAN: Kathy, was that related to
3 this topic? Yes.
4 DR. VINCENT: I have two points. One is
5 that if we're thinking about women with any of
6 these conditions, they often have a cyclicality to
7 their pain no matter what the underlying cause is,
8 and I'm not sure how we capture that. I don't
9 think we capture it very well.
10 We're currently running a trial looking at
11 gabapentin and chronic pelvic pain with no
12 underlying pathology. And one of the things that
13 we did as we were preparing for that was surveying
14 patients as to whether they were more interested in
15 their average pain being reduced or their worst
16 pain. So was it worse for them, the amount of pain
17 they had in general, or were the really bad days
18 worse? Fifty-four percent said they wanted their
19 worst pain reduced and 46 percent wanted their
20 average pain reduced.
21 (Laughter.)
22 DR. VINCENT: So it's an NIH all-funded

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1 study. We ended up with going dual outcomes of
2 worst and average pain, but our statisticians
3 aren't very happy with that for how to analyze it.
4 DR. CHEY: By the way, that's almost
5 identical to the data we have in IBS, like almost
6 identical. So to your point, the majority say that
7 worst pain is most meaningful, but a whole bunch
8 say yes.
9 DR. WESSELMAN: Was there a correlation to
10 the number of comorbidities or the types of
11 comorbidities for those two almost identical
12 subgroups by number?
13 DR. VINCENT: That was literally just a
14 quick patient survey on a website in order to
15 answer that question of what we should be using for
16 our primary outcome. When we actually come to
17 analyze at the end of the trial, then we'll look at
18 that.
19 DR. WESSELMAN: Ian?
20 DR. GILRON: Ian Gilron from Queens
21 University. There's already been a lot of
22 discussion about overlap among symptom-based

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1 conditions like IC, fibromyalgia, migraine. And in
2 terms of trial methodology at least, I know from
3 neuropathic pain, generally we try to exclude
4 competing pain conditions.
5 So if you're trying to enroll somebody with
6 diabetic neuropathy, and their average pain is 5
7 out of 10, and they've got osteoarthritis of the
8 right knee, and it's on average 7 out of 10, we
9 would tend to exclude them because of potential for
10 misattribution of pain and pain intensity.
11 So I'm just wondering, whether for our
12 recommendations whether we need to consider -- or
13 first of all what has been the experience with
14 trial recruitment with overlapping pain. Do you
15 just turn a blind eye? They have coexisting
16 fibromyalgia. Do you just forget about that, or
17 how do we address that in clinical trial enrollment
18 in symptom-based pain conditions?
19 DR. PONTARI: I've got a question for you.
20 So from an anatomic standpoint, my understanding,
21 from the studies from Pittsburgh, and probably you
22 guys, and whoever else, is that there's more cross-

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1 talk between the bowel and the bladder. If you
2 inflame the bladder, you get upregulation in the
3 dermatomes, one above the other, and you get
4 bladder inflammation.
5 So I'm not sure how you could -- we don't.
6 So the first thing is we don't exclude people with
7 IBS in IC trials or prostatitis trials. So I'm not
8 even sure if that's a reasonable thing to do based
9 on the neuroanatomy as far as -- it's a little
10 different than having neuropathic diabetic
11 neuropathy in rheumatology, but because of the
12 neuroconnection, I'm not sure that's a reasonable
13 thing in this condition.
14 DR. CHEY: I completely agree. I think the
15 one thing that's happened in IBS trials, because
16 there is data to suggest that patients with
17 significant psychological comorbidity respond less
18 well to particularly peripherally-acting drugs.
19 So most people have been excluding patients
20 with significant psychological comorbidity, but I'm
21 not aware of -- Tony, do you know of any? I don't
22 think we've excluded any.

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1 DR. LEMBO: Not that I can recall, either.
2 DR. CHEY: Yes. Actually, to your point,
3 though, a more interesting thing -- and this is
4 coming out of this meeting, clearly -- is this idea
5 of deep clinical phenotyping as part of any of the
6 trials that we do. I'm really attracted to this
7 idea of getting a much more comprehensive inventory
8 of not only, in our case, the GI symptoms, but some
9 of the other symptoms that have been discussed this
10 morning.
11 I know Tony and I have suggested that, and
12 we've met with some resistance because of the
13 burden. Obviously, it's a very practical issue,
14 just the questionnaire burden, and also finding
15 things that you don't want to find out.
16 So pretty much narrowly focusing has been I
17 think the theme of the day in most drug development
18 programs. But it would be really valuable if we
19 could do a deep clinical phenotype or deeply
20 phenotype these patients to start to understand
21 these patterns a little bit better.
22 DR. GILRON: Just to get back to that, so if

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1 you had someone with chronic widespread pain and
2 maybe that was their predominant issue, but they
3 happened to come upon your trial, which was an IBS
4 or an IC trial, where do they fit?
5 I mean, should they be included in your
6 trial if their fibromyalgia -- if their upper
7 back/neck pain is equal or more severe than the
8 symptom burden related to their visceral pain? I'm
9 not trying to cause problems.
10 DR. CHEY: No, no, no. Let me just make a
11 comment on this because this raises a point that I
12 meant mention in my talk, but I forgot to. And
13 that is that one way that academic as well as
14 industry investigators have dealt with this is to
15 put a cap on the amount of pain you can have.
16 In other words, you'll notice that the
17 guidance said you have to have at least 3. Well,
18 many trials, not most trials, but many trials will
19 then just say they have to be between 3 and 7 or
20 something like that. And so if you're the kind of
21 patient you're referring to as having a lot of pain
22 all over the place all the time, those patients get

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1 excluded during the baseline period.
2 So that's one way of dealing with that
3 because, again, I think that the prevailing wisdom,
4 whether it's right or wrong, is that those patients
5 tend not to respond to certainly peripheral-acting
6 therapies.
7 DR. WESSELMAN: Chris?
8 MS. VEASLEY: Chris Veasley with the Chronic
9 Pain Research Alliance. Our organization deals
10 specifically with overlapping conditions, and we
11 have worked with industry. Industry has tried to
12 enroll patients, whether it's low back pain, IBS,
13 IC, vulvodynia, other conditions, that don't have
14 other pain disorders. The problem is that they
15 don't have enough people for the trial. So what
16 most are doing is allowing patients to have other
17 conditions, other pain disorders, but they're not
18 tracking it during the trial.
19 For example, if somebody with IC has also
20 migraine, and they're on day 15 of their trial, and
21 they have a migraine attack, that's not being
22 tracked. So that's obviously an important

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1 indicator, and it's certainly something that we
2 need to deal with because there's a huge literature
3 base showing that the more sites of pain you have,
4 the higher treatment recalcitrance you have.
5 So it has to be affecting what outcomes are
6 coming out of clinical trials, and I agree with
7 you, we need to have a recommendation as to either
8 how we handle that or how we track it, and
9 understand what the bidirectional relationship with
10 that is, just like we track mood and sleep.
11 Just going back to what Andrew said, I fully
12 appreciate the comment about central sensitization
13 because it's discussed very much in this community.
14 Really, what we're talking about is pain syndromes
15 that are driven by more CNS, more CNS-driven pain
16 syndromes with mechanisms like central
17 disinhibition and kind of what Clifford Woolf will
18 describe as dysfunctional, a category of
19 dysfunctional pain syndromes.
20 As Michel mentioned, the two patient-
21 reported outcomes or surveys that are most
22 indicative of having multiple conditions have been

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1 some measure of general widespread pain and number
2 of somatic symptoms.
3 I'm going to push the panel a little bit
4 further because my question to you is, we're
5 looking at whether improvement in organ symptoms,
6 so whether it's bowel function, bladder function,
7 and pain as pain goes down and does that improve,
8 how does that correlate with overall health-related
9 quality of life and psychosocial function?
10 I'm very familiar with the vulvodynia
11 literature, which is to say that if pain improves
12 that quality of life or function, whether it's
13 sexual function or physical function, does it
14 necessarily correlate with that? And we've
15 certainly seen in that in the general pain
16 community.
17 I'm wondering, in IC and IBS, has that been
18 studied? So if you have patients whose pain is
19 improving, their bowel function or bladder function
20 is improving, does that correlate with an
21 improvement in health-related quality of life and
22 psychosocial functioning, and is that dependent

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1 upon time? So basically patients who have new
2 onset symptoms versus those who have pain for many
3 years?
4 DR. LAI: I think they do correlate in the
5 IC literature.
6 DR. CHEY: Yes. And I think as well,
7 certainly not a perfect correlation, but generally
8 speaking, the patients that have experienced a
9 meaningful improvement in their abdominal pain are
10 the ones that tend to experience an improvement in
11 at least disease-specific quality of life.
12 I must say that, as an interesting point
13 relative to the question that you posed, our trials
14 have been very consistent in showing disease-
15 specific quality-of-life improvements. They've
16 been less consistent in showing general quality-of-
17 life improvements.
18 So I'm not familiar with specific
19 analyses -- Tony might be -- for a general quality
20 of life, but for disease-specific quality of life,
21 one of the main drivers of improvement of disease-
22 specific quality of life is pain.

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1 DR. WESSELMAN: I think first was Frank,
2 then John, and then Mark.
3 DR. TU: Thanks. Frank Tu from NorthShore
4 Health. So if you go back to the stated goals for
5 the meeting, which seems to center around this idea
6 about defining endpoints for trials for chronic
7 pelvic pain and irritable bowel syndrome, it seems
8 like there's several dichotomies that keep on
9 coming back and forth.
10 To speak specifically, this current
11 discussion, what Roger said about is there a way to
12 distinguish visceral versus somatic, it seems to be
13 one of the critical questions. And the other one
14 is this point that Ralph and Andrew have talked
15 about, about whether or not we can measure central
16 sensitization as a meaningful, stable construct in
17 patients.
18 I'm still struck by this idea that we might
19 be able to define subgroups of patients, and that
20 perhaps one of the critical things to do here is to
21 attempt to identify cleaner visceral-dominant
22 patients versus cleaner somatic-dominant patients;

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1 clinical exam. Henry's talked about pelvic-floor
2 exam. Andrew's talked about vulvar skin
3 assessment. No one's brought up things like doing
4 bladder distention or anal manometry, but those are
5 your obvious provocative measures that could
6 potentially be used.
7 Is that within the scope of what we're
8 trying to do here, to actually see if we can define
9 subgroups that would be described as being
10 responders in subgroup A versus B based on some
11 sort of a winnowing test?
12 DR. PONTARI: Frank, who can you do bladder
13 distinction for?
14 DR. TU: Your patient who's got bladder
15 symptoms, you simply can do a standardized
16 challenge on them.
17 DR. PONTARI: You don't mean a
18 hydrodistention. You mean just a bladder fill.
19 DR. TU: Drink on a consistent basis using a
20 parameter like we use at MAPP. Those are all
21 examples, but it seems like that's a critical
22 question about saying that if a person fails on a

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1 vulvodinia trial, for example, is it because they
2 never had vulvar skin sensitivity, and in fact they
3 just had muscle tightness?
4 These are not always worked out in these
5 broader trials. Typically, we'll use a cotton
6 swab. I think the vulvar trial is a little more
7 consistent in trying to define a pure subgroup.
8 But a lot of these IBS trials -- it'd be
9 interesting if, Bill, you could comment. Has
10 anyone tried to track and see if you are not a
11 viscerally sensitive IBS patient -- so you have all
12 the symptoms, but you have no meaningful anal
13 manometry results, like you can be distended up to
14 a large level and you don't display bother, are you
15 more or less likely to respond to a given drug?
16 That seems like that would be a critical question
17 on endpoints.
18 DR. CHEY: Yes. So there's not a whole lot
19 of literature on this, but there is some literature
20 on this. And the bottom line is, unfortunately,
21 visceral distention, like for example, rectal
22 balloon distension or sigmoid balloon

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1 distension -- which was really popular for a period
2 of time. I grew up doing distension studies in the
3 lower GI tract as a marker of the biomarker for
4 visceral hypersensitivity, and it turns out it's
5 not a very good biomarker for visceral
6 hypersensitivity, certainly not in terms of
7 predicting response to therapy.
8 So unfortunately, the models -- for example,
9 people for a while were doing animal studies with
10 visceral distention to sort of predict whether
11 there would be a pain response in IBS patients.
12 And at least to my knowledge -- Tony, correct me if
13 I'm wrong -- it really did not bear fruit. And
14 we've as a community now gotten away from doing
15 visceral hypersensitivity testing with balloon
16 distention.
17 Now, I'm convinced that you're right. I'm
18 convinced that the issues that you've identified
19 are at the heart of the matter in terms of trying
20 to subgroup these patients top-up/bottom-down. But
21 as I said earlier, I really think that there are
22 many patients where it's both.

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1 So it's not going to be as simple as doing
2 one thing to identify one element that's abnormal.
3 Unfortunately, I think that the patients have a
4 number of different issues, mechanistic issues,
5 that are going on, that conspire to cause their
6 symptom experience.
7 DR. LAI: Do you really think a balloon
8 distension can actually distinguish the central
9 group from the peripheral group? Because I think
10 even the central group is probably going to be
11 showing sensitivity to balloon distention.
12 DR. CHEY: Absolutely.
13 DR. LAI: And if the peripheral group does
14 so, I don't know.
15 DR. CHEY: I can tell you unequivocally at
16 this -- I shouldn't say that.
17 (Laughter.)
18 DR. CHEY: I should never say unequivocally.
19 But my interpretation of the data as it's been
20 conducted to date is that, no, it does not help you
21 to distinguish.
22 DR. RAPKIN: In the UCLA group, they found

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1 it more characteristic of women than males to have
2 hypersensitivity with balloon distention.
3 DR. CHEY: The UCLA group did find a
4 correlation between severity of abdominal pain and
5 sensitivity to visceral balloon distention, but
6 there was a lot of overlap. So the problem is
7 that, yes, there are statistically significant
8 differences, but could you use it as a biomarker to
9 distinguish between groups? Probably not.
10 Probably not.
11 DR. TU: In follow-up to that, I just wanted
12 to comment on it. It seems like with Andrew and
13 Ralph here, we can't just casually go off this
14 question of what does it mean to have central
15 sensitization in these conditions because that's
16 one of the probably biggest -- whatever that is, if
17 you say we can see it, it smells like central
18 sensitization versus something you formally define
19 with some sort of dynamic allodynia or some other
20 sort of a measure.
21 I think it's important not to mix up somatic
22 sensitivity, which the Michigan group has spent a

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1 lot of time working on, from true measures of
2 physiological central sensitization.
3 If you look at work by Steve Bruehl's
4 colleague at Vanderbilt, Lynn Walker, amongst
5 children with functional abdominal pain, there's a
6 small proportion that have very high levels of
7 somatic sensitivity.
8 If you follow them five years later, they
9 still have very high levels of questionnaire-based
10 answers, like a 50-item complaint checklist. And
11 there's something very different about that 15 to
12 20 percent that has 5 years of unrelenting somatic
13 sensitivity that is not necessarily correlative
14 with what their physiological measures on QST would
15 be, I suspect.
16 I think it's important not to drag those two
17 under the same group. It's easy to do as a
18 clinician. I try to do that every day, but I've
19 heard enough people say you can't do that to be
20 casual and say, "Somatic sensitivity is central
21 sensitization."
22 DR. CHEY: By the way -- and I suspect this

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1 would be true of the other conditions -- patients
2 that have chronic symptoms, that patient does not
3 have IBS. I mean, think about the definition.
4 It's related to defecation, associated with change
5 in stool frequency or associated with change in
6 stool form.
7 If a person just has pain all the time
8 that's unrelated to those issues, by definition,
9 they don't have IBS. They've got something else.
10 DR. WESSELMAN: We have about five more
11 minutes left, so John, you had a question, and then
12 Bob -- John, Mark. So then Bob.
13 DR. DWORKIN: I don't remember. I think it
14 might have been Michel who showed the slide of the
15 pain scale that Pfizer used in developing
16 gabapentin and pregabalin. And their wording
17 was -- was it you, Mike?
18 DR. PONTARI: It was a pregabalin trial. It
19 was our --
20 DR. DWORKIN: Yes, and that was from John
21 Farrar's article. The wording of that question is
22 very interesting. It was, "Please pick the number

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1 that best describes your pain in the past
2 24 hours." They didn't use either average pain or
3 worse pain.
4 So it seems to me that based on the
5 fascinating data that Katy just presented, maybe we
6 should go back to what Pfizer was using with
7 gabapentin and pregabalin; get rid of these weird
8 words, "average," "worst," and just ask patients
9 what number best describes their pain. And that
10 approach would have satisfied your statisticians,
11 Katy, because then you'd just have one question
12 instead of two.
13 Actually, I don't know historically how it
14 was we've now ended up with this question about
15 whether it's "average" or "worst" when we started
16 off 20 years ago with "best describes," but it
17 sounds like John's going to answer it.
18 DR. FARRAR: "Answer" I think is too strong
19 a word. I think what I'd like to do is to perhaps
20 explain that phenomenon, which is that everyone
21 describes pain differently, and we just need to
22 come to grips with its subjectivity.

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1 The issue with any scale in a clinical trial
2 is it just needs to be consistently used by the
3 person over the length of the trial. And then if
4 their pain, or whatever, is going to get better,
5 then it will be reflected by that.
6 The problem is, in conversations with people
7 who study pain in animals or who are very basic
8 science oriented, or who have a very clear
9 understanding of what it means to have acute or
10 chronic pain, or what does worst pain mean, or what
11 does average pain mean -- because it may be that if
12 you ask people about their pain without specifying,
13 some are going to answer with regards to its worst,
14 as in 58 percent, you said, or something, 56, and
15 46 percent are going to answer with regards to
16 average because that's what's most important.
17 That doesn't bother me particularly if you
18 think that the treatment that you have would work
19 for both of those instances. I think it might
20 bother you if in fact you have a treatment that
21 just gets rid of the worst pain. And the obvious
22 example of that would be something like trigeminal

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1 neuralgia, where you have these acute episodes of
2 very severe pain and nothing in between.
3 There is no right answer, I think, to that
4 question. I think that you gather information by
5 being careful about what you measure, and then it's
6 important to think about how that affects how you
7 try and interpret the results.
8 DR. DWORKIN: Sharon?
9 DR. HERTZ: Laurie Burke used to always
10 describe work that was done. Laurie Burke is
11 somebody who used to work at FDA, and she's on the
12 outside now, enjoying life.
13 (Laughter.)
14 DR. HERTZ: But she's described studies in
15 which when you look at people's report of average
16 pain and you look at people's report of worst pain,
17 the reality is, average pain pretty much skews
18 towards worst pain because if you do a patient
19 diary, and on a couple days, they're scoring 2 or
20 3, and a couple of days, they're scoring 8 or 7,
21 you can average that pretty easily. But if you
22 just ask them to think about a week and average

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1 their pain, that too is not coming to mind nearly
2 as much as that 7 or 8.
3 So the reality is, as long as whatever the
4 processing is -- sort of what John just said. As
5 long as whatever it is they're reporting is
6 consistent, it kind of doesn't matter. But we just
7 need to understand that when we ask people to
8 average their pain, that's not a skill that most
9 people can do that would reflect an actual
10 averaging of pain diary recordings.
11 DR. FARRAR: That's exactly right, and it
12 gets to this issue, which was said earlier, which I
13 didn't know that IBS actually used a global
14 question for many years, which one can argue that
15 really the question you want to ask is, overall,
16 how bad is your life or how bad is the pain,
17 allowing the person to integrate those pieces into
18 a picture. It drives people nuts if you want to
19 try and dissect it into pieces because you can't.
20 As long as the treatment that you're focused
21 on is hypothesized to affect both the worst amount
22 of pain that patients have or the average amount of

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1 pain that they have, then I think it's fine. And I
2 honestly believe that in most cases, with most
3 drugs that we're using these days, that's the case,
4 so I don't have a problem with it.
5 It is clear that patients remember worst
6 pain better probably, like on Tuesday I had a
7 really bad pain as opposed to on average. I would
8 argue, though, the other aspect of worst pain is
9 that you get a bigger response in worst pain. But
10 we looked at a nice study, and we did a nice study
11 where we looked at that. And if you actually
12 calculate the percent pain, change in pain with
13 worst and average, it's identical, at least in
14 post-herpetic neuralgia and diabetic neuropathy.
15 So I'm agreeing with you. I think what
16 we're getting at here is that pain is really a more
17 global measure than we think, and it's not
18 necessarily the connection between nociceptor and
19 the brain that we're actually measuring. We're
20 measuring more than that.
21 DR. WESSELMAN: With this being said, I just
22 got a note from Bob. So the webinar is going to

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1 start in this room at 12:00, which is basically in
2 five minutes, and lunch is next-door. So we would
3 like to conclude this session, eat, and then watch
4 the webinar, and be back here at 1:00 for the next
5 session.
6 (Applause.)
7 (Whereupon, at 11:54 a.m., a lunch recess
8 was taken.)
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1 AFTERNOON SESSION
2 (1:06 p.m.)
3 DR. SMITH: We're going to go ahead and get
4 started. So this next section that we have after
5 the lunch break is now going to focus on FDA
6 perspectives and approaches to different both
7 outcome assessments, clinical endpoint development,
8 and also how they think about three of the
9 different conditions, so prostatitis, IBS, and I
10 guess interstitial cystitis.
11 So we're going to cover those things this
12 afternoon, and then we'll have a discussion panel
13 at the end. For the most part, we're going to
14 save, again, questions, really process kinds of
15 questions, until the discussion period.
16 Dr. Wiederhorn did ask that he saved time in his
17 talk specifically for clarifying questions. So for
18 his talk, we will allow for some clarifying
19 questions.
20 So the first person I'm going to introduce
21 here is Sarrit Kovacs. She's a reviewer in the
22 clinical outcomes assessment group at FDA. So

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1 Sarrit?
2 Presentation – Sarrit Kovacs
3 DR. KOVACS: Good afternoon. So I'll be
4 presenting an FDA perspective on clinical outcome
5 assessments, and I will be presenting my
6 perspective.
7 Today, I'll be presenting four main topics,
8 the importance of capturing the patient voice by
9 encouraging patient-focused drug development or
10 PFDD; the 2016 update to the 21st Century Cures Act
11 legislation, as well as FDA flexibility in getting
12 the patient voice heard; then a roadmap to
13 selection or development of a clinical outcome
14 assessment or COA by focusing first on defining the
15 target patient population and conceptualizing
16 clinical benefit for those patients.
17 Next, I'll discuss the importance of
18 establishing the content validity of a COA with
19 evidence from qualitative research with patients to
20 ensure that the concepts of interest are being
21 assessed properly. And last, I'll describe some
22 considerations when using COAs to assess patient

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1 symptoms of pain and urgency.
2 So the patient's voice is important to
3 consider when developing patient-reported outcome
4 or PRO tools intended to assess how patients feel
5 or function. Patient-focused drug development or
6 PFDD is about engaging the patient throughout the
7 spectrum of drug development activities. And as
8 part of FDA's commitments under PDUFA V, FDA was
9 tasked with conducting public meetings with
10 patients and patient advocates focused on 20
11 specific diseases and conditions, and FDA has
12 conducted more than 20 to date.
13 Each PFDD meeting resulted in the voice of
14 the patient report that capture the patient and
15 patient advocates' perspectives and experiences
16 both from participants who attended in person and
17 those who participated via WebEx.
18 The 21st Century Cures Act was enacted into
19 law on December 13, 2016 and primarily affects
20 activities of the Department of Health and Human
21 Services and its agencies. And part of the aims of
22 the Cures Act is to increase the involvement of

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1 patients and their perspectives in research and in
2 the medical products development process. It
3 emphasizes the need for patient engagement and
4 directs the FDA to include the patient's voice in
5 drug development and review.
6 Section 3002 of the Cures Act is focused on
7 PFDD. FDA is required to publish guidance
8 documents for industry addressing the topics listed
9 here on this slide, including methodological
10 approaches to collection and analysis of COAs for
11 the purpose of regulatory decision-making. FDA is
12 also required to conduct a public workshop on COA
13 and better ways to incorporate COAs into endpoints.
14 PFDD will also aid in providing evidence to
15 establish whether treatments are in fact providing
16 clinical benefits to patients. Clinical benefit
17 can be measured directly or indirectly. Direct
18 evidence of clinical benefit is derived from
19 studies with endpoints that measure survival or how
20 patients feel and function in daily life, for
21 example using a patient-reported outcome or PRO
22 tool.

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1 Indirect evidence of clinical benefit is
2 derived from studies with endpoints that measure
3 other things that are related to how patients
4 survive, feel, or function, for example surrogates
5 or biomarkers such as endoscopic results. Indirect
6 assessment means impaired justification for its
7 value as a replacement for how patients survive,
8 feel, or function.

9 So what is a COA? A COA is an assessment of
10 a clinical outcome. It could be made through a
11 report by a clinician, a patient, an observer, or
12 through a performance-based assessment, and there
13 are four types.

14 The remainder of my talk, I'll focus
15 primarily on PROs, a type of COA based on a report
16 that comes directly from the patient about the
17 status of his or her health condition. PRO tools
18 can be administered via self-report or interview
19 and could include both a rating scale or an event
20 log such as a bowel movement or urinary frequency
21 diary.

22 FDA has developed a number of tools to help

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1 guide the development of fit-for-purpose COAs, and
2 I'll give a brief overview of the first three tools
3 listed on this slide, on my next few slides. And
4 in terms of the last two tools listed here, FDA
5 developed the 2014 Drug Development Tool, or DDT,
6 Qualification Guidance for Industry, which includes
7 information on the process related to CDER's COA
8 DDT Qualification program.

9 In 2016, FDA compiled a pilot COA compendium
10 as a communication tool for industry in an effort
11 to foster PFDD by collating and summarizing COA
12 information used to support labeling claims in many
13 different diseases and conditions. And it's
14 intended to provide clarity and transparency and to
15 be used as a starting point for early drug
16 development.

17 I'm sure some of you are familiar with FDA's
18 2009 Tri-Center PRO Guidance for Industry, and this
19 guidance defines good measurement principles to
20 consider when selecting or developing a well-
21 defined and reliable PRO measure intended to
22 provide evidence of clinical benefit to patients.

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1 The goal is to avoid labeling claims or statements
2 that may be misleading or false.

3 The Code of Federal Regulations or CFR is a
4 codification of the general and permanent rules
5 published in the Federal Register by the executive
6 departments and agencies of the federal government.
7 And Title 21 of the CFR is reserved for rules of
8 the FDA.

9 Part 314 of Title 21 relates to applications
10 for FDA approval to market a new drug, focusing on
11 adequate and well-controlled studies that include
12 methods of assessments such as COAs that are well-
13 defined and reliable, which is critical for drug
14 approval and labeling.

15 There must be sufficient empiric evidence to
16 support the COA's use in a target patient
17 population, that the COA is measuring the right
18 thing in the right way in a properly defined
19 patient population, and the COA scores accurately
20 and reliably quantify changes in patient scores
21 over time. This is important in order to be able
22 to confidently attribute patients' improvement to

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1 treatment effect.

2 All types of COAs, not just PROs, can
3 benefit from the good measurement principles
4 described within the PRO guidance. It's important
5 to note that this guidance provides an optimal
6 approach to PRO development. However, both
7 flexibility and judgment are necessary to meet the
8 practical demands of drug development and to ensure
9 data integrity and interpretability.

10 We know that not every step of the
11 instrument development and evaluation is
12 necessarily relevant or feasible in the context of
13 an individual drug development program, for example
14 pediatrics, rare diseases, and in the spirit of
15 flexibility, we are encouraging drug sponsors to
16 leverage existing data and existing instruments
17 before embarking on developing a novel COA when
18 possible and feasible.

19 So next I will present the roadmap to
20 clinical outcome assessment, selection, and
21 development. As listed on a previous slide, the
22 roadmap is one of the tools developed by FDA to aid

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1 in PFDD, and there's a link on the slide to a more
2 detailed version of the roadmap if you want.
3 This tool has been extremely instrumental in
4 helping FDA and external stakeholders to
5 systematically think through the issues that need
6 to be considered in sequence before making final
7 decisions on clinical trial endpoints.
8 So again, we recommend careful consideration
9 of column 1 and first understanding the disease or
10 condition, including the natural history and
11 patient subpopulations. Important for today's
12 discussion, we need to consider the patient
13 perspectives regarding what's most important and
14 relevant to them.
15 After this, we can move to column 2 and
16 conceptualize a treatment benefit or clinical
17 benefit by identifying the concept of interest to
18 assess and treat as well as identify in the context
19 of use or targeted patient population for drug
20 development and the appropriate COA type. Only
21 after these two columns' activities are performed
22 should one embark on identifying an existing or

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1 developing a novel COA appropriate for its specific
2 use, shown in column 3.
3 Now, we'll move on to establishing content
4 validity of a PRO tool with evidence from
5 qualitative research with patients. As listed on a
6 previous slide, the wheel and spoke diagram is also
7 another tool developed by the FDA to aid instrument
8 developers in developing COAs for use in clinical
9 trials. This is an extremely pared-down version of
10 the diagram.
11 For now, I'll focus on spoke 2, which is
12 relevant to the FDA's assessment of whether a COA
13 is well defined and reliable, acceptable to support
14 medical product approval, and suitable to support
15 labeling claims.
16 Empiric evidence should be generated
17 according to good measurement principles to support
18 the content validity and psychometric properties
19 and performance of the COA, and this is regardless
20 of whether one is using an existing or developing a
21 new COA.
22 Content validity is the extent to which the

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1 COA measures the concept of interest, and it
2 includes evidence that the items and domains of the
3 COA are appropriate and comprehensive relative to
4 its intended measurement concept, and the
5 population, and use.
6 For FDA, the most critical consideration is
7 whether content validity has been established, so
8 qualitative data supporting content validity. And
9 if that's not provided or not sufficient, the
10 agency can't review or interpret any quantitative
11 data that's submitted to support the psychometric
12 properties or performance of the instrument.
13 So establishing content validity of the PRO
14 tool requires evidence from qualitative research,
15 so focus groups, one-on-one interviews with a
16 sample of patients that matches the targeted
17 eligibility criteria for the clinical trial. The
18 qualitative research should provide evidence that
19 the tool's instructions, items, and response
20 options are relevant, meaningful, appropriate,
21 comprehensive relative to the intended measurement
22 concept and to the targeted patient population.

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1 There are some content validity
2 considerations on which we focus for PRO tools.
3 For example, are we asking the important and
4 relevant questions of the patients in the
5 assessment? Do patients consistently define and
6 understand the concepts in the way intended? For
7 example, can patients distinguish among abdominal
8 pain, cramping, discomfort in consistent waves?
9 Do they experience abdominal bloating and
10 divergent waves? Do some patients experience
11 bloating as an internal feeling of fullness or
12 tightness or, as other patients may describe it or
13 interpret it, as a physical distention or swelling
14 of the abdomen?
15 Are differences between adjacent response
16 options meaningful to patients? For example, can
17 patients meaningfully distinguish between a
18 response option of a little versus some, quite a
19 bit versus very much, severe versus very severe?
20 In other words, would a one-category improvement
21 from baseline necessarily constitute a meaningful
22 improvement to the patient?

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1 I'll now discuss the use of COAs for
2 assessment of pain and urgency in clinical trials.
3 Irritable bowel syndrome or IBS guidance per
4 industry recommends evaluation of abdominal pain
5 using the 11-point NRS, assessing patient's worst
6 abdominal pain in the past 24 hours.
7 Analgesic indications guidance for industry
8 states that pain intensity can be measured by a
9 numeric rating scale such as the 11-point pain NRS,
10 or Visual Analog Scales, or categorical scale, but
11 that there are advantages and disadvantages to
12 each, and it's preferable to use a scale that's
13 more sensitive to change and more interpretable,
14 such as a disease-specific pain measure.
15 The BPI short form, item number 3, is an
16 example of an 11-point NRS, and it's a well-
17 documented measure of pain and appears reasonable
18 for use to assess patient's pain intensity.
19 For consistency, we do recommend that there
20 are verbal anchor descriptors, at least for 0 and a
21 10 rating. And if the sponsor plans to assess
22 worst pain in the past 24 hours, we recommend that

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1 the word "worst" and the recall period of past
2 24 hours or last 24 hours are both included as part
3 of the instructions and items for the PRO to
4 maximize the chance of obtaining valid, reliable,
5 and consistent data.
6 In contrast to the NRS, the pain Visual
7 Analog Scale or VAS is a continuous scale comprised
8 of a horizontal or vertical line usually about
9 10 centimeters in length, or exactly 10 centimeters
10 in length, anchored by two verbal descriptors for
11 each symptom extreme.
12 There are some concerns that the VAS may be
13 imprecise because patients are required to visually
14 differentiate increments in the line without any
15 label tick marks and there can be sometimes
16 inconsistencies in the length of the line due to
17 formatting issues, especially with paper due to
18 photocopying or printing.
19 So in principle, electronic VAS would be
20 preferable if the sponsor uses a single electronic
21 platform throughout the study and patients are
22 restricted from zooming in or out or stretching the

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1 line.
2 There are some challenges and considerations
3 to keep in mind when assessing patient's pain. The
4 localization of pain on which the patients should
5 focus should be clearly specified in the
6 instructions and wording for the PRO. For example,
7 should patients focused on lower abdominal pain
8 below the bellybutton, pelvic area, or upper
9 abdominal area? And it's useful to include a
10 diagram of a body with a location of the pain
11 circled in order to focus the patient and increase
12 consistency across patients' responses.
13 It's critical to conduct qualitative
14 research to obtain the patient input as to where
15 exactly the pain is being experienced. Patients
16 should be interviewed also regarding what the most
17 appropriate and feasible recall period would be for
18 their symptoms, and then that chosen recall period
19 should be clearly stated in the items,
20 instructions, and wording to ensure consistency
21 across patients' responses.
22 For some conditions, having patients report

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1 on the worst pain is appropriate, whereas in other
2 conditions, it may make more sense to look at the
3 average of their pain, and this should be explored
4 with qualitative research with patients.
5 So when assessing patient pain intensity as
6 a prespecified endpoint intended for labeling
7 claims, it's important to capture also concomitant
8 medication or analgesic use. For example using a
9 patient-reported log at baseline and throughout the
10 trials as capturing these data would better
11 characterize the patient's pain experience and aid
12 in interpretability of the pain data.
13 In addition, drug sponsors should optimize
14 the frequency and timing of pain assessments in
15 order to capture meaningful data, and consideration
16 must be made with regard to measurement of pain,
17 whether it's an episodic or chronic pain condition.
18 There are some identified challenges in
19 using COAs for the assessment of urgency, whether
20 it may be bowel urgency or urinary urgency. There
21 are some conditions where patients' experiences
22 with urgency are considered when diagnosing the

<p style="text-align: right;">Page 201</p> <p>1 condition. For example, urinary urgency 2 characterizes overactive bladder syndrome. Pain 3 associated with urinary urgency characterizes as 4 interstitial cystitis. Patient input is needed to 5 better define the concepts of bowel urgency and 6 urinary urgency. 7 It's important to note that it is difficult 8 to measure your urgency adequately without knowing 9 what level of severity and frequency of urgency is 10 considered to be normal functioning and what's 11 considered normal to the patient. There's also a 12 need for qualitative research with patients to 13 better establish what's considered a meaningful 14 improvement in feelings of urinary urgency or bowel 15 urgency. 16 Both clinical and statistical significance 17 in findings will need to be demonstrated. 18 Sometimes, small changes in PRON point scores can 19 yield statistically significant clinical trial 20 results, but these small changes in patient scores 21 may not necessarily be clinically meaningful and 22 may not indicate clinical benefit.</p>	<p style="text-align: right;">Page 203</p> <p>1 early consultation and close collaboration with FDA 2 throughout the drug development. This slide shows 3 three pathways for engagement with CDER and to 4 obtain COA review and advice. 5 The first pathway is within the context of 6 an individual drug development program. Here, we 7 review drug sponsor submissions and provide advice 8 on the sponsor's proposed COA strategy when a COA 9 is intended to support a labeling claim, even as 10 early as the pre-IND stage. 11 The second pathway is within CDER's drug 12 development tool qualification program outside of 13 the IND pathway, where we can work with instrument 14 developers to create and qualify COAs that meet 15 unmet public health needs and can be used publicly 16 across multiple drug development programs. 17 The third and final pathway is through the 18 Critical Path Innovation Meeting or CPIM process, 19 where an instrument developer or drug company can 20 have an informal discussion and receive general 21 non-binding feedback from the FDA on a COA in early 22 phases of development, outside of an individual</p>
<p style="text-align: right;">Page 202</p> <p>1 I have here a few practical considerations 2 to keep in mind when including COAs in clinical 3 trials after content validity has been established. 4 The first is that phase 2 trials represent an 5 opportune time to evaluate psychometric properties 6 in performance of a COA, including what constitutes 7 clinically meaningful within patient improvement in 8 scores prior to initiating a pivotal phase 3 trial. 9 Second, patient global impression of 10 severity and change scales should be included as 11 anchor scales in both phases 2 and 3 to help 12 determine and confirm what magnitude of improvement 13 may be meaningful to patients. 14 Third, the COA items and response options 15 included in clinical trials should be the same 16 across phases 2 and 3 for comparability of the 17 data. And lastly, psychometric evaluation study 18 protocols should be submitted to FDA for review and 19 comment before initiating those studies. 20 To meet the challenges of patient-focused 21 outcome measurement and to ensure that COAs are fit 22 for purpose for drug development, we recommend</p>	<p style="text-align: right;">Page 204</p> <p>1 drug development program. 2 To summarize, the patient voice is important 3 to consider when develop PRO tools, intended to 4 assess how patients are feeling and functioning in 5 their daily lives. There are regulatory standards 6 that need to be followed to determine whether a COA 7 is well defined and reliable and adequate for use 8 in clinical trials. However, FDA maintains 9 flexibility in our evaluation of the evidence, 10 taking into account the evidentiary standards, 11 feasibility, and practicality. 12 I presented some challenges and 13 considerations to keep in mind when assessing 14 patients' pain and urgency as clinical trial 15 endpoints. Early planning and discussion with FDA 16 is important to ensure that clinical trial 17 assessments are fit for purpose and measure what's 18 most important to patients. 19 FDA has developed numerous tools and 20 pathways for COA development, review, and advice, 21 and FDA is open to engagement early and throughout 22 clinical trial endpoint development.</p>

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1 There are some links.
2 (Applause.)
3 DR. SMITH: Thank you, Sarrit.
4 We next have Laura Lee Johnson, who is the
5 acting director of the Division of Biometrics III
6 at CDER in FDA.
7 Presentation –Laura Lee Johnson
8 DR. JOHNSON: Hello, everybody. It's nice
9 to be here today. The Division of Biostatistics
10 III actually oversees many of and helps service
11 many of the clinical divisions that you're hearing
12 from today at FDA, although actually not with
13 Sharon Hertz. She is in a different division that
14 my friend, Tom Permutt, actually is the director
15 of. But we work very closely together because I
16 help oversee all of our patient-focused drug
17 development work across the Office of Biostatistics
18 and in conjunction with several of the other
19 centers.
20 So actually, this disclaimer is the wrong
21 one because my slides still haven't finished
22 clearance. But they were cleared in different ways

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1 for other talks, so hopefully it's okay. So I'm
2 just talking for myself.
3 This is from our multiple endpoints
4 guidance. The primary endpoint for determining
5 that a drug is effective should encompass one or
6 more of the important features of the disorder. It
7 should be clinically meaningful.
8 Now, Sarrit was talking about assessments.
9 She talked about measurement. We talk about
10 outcomes. I'm talking about endpoints. So we're
11 going to go a little bit through what is an
12 endpoint, and I'll give you some of our technical
13 definitions for that.
14 What is the statistical analysis, which is
15 really how I'm going to take all this data, and
16 then how are you going to interpret what comes out
17 of that analysis, not just that you looked at the
18 p-value at the end, but what is it that's really
19 interpretable there? But even sometimes those p-
20 values depend a lot on that analysis.
21 Then something that's dear to my heart is
22 how do we discuss promotional materials? And I

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1 will tell you, at the end of the day, whenever I
2 get fully stuck, what I think about is, what goes
3 into labeling, what is going to be on that Super
4 Bowl ad, and now let me work backwards; that, and
5 then what do I hear all the patients talking about,
6 all the murmuring in the room?
7 So a lot of my work, I've learned by
8 standing in the coffee shop lines and just
9 listening to the people around me. What is it that
10 they're talking about? What is it that's important
11 or that they are entrusting having changed?
12 So where a lot of these definitions are
13 found are actually in this living document called
14 BEST. So for a long time, within NIH and FDA and
15 between the different agencies, we had different
16 definitions of things like the word "biomarker."
17 So we were told we had to sit down and do
18 something about that, and this is on the National
19 Library of Medicines website. You will find all
20 these definitions in there, and as they change,
21 then these slides are out of date.
22 But we have an assessment, so that's the

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1 interpretation or evaluation of the measurement.
2 The measurement is this value you've got using some
3 test, tool, or instrument. And remember, that
4 could be from a lab. It could be from a patient-
5 reported outcome. It could be from a lot of
6 different things.
7 You have some similar words, but I want to
8 focus on the endpoint. So remember, we've talked a
9 lot this morning. People talked about symptoms.
10 They talked also a lot about really how you kind of
11 diagnose people. You talked about concerns.
12 The endpoint may not address all of the
13 diagnostic criteria, for example. Now, a lot of
14 people sometimes think that it has to, but in fact,
15 it may not. What is going to actually change?
16 What is your actual question?
17 Your ability to predict something about a
18 person may in fact not be -- unless that is what
19 you're studying, your question is about, it may not
20 be the appropriate efficacy endpoint that you're
21 interested in.
22 So there are a lot of different ways that we

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1 have a lot of different measurements and
2 assessments, but it may or may not be tied to the
3 endpoint for the question of the study.
4 So here, I want you to think about the
5 precise definition, types of assessments, timing of
6 the assessments, the tools that are being used.
7 Like, sometimes, I just see, literally, it's like
8 physical function. I don't know how they're
9 measuring it. I don't know what they're measuring,
10 when they're measuring. But they say physical
11 function will change, so that's supposed to be on a
12 hypothesis test. It makes it very exciting.
13 Anyway, so other details, how the multiple
14 assessments within an individual are going to be
15 combined. And this gets back to this concept, if
16 you're going to ask people about a 24-hour recall
17 and you're going to have many momentary
18 assessments, are you going to ask them to fill out
19 a daily diary every day for how many weeks? Are
20 they just going to do it for a couple of weeks at a
21 few different periods of time? What is it that
22 people are doing, and how am I going to sum this

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1 up?
2 So what Sarrit was talking about many times,
3 I think -- and we focused on it, and we have to
4 because that's how you build in quality, because
5 when I get to the endpoint, all that quality work
6 up front is what lets me know that now I have a
7 chance at actually having an endpoint that's going
8 to be reasonable and useful.
9 So the endpoint relates to the concept and
10 the measure, but you also have to think about the
11 statistics and that summary. And realistically we
12 also think about this idea of the sensitivity, but
13 is it going to likely predict benefit? And I say
14 that because sometimes you have things that just
15 will never change.
16 So I work also with a lot of cancer studies.
17 If you've had a surgical resection for prostate
18 cancer and now you have problems with your sexual
19 function, they don't have a way to deal with that.
20 That is not what their cancer therapies are going
21 to be dealing with. They're like, it is important,
22 but their new chemotherapeutic agent isn't going to

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1 change that.
2 So we also have to think about what is it
3 that's actually the reasonable endpoint for you.
4 If it's something that's important, but it's not
5 going to change for 2 years and you have a 6-month
6 study, again, what's reasonable?
7 Now, as a statistician, I also want to talk
8 about the wrong analyses. So a lot of times, we
9 assume things are continuous. We talk a lot about
10 our 0 to 11, and it's like, yeah. And I'm not here
11 tomorrow, but I know John is, and we've been on
12 panels together, so I know he'll take care of this.
13 But we think a lot of times about you have
14 the same interval or distance between responses on
15 a scale, and we don't. And there have been various
16 studies, especially in the pain literature, to talk
17 about this. So we really need to be doing more
18 ordinal analyses and fewer continuous analyses at
19 times.
20 Now, sometimes it doesn't matter. I'll be
21 honest. But sometimes, it really does. And
22 thinking about -- we like the mean. Right?

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1 Everyone thinks about means. They think about
2 changes in means, differences in means, stuff like
3 that, but as Sarrit and others have mentioned, that
4 mean difference between arms, it might be easier to
5 show that difference, but it's really difficult to
6 interpret the meaningfulness of the difference,
7 which is why, many times -- and you'll see this in
8 the PRO guidance -- we talk about, yes, you might
9 be testing it at the population or the group level,
10 but then you also want to do analyses that look at
11 the individual level.
12 So we'll talk a little bit more about that
13 moving on. Sometimes people say the mean total
14 symptom score changes, and, again, what exactly has
15 changed?
16 Now, what did work for one of the
17 applications that we had was the mean number of
18 symptom-free days. So they actually did have a
19 continuous variable, and we said, okay, great. You
20 have a difference, statistically significant. We
21 don't know what it means. But then they actually
22 had the mean number of symptom-free days and

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1 compared that.

2 So we also looked not only at that, we

3 looked at how many patients, actually, what percent

4 of them had a drop in certain number of episodes.

5 And we had qualitative information. They had done

6 interviews with patients, and they had a nice,

7 representative sample. And from there, they said,

8 yes, this is the amount that matters to us. So

9 with that information, we were able to help make a

10 determination.

11 Now, these mean symptom-free days -- and

12 again, you've got to talk to people because a lot

13 of times, there are trade-offs in these symptoms,

14 but they may be willing to make a certain trade-

15 off. With the evidence, we're willing to look at

16 that because not all symptoms are expected to go to

17 zero.

18 So maybe it's not symptom free, but as one

19 of my previous bosses when I was at NIH used to

20 say, she's like, "Listen, my pain was at a 10, and

21 now it's at an 8, and I'm still sitting on my

22 couch, and I can't play with my kids. I don't

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1 care. You have not solved my problem."

2 So when do we use ordinal regression? More

3 frequently than we see it, but we should be using

4 it more and more. But that's not all that

5 interpretable, either, so it's not like I solved a

6 problem too much.

7 The key thing to remember is that the

8 instrument is not your endpoint. You have to think

9 about the timing, the frequency, and what really

10 should matter for you. So let's think about this

11 PRO that measures symptoms, is used in trials, and

12 this not dealing with the topics of today, but I

13 want you to extrapolate it.

14 I had one, they're measuring all the

15 symptoms, except the patients in these trials end

16 up in the hospital, they may die, and some of them

17 end up being put on mechanical ventilation. So

18 they cannot answer for themselves, we are told.

19 So what's the endpoint in the trial? Well,

20 they just wanted to use the PRO. We said, well,

21 now you've got missing data. But it's not missing.

22 I know where these people are.

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1 So what my endpoint really needed to be was

2 something about the severity of the disease, which

3 is a combination of symptom information, when I

4 have it, or that they have gotten so sick, or died,

5 then in fact I need to put that as that higher end.

6 So I saw the RADAR paper, and DOOR, and

7 stuff like that, and those are things that I think

8 can be very useful. I'll be honest, not a lot or

9 all of our clinical divisions -- some of them have

10 probably never heard or thought about it, but I

11 know that Lisa LaVange and other people in our

12 office have done a lot of work in this area and are

13 very interested in it.

14 But you've got to think about what your

15 endpoint is, that everybody can have measured and

16 what it means. So you have these lovely daily

17 diaries. The problem is, again, what's the

18 analysis? Next to never, do I see people actually

19 take every single day. How many days can be

20 missed? Why are they missed?

21 So we go down to, like, item-by-item, day-

22 by-day sensitivity analyses when we're looking at

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1 these. That's what we're now instructing our

2 reviewers to do, because we found so many issues.

3 And it's something, though, to figure out in your

4 development phase, and as you're doing the ongoing

5 development, where might this be missing and how

6 can we improve the efficiency of our trials?

7 So responder analyses in the traditional

8 sense, I make a line in the sand. These people

9 have responded, these people have not.

10 Statisticians in general hate these.

11 One of my colleagues has actually now done

12 some research, but we haven't verified it yet. The

13 problem is, sometimes you might actually get a gain

14 in power. We always say you won't, that when you

15 use a continuous outcome, you have more power. But

16 every once in a while, something weird happens with

17 a variance. You have a bimodal distribution. You

18 might -- it might work out. But the problem really

19 for me is that we never know what the heck this

20 definition is, like next to never.

21 Now, I also have psoriasis, and the

22 dermatology and dental group in my

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1 organization -- and for them, you clear. Okay.
2 Well, when you see clearance and you hold that
3 clearance, then they're considered a responder.
4 Fine. There are some things that you can actually
5 measure. But the threshold, also many times we set
6 it the same across all the patients, and that may
7 not be realistic depending on the baseline for the
8 patients that are coming in.
9 So what is it that different patients want?
10 But it needs to be -- and we do this in the rare
11 diseases. I was listening this morning, and I was
12 like I should have just put in more of my rare
13 disease slides where we kind of had this pick-your-
14 own-symptom approach. But you have to measure
15 everything in everybody, pretty please with sugar
16 on top, but you usually need larger sample sizes
17 when you're going for responder analysis.
18 I have seen some of these that are called
19 more continuous responder analyses, where really
20 what they're doing is they're doing their standard
21 actually mean comparison between study arms.
22 They're really plotting a continuous distribution

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1 function, but they call it a continuous responder
2 analysis.
3 What's nice is when people are fighting
4 over -- and you do this, really -- it's not a
5 statistical test. You say this might be my
6 responder definition or this other number. Are my
7 curves separated all the way through? But if you
8 actually do any type of area under the curve type
9 of test, it's the same as doing an ANOVA pretty
10 much, just so you know.
11 But again, I get back to this idea that
12 chronic isn't stable. Then you have episodic. So
13 does the mean matter? How many days? Like what am
14 I averaging and what's the endpoint for any of
15 these?
16 This gets back to this idea, if I have 10
17 relevant symptoms but patient A only has 1, patient
18 B has 3, they've picked their symptoms, what's my
19 endpoint? Do I need them all to resolve?
20 I have one set of data where they said that
21 they wanted no numeric worsening, to which I then
22 asked, so you've got a 0 to 10 score. You're

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1 averaging this on data. Really, if it changes by
2 0.1, do we care? I mean, maybe we do, but does
3 that mean that we don't approve the product?
4 So when you talk about no worsening, it's a
5 statistical test to me. Is it non-inferiority? Is
6 it superiority, but going in the negative
7 direction? What is it that we mean when we say no
8 worsening? You have to really define this for the
9 statisticians, and think about it clinically, and
10 think about the relevance of what we're doing.
11 So another topic that we sometimes see is
12 this time to event. So they'll tell me time to
13 pain progression or time to some type of symptom
14 deterioration, although traditionally people
15 thought about this; just they had an MI, or a
16 stroke, or whatever.
17 But the problem here is, again, I've got to
18 define what is that event. They never had the
19 event at baseline or that symptom at baseline.
20 This can in fact be sometimes a useful analysis.
21 Do they ever develop it in the time to that? So
22 sometimes, if you're looking at progressive

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1 diseases, this might be useful, but you have to be
2 able to define it.
3 This is what many people have for their
4 missing data plans.
5 (Laughter.)
6 DR. JOHNSON: And you can't. So just be
7 aware that, at least at CDER and the FDA, we have
8 instructed all 200 plus of our statisticians that
9 they should assume missing not at random, so not
10 missing at random. A lot of things that come in
11 have the analysis assumption at least of missing at
12 random. This means something to about 4 people at
13 most in this audience, but just know sensitivity
14 analyses don't assume missing at random.
15 So what's the endpoint? We've got to focus
16 on this. What is that statistical analysis? How
17 does it tie to it? How are we going to interpret
18 it? And how do we discuss it?
19 So I was excited to see the multiple
20 endpoints guidance sent out to everybody. This is
21 a draft. I don't think we're still accepting
22 comments on it, although if people have comments,

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1 go ahead and send them, and we'll figure out a way
2 to handle that.
3 But it's trying to focus to say our world
4 many times is broken into co-primary endpoints,
5 where you must establish efficacy on all of these
6 primary endpoints. And you now have a multiplicity
7 problem here because if you don't win on all of
8 them, you're out. So that's really essentially one
9 test. But we're testing them individually. It's
10 not a composite.
11 Then that next bullet is at least one of
12 several primary endpoints is sufficient. So when
13 we say that, our goal there is, we know that there
14 is a lot of heterogeneity, or we don't really know
15 which endpoint exactly it is, but we know this
16 constellation of symptoms and there may be various
17 ways to measure them. We're not sure. We're going
18 to put them all out there. But we're basically
19 saying, if you went on any one of them, and it's
20 clinically significant and statistically
21 significant, that's good enough.
22 So these are actually pretty different

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1 because sometimes when I'm in co-primary land, I'm
2 like, if you don't solve both of these very
3 important problems, no. And this one, I'm like,
4 listen, if you can solve any one of these problems,
5 go forth.
6 Then I have composites. Composites get
7 misused a lot. Composites were put together
8 thinking about things like MACE, so thinking about
9 these rare events like, okay, you might die, you
10 might have a heart attack, you might have these
11 very big things but rare and important.
12 So I'm going to combine it together to have
13 one clinical endpoint to be able to count all of
14 these potential events that could occur.
15 But that's not how it gets used any more.
16 People say, oh, all these things are kind of
17 important. I'm going to combine it together, and
18 usually it's basically one score at the end, a lot
19 of times equally weighted even when there shouldn't
20 be equal weighting to it.
21 But it can harm you because you may have
22 some things that just never move, and that's going

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1 to drag down your power. Then you have other
2 elements here that you have this continue, so
3 people end up making a bunch of responder analyses
4 or responder definitions and one big responder
5 analysis and they really don't know what the
6 responder thresholds should be.
7 So a lot of composites we see shouldn't be
8 composited into a single endpoint. And then also I
9 have to describe it again. I have to write it out
10 so my grandmother would have understood it, and
11 that doesn't work so well.
12 Then we also talk about multi-component
13 endpoints and these clinically critical endpoints.
14 They're too frequent as the primary endpoint, but
15 we want to make sure people have them in there.
16 And sometimes, you lose on a primary. Like, you
17 want a mortality. And there are actually some
18 methods that we have in publications that talk
19 about how you can save alpha and recycle alpha, so
20 that you can recycle your type 1 error there and
21 maybe even actually get to that. So George
22 Kordzakhia has those papers.

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1 So an endpoint hierarchy, we think about
2 primary, secondary -- we go in some various orders,
3 how we're going to spend out that alpha. But in
4 general, if you don't include your endpoint in the
5 multiplicity plan, then we consider it exploratory.
6 I don't care what you call it. Your protocol can
7 say it's a secondary. If it's not in your
8 hierarchy, we consider it exploratory, and now you
9 have to convince us it's so important that it's
10 going up.
11 So it's always generally things like that.
12 But if you're not pre- and well-defined endpoint,
13 alphas not allocated, please don't get mad and
14 contact your congressman and Janet Woodcock because
15 we're going to probably say it's not going to
16 section 14.
17 But we have all these badly behaved
18 endpoints, too. Not all endpoints, even when
19 they're common, are good. Percent change is a big
20 one. It behaves very badly although it is very
21 common.
22 Change scores in general are troubling.

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1 Responder definitions, we've already talked about.
2 Now, there's this great page from Vanderbilt. They
3 put it up. I'm not saying FDA agreed to it, but I
4 think it does a very nice job of explaining in
5 medical school wording what some of the problems
6 are with these.
7 Now, the other problem is, sometimes you've
8 just got to make a choice and move forward. So if
9 you don't understand meaningful change for your
10 continuous endpoint or variable, don't assume you
11 know it for a binary responder variable or time to
12 event.
13 These are my conclusions. The problems with
14 assessments will lead to issues with the endpoint.
15 Again, build in quality everywhere you can. The
16 assay, the tool, the instrument, they are not your
17 endpoint. I like endoscopy. It's not an endpoint.
18 You've got to go a little past that. But many
19 endpoints don't match the situation. They hurt
20 your interpretability. And you've got to choose
21 the analyses and conclusions you want, thinking
22 about the whole picture in mind. So thank you very

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1 much.
2 (Applause.)
3 DR. SMITH: Thank you, Laura Lee. The next
4 person we have is Roger Wiederhorn and who's a
5 medical officer at the Division of Bone,
6 Reproductive, and Neurologic Products at FDA. And
7 he will be taking a few clarifying questions
8 because he saved some time.
9 Presentation – Roger Wiederhorn
10 DR. WIEDERHORN: Thank you. I'm Roger
11 Wiederhorn. I'm a medical officer at the Food and
12 Drug Administration in the Division of Bone,
13 Reproductive, and Neurologic Products.
14 Essentially, I'm a subject content analyzer,
15 working with regulatory requirement restraints.
16 They let me out today to talk, though.
17 Now, from the standpoint of a regulatory
18 perspective on interstitial cystitis, the initial
19 study that we engage, that comes before the Food
20 and Drug Administration for a new drug, is called
21 an investigational new drug application. This is a
22 request for authorization from the FDA to

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1 administer an investigational drug or biologic
2 product to humans.
3 The IND needs to include the following: a
4 protocol, chemistry manufacturing and control
5 information, pharmacology and toxicology
6 information, and previous unit experience with the
7 investigational drug, as some of them have been
8 used before for other indications.
9 This is reviewed within a 30-day period. We
10 receive approximately a thousand or more INDs per
11 year and approximately we review for the following
12 issues.
13 Are there risks to the clinical participants
14 in the trial acceptable? Is there adequate safety
15 monitoring? Has the sponsor submitted sufficient
16 supporting data to establish relative safety for
17 the proposed indication? And is the trial design
18 adequate to meet its intended objectives? At the
19 end of 30 days, if the sponsor does not hear from
20 us, they are free to proceed.
21 Now, as part of the NDA process, or the IND
22 process, rather, safety issues are identified,

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1 effective and tolerable doses are established,
2 proof of concept that the drug works is documented,
3 and the sponsor following this may submit a new
4 drug application to the FDA once all drug
5 development activities have been deemed sufficient
6 by the sponsor.
7 Now, usually the sponsors will meet with the
8 FDA prior to submitting such an application for
9 pre-NDA meetings so that we can reach agreement
10 that these studies are adequate. In other cases, a
11 special protocol assessment occurs where they'll
12 actually show us their phase 3 protocols. We will
13 critique them and ask for improvements prior to
14 submission.
15 Now, in addition to the NDA review that I
16 just mentioned, the NDA must contain adequate
17 numbers of patients to assure safety. These are
18 minimum requirements depicted in this slide by ICH
19 E-1 agreements. 300 to 600 patients exposed for 3
20 to 6 months at the acceptable or contemplated
21 clinical dosage is required to detect an adverse
22 event frequency of 0.5 percent to 5 percent. We

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1 would like to have approximately a hundred patients
2 exposed for a year for long-term safety monitoring.
3 The total number of patients treated with
4 investigational drug is anticipated to be about
5 1500. Now, these are minimal exposures. Drugs
6 that treat chronic, non-life-threatening conditions
7 are really for those. But depending on the
8 circumstances, larger trials may be required.
9 Not all phase 3 trials are successful, and
10 between 2000 and 2012, the Food and Drug
11 Administration approved 50 percent of 302 new
12 molecular entity applications during the first
13 submission. The deficiencies that did not result
14 in approval include efficacy alone for 32 percent;
15 safety, 26 percent; both safety and efficacy,
16 27 percent; and chemistry manufacturing and
17 controls or labeling, 15.2 percent.
18 Now let's talk specifically about
19 interstitial cystitis, which is what I've been
20 tasked to discuss. Dr. Lai has given you a very
21 good presentation of the clinical aspects of that.
22 I'm going to just quickly summarize them again.

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1 It's a syndrome. It's characterized by
2 urinary frequency, nocturia, urgency, suprapubic
3 pressure, and pain with bladder filling, relieved
4 by emptying. Cultures are negative for infection.
5 There's no precise definition of interstitial
6 cystitis. The etiology and pathogenesis of this
7 disease are unknown. Evidence-based definitions of
8 the disease are lacking, and our understanding of
9 this condition relies largely on expert opinion.
10 Now, what are the NIDDK criteria? I'm going
11 to briefly summarize those. Admittedly, there's
12 controversy as to whether or not glomerulations are
13 significant at all. But to be diagnosed with
14 interstitial cystitis, patients must have either
15 glomerulations on cystoscopic examination or
16 classic Hunner's ulcer, and they must have either
17 pain associated with the bladder or urinary
18 urgency.
19 You must have, again, for inclusion in
20 trials that the FDA requires for approving a new
21 drug to treat interstitial cystitis, glomerulation
22 or Hunner's ulcer, the pain that we've talked about

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1 associated with the bladder, urinary urgency for 9
2 months. You have to have a small-capacity bladder
3 based on cystometry, and you have to have an
4 intense urge to urinate at 150 ccs of urinary
5 volume. Daytime frequency of greater than 8 for at
6 least 9 months is required. And again, you're
7 excluded if you don't have or fulfill any of these
8 criteria, if you have involuntary bladder
9 contractions and if you have the absence of
10 nocturia.
11 These are a little bit out of order. The
12 regulatory reason why we insist on the NIDDK
13 criteria is to define a homogenous population of
14 interstitial cystitis patients suitable for
15 enrollment in clinical interstitial cystitis
16 trials.
17 These criteria are not to define the
18 disease, but to ensure that in any group studies
19 that adhere to these inclusion/exclusion criteria,
20 the populations will be relatively comparable.
21 Now, it's assumed that all these patients
22 will present with symptoms of urgency and what they

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1 consider frequency. So these symptoms are not
2 included as positive factors.
3 A rough estimate of the prevalence of this
4 disease using IC NIDDK criteria or suggestive
5 criteria compatible with NIDDK is 0.1 percent to
6 2.3 percent in the U.S. population.
7 Now, what are the measurable symptoms of
8 interstitial cystitis? Pain obviously is
9 paramount. We've heard several presentations today
10 on how pain can be qualified. Is it severe? What
11 type of pain? Is it constant? Is it there every
12 day? Is it visceral? Is it somatic?
13 This really hasn't been well defined. It's
14 been thought about. And I also want to point out
15 that consideration of pain alone does not do
16 adequate service to patients who have interstitial
17 cystitis, and in fact, it may take our attention
18 away from the other features or other facets of
19 this disease.
20 This is a severe, debilitating disease, and
21 I don't want anyone to make light of it for
22 patients who have it. It's very variable. Urinary

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1 frequency is something that should be considered,
2 how often do they get up at night? Urgency, as
3 Dr. Kovacs just showed, is hard to measure. We
4 don't have an acceptable measure or way of
5 reporting it at this point. And Dr. Lai has
6 alluded to flares of the disease. That may or may
7 not be something that could be built into our
8 protocols for us to look at.

9 Now, Elmiron is a drug that was approved for
10 interstitial cystitis. The endpoints used for
11 approval were really measures of pain. This was
12 approved in 1996, and it's classified as an orphan
13 drug. I'm using that just for an example.

14 Dr. Kovacs has talked about PROs. And from
15 my standpoint, patient-reported outcomes allow the
16 capture of disease aspects not felt to be
17 previously quantifiable or discernible. And in
18 some cases, it's a formidable undertaking for
19 anyone to undertake the development of a PRO. But
20 in doing so, new aspects of the disease may be
21 discovered in addition to developing a measurement
22 instrument.

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1 The virtue of PROs is they come directly
2 from the patients, so we put the patient back in
3 the mix saying what's important to you about your
4 disease?

5 At the current time, PROs are not used to
6 diagnose IC or as efficacy endpoints, as none have
7 been shown to be accurate and reliable. Now, if
8 you're going to develop a drug or PRO for
9 interstitial cystitis, what are some protocol or
10 design considerations?

11 Generally speaking, we want two double-blind
12 placebo-controlled studies. You must specify the
13 baseline maintenance therapy that's acceptable
14 because patients who have severe interstitial
15 cystitis, it would be unethical to take them off
16 the medication.

17 Flares should be defined, and criteria of
18 severity stated as well as what indication you will
19 use in the protocol for rescue therapy. In other
20 words, we don't want patients to drop out because
21 they're unhappy with how they're doing in your
22 protocol, unless your therapy may allow them to

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1 continue. That will need to be documented and to
2 be one of the things that's measured, and what type
3 of rescue medication you're going to use has to be
4 prespecified.

5 Now, going forward, what's needed? We
6 really need -- and Dr. Lai and I are in agreement
7 about this -- non-invasive diagnostic methods for
8 IC. Cystoscopy and cystometrics are invasive. We
9 need biomarkers and other diagnostic tests that can
10 be easily done.

11 Now, well-defined and reliable measure of
12 urgency is also necessary. Patient-reported
13 outcome has already been suggested, and the FDA
14 currently wants electronic source data in clinical
15 investigations as opposed to paper submissions.

16 Now, I've given you a very high-level view
17 of what's going on. I have additional slides to
18 talk more in detail about the various steps in
19 development of the drug, or again, I'm not sure I
20 gave you what you were looking for with this, so
21 that's why I left extra time to field questions.
22 (Applause.)

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1 DR. WIEDERHORN: Thanks. Are there any
2 questions?

3 DR. PONTARI: I guess the point is that you
4 can't develop a PRO without the criteria first;
5 correct?

6 DR. WIEDERHORN: Without doing what?

7 DR. PONTARI: Before you can develop the
8 PRO, you need the criteria resolved first.
9 Correct?

10 DR. WIEDERHORN: Well, no. We have criteria
11 at this time. They're the NIDDK criteria. You may
12 not agree with that, but that would be the basis on
13 which we would at this time ask patients to be
14 interviewed, to characterize interstitial cystitis.

15 So we have criteria. They're old. At the
16 current time, we're not aware of anything better.

17 Now, I know there are studies showing comparable
18 patient groups might have comparable outcomes, but
19 we would like data-driven outcomes to verify that.

20 Yes?

21 DR. BUTTERFIELD: The criteria used are
22 focused on obviously patients with defined IC that

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1 have either Hunner's lesions or glomerulations.
2 And as Dr. Lai and Dr. Pontari were talking about,
3 there's obviously the BPS patients or patients that
4 may not have a defined or visible inflammation in
5 the bladder.
6 So it seems to me that, if you were to use
7 this criteria, you really would be only selecting
8 an IC population. So what would you recommend for
9 people developing drugs for bladder pain syndrome?
10 DR. WIEDERHORN: Well, at the current time,
11 those are our only criteria for IC. Both classical
12 IC and BPS are a multi-factorial disease with
13 multiple causations. If you stick to the NIDDK
14 guidelines, there may be less possibilities within
15 that group than there is in bladder pain syndrome.
16 We really don't know what's in the bladder
17 pain syndrome definition. What we have done,
18 however is that we have met with companies who are
19 interested in developing bladder pain syndrome
20 drugs. And what we've said and advised was that
21 you need to have a 3-track protocol, which would
22 include placebo, classical IC patients, and painful

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1 bladder pain syndrome patients, and let's see how they
2 do. Do they behave comparably? Do they behave
3 differently? Because if they behave differently,
4 we may be surprised to find that the drug works
5 better in bladder pain syndrome without an IC or
6 vice versa.
7 But the point is, we don't know at the
8 current time what bladder pain syndrome is, we
9 don't know how many different causes there are.
10 They're all expert opinion and so we're arguing
11 based on expert opinion that there's less
12 variability within the classically defined IC
13 patients than there is in the painful bladder
14 patients. And that's expert opinion. We don't
15 have evidence for that.
16 Yes?
17 DR. DWORKIN: So what you're asking us to
18 do, of course, is onerous, which is a study --
19 DR. WIEDERHORN: It is.
20 DR. DWORKIN: -- that's stratified for
21 classic IC and also BPS without you giving them any
22 assurance that, at the end of the day, all of that

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1 money and effort is going to pay off.
2 So I guess my question is, is there anything
3 a sponsor could do data wise in terms of providing
4 you with evidence that would allow you to move
5 forward from the 30-year-old definition to a more
6 modern definition that includes BPS within a kind
7 of expanded IC/BPS, or does it have to be an
8 onerous clinical trial?
9 DR. WIEDERHORN: I think I would defer -- I
10 participated in the MAPP. I'm participating with
11 the NIH in the Lower Urinary Tract Research
12 Network. But I would defer to Dr. Clemens on that
13 because the idea is, are we going to have data-
14 based phenotypes that we would feel comfortable
15 with?
16 I'm not aware of that yet, and I know it's
17 onerous, and it's also a factor in why a lot of
18 development hasn't occurred. The interesting thing
19 is when you read the transcripts of the 1988 NIDDK
20 criteria and stuff, a lot of the theory and stuff
21 is very similar to what we're reading now. Yes,
22 there's a few new wrinkles and stuff, but we

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1 haven't gone forward very much at all with the
2 field. I agree with you, it's onerous.
3 DR. CLEMENS: I guess one comment I'd make
4 is that the 1988 criteria were entirely not
5 evidence based. So why is it that we're using
6 30-year-old non-evidence-based criteria and don't
7 have openness to using contemporary criteria, which
8 are admittedly not completely evidence based?
9 An example, and the one that particularly
10 bothers me, is the cystometrics. We don't ask
11 people with chronic back pain, see how much you can
12 lift or et cetera. It's a painful test for
13 patients that has been just completely abandoned
14 for IC patients.
15 So it's more of I guess a somewhat editorial
16 comment. But ultimately, I think there are data
17 that I'll show tomorrow that will provide some
18 evidence that there are differences between
19 patients, and that, at least from looking at
20 treated, natural history, et cetera, do seem to
21 distinguish between patients.
22 But ultimately, the one we talk about, if

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1 what we're saying here is that we need biomarkers
2 for IC, that may never happen. So I think perhaps
3 what we're looking for is there a way that, for
4 instance that -- for instance, could the NIDDK
5 potentially convene another summit and try to put
6 together, do the best we can, what is the current
7 data that we have, but understanding that going
8 into that, some of it's going to be evidence
9 based -- or some of it's going to be opinion, but
10 there's been probably an improvement in the opinion
11 over the last 30 years.

12 DR. WIEDERHORN: I had a conversation with
13 Dr. Star, just saying what you did, because he
14 asked us, when is the FDA going to change the
15 criteria, and I'm going to say when the NIH has a
16 meeting. It's sort of the chicken or the egg. We
17 stick to this because at least we feel we have a
18 firm foundation as to who's included in the trials.
19 It's not for decision-making clinically, clearly.
20 The idea is we want to have a uniform patient
21 population we're testing.

22 DR. CLEMENS: I was going to say, perhaps

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1 those taking notes for this, it would be nice to
2 have that in the records, that then some of us can
3 maybe talk to Dr. Star and see what we can do.

4 DR. SMITH: This is probably a great place
5 for us to stop, and we'll take a break and come
6 back at 2:30. Thank you.

7 (Applause.)
8 (Whereupon, at 2:07 p.m., a brief recess was
9 taken.)

10 DR. SMITH: We have two more talks and then
11 the discussion period. This next talk will be by
12 Jordan Dimitrakoff, who's a medical officer at the
13 Division of Bone, Reproductive, and Urologic
14 Products at FDA.

15 Presentation – Jordan Dimitrakoff

16 DR. DIMITRAKOFF: Thank you. Thank you for
17 the kind invitation. Thank you for having me. I
18 am another one of the medical officers in the
19 Division of Bone, Reproductive, and Urologic
20 Products at the FDA. The disclaimer is very
21 important, since you will see that some of the
22 things that I will talk about do not really reflect

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1 the views of the FDA or the Division of Bone,
2 Reproductive, and Urologic Products, where I work.

3 So in the interest of transparency, I
4 haven't actually seen any of the slides --
5 (Laughter.)

6 DR. DIMITRAKOFF: -- which I think is a good
7 thing, and you will see why. My talk has two
8 parts, and I didn't put this in a separate slide,
9 but the first part really talks about some of the
10 things that we've been talking about the whole day,
11 and the second part actually talks about
12 biomarkers.

13 So you heard from Dr. Pontari in the morning
14 about prostatitis and chronic pelvic pain syndrome.

15 I just want to make a comment. The talk is listed
16 in the agenda as Regulatory Aspects of Chronic
17 Prostatitis, but I think everyone knows that,
18 realistically, I will actually not be talking about
19 the inflammatory type of prostatitis. I'll be
20 talking mostly or exclusively about chronic pelvic
21 pain syndrome.

22 So again, Dr. Pontari expertly described the

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1 NIH classification, which has been around since
2 1999. The previous slide actually showed you a
3 nice outline of the four categories of prostatitis
4 syndromes. And what we're really focusing on today
5 is chronic prostatitis or chronic pelvic pain
6 syndrome. This is the category 3 in the NIH
7 classification.

8 This description is the original description
9 that comes from a letter that was published in JAMA
10 from Drs. Krieger, Nyberg, and Nickel at the time.
11 It was in 1999. And I think it nicely describes
12 the characteristics of this category 3, chronic
13 prostatitis/chronic pelvic pain syndrome, or as we
14 usually call it now, CPCPPS.

15 Basically, it's another one of the chronic
16 pelvic pain syndromes. It's in males, and that's
17 why, hence, the prostatitis part. And it by
18 definition is characterized by pelvic or perineal
19 pain, which arbitrarily at the time was defined as
20 being present for at least 3 months within a
21 6-month period with or without varying symptoms, as
22 we talked about in the morning and with or without

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1 erectile dysfunction or sexual dysfunction.
2 So I just wanted to make sure that -- again,
3 I wanted to reiterate some of the points that
4 Dr. Pontari made in the morning, that although CP,
5 chronic prostatitis, and CPPS, chronic pelvic pain
6 syndrome, are usually combined in clinical
7 practice, it is unclear at this time whether it is
8 appropriate to combine them for the purposes of
9 clinical trials, which are intended to support a
10 specific approval of a drug therapy.
11 So the reason for this, as I understand and
12 this highly educated audience understands it
13 better, is that CP and CPPS may actually reflect
14 different conditions with different underlying
15 etiology and different pathophysiologic mechanisms.
16 So again, this is a point which has been
17 very well made in the literature by Dr. Pontari,
18 Dr. Krieger, and the chronic prostatitis network at
19 the time, and more recently by the MAPP network,
20 that CPPS, the chronic pelvic pain syndrome, is a
21 vague condition.
22 The source of the pain is really unclear.

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1 And most of the time, when we see a male patient in
2 clinical practice, we categorize it as chronic
3 prostatitis or chronic pelvic pain syndrome, as I
4 mentioned earlier, but the reality of this is that
5 the pelvic pain could actually be originating from
6 a lot of different structures in the pelvis, the
7 prostate, the pelvic floor, the bladder, as we
8 talked about earlier, in the people that probably
9 have a localized pain condition. And CPPS could
10 and probably does represent a number of different
11 heterogeneous disorders.
12 So there is an urgent need -- and the FDA
13 really acknowledges and understands that, that
14 there is an urgent need to learn more about CP and
15 CPPS and what these conditions actually are. And
16 that feeds nicely into the discussion we've been
17 having the whole morning, going into this afternoon
18 today, that one potential approach to do that is to
19 phenotype patients or to try to characterize them
20 as best as we can clinically and using biomarkers.
21 So the next three slides -- I always hate
22 people that show slides and say, oh, this is a very

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1 busy slide and don't really pay attention to this.
2 So I'm actually going to walk you through the
3 slides. This is just an overview of what the
4 slides are.
5 But this was really a dream. It was a dream
6 which turned into a hypothesis, which we wrote as a
7 proposal to the MAPP network back in 2008. So I
8 say that I haven't seen these slides, and these
9 slides are actually 10 years old.
10 So 10 years ago, the idea was, well, how do
11 you actually approach patients with chronic pelvic
12 pain syndrome. And we wrote this grand proposal in
13 response to the RFA, which was issued by the NIDDK
14 for the MAPP network.
15 So the idea was -- I know that the colors
16 are nice; I hope they project nicely, as you will
17 see on the other slides. But you can ignore the
18 population at the top. This was just a sample
19 population.
20 If you start with a population of patients
21 that are predisposed to pain or have some degree of
22 pain predisposition, how do you actually tease

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1 apart the systemic versus the local factors that
2 might be involved?
3 I'm just a simple urologist. I don't know
4 as much neuroscience or any of the neurologic stuff
5 as the people in the room. So at that time, I
6 tried to think how would I actually do a study
7 looking at the different factors that might
8 underlie chronic pelvic pain syndrome?
9 There have been different theories, and the
10 theories are listed on the left side. And these
11 are different theories, at least for, at the
12 time -- that was in 2008 -- 2007, December
13 2007-2008 -- of what causes prostatitis and chronic
14 pelvic pain syndrome. There's a theory about
15 dysfunctional voiding. There's a theory that it
16 occurs after trauma, after infection, inflammation,
17 nerve damage, and autoimmunity.
18 Then there are all the other systemic
19 factors that we have been hearing about in the
20 literature that some patients are different. There
21 is dysregulation of the HPA axis. There is
22 dysregulation of sympathetic neurosystem. And

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1 again, you can totally tell these apart because
2 this is not evidence based. This was just a
3 hypothesis-generating study, which was required in
4 the RFA.
5 Then we propose some cohorts that we can use
6 potentially and that we had, that we can look at,
7 and then look at this whole sequence of events,
8 which is totally probably irritating to you because
9 it's, again, not evidence based, and it was based
10 off some neuroscience papers that were contributed
11 by the participants at that time.
12 I hate to talk about central sensitization
13 because we heard about this in the morning, but
14 again, this is the urologist's view of the life
15 beyond Fifth Avenue.
16 So this was the phenotyping plan that we
17 proposed in the grant. And again, just to give you
18 a better idea of things that you were asking about
19 in the morning, what I thought at the time was, as
20 a urologist, what do you do?
21 Well, the NIH at the time in the RFA didn't
22 want us to say what criteria we were going to use

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1 to record patients because they didn't want us to
2 get married to the 1998 NIH IC criteria. So the
3 way we decided to go around that is they said,
4 well, we will tell you what the criteria will be.
5 That's why there's an asterisk, and you see it on
6 the next slide. But it says that the patients will
7 be recorded based on the criteria, which is what
8 the MAPP is doing.
9 I'm not part of MAPP. I don't know what's
10 going on in the MAPP. I haven't been ever a part
11 of the MAPP, so I'm just talking as a person who
12 conceptualized that at the time.
13 So the idea was, well, if you take patients
14 that meet criteria and don't meet criteria, the
15 other idea was to look at patients with overlapping
16 conditions. And the RFA wanted us to look at
17 patients with urologic chronic pelvic pain
18 syndrome, which is the UCPPS abbreviation, and at
19 least one other comorbid condition.
20 At that time, again, they were listed in the
21 RFA, and we decided to look at fibromyalgia, CFS,
22 or IBS. That was my list. Again, this shows the

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1 limits of my understanding, but these are all the
2 questionnaires I could think of at the time. And
3 of course, the comment was that no one can actually
4 fill out those questionnaires because they were so
5 onerous.
6 But the idea was, well, if you take all
7 these patients -- one of the major challenges, as
8 you've heard in the field, is there's a
9 belief -- and I understand from what I heard in the
10 morning that it's not so much of a belief, but it's
11 becoming more evidence based.
12 There is a reality actually in the clinic
13 that we know that there are patients who
14 have -- people call it different things -- pelvic-
15 based disease and people who have symptoms, which
16 are outside of the pelvis.
17 So my simplistic thinking at the time was,
18 well, how do I know? Well, maybe do a pelvic-floor
19 MRI on everyone and look at the pelvic floor. And
20 if the pelvic floor is fine, we'll just see, well,
21 they probably have systemic disease, and if it's
22 not fine, then they probably have a localized

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1 disease. And that's why you have this thing at the
2 bottom, which says pelvic-floor MRI, spectroscopy,
3 and all those different things, which are outside
4 of my area of competence. Then at the same time,
5 the idea was, well, we'll probably do an MRI of the
6 brain, which is what the MAPP is doing right now.
7 So the idea was, again, taking people who
8 meet the criteria, looking at the symptom domains,
9 then looking at a way to somehow differentiate
10 between people who have pelvic disease versus those
11 who have outside-of-the-pelvis disease, and then in
12 the next step put everyone through -- that's the
13 thing you see at the top.
14 So then the next thing is looking at
15 biomarkers, and then the biomarker part was, again,
16 not evidence based, but it was an idea of looking
17 at people and looking for evidence for evaluating
18 their hypothalamic-pituitary adrenal sympathetic
19 nervous system, look at different biomarkers in the
20 blood.
21 This is all from the literature in this
22 area. We came up with an arbitrary score, which

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1 hasn't been validated, but it was just an idea at
2 the time, look at the adrenal and then look at the
3 pain memory or system and do some sort of
4 genomic/proteomic evaluation.
5 So that was just a dream, and that was the
6 way I would still think about a lot of those
7 patients. And here is the asterisk, which says
8 that patients will be diagnosed using the 2008
9 NIDDK criteria at the time.
10 So the real challenge, as we talked about,
11 again, is that in these patients, it's actually
12 good to have a biomarker. It's a good idea to have
13 some measurement. And Dr. Laura Lee Johnson gave
14 you a very nice outline of how the FDA actually
15 looks at endpoints and biomarker endpoints.
16 So I actually wanted just to give you a few
17 bits of the regulatory approach to biomarkers from
18 the point of view of the FDA. This is the
19 definition of a biomarker. It's something that
20 measures and is indicative of a normal pathogenic
21 biological process or response to an intervention.
22 These could be molecular, histologic, radiographic,

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1 physiologic.
2 It's not a COA. It's not a clinical outcome
3 assessment about which you heard from Sarrit Kovacs
4 earlier. But again, the biomarkers may be used by
5 the clinical and the research community for a
6 number of different things.
7 I think these are very important points when
8 you think about the biomarker, which I didn't think
9 about when I was doing research. But now, looking
10 at this from the regulatory point of view, it's
11 important to have reproducibility of data, to have
12 adequacy of the analytic device, and feasibility of
13 the marker should the drug be approved.
14 I think we are quite far away from this in
15 the CPPS field now, but I think it's helpful to
16 think about those things up front before designing
17 trials. Again, I think it's very good. I urge you
18 to review this source. It was a very nice public
19 workshop, which was FDA and the Duke Margolis
20 Center for Health Policy.
21 There is a very nice YouTube video where you
22 can watch the whole public workshop, which was just

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1 a couple weeks ago. And it talks about biomarkers
2 in a different setting, but I was listening to
3 this, and I heard so many things that are really
4 relevant to the field of CPPS.
5 The one thing that I think is very important
6 when you think about the biomarker -- and I sense
7 that is some of the talks in the morning -- is to
8 think about the context of use, which is the second
9 definition here.
10 The FDA has a regulatory process and
11 requires a statement that fully and clearly
12 describes the way the medical product development
13 tool is to be used and the medical product
14 development-related purpose of the use.
15 So what this means is that -- and I'm sure
16 I'm not telling you anything new; you are familiar
17 with all those things -- it's important to think
18 about the biomarker in terms of biomarker for
19 research purposes, biomarker for diagnostic
20 purposes, and biomarker for prognostic purposes.
21 And these are all different things, and there are
22 different ways to quantify those.

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1 There is an important analytical evaluation
2 and clinical validation process, and, again, those
3 are very well described. We do have a guidance and
4 I've listed this on the last slide. But I will
5 also urge you, if you're really interested into
6 biomarkers -- and I know that the MAPP has a large
7 biomarker group that's probably involved in this.
8 I urge those of you that are interested in
9 biomarkers for chronic pain, chronic pelvic pain,
10 to review this white paper, which was put together
11 by a consortium, by the FDA and the C-PATH
12 Institute. It's available again at this Duke
13 Margolis Center for Health Policy website.
14 It's a very nice paper describing all the
15 challenges of how you actually define, how do you
16 develop, how do you discover, how do you define,
17 and how do you actually analytically and clinically
18 validate a biomarker?
19 So a lot of the things we're talking about
20 in the morning were mostly related to the clinical
21 validation. Again, you have to remember that there
22 is also a process of analytical validation, which

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1 is not easy.
2 So I had to show you this figure, but it
3 relates to my next slide, and one of the people
4 reviewing my slides made a comment that if I show
5 the next slide, you wouldn't be able to understand
6 the context of the slide.
7 So this is a figure from Dr. Schaeffer's
8 paper in the New England Journal of Medicine. It's
9 a procedure that we used to do in the prostatitis
10 field. It was described in 1968 by Edwin Meares
11 and Tom Stamey. And it was an interesting way to
12 think about this because at the time, they actually
13 described this as a procedure of proving that
14 someone actually has bacteria in their prostate.
15 So the idea was how do you know, how do you
16 find out if a patient has bacteria in their
17 prostate. Well, what you basically do is, you take
18 a first void urine. They urinate in the morning
19 with a full bladder. Then they stop, and you take
20 a second sample. And then you basically do a
21 prosthetic massage, where you push on the prostate,
22 you get the fluid, and then you make the patient

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1 urinate afterwards.
2 So the idea was that if you have bacteria,
3 the way they described it, in the so-called VB3
4 sample, the sample after the prostate massage, and
5 if the bacteria are in a higher number than the
6 VB2, then the bacteria are probably coming from the
7 prostate. If you have bacteria in EPS, which is
8 the expressed prostatic secretion, and you don't
9 have the same bacteria in the first or the second
10 sample, they are probably coming from the prostate.
11 So Dr. Nickel actually published a paper
12 about 10 years ago where he proposed using just one
13 sample before and one sample after, so the VB2
14 sample is called pre-M, which is pre-massage, and
15 then the urine after the prosthetic massage is the
16 post-M.
17 So the idea is if you compare the two
18 samples, and if you find something in the post-M
19 you don't find in the pre-M, that means it's coming
20 from the prostate. So my time is up, but I'll just
21 finish. I have one more slide.
22 So that is what we did at the time. And the

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1 dream was, well, if you take pre-M and post-M
2 patients' urine samples from patients with CPPS,
3 you put this in a mass spec, do a programmatic
4 study, and then you use bioinformatics to look at
5 patterns, you would probably eventually be able to
6 come up with a biomarker. But at the same time, if
7 people have systemic disease, maybe you can look
8 for biomarkers in the blood and do the same thing.
9 So the dream really I think in the biomarker
10 field, and prostatitis, and CPPS, is to have
11 something like this, which is a very old slide
12 again from the cancer field, where you would
13 actually take a patient, not probably do a biopsy,
14 but have like a non-invasive way of doing this, and
15 that's why we're using urine to look at the genes,
16 the proteins, and then come up with an
17 individualized approach to the patient.
18 So I'm sorry. I probably ran out of time.
19 This is what a biomarker will actually give you,
20 what kind of information it will give you. And
21 just in conclusion, just to say that once we have a
22 good handle on what those conditions are, we can

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1 best tailor the inclusion/exclusion criteria for
2 clinical trials.
3 Again, as Roger mentioned earlier in IC, the
4 idea here is to have a homogeneous group of
5 patients in a trial that may be able to give us an
6 opportunity to detect treatment response if one
7 exists as opposed to enrolling different people
8 having the syndrome and a heterogeneous population,
9 some of which might not respond to treatment, and
10 that would dilute the therapeutic effect.
11 So this is the final slide, and I just
12 wanted to state that at this time the likely
13 endpoints for trials in CPPS, the chronic pelvic
14 pain syndrome, in men would be PROs, which look at
15 patients' pain, plus/minus voiding dysfunction,
16 plus/minus erectile dysfunction, going back to
17 definition.
18 There is a PRO guidance that Dr. Kovacs
19 mentioned already, but I'm not aware at this time
20 of any PROs that are validated by the FDA for drug
21 registration trials for CPPS.
22 So these are the references, and I have to

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1 thank three people at least, my team leader,
2 Dr. Kaul; our deputy director, Dr. Gassman; and our
3 division director, Dr. Hylton Joffe. Thank you for
4 seeing this.
5 (Applause.)
6 DR. SMITH: Thank you so much,
7 Dr. Dimitrakoff.
8 We have Lesley Hanes next, and she is a
9 medical research analyst at the Center for Drug
10 Evaluation and Research at FDA.
11 Presentation – Lesley Hanes
12 DR. HANES: Good afternoon. I'm Lesley
13 Hanes. I'm a medical officer in DGIP, which is the
14 Division of Gastroenterology and Inborn Products at
15 the FDA. Thank you for inviting me to speak to you
16 today about some of the select challenges in IBS
17 clinical trials and to provide a regulatory
18 perspective in new drug development for the
19 treatment of IBS.
20 So a lot of what I'll say today is a recap
21 of what you heard from my FDA colleagues, from
22 Dr. Chey, but hopefully you'll be able to glean

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1 some new information or have some questions for me
2 during the panel discussion.
3 I think it does highlight what I'll speak
4 about, even though it's some of the similar things
5 they've heard before. It's because we're
6 collaborating together, so we're pretty much all on
7 the same page.
8 So I have no disclosures, and these are my
9 views, not necessarily of the FDA or DGIP. Today,
10 this is a brief overview of my discussion, a plan
11 to talk about basic regulations for drug approvals,
12 because this is an FDA talk; select challenges,
13 including pain-related outcomes in IBS trials
14 intended to support drug approval; and the FDA
15 guidance for industry regarding IBS and how it can
16 be used to address some of these challenges.
17 Since I'm giving the regulatory perspective
18 on the challenges in drug development in IBS, the
19 first couple of slides will review the laws and
20 regulations that guide regulatory work.
21 In brief, an improved drug must meet each of
22 the following statutory requirements for the

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1 proposed patient population. The benefits must
2 outweigh its potential risk. There are specific
3 manufacturing requirements that are required. And
4 it needs to have labeling that is evidence based
5 and adequately provides guides providers and
6 patients to use the drug safely and effectively.
7 The 1962 Drug Amendments to the Food, Drug,
8 and Cosmetic Act requires the establishment of drug
9 effectiveness as a prerequisite for marketing
10 approval and that the effectiveness is demonstrated
11 by substantial evidence.
12 So what does this evidence entail? The
13 evidence includes the findings from trials that are
14 designed well enough to distinguish the effect of a
15 drug from other influences such as spontaneous
16 change, placebo effect, or biased observations.
17 And typically two adequately well-controlled
18 studies are required to support a new drug
19 approval.
20 As you have heard, a key goal of any
21 clinical drug development program is to demonstrate
22 safety and benefit of therapy. How is benefit

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1 defined? It's defined as a favorable effect on a
2 meaningful aspect of how a patient feels,
3 functions, or survives as a result of treatment.
4 It must be clinically meaningful,
5 measurable, and interpretable. And in accordance
6 to the statutory requirements, this observed
7 clinical benefit is described in labeling as a
8 claim or claims using words that represent the
9 measured concept.
10 So moving forward, we'll focus on how this
11 relates to the development of treatments for
12 patients with IBS. In brief, as you have heard and
13 you're well aware, IBS is considered to be a
14 functional GI disorder, and this group of disorders
15 have also been referred more recently as disorders
16 of gut and brain interaction.
17 It describes a spectrum of GI conditions in
18 which patients experience signs and symptoms over a
19 chronic time course that can be unpredictable in
20 nature with exacerbations that can be disabling to
21 patients.
22 There are no known anatomical, structural,

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1 or biochemical abnormalities at this time, and
2 signs and symptoms are believed to be related to
3 abnormal intestinal motility perception and brain-
4 gut communication.
5 Because there are no objective markers such
6 as abnormal colonoscopy or endoscopy, diagnosis is
7 made on patient-reported signs and symptoms. And
8 as mentioned earlier this morning, the Rome
9 criteria is typically used as the diagnostic
10 criteria in functional GI disorders. And this is
11 the Rome criteria. You heard about this this
12 morning.
13 With the basic regulations in mind and the
14 characteristics of IBS, we have worked with
15 multiple stakeholders, including most of you,
16 including patients, pharmaceutical companies,
17 academia, and professional societies during the
18 drug development process. Partnership among
19 stakeholders can facilitate the drug development in
20 a variety of ways, including assisting in the
21 identification of clinically meaningful,
22 measurable, and interpretable endpoints; assisting

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1 in identifying acceptable designs for trials that
2 can enroll and answer key questions; and sharing a
3 commitment to the completion of successful drug
4 programs.
5 The FDA recognizes that the patient
6 perspective is key to informing the drug
7 development process. And as Dr. Kovacs mentioned,
8 a public meeting on functional GI disorders
9 relating to patient-focused drug development was
10 held in 2015. They provided a lot of information
11 for us.
12 So this leads to us talking about the
13 fundamental regulatory aspects of the drug
14 development process, which you are for the most
15 part aware of. In this process, we encourage
16 pharmaceutical companies and investigators to meet
17 with us to discuss their proposed trial objectives,
18 design details, endpoints, and current findings at
19 various stages of development, including at the
20 pre-IND or investigatory new drug period; at the
21 end of the phase 2 period when the proof of concept
22 and the treatment dose or doses are determined for

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1 future phase 3 trials; and at the pre-NDA or the
2 new drug application stage as well.
3 So these meetings can help to facilitate
4 mutual understanding, provide guidance, and enable
5 drug development programs to gain further insight
6 into the FDA regulations for new drug approvals.
7 It can also potentially help to prevent harm in the
8 drug development process and optimize the
9 demonstration of efficacy.
10 So there are many challenges in IBS drug
11 development from a regulatory perspective, and here
12 are some select ones. As discussed in depth by my
13 COA colleagues earlier, we rely upon patient-
14 reported outcomes for the assessments of symptoms
15 and disorders such as IBS, since these can
16 represent direct measurements of treatment benefits
17 regarding how a patient feels or functions.
18 For conditions like IBS and other functional
19 GI disorders, input from patients regarding their
20 signs and symptoms is essential, but can be
21 challenging to conceptualize, measure, and analyze
22 in itself.

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1 So one commonly-faced challenge includes
2 differentiating concepts of abdominal pain and
3 pain-related symptoms for efficacy endpoint
4 definitions and analysis. And this was discussed
5 in depth this morning, particularly the question
6 of, are abdominal pain and abdominal discomfort
7 describing the same symptom?
8 In the May 2015 public meeting on GI
9 disorders at the FDA, a large majority of patients
10 identified abdominal pain and discomfort as the
11 most meaningful symptoms to them, but as separate
12 entities, as you have heard. Abdominal pain was
13 described as being temporary in nature, crippling
14 at times, and that a variety of different types of
15 pain existed, including constipation pain and
16 intestinal spasms.
17 In contrast, abdominal discomfort was
18 described as a duller sensation that was pervasive,
19 last hours, and could be perceived as bloating,
20 gassiness, fullness, flatulence, and the sensation
21 of incomplete evacuation.
22 So how about abdominal distension and

<p style="text-align: right;">Page 269</p> <p>1 bloating? Are they redundant with pain or 2 discomfort? Half of the participants during that 3 meeting identified distension or bloating as 4 significant as well, but they also considered it to 5 be distinct from pain, but could be related to 6 discomfort.</p> <p>7 Note this information was gathered from an 8 open meeting format and points to the importance of 9 addressing and distinguishing what and how symptoms 10 and signs are measured as endpoints during the 11 clinical development process.</p> <p>12 For the evaluation of treatment efficacy, 13 most clinical research in IBS focuses again on 14 abdominal pain, intensity, or severity as you have 15 heard, as well as stool frequency and consistency. 16 However, there are definitely additional signs and 17 symptoms, such as those listed here, and there are 18 more that are key to the patient's experience.</p> <p>19 For clinical trials, it's important to 20 understand whether the concepts that are being 21 measured are intended for use as primary endpoints, 22 secondary endpoints that may potentially support</p>	<p style="text-align: right;">Page 271</p> <p>1 and continuing to monitor the risk in the 2 postmarketing period, realizing that IBS in itself 3 is not a deadly disorder or disease. And so we 4 want to make sure that the benefit definitely 5 outweighs the risk of therapy.</p> <p>6 We emphasize it's important to leverage 7 smaller earlier studies such as phase 2 trials to 8 adequately explore and identify optimal drug doses 9 and potential efficacy endpoints to be used in the 10 phase 3 trials to help ensure program success. The 11 establishment of clinically meaningful and 12 acceptable improvements in signs and symptoms are 13 essential prior to the larger studies.</p> <p>14 Instead of comparing the average changes 15 observed across treatment groups with the numeric 16 differences and means, which may not be clinically 17 meaningful on the patient level, we have suggested 18 that investigators assess within patient clinically 19 meaningful changes from baseline and signs and 20 symptoms.</p> <p>21 Accordingly, at this time point, the 22 guidance, which I'll get to, recommends the</p>
<p style="text-align: right;">Page 270</p> <p>1 labeling, or as exploratory ones. If they're 2 intended to support labeling, then the concepts, as 3 you have heard, must be clearly defined and 4 measured in a reliable and valid way for labeling 5 purposes.</p> <p>6 For example, although straining has been 7 proposed as secondary endpoints in many clinical 8 trials, it has not always been well defined. 9 Patients have equated straining to effort, time, 10 and pain associated with stooling and a lot of a 11 variety of other kind of qualities. So we 12 definitely suggest that qualitative investigations 13 regarding the interpretation and meaningfulness of 14 these concepts are vetted prior to phase 3 trials. 15 We spent a lot of time talking about these concepts 16 in our dealings.</p> <p>17 Additional select challenges, here are some 18 of the ones that we encounter during our evaluation 19 of the drug development programs, and I'm going to 20 talk about some potential solutions as well.</p> <p>21 These include weighing the benefit versus 22 risk of IBS therapies in the drug review process</p>	<p style="text-align: right;">Page 272</p> <p>1 conduction of responder analysis. That compares to 2 a proportion of patients within each treatment 3 group who meet a definition of being an overall 4 responder, and I'll talk a little bit more about 5 this in the future regarding the pain assessment.</p> <p>6 We also advocate that trials are designed to 7 target more than one IBS sign or symptom, given the 8 proposed mechanism of the drug, since having a 9 narrow focus can create challenges in itself in 10 addressing the effect and outcome of other relevant 11 signs and symptoms. For example, trials that focus 12 on the primary endpoint on the evaluation of 13 abdominal pain intensity by itself may not 14 adequately assess whether abnormal defecation 15 improves, remains unchanged, or worsens with a 16 specific treatment.</p> <p>17 Regarding the placebo response rate, we 18 recognized that this could be high in multiple IBS 19 trials, and this can represent a challenge in 20 demonstrating that treatment effect size, 21 particularly when it's not very large. And we know 22 that in IBS trials that there typically isn't a</p>

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1 very large effect size. Therefore, we suggest
2 using trial designs -- perhaps this might be
3 controversial -- with a placebo run-in period for
4 removal of placebo responders prior to
5 randomization.

6 In addition, adequate trial duration is
7 needed to assess drug safety, efficacy, and
8 treatment durability, particularly for therapies
9 that are intended for chronic treatment of IBS.

10 So you've heard about and you've read about
11 and rely upon the FDA guidance, and this is the
12 guidance for industry for IBS. It's used to help
13 address and select other challenges in drug
14 development. It was developed in 2002, and it's
15 based upon the Rome diagnostic criteria and
16 published literature.

17 It includes acceptable and provisional
18 endpoints in trial design recommendation for the
19 evaluation of drugs to treat patients with IBSC, in
20 particular, and IBSD, and provides recommendations
21 for which trial design development can continue to
22 evolve. So we recognize that there is still

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1 evolution. This is not hard in stone, necessarily,
2 but to evolve within our regulatory framework.

3 These recommendations may assist in
4 developing treatments to address the needs of
5 patients while the work of increasing and vetting
6 out reliable PRO instruments for FDA qualification
7 continues.

8 In the guidance in general, we recommend a
9 primary endpoint that measures the effect of the
10 treatment of two major IBS signs and symptoms in
11 support of the indication for the treatment of IBS.

12 This is the IBS pain intensity and abnormal
13 defecation. For abnormal defecation, typically,
14 trials in IBSC assess stool frequency and IBSD
15 trials assess stool frequency as primary endpoint
16 components. And we recommend that these components
17 are evaluated in trials even as secondary endpoints
18 if they are not part of the primary endpoint.

19 In regards to assessing a clinically
20 meaningful change and pain intensity, the guidance
21 recommends the incorporation of a defined responder
22 endpoint and analysis at this time. This is

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1 particularly for the abdominal pain intensity
2 responder, and it's defined as a patient who
3 experiences a decrease in the worst abdominal pain
4 of at least 30 percent compared to baseline in the
5 past 24 hours.

6 Patient is to be categorized as an overall
7 responder if they achieve a prespecified
8 improvement in weekly or daily response for at
9 least half of the weeks or days of treatment. So
10 if they're treated for 12 weeks, then it's 6 weeks
11 that they have to show that they were a weekly
12 responder.

13 To note, regarding the 30 percent reduction
14 in pain intensity in comparison to baseline, this
15 was primarily based on published literature of
16 other chronic pain conditions at the time of this
17 publication, such as rheumatic arthritis. So it
18 may or may not affable to patients with IBS, but it
19 sounds like there's been some additional work that
20 has been done and is continuing to be done.

21 Therefore, we do recommend conducting
22 additional responder analysis that evaluate greater

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1 reductions in pain with treatment that may be more
2 beneficial, so perhaps a 40 or 50 percent reduction
3 in pain intensity or more, as well as evaluation of
4 cumulative distributions of various amounts of pain
5 reduction.

6 We also recommend that sponsors perform
7 qualitative work to see if these and other
8 thresholds can be validated in IBS populations for
9 further use as key endpoints in analysis and
10 trials.

11 Working backwards a little bit, in light of
12 the Rome criteria and the related components of the
13 recommended primary endpoints that you heard about,
14 the guidance suggests the following entry criteria
15 for patients with IBSC and IBSD, and this has been
16 discussed.

17 The important thing that we note is that
18 patients who enter the trials, we ask to have
19 sufficient clinical manifestations of
20 symptomatology, whether it's this symptomatology
21 that is chosen for entry criteria or other signs
22 and symptoms, just so that there can be a

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1 demonstration of clinically meaningful improvement
2 with treatment.
3 These are the final thoughts. In
4 conclusion, there are many challenges in the
5 clinical development of IBS therapies. Presented
6 today were just select ones. We recognize that
7 there are definitely more. We encourage early and
8 often collaboration in the drug development process
9 and recognize that collaboration is key to
10 addressing challenges.
11 My final pearls are that in the IBS drug
12 development, consider leveraging phase 2 trials to
13 optimize programs assessed by clearly defining
14 endpoints, defining clinically meaningful treatment
15 response, and then subsequent effect size versus
16 the treatment arms; identify appropriate doses for
17 phase 3 trials in IBS; and consider the placebo
18 response rate in these trials.
19 This is thank you to my team leader, who is
20 here, another medical officer, my division
21 director, and the director of the ODED [ph], FDA.
22 (Applause.)

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1 Q&A and Panel Discussion
2 DR. SMITH: Now I'm going to call all of the
3 people who were just speaking during this session
4 since lunch to come up and sit with us up here for
5 the discussion.
6 Does anyone have any questions? I see Steve
7 in the back.
8 DR. BRUEHL: I've got an ignorant question
9 referring to something that was mentioned earlier.
10 So it's clear that some of these disorders have
11 multiple components that are somewhat independent.
12 So you've got -- like an IC, you might have pain as
13 one key component, and then you've also got urgency
14 possibly as a second component. And it's a totally
15 different thing. And clearly, the talks we heard
16 said it doesn't make sense to lump those into one
17 measure necessarily.
18 If I understood right, I think that somebody
19 mentioned the idea of having co-primaries, so you'd
20 have pain and urinary symptoms as co-primaries. So
21 I'm just wondering, pragmatically, if you do that
22 a priori, and your trial shows efficacy on one but

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1 not the other, is that accepted?
2 I mean, can you still get the drug approved
3 for the one that it was significant for? And then
4 what is the labeling like on something like that?
5 Is it just descriptive to say it may also change
6 these other things, but we didn't show it
7 significantly? I'm just kind of wondering how all
8 that would work.
9 DR. JOHNSON: I'll start with the types of
10 endpoints, and then I'll let my clinical colleagues
11 tell you what they think is relevant or not. And I
12 think for all of these, it's always a discussion
13 that comes up.
14 You all are supposed to be thinking about
15 endpoints, so part of that discussion before you
16 let them out the door tomorrow is if you had a
17 therapy that only changed the pain, but never
18 changed the urgency, is that worthwhile for
19 patients? If you had one that only changed the
20 urgency, but didn't change the pain, is that
21 worthwhile for patients?
22 I say that because that bullet under

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1 co-primaries describe exactly that, where you have
2 two primaries and there are various ways that you
3 can handle how you designate the alpha for them.
4 There are a lot of ways you can do it.
5 But basically it says, if you win on either
6 one of these, you've won. But you still are going
7 to have to report everything. Let me be clear.
8 But on co-primary, it's saying, when you have a
9 co-primary and it would say I won on pain, I did
10 not win on urgency, that means it's a no-go.
11 So it depends on what the patients think is
12 really important, and what you all are thinking is
13 important, to decide that you've actually made a
14 step. But in writing it, we'll write what it
15 changed, what did not change. That's how you write
16 them out.
17 DR. DWORKIN: So I have a follow-up
18 question, Dr. Johnson. The kind of classic
19 co-primary that you just tried, there has to be
20 significance for pain and significance for abnormal
21 defecation or urination, otherwise nothing. Right?
22 And hat we just saw was a kind of composite of

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1 those two things, pain and abnormal defecation or
2 urination, where a patient gets classified as a
3 responder, and that the analysis is done on that
4 responder composite.
5 As a statistician, could you comment on the
6 advantages and disadvantages of those two very
7 different approaches, co-primary pain and abnormal
8 defecation, urination versus this somewhat
9 complicated composite responder?
10 DR. JOHNSON: So you don't necessarily have
11 to also have a composite responder. That's a third
12 way.
13 DR. DWORKIN: Exactly. So what are pros and
14 cons?
15 DR. JOHNSON: So I can talk about that, but
16 I don't know if -- do you want to talk a little bit
17 about it first?
18 DR. WIEDERHORN: The co-primaries?
19 DR. JOHNSON: Well, about which one we're
20 looking for.
21 DR. WIEDERHORN: Well, it depends on the
22 particular indication. Like for overactive

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1 bladder, we have two co-primary endpoints, which
2 are urinary frequency and incontinence. And the
3 sponsors have to win on both for that. So it
4 really just depends on the specific disease.
5 DR. DWORKIN: But my question was for, IBS,
6 we don't have co-primary, but we still have two
7 different things that are then combined into a --
8 DR. WIEDERHORN: And I think a lot of it is
9 the frequency of each of these endpoints is brought
10 out in the review session. And again, I'm not an
11 expert on IBS, so I can't really answer those
12 priorities.
13 DR. HANES: I could try to take a stab at
14 that. So for IBS, we do recognize that multiple
15 signs and symptoms are important, particularly to
16 include in the primary endpoint. So we think that
17 it's definitely important to look at both abdominal
18 pain, right now its intensity, but could change to
19 frequency or other things perhaps, but we also
20 recognize that abnormal defecation is important as
21 well.
22 So regarding whether it's a component

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1 endpoint, which we kind of call it at this
2 point -- and correct me if I'm wrong, Dr. Johnson,
3 but as component versus a co-primary, it basically
4 depends on the statistical analysis plan and how
5 the alpha is divvied up.
6 So the question bounces back to Dr. Johnson.
7 But right now, it depends on how it's presented in
8 the analysis plan and what people want to spend
9 their alpha on and what they want to take a risk on
10 in terms of not working out to be in the label.
11 DR. JOHNSON: So now I will respond. But I
12 think the problem with many ways that people will
13 do the composite, I think when they see the
14 responder definition in a lot of our guidances,
15 they think they have to do a responder analysis.
16 That is not necessarily the case.
17 Now, some of our guidances do have responder
18 analyses. Also, a lot of the clinical guidances
19 haven't necessarily gone through the statistics
20 office, and we've now changed that process so that
21 they are. But there is some balance and some
22 changing and evolution that has been happening over

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1 the years, so that's another thing that I will put
2 out there. But typically, when you are trying to
3 do a composite, it tends to put you from a research
4 standpoint at a disadvantage.
5 So composites in the fields that we've been
6 talking about today very rarely tend to do well.
7 And I say that because from a mathematical
8 standpoint, a lot of things go wrong. And many
9 times, we're not weighting those well. We end up
10 defaulting to measures that if instead what had
11 happened is that people looked at them individually
12 in their continuous state or their ordinal state,
13 and had done those analyses, and actually figured
14 out how they wanted to set up their testing
15 hierarchy -- and there's some very innovative ways
16 of doing that -- you would have been a lot better
17 off.
18 But being blunt, I think people say, okay,
19 composite, I've got one test, this solves my
20 problem, because they're not willing to get into
21 the innovative part. The math is not that hard. I
22 think a lot of people have done a lot of work to

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1 make it such that the math is easier. But really,
2 the composites for the types of areas you're
3 talking about rarely are how you want to go.
4 That said, that doesn't mean you don't need
5 to address each of the issues inside of what many
6 people are talking about as composites, but instead
7 just do it in a different way as a multiple
8 endpoint.
9 That's one reason this guidance we thought
10 was so important. And it took us close to seven
11 years to get this guidance out, to get it through
12 the political type of clearance process because
13 people get scared when they see statistical
14 guidances.
15 You'll notice that there's some math in the
16 end; there's some Greek symbols back there. And
17 that's actually what we came down to, is actually
18 trying to make it fairly statistical. But the idea
19 there was to say there are many ways to envision
20 this.
21 But we have really in-depth discussions
22 internally and also with our sponsors to say what

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1 is it that you think this substance is going to do?
2 What will it change? And then we have to then
3 think what is the indication.
4 If you have a disease -- I have one where
5 the fundamental aspects, one was a psychological
6 trait and one was a physical trait. But you did
7 not change both of them, you did not fundamentally
8 do anything about the disease.
9 So we said, listen, if you are going to
10 study people with this disease and you are saying
11 that you want this drug to be helping the signs and
12 symptoms of this disease, you must impact both.
13 That's a co-primary.
14 But again, if you have evidence to say, I'm
15 only going to hit one, and people say that it's
16 really important if they can do this; and that's
17 okay if the other one doesn't change or even if I
18 get a little worse, again, you've got to define it,
19 you're going to have to measure everything, but
20 you're only going to allocate your alpha to one of
21 them. Or if you think it might be both, then you
22 have ways of recycling.

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1 DR. HERTZ: Sharon Hertz here. I think
2 going back to the original question, why don't you
3 know by the time you're going into phase 3 what
4 your drug is going to do? Not whether or not it's
5 going to be capable of being successful, but
6 why -- to me, there's a fundamental problem, if
7 you're getting to phase 3 and you're not really
8 sure what you're capable of moving, you probably
9 skipped phase 2, which pretty much doesn't exist
10 anymore for I'm sure of financial reasons.
11 So the idea of going into a phase 3 with a,
12 gee, I'm not sure. I'm not going to have two
13 independent variables and I want either, then how
14 do I label that?
15 In a population of 100 people, 25 had
16 improvement in pain, but a different 25 had
17 improvement with frequency of a symptom. Well, if
18 it's the same symptom and it's become less severe
19 and/or less frequent, so for instance, trigeminal
20 neuralgia, that could be okay. But if it's two
21 different things, then is it just really a
22 meaningful assessment of the drug, and then you

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1 have to start looking at all the details. Did you
2 just miss in some people? Was it just a criterion
3 thing?
4 So a lot of that needs to be kind of worked
5 out in exploratory mode. Is your dosing a little
6 off? Your entry criteria, are they a little off?
7 Where is the problem?
8 Ideally, if you do, if there is early work,
9 which doesn't have to worry about putting all your
10 eggs in a basket, prespecifying, and making a guess
11 at the best stab at it, then phase 3 is most likely
12 going to be more -- let me just say, less
13 worrisome. It's less of a gamble, less nail-biting
14 at the end that you're going to have stuff and then
15 you're going to have to figure out whether or not
16 it meets a regulatory standard.
17 DR. JOHNSON: I do want to emphasize phase 3
18 was supposed to be confirmatory. And especially
19 the dosing part, a lot of times in the early-phase
20 studies, we see very little work done across
21 multiple doses to get enough information.
22 Even when you're doing it, you can put in

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1 some of these endpoints to get an idea of where
2 you're supposed to be going. But we do, under
3 PDUFA VI, if it's past, have an extra meeting. We
4 have two pilot programs in there. One of them is
5 for innovative studies designs. And while a lot of
6 that is to deal with a variety of other study
7 designs, we will have information.
8 This is already in the public knowledge.
9 Starting in FY18, we'll be publishing information
10 in the Federal Register to talk about how to ask
11 for meetings to be part of the pilot program. And
12 an important part of that pilot is knowledge of
13 your study design will be made public prior to your
14 finishing any work or going on the market. So it's
15 kind of a tradeoff. You get extra meetings with
16 the FDA, but we'll be doing discussions beforehand.
17 But I say that because the
18 heterogeneity -- when there are only 24 people in
19 the world, it's very different than when you have
20 many millions of people in the world. So we can
21 borrow a lot from the heterogeneity information
22 we've learned in the study designs and rare

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1 diseases, but not too much. And it is hard. When
2 I come down to it -- and Dr. Hertz said it very
3 well -- what does she write in the label, and work
4 your way out from there.
5 DR. SMITH: Lee?
6 DR. SIMON: Lee Simon. That's me. The
7 question I wondered about is we've heard multiple
8 times today reference to worst pain, and the worst
9 pain in the last 24 hours, the average worst pain
10 in the last week, or whatever.
11 Two years ago, we had a discussion at such a
12 meeting about worst pain. And I work with a group
13 of people that do outcomes in musculoskeletal pain,
14 very different than what we've been talking about
15 today. And when we did cognitive discussions with
16 patients about what worst pain means, we could not
17 get any consistency of understanding about what
18 that meant.
19 So I was wondering if there's actually been
20 work done that actually led to many people at the
21 FDA talking about worst pain in these two
22 indications. And I wondered whether or not there

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1 was actually support for using that concept from
2 the context of patients.
3 Do they understand what it means to identify
4 the worst pain as opposed to whatever pain measure
5 we're going to do, but do they understand worst
6 pain?
7 DR. KOVACS: I think the context of use in a
8 patient population is the most important, so
9 getting the qualitative research done with those
10 patients that are your target for your clinical
11 trial. So maybe worst pain is most important to
12 them or average pain, but the most important thing
13 is just having the consistency across patients, and
14 in the item, and in the instructions.
15 So sometimes, we see a 0 to 10 point scale,
16 numeric rating scale, where it'll say please
17 average your pain across the past 24 hours, and
18 then a zero rating, verbal anchor descriptor as no
19 pain versus worst pain, worst imaginable pain. So
20 then you have kind of conflicting information that
21 patients are getting. So you're averaging your
22 pain across 24 hours, but then the response option

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1 scale is asking about your worst imaginable pain.
2 So we've seen that.
3 I think that the most important thing is
4 just having the consistency and what most of the
5 patients, I don't know, 60, 70 percent of the
6 patients, are saying is applicable to them and what
7 they interpret as the most important measure of
8 pain for them
9 DR. JOHNSON: Yes. And sometimes when you
10 see flares or in the migraine or headaches, we do
11 hear from patients -- when you read through the
12 qualitative work, part of what they're interested
13 in is if they can take something that's really
14 bad -- so if they have some sufferable pain and
15 they can work through it and they can handle that.
16 But it's taking the highs and diminishing the highs
17 to something that they can actually tolerate
18 better, that's a win for them.
19 So there are some that really do distinguish
20 that worst, and it seems like they can -- but I
21 agree with what you just said. It's very kind of
22 what's the patient group, what's that population

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1 you're trying to work in.
2 There are some things that I thought nobody
3 would ever understand, but those patient groups
4 know it, because they live their disease every day
5 and they've heard enough of that vocabulary that it
6 makes sense for them. But that may not translate
7 to another patient group, and that's something to
8 really think about.
9 DR. HERTZ: Lee, what did they understand?
10 Did they understand average pain?
11 DR. SIMON: So it was interesting. So what
12 I've referred to before was the OMERACT process,
13 and we have 52 working groups in outcome measures
14 of rheumatic diseases. And a significant portion
15 of what we do has to do either referentially to
16 pain or actually specifically to pain.
17 Patients do understand, when you ask the
18 question, how much pain do you have right now,
19 which some of us like, some of us don't like, and
20 then some people are pushing, how much average pain
21 have you had over the day, 24 hours, and then you
22 average that over a 7-day period. That seems to

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1 also be understood. But again, this is
2 musculoskeletal pain, and it's not as complex in
3 certain ways as all the other things that are going
4 into these particular syndromes.
5 So I think that it's really important to be
6 consistent, as we've mentioned, in that population
7 that's being studied. I still think that patients
8 in musculoskeletal pain are most consistent in
9 understanding how much pain do you have right now.
10 And if you want to do that over a 7-day period and
11 average that over that 7-day period, that's
12 possible. But consistently, they tell us that's
13 the one they really understand.
14 DR. SMITH: John?
15 DR. FARRAR: I want to ask a couple
16 questions, but a quick comment about that. The
17 problem with right now, especially in
18 musculoskeletal pain, is that the patient has
19 ridden a bus and walked up five flights of stairs.
20 And so their pain right now may not reflect their
21 normal pain during the process.
22 We talked earlier about the fact that

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1 between patients, they don't always understand the
2 question about pain in exactly the same way. But
3 as long as they're consistent about it over the
4 course of the trial, you'll get a reasonable
5 result. So we could talk all day about that or I'd
6 be happy to.
7 But my question really revolves around this
8 issue of multiple endpoints. And whenever we
9 develop a patient-reported outcome that has more
10 than one question in it, it could be considered
11 multiple outcomes. Right? So the SF-36
12 is -- well, actually, it's more, but at least 36
13 separate outcomes, which then get coalesced into a
14 bunch of different subscales.
15 So there are two aspects to the question,
16 one of which -- sorry. And then in thinking about
17 the definition of the chronic prostatitis or the
18 IC, the definition is constituted of pain and
19 urinary symptoms. That's the combination.
20 In the MAPP program, in looking at that,
21 there's a nicely published paper that can't
22 remember whether it was Mike or Henry talked about,

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1 which said you really can't count on those going
2 the same way with the treatment, so that you might
3 want to consistently treat them separately. It
4 seems to me that what we're talking about is being
5 consistent with the biology and what your drug is
6 thought to do, and then thinking about that.
7 But I wondered about your thoughts about
8 patient-reported outcome scales. If the GUPI
9 includes things in both pain and urinary symptoms
10 and it's a validated scale, I guess it could be an
11 outcome. But it is combining two things, and I
12 wonder about your thoughts, Laura.
13 DR. JOHNSON: You can have plenty of
14 different domains inside the same scale, and then
15 you just have a difference. Like, SF-36 doesn't
16 have a total score. SF-36 has 8 different little
17 scores, or you could break it into physical
18 component and mental component, or you could break
19 out the PF-10. But there is no total score there.
20 I think what's important is, for that
21 tool -- I'm not going to talk without having done
22 the thorough review, et cetera, about how good it

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1 is. But let's say it's there, and you have a
2 urinary component, and that pulls together on its
3 own, and you have that pain component, and it pulls
4 together on its own, two separate scores, fine.
5 It might be that one of those scores, even
6 though you're giving the entire instrument -- so if
7 I'm a patient, I'm just answering different items,
8 right, I'm just going through it. But when you're
9 scoring it, when you're writing the hypothesis and
10 you have a hypothesis-tested analysis, it's just on
11 one of those domains. And it might be that you do
12 a co-primary because the decision is both need to
13 move, or it might be that, really, only one of them
14 is your primary endpoint and another one is a
15 secondary or something like that, like whatever
16 you've negotiated with.
17 But yes, I mean, it's not a problem. And I
18 think for a lot of these PROs, the mistake that we
19 see frequently is people try to get a total score
20 when there shouldn't be one.
21 DR. FARRAR: There shouldn't be one.
22 DR. JOHNSON: But at the same time, then

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1 other people go through one, and go item by item by
2 item, and break apart something that really was
3 supposed to be a whole.
4 So you can make a mistake going both ways,
5 but it really depends on how you develop the tool.
6 And when you go through and do that early
7 quantitative work in the tool development, what
8 that evidence is showing you. So you always have
9 an idea of how you think it's going to go, but I've
10 done tool development, and sometimes you're like,
11 oh, these things are hanging together differently.
12 You get more evidence? Yes, that's the way it's
13 supposed to go. That's why it's science and why we
14 try to learn things.
15 DR. FARRAR: So it's really taking things
16 and dividing them because obviously even the
17 urinary scale consists of pressure on filling
18 issues related to frequency, issues related to IBS,
19 constipation, diarrhea, fullness. And how you
20 group those, I think what you saying is it's a
21 scientific question that needs to be answered
22 before you bring it to the phase 3 meeting.

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1 But no matter what you do, you're going to
2 be combining some set of symptoms, and I think the
3 issue would be -- my advice, at least -- and I'm
4 interested in your thoughts on whether it makes
5 sense -- is that it ought to be scientifically
6 based and demonstrated as being a thing that
7 consistently changes together as opposed to being
8 separate.
9 DR. JOHNSON: Yes. There should be evidence
10 for that. Otherwise, it's also going to be very
11 hard for your biostatistician to help you design
12 your trial.
13 DR. SMITH: Hanna?
14 DR. GROL-PROKOPCZYK: So this question may
15 be as much for Bob and Dennis as --
16 DR. TURK: Who are you?
17 DR. GROL-PROKOPCZYK: I'm Hanna Grol-
18 Prokopczyk at the University of Buffalo -- as much
19 for the two of you as for the panelists. But one
20 thing that would help me figure out which of these
21 issues that are coming up that are most salient to
22 the work of this group is to have a clearer sense

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1 of what the end product at the end of tomorrow is
2 supposed to be.
3 So I'm not clear right now whether the goal
4 is to recommend pain outcomes period, or are we
5 going to go into how you measure constipation,
6 diarrhea, and then urinary frequency, and things
7 like that.
8 Secondly, relatedly, is the goal to sort of
9 focus on outcomes for the various conditions
10 independently and possibly with non-overlapping
11 pain measures, or is there also an effort to try to
12 have some comparability in the pain measures that
13 are used for the various conditions?
14 DR. DWORKIN: So Hanna, you'll have to take
15 my word for it, but I started to write out an
16 outline for tomorrow afternoon's discussion.
17 DR. GROL-PROKOPCZYK: I'm getting ahead of
18 myself.
19 DR. DWORKIN: Your question is on numbers 1
20 and 2 on my outline. So you're thinking 24 hours
21 ahead, but those are exactly the questions we'll
22 start off with at 1:00 tomorrow afternoon. It's

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1 really a group discussion. Are we just going to
2 recommend pain outcomes or pain plus abnormal
3 urination, defecation outcomes?
4 Are we just going to focus on primary
5 endpoints or also talk about secondary and
6 exploratory outcomes? But that, we'll all decide
7 as a group tomorrow at 1:00.
8 DR. SMITH: Quentin?
9 DR. CLEMENS: It's Quentin Clemens.
10 Regarding the primary outcome or composite outcomes
11 concept, I think what the IBS field has done nicely
12 is have defined these subgroups. So conceptually,
13 we could do the same in IC, where we have a pain
14 predominant group, in which case, then, the pain,
15 whether it's endoscopy or some other measure, it
16 could be the outcome. And then we could have a
17 urinary predominant group with a certain severity
18 of urinary symptoms, and then the urinary outcomes
19 we know. And that could kind of be a parallel
20 thing.
21 What I want to know from the IBS people is
22 what do you do when they have both? Because I had

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1 a conversation at lunch, and I think they said,
2 "Yeah, that mixed group is a mess." But we went
3 into that a lot in the course of urinary symptoms.
4 So sometimes when you sub categories like this, the
5 patients don't cooperate and you get there in
6 between.
7 So how do you all handle that when you're
8 recruiting patients and conducting these studies,
9 where they have both C and D, or a different --
10 DR. HANES: That's a great question. So
11 typically, there is a spectrum of disease of
12 IBSC/D, and you heard about the mixture. At this
13 point, we haven't seen a lot of studies that looked
14 at IBS or IBS with mixture at this point. Usually,
15 it's typically IBSC or IBSD. And we recognize that
16 on patients with IBSC who are more along the IBSC
17 spectrum are different than IBSD because of their
18 stool characteristics, and what you've heard also
19 about their types of pain, perhaps pain frequency,
20 perhaps pain severity.
21 When the drugs are being developed
22 typically, they are targeted either for IBSC or

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1 IBSD. So pharmaceutical companies, sponsors have
2 come to us particularly for a drug that's for
3 helping the abdominal pain as well as a stool
4 component of constipation or a stool component of
5 diarrhea based on the mechanism of action.
6 I haven't heard of particular drugs that
7 have come in to look at treating both mechanisms,
8 helping constipation and diarrhea at the same time.
9 But perhaps in the future, there will be something,
10 but right now, typically, it's IBSC or IBSD in the
11 mechanism of action.
12 DR. CLEMENS: Are most of the IBS patients
13 in the mixed group? I guess that's just a
14 question? Or I mean, is it a very small group
15 that's both? In other words, are these studies
16 kind of ignoring the majority? I suspect not.
17 But then the other question to follow up is,
18 if you have an IBSC drug and you have a mixed
19 patient, then you just put them in the IBSC, study
20 it, and ignore their D symptoms, and then when a D
21 study comes along, operationally, is that kind of
22 how it tends to work?

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1 DR. HANES: That's a good question. The
2 question is about the prevalence of IBS mixed group
3 versus IBSC and IBSD. I don't have that exact
4 answer. I wish Dr. Chey was here. Perhaps my team
5 knows more about the prevalence of the variety of
6 different subtypes.
7 But what I would say is that, at least in
8 looking at the trials that are proposed, there are
9 entry criteria that further delineate. This was
10 just kind of a brief overview, but there are
11 definitely entry criteria that clearly delineate
12 who's excluded.
13 So for IBSC trials, those who have a
14 predominant diarrhea or more than, say, a number of
15 stools and diarrhea are excluded. So we try to get
16 a more homogeneous population and not completely
17 heterogeneous with a lot of mixture in it. And on
18 the other hand, the same thing for diarrhea, so
19 there are exclusions in terms of how much
20 constipation there is that wasn't presented today.
21 So the goal is to really target what the
22 mechanism of the drug can do. So if it's intended

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1 to treat diarrhea and pain, then we really want a
2 patient population that has diarrhea and not too
3 much mixture. I think that programs are doing a
4 good job in providing this.

5 DR. LEMBO: Maybe I could just comment on
6 those questions. So the traditional literature
7 suggests that it's about a third, a third, a
8 third. More recent literature suggests that many
9 of these mixed are drug induced because patients
10 are searching and desperately trying, and they
11 don't get it quite right with the lmodium or some
12 of the laxatives.

13 Some of this is also induced by the fact of
14 the definitions that we have for Rome, which is not
15 that reliable, because it relies on historical
16 recall from the patients. Even if a physician is
17 reading it, it can be interpreted differently.

18 The Bristol stool scales, which you used for
19 stool consistency, is notoriously difficult for
20 patients to get that right, because they always say
21 the same thing, "What do you mean? At the start of
22 my bowel movement? At the end of my bowel

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1 movement?" And traditionally we have not been able
2 to really guide them. And as some of us have said
3 many times, as long as it's consistent
4 throughout -- and that's not a pun on words -- you
5 do it the same way each time.

6 That being said, we've seen this several
7 times with the rifaximin trial, where we tried to
8 include mixed desperately because we felt that it
9 was mainly a drug for bloating and not necessary
10 for bowel function. And we're surprised to find so
11 few people that actually fit into the category.

12 When you did the baseline -- I mean, by history,
13 sure, but when you go to the baseline, you take
14 them off their drugs, we found that almost all of
15 them fit into the definition of IBSD.

16 The other part is, of course, with these
17 endpoints, it's hard to study these patients
18 because you have to pigeonhole them into the CRD,
19 and that's become a bit of an issue as well,
20 although I know I understand that we can do it for
21 pain, but it's a little bit of a problem.

22 DR. SMITH: Ursula?

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1 DR. WESSELMAN: Ursula Wesselmann,
2 University of Alabama at Birmingham. Now, we
3 discussed comorbidities this morning, and I would
4 like to ask the panel how you suggest we deal with
5 them for a clinical trial.

6 So as we already said, a patient might
7 qualify for the IBS trial, but the patient might
8 also actually qualify to be enrolled in the
9 fibromyalgia trial. And in our own studies, we
10 have sometimes asked patients who had multiple pain
11 comorbidities which one is the one bothering you
12 most, and then to kind of go down the list.

13 But it's often that several chronic pain
14 syndromes bother them the same way. And the way it
15 develops is usually that they start out with one
16 pain syndrome and then develop multiple others. So
17 it would be really key to prevent that situation,
18 where they have multiple pain syndromes.

19 Actually, we just published this month a
20 paper where we looked at patients with visceral
21 pain comorbidities and fibromyalgia, and we could
22 show in a clinical sample that if you treat one

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1 pain syndrome, then the other one gets better as
2 well. So if you treat fibromyalgia, the IBS or the
3 endometriosis associated, pain gets better and vice
4 versa. And there were a few publications in the
5 literature like that that are also comparing,
6 looking at migraine headaches and fibromyalgia.

7 So should those be secondary endpoints, or
8 what would be the best way to recognize these
9 multiple comorbidities that you especially see in
10 visceral pain?

11 DR. WIEDERHORN: Listening to your question,
12 the key thing would be what is the demographics of
13 the population in the clinical trial and what is
14 the epidemiology of the disease, because if you
15 wanted to use it as a secondary endpoint, you'd
16 then have to make sure that you have the proper
17 number, proportion of patients in there to be able
18 to do some kind of stratified or prespecified
19 analysis.

20 So we would want that, and sometimes we do
21 insist that we have a representative population
22 just to do that. I can't give you a specific

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1 example.
2 Jordan, do you have any?
3 DR. DIMITRAKOFF: I don't have a specific
4 example. Thank you.
5 Thank you, Dr. Wesselmann. I think it's a
6 great question because I think, historically, in
7 most of the trials that I am familiar with. I
8 think patients, especially in the process of the
9 CPPS field, patients with severe IBS or severe
10 chronic fatigue syndrome have been excluded.
11 I think this is an arbitrary definition, and
12 in light of what we have been discussing in your
13 work and the other work in the field, it's obvious
14 that this is probably not a representative
15 population. Again, it depends on the definition of
16 severe, like how severe should it be to exclude it.
17 So obviously, I cannot speak for the agency
18 or for the division of what might represent a valid
19 secondary endpoint. But I think the reality is
20 that these patients, as you mentioned, have
21 multiple comorbidities. And if you treat one,
22 another one gets better.

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1 The other reality, I think listening to
2 everything in the morning, is that we already know
3 we actually classify those patients arbitrarily
4 with a localized or systemic disease. And then one
5 day -- it depends on maybe the day or the time of
6 their life, and how do we know that patients that
7 present, were localized as you mentioned, wouldn't
8 become patients with systemic or other pain
9 conditions.
10 I think we probably need to go into this
11 whole big data thing, and the things that we're
12 learning about people now that would probably
13 change the way we phenotype patients right.
14 Sorry. I'm not probably --
15 DR. JOHNSON: I was going to try to give you
16 about four different answers.
17 (Laughter.)
18 DR. WESSELMAN: If I could just
19 comment -- if I can just give one comment in that
20 regard. Like when we started out, for example,
21 20 years ago with the IC studies, the idea was
22 inclusion criteria were that patients who had other

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1 pain comorbidities were actually excluded, only to
2 find out that there's hardly any patients like
3 that. So as you dig into this in more detail and
4 ask the questions, you find out that those patients
5 really exist.
6 An exception to that is probably vulvodynia,
7 the localized vulvodynia, the vulva, previously
8 called vulvar vestibulitis that Andrea mentioned in
9 her lecture. About 50 percent of those patients
10 indeed do not seem to have any other pain
11 comorbidities, and they don't seem to develop them
12 later in life, either.
13 DR. JOHNSON: Yes. So personally I find
14 that, from a generalizability standpoint,
15 problematic, but that's what we regularly see, is
16 that people want a clean sample, so they start
17 excluding.
18 To the extent one of my friends at Cleveland
19 Clinic said to me one day, she's like, "I work at
20 one of those rarified academic institutions, and
21 even my patient population does not look like
22 anything that's ever in a clinical trial." She's

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1 like, "Yeah, I feel like I just need to do my own
2 research on my patients once something comes out."
3 But we do see stratification. So if you
4 know, if you know that there is a comorbidity, we
5 will sometimes preplan those subgroup analyses, and
6 we may even stratify randomization on if they do or
7 do not have another comorbidity or a specific one.
8 So sometimes, it's constellation of
9 diseases. So it might be that you stratify that
10 they have other pain-related disorders, which means
11 you have to check for it and you have to be able to
12 define it, and sometime groups don't want to do
13 that and some do. But then you can preplan those
14 types of analyses, and you can also power your
15 study to be able to look at different results
16 there.
17 We do sometimes see groups that will put in
18 endpoints while generally the general rule is you
19 measure everything and everyone every time. But
20 sometimes there may be a specific measure that
21 you're only going to use in that subgroup because
22 they are the only ones for whom it is reasonable to

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1 do it. But it depends.
2 Actually, you reminded me of an NIH study I
3 was involved in where the center -- it was actually
4 a pain center. I want to say we did it at Stanford
5 with Sean Mackey. But they had four different
6 studies going on, so we actually did a biased coin
7 allocation.
8 So what happened is when patients called in
9 and said that they were interested, we had all the
10 inclusion/exclusion criteria there for all of the
11 studies. So the person was ticking off, and at the
12 end of the interview -- because many of these
13 overlapped, right? So at the end of the interview,
14 it popped up on the screen to say which studies the
15 person was eligible for.
16 So then they described those studies to the
17 patient and found out which ones they were at least
18 interested in, and then did an allocation. And
19 they weighted it based on if we had different
20 recruitment targets and also so that there was some
21 sense of chance going on. But that's one way, that
22 if people are eligible and have multiple

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1 conditions, and it's not a problem to do it.
2 But again, that was an NIH type of study,
3 and we at the FDA do not control necessarily what
4 comes into us, at least to a very little extent.
5 But I think there is a lot more openness than is
6 necessarily seen because we approve or don't
7 approve what has come into us.
8 MS. VEASLEY: Just a quick comment. It
9 would be really helpful to have FDA guidance on
10 that topic because, again, there's a huge
11 literature base showing that the more sites of pain
12 you have, the less likely you are to respond to any
13 therapy.
14 We're working with three companies right
15 now, one on endometriosis, one on IC, and one on
16 low back pain. All three are enrolling patients
17 that have other pain disorders, and none of them
18 are tracking them at all.
19 So when you talk to companies about this and
20 even, like Sean has a colleague -- he mentioned
21 that last week Dr. Collins had a meeting on
22 developing a public-private partnership with

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1 industry and the FDA to develop pain therapeutics.
2 He said 9 out of 10 patients that he treats looks
3 nothing like the one that he enrolls in a clinical
4 trial.
5 So I think, again, this is the middle-of-
6 the-road approach between rigorous science on the
7 end of doing a placebo-controlled randomized trial,
8 but then also on the other end of, what do our
9 patients actually look like.
10 Then just a quick question. Not to make
11 something that's already complicated even more
12 complicated, but we're talking about, I think as a
13 speaker mentioned earlier, for every 2 patients she
14 asked, one side worst pain was more important, one
15 said average pain is most important.
16 All patients are individuals, and all
17 individuals have different preferences. And I
18 appreciate very much the FDA's move and other
19 agencies' move towards patient-focused drug
20 development and patient centricity. But I think
21 sometimes we've gone too far to think that if we've
22 talked to 5 patients, 10 patients, or even

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1 100 patients with any one given disorder,
2 especially something so individualized and
3 personalized like pain, that we understand it, and
4 that's just not the case.
5 There's very big differences between people
6 who have had pain syndromes for 10 to 20 years
7 versus someone who just started having IBS 6 months
8 ago versus somebody who may be in the middle of
9 that spectrum.
10 My question is, are there other disease
11 areas where patient preferences are being taken
12 into account in more of a sophisticated design? So
13 for example, we're talking about this issue between
14 pain and urgency. So for the patient that has
15 urgency, and that's the primary thing that's most
16 important to him or her, are there approaches that
17 are letting patients identify what their patient
18 preference or most important area is and then
19 tracking them? And if no, how far away from that
20 type of a scientific design do you think we are?
21 DR. TURK: Who are you? This is being
22 transcribed, so please say who you are.

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1 MS. VEASLEY: Sorry. Chris Veasley.
2 DR. JOHNSON: So at least in some of our
3 rare disease inborn error areas, yes, we do have
4 some trials that are set up that way. They are not
5 frequent, and I will say from an analysis
6 standpoint we're not 100 percent sure that we're
7 going to do the best job.
8 But it is a new territory and something that
9 I keep encouraging, and I'll be encouraging at the
10 joint statistical meetings again this year. But I
11 think from an analysis standpoint and the
12 interpretation at the end, we need to learn and do
13 more because if everybody chooses a different
14 endpoint, what exactly are they writing into
15 labeling? I think this is something that we do
16 have to figure out.
17 One other comment you mentioned, Karen Cook
18 and I think maybe Dagmar Ottmann also worked on
19 this. They had a discussion with MS patients, and
20 it was actually about pain. And they were trying
21 to get what are the different questions.
22 They had shown them this promised set of

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1 items and said what's missing? But then they went
2 back and said, okay, does this pretty much capture
3 it? Because a lot of times, we look at what's
4 missing, but then if you actually ask the patients
5 if it's good enough, a lot of times, they'll also
6 tell you yes.
7 So I think that's something else that we
8 sometimes need to think about, is that maybe we are
9 covering it well enough. But I do agree -- and we
10 actually have a lot of discussion inside my office
11 about how people, and their perceptions, and what
12 they want change a lot over time and over the
13 course of your illness, and what's important to you
14 changes over the course of your illness.
15 So those are things that, again -- I think
16 actually it was Lee Simon who asked me the
17 definition of an estimate, if I could say it
18 quickly to him. And Lesley was starting, and so I
19 said hey, wait.
20 So this might actually be a place to tell
21 you that's really this kind of this what are you
22 supposed to estimate. But part of it is that

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1 population. What's the target of the research?
2 One thing we have to be careful about without
3 slicing too thinly everything is thinking about for
4 that target of the research, what is it that they
5 care about, what are the variables, what are those
6 endpoints that we are measuring, what's the
7 scientific question for them, because it may be
8 pretty different for different groups and different
9 places.
10 But yes, some people aren't going to move,
11 and that's something we also have to consider. The
12 problem is, most companies, they want people who
13 are going to move, and they will very
14 carefully -- and actually a lot of my NIH
15 investigators used to do the same thing, so I can't
16 say it's only them.
17 But they design a study very carefully and
18 think very carefully about who's going to be in it
19 because they want to see changes. And that doesn't
20 necessarily mean that in the whole global group of
21 people that would then take that therapy, that
22 you're going to see it -- it's a big difference

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1 between efficacy and effectiveness when you think
2 about research. That's why PCORI got their money
3 in many ways.
4 DR. DIMITRAKOFF: I want to go back, if I
5 may, to a point that you make, and I think is an
6 important point, about the importance of how the
7 patient feels. And I think that ties into some of
8 the research about the duration of the flares and
9 how often people have flares.
10 So I think it's important when you collect
11 all this information about PROs and different
12 outcomes to be informed if the patient is having a
13 bad day or a good day. If you're doing a study,
14 it's important to be able to capture all that
15 information. I think it's possible to do that
16 nowadays with all the mobile technologies and
17 electronic diaries.
18 But something else I think that you said is
19 very important is that we need to know -- I think
20 historically people have always tried to look at
21 people with newer diagnoses versus people who have
22 had the disease for a very long time. For example,

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1 I don't mean to open a can of worms here, but
2 talking about CPPS, the field that I know best, and
3 IC, which I know a little bit, there is, for
4 example -- again, it's not evidence based, but
5 there is some clinical mythology about whether IC
6 exists in children or not.
7 So if you actually want to find children
8 that have IC, the idea is that if you actually
9 diagnose IC or CPPS in children, maybe you can
10 prevent them from developing the disease later on
11 in time.
12 So there is a disease, for example, in
13 children, which is called benign daytime frequency,
14 where children start urinating every 15 minutes.
15 It happens only during the day. It doesn't happen
16 during the night. And a lot of pediatric
17 urologists actually believe it's a precursor to IC.
18 So again, going back to the criteria that
19 Roger was talking about, for example, the NIDDK
20 criteria state that you have to be 18 or older to
21 be diagnosed with IC. So if you think about the
22 populations that we should be studying, the

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1 question is can we actually capture specific
2 populations which might be suitable to study both
3 the natural history of the disease and maybe for a
4 specific intervention. I think it's an important
5 point to think about some of those issues when
6 you're designing a trial.
7 DR. WIEDERHORN: Another point that you
8 brought up was the difference between or
9 relationship to pain versus urgency. Urgency, we
10 have no really good definition for in terms of
11 measuring. Pain may be easier. A lot of patients,
12 however, will say that the severe urge to urinate
13 is pain and vice versa.
14 That can confound things, and that's why I
15 think a lot of people will look at pain primarily
16 because they think they can measure that better
17 because we don't have an acceptable measure for
18 urgency. And I think that needs to be further
19 worked out because you're right. It's a very
20 difficult distinction for some patients to make,
21 especially when they're interviewed about it. Some
22 patients will say, "I only decide to urinate when I

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1 have pain."
2 DR. JOHNSON: I also want to comment no
3 something from this morning. A lot of people are
4 talking about correlation. I hate correlation with
5 a blinding passion. But one part of this is you do
6 have things that may be associated, that may be
7 related, but when you're thinking about what should
8 be endpoints, if one thing a hundred percent for
9 everybody at all severities ties to another, you
10 only need one of them.
11 But sometimes things may be associated with
12 each other, but especially on the edges, so for
13 your lower severity, or higher severity groups, or
14 stuff like that, there will be some disagreement.
15 And that's really important. That's also what gets
16 lost when you look at correlation.
17 But it's okay if you have related endpoints,
18 and we can handle that. That's not a problem.
19 DR. DIMITRAKOFF: There's a good paper on
20 the correlation of consumption of chocolate and
21 intelligence in the New England Journal of
22 Medicine, probably your least favorite paper.

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1 DR. JOHNSON: Storks and babies.
2 DR. DIMITRAKOFF: Yes.
3 DR. TU: Frank Tu. I was wondering, would
4 it be possible for you guys to comment on an actual
5 trial that's ongoing, that's on clinicaltrials.gov?
6 I'm just kind of curious about some of the stuff
7 we're discussing, whether it would apply to an
8 actual real-world example if we were then going to
9 try to apply that to guidelines.
10 Full disclosure, I've done work on an AbbVie
11 ongoing trial that is currently in phase 3 that's
12 listed here for a drug called Elagolix, and it runs
13 into the exact same issues you're bringing up.
14 And I've looked this over, and I'm pretty
15 sure that anything I'm saying here is entirely in
16 the public domain because I'm on
17 clinicaltrials.gov, so I don't have any sort of
18 disclosures I have to put on this. But one thing
19 we're kind of curious about is this discussion
20 about the applicability of a trial design to a
21 broader population. It comes up on the Alligolix
22 trial because -- this is where I'd be interested in

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1 your guidance.
2 How do they decide on the exclusion
3 criteria? Is that a back and forth with
4 regulators? Because they pick an extraordinarily
5 narrow sliver of patients to study within a
6 chronic -- they study specifically endometriosis-
7 associated pelvic pain, but their exclusion
8 criteria pretty much takes out anything that is
9 chronic pelvic pain that's not caused by
10 endometriosis. And Katy and I were both talking to
11 each other, saying we don't even know how you would
12 achieve that criteria, but that's the
13 actual -- that's the criteria they settle on for
14 this phase 3 trial.
15 But it results in a trial that we
16 think -- they've got a New England Journal article
17 out on the initial results, but the applicability
18 seems like almost no one. And I was wondering --
19 DR. VINCENT: The general gynecologist
20 recruited to that, not even people who were very
21 specialized pelvic pain, who would be able to
22 detect a pelvic-floor component, for example.

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1 DR. TU: The question is how does the FDA
2 work with a company on trying to decide on
3 ultimately designing a study that would promote an
4 approved drug that would have meaningful utility?
5 And I can say that I understand there's a back and
6 forth because when I was involved in the trial,
7 they did say there was back and forth in deciding
8 how you create these inclusion/exclusion criteria.
9 But I was just rereviewing it, and then
10 several people brought up this very point about the
11 generalizability of these studies.
12 DR. HERTZ: This is Sharon Hertz. So it's
13 interesting to contrast that with what Christin was
14 mentioning, where there was really not much of that
15 kind of specificity going on and not even
16 necessarily particularly good description of who's
17 in the study. One might almost argue that that
18 could better provide some type of real-world
19 broader efficacy assessment.
20 So it goes like this. Sponsors come in, and
21 sometimes they've spoken with you all, and
22 sometimes it's clear they haven't. Sometimes we

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1 get very narrow definitions of a population because
2 early work suggests there's efficacy there. And
3 there may not be much information available on a
4 broader segment of a given indication or diagnosis.
5 So how one weighs the value of an approval
6 for something narrow or pushing for something broad
7 is often something that we don't do. We let the
8 company decide because if I push that company to do
9 a broad population and it fails, then what? Then
10 it means I pushed them to study the wrong
11 population or this drug is no good. It could be
12 either. If they do a narrow population, it works,
13 prescribers don't know how it will function more
14 broadly.
15 So I tend not to be the one to make that
16 decision. We tend not to be the ones to make that
17 decision. I mean, I think there's some situations
18 in which the definitions are more advanced and
19 broadly accepted in terms of populations. But for
20 the most part, especially within pain, it's pretty
21 wide open.
22 So now I'm going to ask you, what's better

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1 for the public, for the public health, for the
2 population, to have a broad study in sort of a
3 mish-mosh of people and you're not 100 percent sure
4 how to predict who it's going to win in, but it
5 certainly wins in some or to have a narrow
6 population of very well-defined patients that you
7 have a very good understanding of the proportion
8 that will respond, but you don't know the
9 generalizability?
10 So that's one question. And I'll say that
11 this is a question to consider in the context of
12 indications where there's just not a lot to begin
13 with. So it's not like we have a ton of things
14 where we can make clear-cut decisions.
15 So I'll turn that back over. I mean,
16 especially in these areas, where I think there's a
17 tremendous amount of unmet need, what is more
18 useful to the community?
19 DR. TU: My own thoughts on this -- again,
20 this s Frank Tu -- is that, obviously, it's a
21 double-edged sword. What happens in clinical
22 practice is you apply a drug that's been studied in

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1 a very narrow sliver of patients to a broad,
2 oftentimes highly comorbid population that has not
3 been allowed entry in the trial. And all manner of
4 side effects erupt that were never seen in any of
5 the initial studies.
6 Their prior drug, the GnRH agonist that is
7 an injectable Lupron, has these problems, massive
8 weight gain in some patients. They're not
9 described in the initial trials, but those patients
10 who have been vulnerable, things were never allowed
11 in the initial trials.
12 On the flip side, the drug was used in
13 conditions like bladder pain syndrome and IBS, and
14 a subset of those patients got better, but they
15 were never allowed into the initial trials, either.
16 So from a public health perspective, it's a
17 question of would you rather have more people with
18 horrific morbid obesity, a small sliver of people,
19 or a small sliver of people that benefit from bowel
20 and bladder, unexpected benefits of this drug? I
21 don't know where the sweet spot is on that, but
22 both things actually happen in real practice.

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1 DR. HERTZ: But let's take out the nasty
2 really bad side effect, which is going to be true
3 even if it was a broad population because the
4 number of people that are often studied in the
5 context of development is somewhat limited.
6 So you may not pick that up anyway, even if
7 the comorbidities that are more susceptible were
8 represented. Right? Because maybe there was one
9 case, and that was going to be written off as not
10 known whether it was DOOR related.
11 So the toxicity piece aside, which is not to
12 say it's not important, but just for the purposes
13 of understanding the efficacy implications, I don't
14 think there's a right answer. This is a preference
15 question. And one could ask patients this, but I
16 think this is very difficult to operationalize.
17 But what is better in the context of an area
18 of great unmet need; specificity that you're not
19 sure how will generalize or some type of effect and
20 you're not sure how to predict who that will be?
21 DR. MARKMAN: My two cents -- John Markman,
22 Rochester, New York -- I think that the problem

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1 with the mish-mosh is I've often felt like we're
2 condemning ourselves to really trivial effects in
3 terms of analgesic benefit.
4 As a clinician, I find it incredibly helpful
5 to see a large magnitude effect, and then I know
6 the risks of applying it more broadly, whether
7 that's the use of oxcarbazepine and trigem
8 neuralgia or Toradol in renal colic. I just feel
9 like seeing those huge facts actually really helps
10 inform my decision-making.
11 So when I see this very tiny separation out
12 of 12 weeks in this very heterogeneous population,
13 I just frankly often struggle with how to match
14 that up with the other 400 options which have
15 trivial effects.
16 DR. ALTEPETER: Hi. I'm Tara Altepeter. I
17 also work in the GI division at FDA. And I guess I
18 would just add to what was already said, that while
19 it's not necessarily our decision, the population
20 that's enrolled, we try to be as descriptive as
21 possible on the labeling to share that information
22 with clinicians and to allow people to draw their

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1 own conclusions and use that information in a way
2 that's most appropriate for you.
3 So I guess I sort of see that as the balance
4 point. And again, all of us sharing a goal of
5 wanting to help promote the success of programs
6 that do have an effect. And I think the more
7 heterogeneous the population is, the less likely
8 you are to be able to see an effect if it's only
9 going to be working in a particular subset.
10 So it is a balancing act, but I think, as we
11 move forward every year in our approach to the
12 labeling and information that we're sharing with
13 prescribers is continuing to change, you'll notice,
14 if you look in that section 14 of the labels,
15 compared to what was in there from a drug that was
16 approved 10 years ago, you're going to see a lot
17 more detail.
18 We're really trying to describe who was that
19 population, what were the different components of
20 the effect; not just, yes, you won, but some of
21 those other components that might be of interest,
22 but may or may not have been part of the primary

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1 endpoint, to give as month descriptive information
2 about what we saw demonstrated in the trial and
3 then allowing the market and the clinician's
4 experience as they start to use the drug to then
5 help guide them to whether or not it's more broadly
6 applicable.
7 But we have seen examples where programs
8 have failed because there was too much
9 heterogeneity, and then we couldn't figure
10 out -- even looking back and doing all these
11 careful post hoc analysis, we couldn't quite point
12 our finger to which one of those 17 confounding
13 things we think might have resulted in a failed
14 trial, even though when everyone really thought
15 that there's a good bio plausibility for that drug
16 being effective.
17 DR. HANES: I was just going to add, I think
18 that I completely agree with both points, and your
19 question and your mentioning of safety issues.
20 Just to let you know, the drug development process
21 doesn't end at the phase 3 level. It doesn't end
22 at the approval or the non-approval of the drug,

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1 that there's definitely a post-approval period.
2 There's phase 4. There are other studies that can
3 be done that are included in the PMRs, or PMRCs, or
4 looking at safety and looking at other endpoints
5 perhaps, or subpopulations of patients that might
6 be critical that are identified later on.
7 So things continue to evolve. The label
8 continues to evolve as well. And so particularly
9 maybe something that's a salient safety issue could
10 be included to the label at a later point if it's
11 seen in a broader population, because we recognize
12 that there are limitations to the studies. We're
13 not looking at thousands and thousands of patients
14 in the populations, so you may not pick up on those
15 rare severe issues, but they could be included
16 later on.
17 DR. LEMBO: I think one of the cases that
18 brings this up -- I think the point you're trying
19 to make is the alosetron trials had an entry
20 criteria for pretty severe significant diarrhea,
21 and when it got to the general population of the
22 more milder case, obviously patients got quite

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1 severe constipation because it was a little too
2 strong for them and subsequently came out at a
3 lower dose.
4 So it can be difficult. I mean, clearly,
5 it's not an easy thing to do. And a postmarketing
6 strategy is obviously important, but that was
7 already too late because those events occurred
8 within weeks of people being on the market, where
9 we're seeing patients with very severe
10 constipation.
11 DR. HERTZ: Let me also just ask a question,
12 and I hope I'm not derailing where you were
13 planning to go, Shannon. So the other question is,
14 then, are there study design characteristics that
15 might help sort through some of this?
16 I'm going to say something now, which some
17 people in here may chuckle about, but there are
18 certain study designs that might help clear some of
19 this. So for instance, what about enriching the
20 population based on an early open-label phase?
21 This is something I get thrown in my face as the
22 worst thing we've ever done, but I still say it's a

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1 fabulous thing.
2 So an enrichment for responders and then a
3 re-randomization -- or then a randomization, and
4 then what that might allow is looking at who in
5 that open-label period -- when you haven't had
6 enough refinement during phase 2, because this
7 should not replace phase 2, and then describing
8 that.
9 So if you wouldn't hide that fact from the
10 labeling, a thousand patients were started in open
11 label; 500 seemed to meet the criteria of the
12 following. They were then randomized. And this is
13 what happened to that population. So you create a
14 narrative, and it's useful for a number of reasons,
15 I think.
16 I have no idea if your indications have ever
17 considered something like that. This is not an
18 area I've worked in directly. But for non-specific
19 analgesics, for whom there's only subpopulations
20 that respond, it seemed to have improved the
21 ability to demonstrate an analgesic effect in my
22 division.

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1 So I throw that out there. And is that
2 something that could be operationalized? It's got
3 pros and cons, but I put that out there.
4 DR. JOHNSON: I'll throw out another one,
5 which we don't see often, but N of 1 studies. Now,
6 depending on the product, an N of 1 study may not
7 work. But those are great types of studies. And
8 if you have episodic, that might be a problem, but
9 if you have the timing and long enough
10 periods -- do people know what an N of 1 study is?
11 It doesn't mean you only study 1 patient. So do
12 people know what a crossover study is?
13 So N of 1 is kind of like multiple
14 crossovers within the same patient. So you enroll
15 maybe 100 patients, but each one of them, they
16 might be, A; B; A, A; B, B. So they're going to go
17 through each period, but it's randomized what
18 they're getting. And there may be washout periods
19 or not depending on how you want to do your timing
20 and what the medication or therapy is.
21 But it's a nicer -- and really, if you think
22 about a lot of doctors, when we talk, that's how

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1 they treat their patients. That's how they try to
2 figure out if something's going to work or not.
3 That's another method.
4 But yeah, the enrichment -- open-label
5 run-ins, again, you have to think about -- we are
6 open to a lot of different study designs. You have
7 to decide how well they'll work and what you're
8 going to say at the end. But as a clinician, a lot
9 of times you're going to put a patient on a drug
10 and see how they're going to do. And if they're
11 not responding well, then you change it.
12 So in that sense, what was just described is
13 not that different than how you practice.
14 John?
15 DR. MARKMAN: John Markman. Can I just
16 follow up to that point about the N of 1 studies?
17 Because I was struck this morning about
18 Dr. Rapkin's point about provoked vestibulodynia.
19 And I just think for a lot of these syndromes,
20 provocation is a really important issue. So it
21 would seem to me, for some of these N of 1 type
22 approaches, provocation and then repeat exposure

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1 would be one of the models.
2 So can you just talk a little bit more about
3 how you think about provocation? Is that a
4 temporal thing? Is that a particular activity?
5 And how much definition is needed around that?
6 Because obviously, what provokes these different
7 syndromes is variable, but I think what I've heard
8 this morning with provocation is a really important
9 consideration.
10 DR. JOHNSON: Clinical colleagues might talk
11 more about that.
12 DR. WIEDERHORN: Going back to the MAPP
13 study, I don't know if any provocative entities
14 have been really confirmed or observed. I mean,
15 anecdotally, for interstitial cystitis, spicy
16 foods, coffee, various triggers, but I don't think
17 that's been substantiated.
18 I think the only thing that I'm aware of in
19 the MAPP study was the fact that if you're going to
20 have a flare, you might have that preceded
21 by -- you guys can confirm this -- two or three
22 days of urinary tract symptoms, and then you have

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1 the flares.
2 Is that true? But I didn't know how you
3 could provoke it for interstitial cystitis because
4 I don't believe these dietary indiscretions, so
5 called, really provoke it. And prostatitis again
6 is the same old song. Don't drink coffee, don't
7 eat spicy foods.
8 DR. JOHNSON: But for vulvodynia, it might
9 be something, yes.
10 DR. WIEDERHORN: Vulvodynia, yes, but I'm
11 not aware for urologic stuff how we could provoke
12 it.
13 DR. DIMITRAKOFF: But for the CPSI -- I
14 think, at the time the CPSI was developed, it was
15 mentioned in the morning that there was an internet
16 survey which asked patients about the most common
17 symptoms, which was done. I think this was a paper
18 published by Dr. Alexander back in 1996.
19 I think one of the consistent symptoms that
20 evolved at that time was pain after ejaculation.
21 I'm not sure how that codes up in the MAPP study
22 more recently. But historically, I don't think

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1 people have actually tried to do provocation
2 studies, at least in the CPPS field.
3 DR. WIEDERHORN: And actually,
4 historically, back when I was training, which was
5 in the Dark Ages, if you didn't ejaculate
6 regularly, you may have gotten prostatitis. And
7 that was true. I was out at sea, and guys on board
8 the ship came down with prostatitis on a regular
9 basis. And the captain of course was very upset
10 with my recommended therapy.
11 (Laughter.)
12 DR. WIEDERHORN: It's unproven.
13 DR. DIMITRAKOFF: They don't know if it's
14 evidence-based, clinical folklore.
15 DR. WIEDERHORN: It's folklore, right. It's
16 folklore. So that's the problem. I'm not aware of
17 how you can provoke this. I mean, we also said if
18 you sit for a prolonged period of time, you're a
19 cab driver, a police officer, as you sit, you're
20 more prone to prostatitis. Medical students got it
21 because they were in lectures all the time. You
22 know, no proof.

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1 DR. SMITH: Go ahead, Jen.
2 DR. GEWANDTER: This is for Dr. Johnson. I
3 was just wondering, when you suggested N of 1
4 studies, are you thinking for phase 3 or more of
5 the earlier experimental studies?
6 DR. JOHNSON: You could probably make the
7 case. I mean, I think N of 1 studies could be used
8 in earlier studies, but if it's a reasonable study
9 design for phase 3 -- I mean, all study designs are
10 open and available for phase 3. They just have to
11 make sense and answer the appropriate question.
12 DR. MARKMAN: I just wanted to go back to
13 this. There are provocations. The 6-minute walk
14 test and the results on a 6-minute walk test, which
15 have been used in some recent approvals, is as an
16 example to me of a provoked symptom. Obviously,
17 it's not pain as the primary, but is as an example
18 of a provocation.
19 DR. HERTZ: We use provocation in a
20 different sense. For managing sprains, for
21 instance, if you measure pain at rest, you're going
22 to get nothing. So the pain is often measured on

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1 standing or walking. So yes, I guess I hadn't
2 thought of that. So that's something that's simply
3 been accepted in that context because it make
4 sense.
5 So for instance, if you're going to talk
6 about vulvodynia and you have behavior that
7 consistently seeks to avoid it, it's going to be
8 very hard to study the drug in that person. And
9 part of the criteria and the conversation that has
10 to occur, then, would probably be, this is
11 the -- if you want to participate, here is what we
12 recommend, and then somehow define what the
13 provocation would be that would be acceptable to
14 put in the study and incorporate that into the
15 study design.
16 DR. DIMITRAKOFF: I think it also goes back
17 to the definition again. It's like what are you
18 trying to reproduce. I think you first have to
19 define it so that you are able to reproduce it. I
20 mean, there have been studies -- I think, again,
21 there was a test in the past, the potassium
22 chloride test, that people used to do, so you can

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1 actually put potassium chloride in the bladder, and
2 people used to claim that this is a test for IC.
3 But at the end of the day, it turns out it's
4 a test of hypersensitivity, and it doesn't really
5 reproduce the condition that you're trying to
6 study. It has huge overlaps with other conditions
7 of bladder sensitivity.
8 So again, I don't have all the information,
9 and I don't know what's going on in the MAPP. But
10 from what I know, I just think that we're not there
11 yet to be able to do a provocation study just
12 because we're not really clear what we're trying to
13 reproduce.
14 DR. WIEDERHORN: I think from a standpoint
15 of provocation, you could also study patients who
16 have a recurrent frequency of either prostatitis,
17 or interstitial cystitis, or recurrent flare
18 frequency of a minimum amount, and then study them
19 for a particular drug. That's not provocation, but
20 at least we're trying to treat the acute entity. I
21 don't know if that answers your concern.
22 DR. JOHNSON: I'm going to think back to the

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1 tampon test, I'll call it, that you were thinking,
2 because this has always been a problem when you
3 have some of these more sexually related issues,
4 which is people, they will choose not to have sex
5 or they don't have a partner at the time for
6 whatever reason. I mean, my sister's married to
7 someone in the Marine Corps. There are a lot of
8 reasons she doesn't have a partner at a time. And
9 what is going in. There can be all sorts of
10 different issues happening.
11 But what you could measure is at the end of
12 each of those periods in that N of 1 study, or in
13 any crossover study, really, is you may have that
14 provocation to see is it still provoking something,
15 so you can standardize that.
16 But what you can also measure is everything
17 in between. So we talk about concomitant
18 medications. And really, in some ways, there are
19 therapies and there are actions that people take.
20 And so if you notice that people are actually able
21 to have encounters with that -- so like suddenly
22 these women now feel comfortable using tampons, for

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1 example, that's something that you want to measure.
2 So understanding what it is and then
3 measuring it throughout, that can sometimes become
4 your endpoint, like you've realized that this is
5 what's changing hopefully in your phase 1 or
6 phase 2, and now that actually evolves into an
7 endpoint more so than just, okay, at the end of
8 8 weeks or whatever, I have this fixed measurement.
9 We've done that in some other pain studies.
10 You'll see that maybe the level of pain remains
11 about the same, but their level of activity
12 changes, or they are no longer using heavier
13 analgesics, they're using less, something like
14 that, where it's kind of the incidental but very
15 important outcome that's there.
16 DR. MARKMAN: John Markman. I just think
17 this is especially important because we're living
18 in an age when we're told to emphasize non-
19 pharmacological strategies first, and the most
20 important non-pharmacologic strategies for many of
21 these patients is avoiding the provocation,
22 wherever their pain problem is.

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1 So when your hands are tied and you're not
2 supposed to use many classes of medications due to
3 adverse events, it's helpful if our designs
4 dovetail with these sort of non-pharmacologic
5 management, which is the cornerstone.
6 DR. JOHNSON: But I think that there's non-
7 pharmacologic management, but also remember
8 avoidance can have a heavy impact on people's
9 lives.
10 DR. MARKMAN: Absolutely.
11 DR. JOHNSON: So there's a wide variety
12 there.
13 DR. HANES: Speaking in terms of IBS and
14 avoidance of diet, that kind of being studied at
15 this time, for a few years, looking at specific
16 diets that could be used, like FODMAP and things
17 like that. But is restriction -- it could be
18 beneficial, but how hard is it to do and how much
19 of a lifestyle changer will that be, and will
20 patients move away from them and prefer to take a
21 pill instead?
22 But I think those things need to definitely

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1 be considered in light of pharmaceutical
2 development, what they're avoiding. Certain foods
3 could be the answer versus taking a drug in and
4 that there is a way to look at both of them at the
5 same time.
6 So I think that's a great question that you
7 have, but restriction is not as easy as it seems,
8 particularly when it comes to something that's
9 essential like food.
10 DR. LEMBO: I'm curious if any of you could
11 comment on the very high placebo rate we see in all
12 these trials. Sometimes the difference between an
13 effective drug and a non-effective drug is simply
14 the placebo was lower for whatever reason.
15 Do you have any suggestions or have you seen
16 any studies like placebo run-ins or other things
17 that you think might be effective or would
18 recommend to us?
19 DR. JOHNSON: So I spent more than a decade
20 working at what is now called the National Center
21 for Complementary and Integrative Health. A very
22 large portion is studying placebo. And I say that

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1 because we in fact had requests for placebo
2 research. And we have some clinicians -- it was
3 interesting because I had clinicians who would come
4 up to me who said, "Well, if I've now learned that
5 this is safe and I have what is twice the
6 clinically important difference using what is
7 essentially a placebo, as a clinician treating an
8 individual patient, I'm okay with it. As a
9 researcher, I'm not." So we would try to balance
10 there. Sometimes this costs \$800. So that's your
11 public health problem versus not.
12 But there are lots of enrichment designs
13 that happen, and I think, in psychiatry in
14 particular, you will see a lot of variety of those.
15 But the other element is to also think about the
16 fact that people in studies tend to do better.
17 So there is a placebo rate that's going to
18 happen in your general population, and then there's
19 the fact that they are in a trial, regardless, that
20 kind of elevates their doing better on anything.
21 The problem with a lot of the enrichment
22 designs are when you say, "I want people to have so

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1 many hot flashes before I enroll them," things like
2 that, is you get a different type of regression to
3 the mean. That will happen. Especially when
4 you're looking at episodes, or severity, et cetera,
5 people tend to go into studies when they are doing
6 not so well, and there is a nature ebb and flow,
7 and then they start going down. So this is a
8 problem when you do some of these run-ins.
9 Another issue that can happen
10 is -- especially now that we have everything on
11 clinicaltrials.gov, which is a great thing. At the
12 same time, people many times know what they need to
13 do to cross that threshold. And we now see
14 increasing numbers of people that are right at
15 those thresholds as they come in.
16 So there's a lot of balance there, but
17 realistically, I think it's also a lot of our tools
18 and trying to measure what you really want. So
19 when we were using the AUA scale for this one
20 urinary study that I did at NIH, literally the
21 standard deviation was 3 times the clinically
22 important difference that we're supposed to be

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1 looking at.
2 So when you have measurement tools like
3 that, you have a problem. And the placebo
4 rate -- and this includes -- we pulled it off of
5 three large trials for an FDA-approved product, and
6 our placebo rate matched pretty much exactly for
7 that trial, and it was twice. So this becomes an
8 issue. But a lot of it, I think, in that case came
9 down to the tools.
10 So we talk a lot about populations and all
11 these other things, but many times, it's how we are
12 measuring people as part of the problem. But also
13 remember, placebo is not benign. You're talking to
14 people and, yes, it's there. It's doing something.
15 So you need to get above and beyond with whatever
16 that new therapy is of basically providing empathy.
17 DR. SMITH: John?
18 DR. FARRAR: I thought Bob might say this.
19 This group, actually, the IMMPACT ACTION group,
20 published a couple of articles about attempts to
21 try and control some of the placebo effects in
22 pain-related clinical trials. I would suggest you

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1 look at that article because I think it covers a
2 number of things that Laura was just talking about
3 and suggests some ways that might be able to get at
4 it.
5 Just to reiterate what Laura said, what
6 happens to the placebo group and what we think of
7 as the placebo effect, i.e., the brain-body or
8 mind-body, are very, very different. Most of what
9 happens to the placebo-treated group is the natural
10 history of disease or their regression to the mean
11 for all the reasons Laura was suggesting.
12 In the mind-body component, there are
13 circumstances where it's relatively easy to
14 understand. So if you're studying a new opioid, it
15 won't happen, but if you're studying a new opioid,
16 we produce endogenous opioid. And people who are
17 in a lot of pain produce a lot more endogenous
18 opioids, so that you could see that they would have
19 a larger placebo effect, even if they weren't in
20 the treated group.
21 But I think, without getting into much more
22 detail about it, there are several published

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1 articles that would be useful in thinking this
2 through. It hasn't been tried in the diseases
3 you're talking about -- well, I don't know that.
4 But we've looked at it with regards to pain and
5 depression.
6 DR. JOHNSON: I think Ted Kaptchuk has also
7 looked at it in IBS, for example.
8 DR. FARRAR: Yes. And of course, there's
9 all of Ted's work and all those other things.
10 DR. DIMITRAKOFF: So there is one paper in
11 the CPPS field, which actually estimated the
12 placebo rate or the placebo effect, that I'm aware
13 of. I think it's also a question of how long that
14 effect lasts, and I think that's what we don't
15 really know.
16 I think sometimes there are studies where
17 people have estimated the placebo effects. And
18 we're talking about numbers and I think this is an
19 important consideration. But it's also important
20 to know how long that effect lasts, because that's
21 an important consideration when you're enrolling
22 patients.

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1 I think in terms of design, I think
2 Dr. Johnson mentioned Ted Kaptchuk's work. And I'm
3 not sure if this is something that he discussed or
4 I read it somewhere else, but I think there is a
5 design where you can do a placebo-controlled trial,
6 and you can actually have a third group where you
7 have patients with a condition, and you promised
8 them that they will eventually get the study drug.
9 And you kind of use them as an active control to
10 your placebo population, because you actually have
11 a way of somehow -- you have some sort of control
12 of treating the patients' expectations or part of
13 the placebo-induced response.
14 I'm not sure in particular if this is
15 correct, so please correct me if I'm wrong.
16 DR. JOHNSON: I think there are a lot of
17 different ways that can be approached. But if any
18 of them was a slam-dunk, you'd be able to just to
19 rattle it off, and people would use it, and we'd be
20 done.
21 DR. WIEDERHORN: Yes. There's another
22 pitfall with placebos that we've encountered, and

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1 that was that we did a study with a run-in period.
2 Placebo responders were eliminated. The non-
3 responders were then randomized, placebo active
4 drug. Guess what? The placebo effect was still
5 the same in the repeat trial. So it depends on
6 what you're studying and your measuring
7 instruments. It can be very tricky.
8 DR. DIMITRAKOFF: I think there is data in
9 the literature that shows it could last up to
10 6 months --
11 (Crosstalk.)
12 DR. WIEDERHORN: I really thought it was
13 much shorter, but you're right.
14 DR. DIMITRAKOFF: Yes.
15 DR. WIEDERHORN: It's much more than I
16 thought.
17 DR. SMITH: Do you want to go?
18 DR. DWORKIN: Sure. So I'd like to go back
19 to this heterogeneity issues just briefly, which
20 was mentioned with respect to interstitial cystitis
21 and the changing diagnostic criteria with respect
22 to newer approaches to bladder pain syndrome.

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1 It seems to me the risks of having two
2 heterogeneous groups of patients in the clinical
3 trial are two that I can think of. One is it makes
4 it hard for the agency to write a label because the
5 label needs to characterize the patients that were
6 studied in the clinical trial.
7 But assuming that bladder pain syndrome IC
8 can be defined by MAPP in a way that could be used
9 in a label -- and I don't know, but I'm imagining
10 that they will get there if they haven't gotten
11 there already. But it seems to me the only other
12 risk of heterogeneity is the sponsor risk.
13 So I guess when I think about the fact that
14 the major risk of heterogeneity, assuming that a
15 label can be written, is a sponsor risk, then I'm
16 sorry if I'm beating a dead horse, but I don't
17 really understand the resistance to moving beyond
18 into the present a 1988 definition, because it's
19 mostly or entirely a sponsor risk.
20 DR. WIEDERHORN: The first comment is there
21 obviously could be better phenotyping even with
22 these large groups, BPS and traditional

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1 interstitial cystitis. That's one of the things
2 we're looking for with MAPP results, was maybe we
3 can identify subgroups that are going to respond.
4 But the second thing is who then defines what these
5 diseases are.
6 In 1988, 1987, the NIDDK criteria, that was
7 done by consensus conference at the NIH. The
8 question is, whose role is it to define or reform
9 things?
10 The other question of course is fairness to
11 approving drugs. You approved me under this, but
12 now you're going to tell me that my competitor gets
13 approved under something else. So there's fairness
14 to the corporations. That's also an obligation as
15 well as fairness to the American people, trying to
16 develop drugs that are effective for a disease that
17 can be debilitating. So yeah.
18 As I said before, I asked Dr. Star this
19 question a couple years ago at one of the
20 meetings -- I forget which one it was -- as to when
21 are you going to have another meeting, because at
22 that point, I was looking to the NIH to look at

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1 this. Now, these are my views. That's not the
2 views of the FDA.
3 DR. DWORKIN: So maybe that will be our next
4 meeting next year. We'll have a meeting to come up
5 with a 2018 definition of IC/BPS.
6 DR. CLEMENS: I'd be happy to attend.
7 (Laughter.)
8 DR. DWORKIN: Please go write into your date
9 book next year at this time.
10 DR. JOHNSON: I'll tell you in a general
11 sense a plan for the heterogeneity plan. If you
12 know you're going to have a high placebo rate, plan
13 for it. I think for a lot of studies, the things
14 that come in, many times our comments are, like
15 this is just wrong; please don't do it. But a lot
16 of times, we're like, you are taking a risk, and by
17 the way, we're trying to give you scientific advice
18 because I can tell right now reading this, you're
19 going to fail because you haven't taken into
20 account what is very clear is a huge problem.
21 So just plan for it. I mean, most of the
22 time, things are fine, but it's a lot of things.

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1 Plan for what you know is a problem. It's very
2 basic.
3 DR. DIMITRAKOFF: Unless there is a patient
4 with a monogenetic phenotype, and someone comes up
5 with a drug within the next year, and then it would
6 be good.
7 DR. DWORKIN: But that will be an N of 1
8 trial.
9 (Laughter.)
10 DR. SMITH: Jen, and then we'll go to Rob?
11 DR. GETWANDTER: So I was actually thinking
12 about the N of 1 trials again, and when I think of
13 them, I think of breakthrough cancer pain, which
14 the whole trial can be done maybe within 7 to
15 10 days.
16 So I was wondering if some of the content
17 experts for IBS, IC, and prostatitis could comment
18 on how often patients are having these very
19 cyclical pain flares, how long they take, how long
20 it would take to have another one. So in essence,
21 would it be feasible to be doing these kinds of
22 N of 1 studies for the acute flares in a reasonable

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1 amount of time.
2 DR. LAI: For IC, I think flare happens
3 fairly often. More than 90 percent of the patients
4 will report some kind of flare. It varies in terms
5 of duration. It could last anything from a week to
6 a few days to one days to a few hours. Some people
7 describe minutes' long flares.
8 So it becomes I think perhaps difficult if
9 you're doing an N of 1 because of the natural
10 history of somewhat unpredictable flares happening.
11 That's one consideration, and washout is another
12 thing you can think about.
13 It is common, but it does impact the quality
14 of life. We did some studies, what changes during
15 flares. We looked at pain, and we looked at
16 urinary frequency, urgency, and they all go up.
17 You expected them to go up. But at the same time,
18 it affects quality of life.
19 The longer flares, things that lasted more
20 than a day, maybe up to a week, affects quality of
21 life more than a timely little so-called flare that
22 lasts a few minutes.

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1 So there are some qualitative -- and also we
2 did some focus groups, some qualitative,
3 quantitative data on these. So this could
4 potentially be useful as potential things to look
5 for in future clinical trials or a study.
6 DR. LEMBO: In IBS, I think it's probably
7 similar that there's a wide variation. I'm not
8 aware of any clustering between a specific number
9 of days. But in trials, I mean, we get down to who
10 comes into the clinical trials, that's the
11 intermittent pain that people just have
12 intermittently such as meet the Rome criteria, they
13 almost never come into trials. We don't see them
14 in clinic. Most of the patients have pretty
15 regular frequency.
16 They do get worse, and there will be some
17 fluctuation based on a variety of factors. We're
18 doing several studies now. Right around the
19 elections, we had tremendous flares with patients.
20 (Laughter.)
21 DR. LEMBO: That was the reality. Every
22 patient came by. And women will report worsening

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1 systems around menses. I mean, there's a whole
2 bunch of factors that come in. And that's why, as
3 you've said, you need to factor that into the size
4 of the trial, and that's why you have these control
5 groups.
6 As far as the N of 1, crossover designs,
7 particularly in IBS, are not realistic to do
8 because patients never get back to baseline. And
9 it's been shown over and over again. It may take a
10 tremendous amount of time because the placebo
11 effects were long-lasting.
12 As you appropriately stated, there are
13 numerous factors that go into why people may or may
14 not respond. One of the things that we see over
15 and over again now is that it's all of the non-
16 specific effects that are occurring.
17 The classic example in our current trials
18 where we actually are talking to patients
19 afterwards is you got the placebo. Why did you get
20 better? Well, I changed my diet. You said don't
21 change it, but I changed it. That continues on
22 afterwards, so they never get back to their

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1 baseline. That's our experience. So we really
2 stay away from crossover designs.
3 DR. JOHNSON: That's actually one reason I
4 kind of like the N of 1 versus a straight-up
5 crossover because you cycle through multiple times
6 that you get to be in that placebo or whatever your
7 active control arm is. So you kind of get away
8 from the problem that they never come back
9 completely to baseline.
10 As long as you can have somewhat of a
11 washout of whatever that new therapeutic is -- and
12 again, it doesn't work for everything, but that's
13 one part that's nicer compared to just a simple
14 crossover.
15 DR. DWORKIN: I'd like to ask everyone about
16 discomfort. Over the course of the day, there were
17 a bunch of mentions of pain and discomfort or pain
18 or discomfort. And my sense is that there's no
19 validated measure of discomfort, so it's not like
20 pain where we all agree that a 0 to 10 scale or a
21 visual analog scale is well enough validated to be
22 a primary endpoint. So does that mean -- and now

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1 I'm fast-forwarding to tomorrow's discussion.
2 Does that mean that, at most, discomfort is
3 a secondary or exploratory endpoint because we just
4 don't have a measure that would allow it to be
5 primary, or did someone know about a way of
6 measuring discomfort that's just kind of reasonably
7 well validated?
8 DR. DIMITRAKOFF: As I said in my
9 presentation, I'm not aware of any instruments that
10 have been used at least in the CPPS field, but I
11 think part of the reason is that discomfort
12 probably means different things to different
13 people.
14 DR. DWORKIN: We don't know.
15 DR. DIMITRAKOFF: So it's probably like
16 validation.
17 DR. DWORKIN: So the same way that Charlie
18 Cleeland started work on that brief pain inventory
19 four years ago, someone -- maybe not someone in
20 this room, but someone somewhere should start work
21 on a kind of brief discomfort inventory that in
22 30 years could be incorporated into clinical trials

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1 of conditions where discomfort is an important
2 symptom.
3 Are you volunteering, John?
4 DR. FARRAR: No.
5 (Laughter.)
6 DR. FARRAR: I had a comment, though.
7 DR. HERTZ: Add fatigue in with that one.
8 DR. DWORKIN: What?
9 DR. HERTZ: Add fatigue into that.
10 DR. DWORKIN: That's right. Fatigue, yes.
11 MALE SPEAKER: Add urgency.
12 DR. FARRAR: So the 0 to 10 scale works fine
13 for fatigue, and the PROMIS measures do pretty
14 well, and the frequency as well, and you can count.
15 The issue about discomfort I think is an
16 interesting one because in our patient population,
17 I see a fair number of palliative care folks who
18 get chemotherapy, and they'll talk about the
19 numbness and tingling they get from the neuropathy
20 as uncomfortable.
21 The question is, does it bother them enough
22 to need some treatment or not? And I would argue

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1 that the same might be said about pain, which is
2 probably the best post-operative measure; is this
3 okay? Could you go to sleep this way, or do you
4 need anything else?
5 So I think that there is the potential for
6 measuring that. What I was going to say, though,
7 is that discomfort becomes painful. I have had
8 patients who come in and say this is uncomfortable.
9 Yes, I'd like a little treatment. And then when it
10 doesn't work, they say, "This really is starting to
11 hurt now."
12 So I'm wondering actually whether -- I have
13 never seen a patient who comes in and says this is
14 so uncomfortable, I can't stand it. Now, maybe
15 there are people who do that, but mostly they come
16 in and say their pain --
17 DR. DWORKIN: Think about itching. Itching
18 is not painful, but it can often be intense enough
19 that you can't stand it.
20 DR. JOHNSON: There's a lot of itching --
21 DR. FARRAR: I agree. So I guess what I'm
22 saying is that I think discomfort covers a bunch of

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1 different symptoms, like this urgency is so
2 uncomfortable, so discomforting. And I wondered
3 whether discomfort is really a symptom unto itself
4 or whether it's really just part of others.
5 I honestly don't know the answer to that,
6 but I think it might be worth looking at.
7 DR. DIMITRAKOFF: I think there is a
8 part -- I'm sorry.
9 DR. SMITH: Go ahead.
10 DR. DIMITRAKOFF: There is also a cultural
11 element. I think there is also a way of how people
12 perceive discomfort. Your words actually remind me
13 of a discussion I had with a colleague about 10 or
14 15 years ago, and we were just talking about
15 various -- I'll just give you a very clean-cut
16 example.
17 We were talking about dysuria, which is a
18 very clean term, and we know what it means in North
19 America. But then in other parts of the world, it
20 turned out that -- it was part of another project,
21 but he was working with someone who was studying
22 people with dysuria. And the people in the other

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1 specific population actually, for them dysuria
2 meant obstruction, difficulty urinating to the
3 degree where they would be uncomfortable enough to
4 call this what we call dysuria here, which is
5 painful urination.
6 So I think it's a perfectly valid example of
7 what you are saying, that it is actually very
8 important.
9 DR. SMITH: Hanna, did you have a comment
10 about this specifically because there are a few
11 others -- okay, go ahead.
12 DR. GROL-PROKOPCZYK: Just really quickly,
13 for what it's worth, when I worked with WHO data
14 from 10 countries, where people are asked to rate
15 pain and discomfort, the two were extremely closely
16 correlated. But it occurs to me that maybe
17 discomfort more than pain is really
18 context-specific because when Lesley Hanes was
19 speaking, it seems like there's ambiguity in some
20 cases whether discomfort can be a synonym for
21 bloating, or could it be a synonym for some other
22 more specific symptom.

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1 So it seems like maybe that's something
2 you'd get into before you start designing the
3 discomfort scale.
4 DR. SMITH: Did you have a comment about
5 this, too?
6 DR. CLEMENS: Yes. I was interested in
7 Bill's talk, where he showed that 40 percent of the
8 IBS patients didn't report pain. It appears that
9 the IBS field has chosen to exclude that
10 40 percent, perhaps wanting to have more internal
11 validity or more homogeneity to the population, and
12 the IC world is uncomfortable currently at least
13 with excluding that 40 percent.
14 I wonder if it's more of the nature of
15 visceral pain or where patients think of pain as
16 burning themselves when they're cooking or
17 something. This is inherently different, and some
18 people just don't view it as -- they're never going
19 to call it pain.
20 They're going to use another term for it.
21 And the concern is from the academic world that if
22 we could educate them in 30 seconds about what

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1 we're referring to, to pain, they'd say, yes, I
2 have pain, because what I have definitely meets
3 that IASP definition.
4 So that may be where some of the concern is,
5 that at the end of the day, it's perhaps semantics
6 or terminology that's getting in the way of us
7 studying the type of patients that we all would
8 like to study and help. And at least for me, I
9 think that's one of the concerns I have, that it's
10 more of an education thing than it is
11 perhaps -- the patients and the communication thing
12 than anything else with some of them.
13 DR. LAI: I don't think it's totally a
14 cultural thing at least in interstitial cystitis.
15 There are some patients here that I see regularly
16 who say that it is not pain, but it's pressure.
17 It's very intense bladder pressure, but it's not
18 pain. Is it 0 to 10? Is it pain? Is it 1? No.
19 It's not pain. It's pressure.
20 So there are people who actually perhaps not
21 get to the point to see you that they complain
22 about pain.

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1 DR. CLEMENS: They're urinating every
2 30 minutes.
3 DR. LAI: They're urinating every
4 30 minutes, driving them crazy.
5 DR. CLEMENS: It's having a substantial
6 impact, whatever it is.
7 MS. VEASLEY: Chris Veasley. Some women
8 with vulvodynia will say the same thing. They'll
9 say, "I have burning. It's not pain." We'll say,
10 "How is your pain?" "I don't have pain. I have
11 burning."
12 I want to just quickly go back to something
13 that Sharon mentioned just to answer your question,
14 I think, as yes. We would like to be able to know
15 which drugs are working in different subgroups of
16 patients with these conditions, and we would like
17 to be able to use different methods like enrichment
18 to do that.
19 The problem is that we know these conditions
20 are heterogeneous, but we don't know how or what we
21 should be using to phenotype. I mean, the whole
22 reason why MAPP began is because all these IC

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1 trials failed. So they had to take a step back and
2 say we need to understand this better before we
3 start trying to move forward with larger clinical
4 trials.
5 I think MAPP and ARP are beginning to really
6 be informative about what some of those different
7 domains need to be and how we can better
8 characterize and phenotype patients. But until we
9 have that information, I don't think we can do what
10 you asked.
11 Just one quick observation. Having worked
12 in this area with these different conditions and
13 ones that aren't addressed here, it seems to me
14 that there is something different about IBS because
15 IBS has been more successful in getting positive
16 trials and approvals versus these other conditions.
17 There's no approvals for vulvodynia. I see trials
18 keep failing.
19 I'm wondering if it's because, one, maybe
20 there's more corporate involvement in IBS, are
21 there more trials going forward, i.e., the larger
22 percentage of approvals? Do we know molecularly

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1 something different about IBS? There are other
2 targets that are being more specific.
3 Is there something different about the way
4 IBS trials are being conducted than some other
5 trials in this area? I mean, what might be some of
6 those differences?
7 DR. HANES: I would say that is hard for me
8 to answer that question. So basically the question
9 is, what is different in the IBS trials versus IC
10 trials or vulvodynia and those type of trials -- I
11 believe that's what you're asking -- that's making
12 the allowance of drugs to be approved in IBS versus
13 perhaps other disease processes?
14 So I can't speak upon the other disease
15 processes since I haven't worked in them, so I
16 don't know necessarily about their trial structures
17 or what sponsors have proposed and what the
18 discussions have been with the FDA during the
19 process.
20 I think that every division at the FDA,
21 although there are a lot of similarities, there are
22 differences. So what DGIP, the GI division, might

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1 encounter in working with sponsors, and companies,
2 and investigators might be completely different
3 than what DBRUP is doing or not doing, but what has
4 been presented to them from the outside.
5 So it's definitely a working relationship
6 with pharmaceutical companies and investigators to
7 try to lead to the best optimal drug development
8 process.
9 DR. HERTZ: I think just to build on, where
10 is the opportunity to explore those questions? So
11 for instance, the drugs for IBS, it sounds like
12 they pretty much affect the defecation pattern, and
13 then there's also an effect on pain.
14 So are there any products for IBS that are
15 neutral on the actual bowel function but also
16 affect pain, and have those been tried in these
17 other areas, where maybe the target is not local,
18 but central? I don't know if that work's been
19 done, but that might be something for consideration
20 as a way to expand success.
21 DR. HANES: I definitely agree. I think
22 that it does get back to the basics where the

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1 mechanism of action is being proposed. Is it being
2 proposed on a molecular physiologic level? Do they
3 have, say, a receptor that they are targeting, or
4 do they not know how the drug works, and they think
5 it might be a central way that it's working versus
6 a localized intestinal way that it's working?
7 So I think it definitely depends on the
8 concept of the drug, what has been shown in animal
9 models starting from there, and then what's been
10 shown or what's being proposed to occur in the
11 human.
12 So I think that's a huge part of it, too.
13 And we have seen proposals looking at one aspect of
14 IBS, so looking at either the abdominal pain aspect
15 or the defecation. And the biggest thing with
16 those -- which we don't discourage, we want to see
17 a variety of different drugs that might help
18 components of IBS because patients need that, and
19 they might not necessarily suffer too much with
20 belly pain, but they suffer more with defecation
21 issues.
22 So I think that we welcome evaluating and

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1 helping with multiple drug development processes,
2 but the issue with that is that we want to make
3 sure that symptoms aren't worsening in the ones
4 that it's not being targeted to or at least that
5 it's being addressed.
6 So say a drug is targeting abnormal
7 defecation. We want to make sure that at least the
8 programs are really looking sincerely at abdominal
9 pain as well, making sure that it's not worsening,
10 and that they're identifying whether there's any
11 problems with that.
12 I'm not sure if that answered your question.
13 I'll let my colleagues answer in terms of kind of
14 what they've been doing. But I would say that at
15 least in my experience -- I've only been with the
16 FDA for two years, but there is a lot of contact
17 between FDA and collaborators, and there's frequent
18 meetings with companies. And they definitely
19 present their protocols for the most part, and we
20 try to work with them. So I think that's a good
21 thing. It happens universally.
22 MS. VEASLEY: I guess just the

1 recommendation would be, theoretically, we don't
2 think there's a big difference among these
3 disorders, to take a deeper dive in looking at how
4 clinical trials are conducted across these
5 conditions and see if there's lessons learned or
6 better practices that are being applied to IBS that
7 could be applied to other conditions.

8 DR. JOHNSON: So that might be something
9 that the NIH -- a lot of our reviews are public for
10 at least those approved drugs, and then there are a
11 lot of others. So that's something I think Sharon
12 Hertz laid out kind of a nice plan of ways that you
13 could look at that and see what could come up.

14 DR. SMITH: Let me be respectful of the fact
15 that it's 5:00. I know there were two other
16 questions. Is it possible for those to wait until
17 tomorrow during our discussion period, or are there
18 pressing questions that you want to get in today?

19 (No response.)

20 Adjournment

21 DR. SMITH: No? Okay. So why don't we end
22 now? Dinner will be at 7:00 p.m. on the mezzanine

1 level. So we'll see you all then. Thank you so
2 much for today.

3 (Applause.)

4 (Whereupon, at 5:02 p.m., the meeting was
5 adjourned.)

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