

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

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Page 1

1 ACTTION
2
3 INITIATIVE ON METHODS, MEASUREMENT, AND PAIN
4 ASSESSMENT IN CLINICAL TRIALS (IMPACT-XX)
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7 Recommendations for the Assessment of Pain
8 Outcomes in Clinical Trials of Chronic
9 Pelvic Pain and Irritable Bowel Syndrome
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Page 3

1 P R O C E E D I N G S
2 (8:35 a.m.)
3 DR. SMITH: Good morning, everyone. We are
4 going to get started, so if you can take your
5 seats, that would be very helpful. Thank you.
6 The first speaker we are going to have this
7 morning is Dr. Jennifer Gewandter. She is an
8 assistant professor in the Department of
9 Anesthesiology at the University of Rochester.
10 Presentation – Jennifer Gewandter
11 DR. GEWANDTER: Good morning, everyone.
12 Thank you for being on time. It's very nice. This
13 morning, I am going to be talking about a
14 systematic review that we did looking at all of the
15 clinical trials in the areas we have been talking
16 about today that we found.
17 The objective of our systematic review was
18 to summarize eligibility criteria and outcome
19 measures from previous RCTs in order to inform our
20 discussion and recommendations for future trials.
21 When designing the coding manual for this review,
22 we thought about a few things that we have already

Page 2

C O N T E N T S	PAGE
AGENDA ITEM	
1 Systematic Review of Chronic Pelvic Pain and	
2 IBS Clinical Trials: Pain Outcome	
3 Measures and Inclusion Criteria	
4 Jennifer Gewandter, PhD, MPH	3
5 Lessons Learned from the Multidisciplinary	
6 Approach to the Study of Chronic	
7 Pelvic Pain (MAPP) Study	
8 Quentin Clemens, MD	19
9 Lessons Learned Along the Path to	
10 Qualification of an IBS Outcome Measure	
11 Stephen Joel Coons, PhD	50
12 Q&A and Panel Discussion	72
13 Moderators - Dennis Turk and Jennifer Gewandter	
14 Group Discussion: Recommendation for the	142
15 Assessment of Pain Outcomes in Chronic	
16 Pelvic Pain and IBS Clinical Trials	
17 Adjournment	244
18	
19	
20	
21	
22	

Page 4

1 covered today, that there are multiple symptoms and
2 we have to control false positive rates. They
3 sometimes include recurrent pain, pain affected by
4 the other symptoms as well as activity-specific
5 pain; many potential causes of lower abdominal pain
6 that we have to rule out if we want to have a
7 homogenous population, as well as this idea that we
8 have mentioned of overlapping conditions.
9 For my presentation, I am just going to
10 outline our systematic review methodology and then
11 the characteristics of the trials that we found and
12 then summarize the trial inclusion and exclusion
13 criteria; the outcomes measures and endpoints,
14 which I think Dr. Johnson did a good job of
15 describing what the difference between those two
16 things are; and summarize the methods that were
17 used to adjust for multiplicity in these trials.
18 First, I just wanted to acknowledge that
19 this was a group effort. A lot of you in the
20 audience were involved in the planning as well as
21 in the feedback stage, and this manuscript is in
22 preparation.

Page 5

1 For our review, we included the conditions
2 that we are talking about today as well as a term
3 for chronic pelvic pain. We searched on the
4 condition names and the word "pain." We also
5 searched on drugs that are approved by the FDA or
6 EMA for these conditions to see if we could find
7 any other trials.
8 Inclusion criteria for the systematic review
9 was that the trial was randomized, it was a
10 pharmacologic treatment, it either treated one of
11 the conditions that are listed and that we're
12 covering today, or included patients with chronic
13 pelvic pain and they didn't require specific
14 etiologies. The trials had to be double-blind and
15 have at least one pain-related outcome reported in
16 the abstract, and this could include discomfort.
17 Our search resulted in 121 articles from the
18 first search, and then two additional articles from
19 the second search that we didn't identify in the
20 first search.
21 Here is the breakdown of what we found in
22 terms of the conditions. The majority of the

Page 6

1 articles reported trials for irritable bowel
2 syndrome, and then interstitial cystitis and
3 chronic prostatitis were the second most common.
4 We didn't find a lot of trials that included a
5 broad pelvic pain indication or vulvodynia.
6 The majority of the trials were published
7 after 2000. And interestingly, only about
8 25 percent of them investigated drugs that we
9 consider to have a putative pain mechanism, so
10 things like opioids, anticonvulsants,
11 antidepressants. Everything else looked at things
12 like anticonstipation, antidiarrheal agents. A
13 little over half were sponsored by industry.
14 Now I'm going to talk about the inclusion
15 and exclusion criteria. What I'm showing here are
16 the percentage of trials that had these inclusion
17 criteria. The darker bar is IBS, and then the
18 other bar is pelvic pain put together. The most
19 common inclusion criteria was a minimum duration of
20 pain, and then the second most common was an
21 established diagnostic criteria. For IBS, that is
22 the Rome criteria.

Page 7

1 One thing that I noted that was interesting
2 was that fewer than half the trials in both the IBS
3 and the pelvic pain group included a minimum
4 severity of pain, and that is something that in the
5 pain conditions that I think about on a daily
6 basis, we would always include in a trial. I'm
7 blanking on what they are because of the dot, dot,
8 dot. It's a minimum score on a composite measure,
9 so like the prostatitis composite score was
10 inclusion criteria for the pelvic pain trials.
11 The second-to-last one is diagnosis by a
12 clinician without any kind of definition really,
13 and then the third one was some kind of imaging.
14 So this was common in things like interstitial
15 cystitis that Dr. Lai talked about yesterday.
16 Is there any way I can stop for a second?
17 Sorry.
18 (Pause.)
19 DR. GEWANDTER: Thank you for your patience.
20 For exclusion criteria, the most common
21 exclusion criteria was a comorbid condition that
22 could be associated with abdominal pain. This

Page 8

1 ranged from things like a UTI to a kidney stone to
2 cancer. The next most common was an imaging or
3 exam or lab testing to try to identify these
4 things, so a test for infection.
5 A lot of trials prohibited use of certain
6 drugs, which I will talk about the different types
7 in a minute; abdominal surgery, alcohol or drug
8 use, as well as psychiatric conditions.
9 The drugs that were prohibited, opioids were
10 commonly prohibited. Then often, there was a
11 phrase that said "treatments for the condition,"
12 but it wasn't specified what that meant;
13 antidepressants, anti-inflammatories. Some trials
14 just stated all analgesics were excluded. Hormones
15 were excluded sometimes, and anticonvulsants.
16 Now I am going to change to primary outcome
17 measures and endpoints. Just so we are on the same
18 page about the denominator in my summaries,
19 86 trials or 69 percent identified one or multiple
20 primary outcome measures. The others just didn't
21 identify one. An example of an outcome measure is
22 the 0 to 10 pain numerical rating scale. That is

Page 9

1 what I am talking about when I say a measure.
2 Then 67 or 54 percent of the trials
3 identified a single primary endpoint. What I mean
4 by that is something like response defined as
5 30 percent improvement in pain intensity at trial
6 endpoint. These numbers are what's used for the
7 denominator and the percentages in my next set of
8 slides.
9 The most common primary outcome
10 measure -- there really weren't that many
11 commonalities, I think, as one takeaway from these
12 slides -- was a composite pain and non-pain outcome
13 measure, which was used a lot in the IC and
14 prostatitis studies; this idea of an overall
15 symptom relief that was specific to the disease, so
16 please rate your IBS symptom relief.
17 IBS or abdominal pain and discomfort relief
18 was common, and then less common was just a measure
19 of pain intensity. Sometimes people identified
20 multiple primary outcome measures, one of which was
21 pain intensity. Then the next most common was a
22 symptom relief question that was not specific to

Page 10

1 disease, so just please rate your symptom relief in
2 general.
3 I also summarized the non-primary outcome
4 measures. Interestingly, pain intensity was very
5 common for a non-primary outcome measure and also
6 diaries of either non-pain symptoms and signs, so
7 like number of urinations, number of defecations.
8 Quality-of-life measures that are specific
9 to the disease were included frequently, as well as
10 measures of depression, anxiety, and quality of
11 life that was not specific to the disease, so
12 something like the SF-36.
13 Now I want to cover how the articles turned
14 those measures into endpoints. I presented this a
15 little bit differently, mainly because if you just
16 take a quick look at the numbers, there is not a
17 lot of commonality between the trials. So what
18 I've done here instead is group them into families.
19 The first family are responder endpoints
20 that are based on over a certain percentage of
21 time, so how the patient is responding in, let's
22 say, 6 out of 12 weeks, for example. The things

Page 11

1 that people use for defining response was adequate
2 pain relief for a certain percentage of time,
3 adequate IBS symptom relief for a certain
4 percentage of time, adequate pain relief and
5 improved bowel movements for a certain percentage
6 of time, and that would include the definition by
7 the FDA, like the FDA guidance would be included
8 in there, and adequate improvement in stool
9 consistency over a certain percentage of time.
10 Then there were also response endpoints that
11 were based on a single time point, so for example,
12 just the endpoint week, so adequate symptom relief
13 at endpoint, adequate improvement in pain and non-
14 pain composite outcome measure at endpoint, and
15 adequate improvement in stool consistency at
16 endpoint.
17 Then there were the severity endpoints, so
18 just comparing. This would be like a T-test,
19 continuous outcome measures, comparing the severity
20 or change from baseline in pain at endpoint; the
21 severity or change from baseline in pain and
22 non-pain at composite at endpoint; and again, stool

Page 12

1 consistency or constipation at endpoint.
2 Also, a couple of the trials -- there is a
3 typo there; sorry, that should be a zero for the
4 pelvic pain -- included a biomarker endpoint, so
5 that was interesting. Again, these are primary
6 endpoints.
7 Then there were a couple miscellaneous that
8 were like a model that incorporates a bunch of
9 different times over the study like repeated
10 measures ANOVA. Then there were a couple
11 single-dose studies, so summary of change in pain
12 intensity at specific time after receiving a dose
13 of the treatment. And I just put the other in for
14 completion, but if they only occurred in one trial,
15 I did not summarize them here.
16 Methods to adjust for multiplicity, the
17 endpoints that I just talked about, some of them
18 can combine two symptoms into one outcome in order
19 to incorporate two symptoms without inflating your
20 false positive rate or type 1 error rate, but you
21 can also do this statistically by adjusting for
22 multiplicity.

Page 13

1 So 71 or 57 percent of the articles did not
2 identify a primary analysis. This would be not
3 only identifying the primary endpoint, but then
4 also describing how you were going to do the
5 statistical analysis in sufficient detail.
6 Thirty-five percent of the articles identified one
7 primary analysis, and 7 percent identified multiple
8 primary analyses, and of those 9, 7 adjusted for
9 multiplicity.
10 The methods that were used were primarily a
11 gatekeeping strategy. Forgive me if I'm boring you
12 and you already know this, but gatekeeping is when
13 you have two primary outcome measures but you give
14 then an order. Let's say the first one would be
15 pain, and you do an analysis on the pain outcome.
16 If it's positive, then you can do an analysis on
17 the constipation outcome, and your significance
18 level could be 0.05 for both of those analyses.
19 But you wouldn't move forward if the pain outcome
20 was not positive.
21 Then one trial used Bonferroni correction,
22 which is when you split the alpha between two

Page 14

1 analyses, so you have to get a 0.025 for both
2 analyses for the trials to be considered
3 positive -- either one can -- sorry -- hit 0.025.
4 Just in conclusion, our review identified
5 high variability in entry criterion outcome
6 measures even within these end-organ conditions.
7 There were deficiencies in identifying single
8 primary analyses or adjusting for multiplicity in
9 the articles. But they did give us multiple
10 examples of methods to combine symptoms into single
11 endpoints or adjust for multiplicity; again, these
12 responder definitions using different baseline,
13 different time frames within the trial like over
14 the whole trial or at the endpoint, composite
15 outcome measures as well as gatekeeping and
16 Bonferroni approaches.
17 For the purposes of our discussion later
18 this afternoon, I just wanted to quickly mention
19 some of the methods that you can use to adjust for
20 multiplicity, or combine outcome measures, or
21 combine endpoints that weren't covered in the
22 systematic review.

Page 15

1 One of them was mentioned yesterday, this
2 idea of co-primary analyses. You do an analysis
3 for pain and an analysis for constipation. They
4 both have to hit at 0.05 for your trial to be
5 considered a positive trial or note that the
6 treatment was effective.
7 There are stepwise procedures that are like
8 a Bonferroni correction, but they are a little bit
9 less strict. For example, Holm where let's say you
10 have two outcomes, you do an analysis on both those
11 outcomes. As long as one of them hits a p-value of
12 0.025, the next one can hit a p-value of 0.05 and
13 you can still consider the trial positive.
14 Then finally, there is this relatively new
15 methods that rank participants based on their
16 combined treatment response on multiple outcomes.
17 An example is DOOR, which we distributed an article
18 on this by Scott Evans. I am just going to try to
19 explain it. I am not a statistician, but I just
20 want to give you the 30,000-foot view of this.
21 An example of this would be if you want to
22 incorporate in your endpoint how patients respond

Page 16

1 to pain but also whether they take rescue
2 medication or not. One of the main advantages of
3 this type of analysis is you can incorporate
4 competing interests. If you take rescue
5 medication, your pain might look better, but that
6 might not necessarily mean you're a better
7 responder because you've taken rescue medication.
8 In order to do this analysis, you rank
9 participants. This might be an example ranking
10 scheme. Patients who improve by greater than
11 50 percent on their pain and they take no rescue
12 medication, that's the best outcome. Then the next
13 outcome would be that they improve by 50 percent,
14 but they took rescue medication greater than
15 20 percent of the days.
16 Then the next would be they have less than a
17 50 percent improvement in pain, but they don't take
18 any rescue medication. Then finally, they have
19 less than a 50 percent improvement in pain, and
20 they also were taking a bunch of rescue medication.
21 You can obviously use finer gradation for
22 this, and you might not necessarily agree with the

Page 17

1 order that I put here, which is one of the
2 challenges of the method. So you rank patients
3 based on these criteria. And what the DOOR
4 probability tells you, when you do the analysis, is
5 the probability that a randomly selected patient in
6 arm A has a more desirable outcome than a patient
7 in the control arm.

8 The advantages of this method are that it
9 uses outcomes to analyze the overall patient
10 experience rather than patients to analyze each
11 individual endpoint. When you do a co-primary
12 analysis, you might show that, overall, people have
13 improved pain and, overall, they have improved
14 constipation. But the patients who improved in
15 pain could be completely different than the
16 patients who improved in constipation, so you don't
17 really know what their overall experience is.

18 It has this appealing probability
19 interpretation that we usually can't do with
20 frequent [ph] statistics that people like. And
21 again, it deals with this competing outcomes issue
22 of if I take more rescue, my pain will be lower,

Page 18

1 but that doesn't necessarily mean the drug was
2 better.

3 It may have more power than a dichotomous
4 composite responder analysis. The responder
5 analysis that the IBS guidance gives us where you
6 have to be a responder, you have to improve
7 50 percent on pain and somewhat on the constipation
8 scale, or the stool consistency scale, because
9 that's just a dichotomous analysis, this might have
10 more power than that.

11 The limitations are developing that ranking
12 scheme -- you know I made up -- so how much input
13 do you need from patients, how do you decide what
14 those ranks are. Also, just like any composite
15 measure, the differences could be driven by a
16 single measure. It could be all driven by if you
17 did this for pain and constipation. The change in
18 the probability could be all driven by pain, but
19 constipation could have not changed. But that is
20 true for any composite.

21 With that, I will thank everyone again who
22 was involved in the systematic review, as well as

Page 19

1 Dr. Evans for reviewing my slides and hopefully
2 preventing me from embarrassing myself.
3 (Applause.)

4 DR. SMITH: All right. So next, we have
5 Dr. Quentin Clemens, who is a professor of urology
6 at the University of Michigan Medical Center.

7 Presentation – Quentin Clemens

8 DR. CLEMENS: Thank you, and I have really
9 enjoyed the discussion and meeting so far. There
10 was a lot of talk yesterday about the MAPP, so I
11 just want to bring everyone up to speed about the
12 organization and some of the main findings.

13 A couple points about the title slide, we
14 have two Ps, so we are part of the club.

15 (Laughter.)

16 DR. CLEMENS: The other is that as someone
17 who is involved every day with the data analyses, I
18 always feel tempted to put the title being
19 questions unearthed by the MAPP rather than lessons
20 learned because it is very tempting as you are
21 always thinking of the weaknesses of what you found
22 or what is the next analyses. But I will do my

Page 20

1 best to summarize what we have found to be the main
2 findings.

3 MAPP stands for Multidisciplinary Approach
4 to the Study of Chronic Pelvic Pain. Someone asked
5 me Friday evening what does MAPP stand for, and
6 even I got it wrong because I put a urologic in
7 there. This is the official title, but we just
8 refer to it as MAPP.

9 It is funded by the NIDDK, and we are
10 dedicated to studying IC and chronic prostatitis,
11 and we have coined a term, "urologic chronic pelvic
12 pain syndrome," to encapsulate both of those
13 conditions.

14 A little editorializing here, when a man has
15 pain essentially from the nipples to the knees and
16 it is not associated with bowel movements, they
17 tend to come to see urology, and often they get
18 diagnosed with chronic prostatitis, chronic pelvic
19 pain syndrome. And that is not inappropriate
20 necessarily. We're used to it.

21 Women are different. When they have pelvic
22 pain, they see a gynecologist. And if the pain

Page 21

1 tends to be focused on the bladder, then they
2 ultimately sometimes find their way to urologists
3 and get diagnosed with IC.
4 So we are combining these two conditions,
5 but they are actually not the same. There is a
6 whole population of women out there who have pelvic
7 pain. It's not endometriosis necessarily, and it
8 is not associated with the bladder. We are not
9 studying them in this.
10 For instance, you would expect that if we
11 compare men and women using these criteria, that
12 the women will have more bladder symptoms because
13 that is the definition of IC, and what we are
14 seeing, that's what we found. As we noticed
15 yesterday, we were surprised a little by how many
16 bladder symptoms men have, but I think as we think
17 about what we are studying here, I think keeping in
18 mind that these are a little bit apples and oranges
19 is useful.
20 Why do we need MAPP? Well, we haven't made
21 much progress in helping these patients. We in
22 urology and urogynecology had not, before the MAPP,

Page 22

1 really worked closely with smart people like
2 yourselves. There is more and more of a feeling
3 that these patients represent probably a
4 multiplicity of different etiologies; in other
5 words, there is a need for phenotyping. And
6 hopefully if we get a better understanding of
7 subgroups, that will lead to more targeted
8 therapies and better outcomes.
9 It is organized. There are six main what we
10 call discovery sites listed here. One of the
11 smartest things the NIDDK did is they required that
12 each site have a non-urology investigator as a
13 co-PI. I work with Don Clauw. UCLA has Emeran
14 Mayer, et cetera, et cetera; Dedra Buchwald from
15 University of Washington. That has been for me the
16 best experiences about this, and it brings more
17 energy and more insight, so that's been really
18 good.
19 Then we have some specialized discovery
20 sites that don't recruit patients but conduct some
21 other ancillary studies; the data coordinating
22 center, which Dick Landis here runs, and a tissue

Page 23

1 and technology core at University of Colorado; then
2 of course the NIDDK. And there is an oversight
3 executive committee. Mike Pontari is a member of
4 that.
5 Here is a nice map that shows we have a
6 fairly decent geographical representation,
7 including Canada.
8 The goals are to better understand the
9 treated natural history of UCPPS; identify clinical
10 and research factors that hopefully will define
11 relevant subgroups, which can inform future
12 clinical trials and address underlying disease
13 pathophysiology.
14 Our inclusion criteria were really quite
15 broad. They had to have a clinical diagnosis of IC
16 or CP. I think that is important. There were some
17 patients that found their way to us that maybe saw
18 an ad, and so we made allowances to say, well, they
19 tell us they were diagnosed with IC.
20 So what we made sure is that there was some
21 clinical evaluation done when they came to the
22 initial appointment by a clinician, just talked to

Page 24

1 them a bit about their symptoms and make sure it
2 wasn't obvious they had endometriosis or something
3 along those lines, as opposed to some idea where we
4 would advertise widely and anyone with the right
5 types of symptoms could get in. We wanted to be
6 sure as best we could that these really were IC and
7 CP patients.
8 We talked about exclusions a bit yesterday.
9 These are pretty standard across trials and
10 studies.
11 We did want to examine whether those with a
12 short duration of symptoms were different, those
13 with longer, so we oversampled for subjects with
14 less than 2 years of symptoms. That is what we
15 defined as early.
16 Now, to cut to the chase, it didn't really
17 matter very much in the analyses we've done, so we
18 haven't followed up much with that in MAPP II, but
19 it turns out that the patients with short durations
20 of symptoms really tended to not look much
21 different at all than those with longer duration.
22 Then we had two control groups. One were

Page 25

1 those with no urologic symptoms at all, and the
2 other was patients diagnosed with fibromyalgia,
3 IBS, or chronic fatigue. The RFA specifically
4 focused on those three conditions, so we focused on
5 those three conditions.
6 We did not recruit intentionally people with
7 migraine or other conditions that are typically
8 part of that chronic overlapping pain condition
9 group. This was our positive control group.
10 You-all, I'm sure, are very interested. I
11 didn't list all the questionnaires because most of
12 the audiences don't care too much about them, but
13 all kinds of different, psychosocial symptoms,
14 catastrophizing, IPIP questionnaire, et cetera,
15 et cetera. This was about a 2 to 3-hour battery of
16 questionnaires that were administered, a lot of
17 details about their urologic symptoms, of course,
18 psychosocial symptoms, pain symptoms in general,
19 the body map.
20 The physical exam was fairly minimal. In
21 MAPP I, we asked do they have pelvic tenderness,
22 pelvic muscle tenderness, yes or no. In MAPP II,

Page 26

1 we are doing more of a detailed, which pelvic
2 muscles are tender, and also importantly, does the
3 exam reproduce at least some of your symptoms to
4 try to get a little more detail about that.
5 We obtain bio specimens. We did
6 neuroimaging and QST, and I will talk about those a
7 bit at the end. It took some time to get those all
8 up and running for a variety of factors. I don't
9 think there had been a multi-institutional group
10 like this who had ever done neuroimaging before.
11 So it's always been one-off. One site does
12 something; another site does something.
13 So we get everyone together, agree on a
14 protocol, make sure all the scanners were
15 equilibrated equally, et cetera.
16 As a result, the number of subjects who have
17 the questionnaire data, the QST, because that took
18 some time, and the neuroimaging, when you do that
19 Venn diagram, it's actually pretty small for
20 MAPP I.
21 In MAPP II, now we're halfway done with
22 recruitment. We already have way more patients who

Page 27

1 have had all three together than we do in MAPP I.
2 So there is an example of some of the advances you
3 can make with continuing things.
4 This is the flow. The subjects were
5 recruited, as I mentioned. All of them, including
6 the controls, of course, did the baseline
7 phenotyping that I just described. Then for the
8 controls, they were done. Then the UCPPS patients
9 were then followed for a year. They came back at
10 6 months and 12 months and had pretty much the same
11 assessment except no QST or neuroimaging. That was
12 just done at baseline.
13 Also, throughout the year, they underwent
14 biweekly internet assessments. So they were paid
15 about \$5 to do that. And I'll show you, but they
16 really were very compliant with that. So we have a
17 huge amount of data, a lot of repeat measures,
18 et cetera.
19 Then people who were in the study then were
20 eligible to have site-specific studies done, kind
21 of as add-ons, based on the interest of the various
22 sites. Importantly, there on the right, the

Page 28

1 regular treatments were allowed. We tracked that
2 to some degree. Every 2 months, we assessed what
3 treatments they were currently undergoing, so we
4 had some idea of the treatments, but not super
5 closely following that.
6 This is a treated natural history study.
7 This is sites that we think know what we are doing
8 in terms of treating this, and so there are a
9 variety of different treatments that were
10 prescribed. So when we talk about someone who got
11 better, they got better based on probably the
12 treatments they received.
13 We recruited overall 424 UCPPS patients,
14 415 healthy controls, and 200 of the positive
15 controls. As you can see, the positive controls
16 were mostly women just because they tend to have
17 those conditions more commonly.
18 The first point is that we found using
19 baseline data that our MAPP subjects look similar
20 to those that were previously reported in the
21 literature. Mean symptom duration, 8 to 9 years.
22 We used some of the symptom scores that could be

Page 29

1 compared with older studies as well and looked very
2 similar.
3 The other here is 83 percent missed no more
4 than 3 of the 26 planned contacts throughout the
5 year. So it's really a tribute to the patients and
6 also speaks to how desperate they are to find
7 better treatments. They are very willing to bend
8 over backwards for us to help.
9 A couple of the themes that have emerged as
10 being as important: The one is the degree of
11 widespreadness of pain is important. Here we're
12 finding body maps to be increasingly useful, so if
13 we define pelvic pain only as those three regions
14 there, we understand that the IBS people are going
15 to say, wait a minute, that's our area, too.
16 We are looking into that more, and in
17 MAPP II, we have actually divided the abdomen into
18 some different quadrants to try to help. We also
19 have the CMSI instrument, which has a module for
20 IBS. So if bowel symptoms are reported, then there
21 is a separate model triggered to really go through
22 diagnostic criteria. So we have those data that we

Page 30

1 can look at.
2 This was essentially a baseline tool. We
3 have found that those who have more widespread
4 symptoms have worse urologic pelvic pain. In
5 MAPP II, we have repeated measures for this,
6 including during a run-in period to look at the
7 stability and help to define the phenotype maybe
8 better at baseline. Also, we have severity as a
9 measure. This doesn't.
10 So ultimately, maybe if they have trivial
11 head pain, we might exclude them as having pelvic
12 pain and beyond, for instance. So we're trying to
13 look into this in more depth, and we are looking at
14 it in more depth.
15 In terms of the psychosocial symptoms, our
16 urologic patients are every bit as affected in this
17 regard as fibromyalgia, IBS, chronic fatigue
18 patients. As you might expect, if you have these
19 chronic fatigue syndrome, et cetera, symptoms, you
20 are more worse off. You are worse off, worse
21 quality of life, worse psychosocial symptoms.
22 We found about 40 percent of the females and

Page 31

1 30 percent of the male subjects had one of these
2 diagnoses. And then of course it goes up if you
3 add migraine and other types of overlapping pain
4 conditions. This has been reported previously for
5 women, not so much for men, so it's somewhat novel
6 data, examining this as closely as we did for the
7 men.
8 We discovered what we call bladder
9 sensitivity phenotype, and this was briefly
10 mentioned yesterday. The first point is that men
11 had more bladder symptoms than we thought. This
12 doesn't mean that all the men have IC, but what it
13 does mean is we should pay attention to that when
14 seeing the patients because it does seem to
15 correlate with a worse quality of life and would
16 suggest if we helped to address those bladder
17 symptoms -- or I guess the other way to say it, if
18 we ignore the bladder symptoms, which I think is
19 perhaps what is done not too rarely, we won't be
20 able to help them as much. And this bladder
21 hypersensitivity seemed to be associated at
22 baseline with worse quality of life and more severe

Page 32

1 symptoms overall.
2 Jamie Griffith, who's a psychometrician at
3 Northwestern, led this where we basically looked at
4 unstructured factor analysis at baseline of the
5 symptoms and found that two factors emerged: pain
6 and urinary symptoms. This was similar in men and
7 woman. Then we also looked longitudinally and
8 found that not only did they look different at
9 baseline but they tracked differently. So this was
10 the subject of a good bit of discussion yesterday.
11 To date, a lot of the outcomes for these
12 trials have been composite scores for urinary and
13 pain, and so what this leads to is a conclusion
14 that we probably should have pain outcomes and
15 urinary outcomes separately.
16 In fact, John Farrar has led an activity,
17 grant that has been written up to try to
18 retrospectively look back at the existing clinical
19 trials, try to separate, the best we can, men and
20 women into pain or urinary phenotype, and look at
21 the types of treatments they get, and see if by
22 doing that -- and in having pain and urinary

Page 33

1 outcomes, which we can derive from the trial data,
2 see if we can examine this concept using existing
3 data to see if it pans out that perhaps some of
4 these negative studies might look positive if we
5 subcategorize them like we are proposing in MAPP.
6 When we looked at longitudinal data for
7 whether patients get better or worse, the first
8 concept was to just look at the slope of the
9 symptoms. This is a pretty stable of group of
10 patients that don't tend to change their symptoms a
11 heck of a lot over time. So using a slope, most
12 everyone just ended up looking stable.
13 We looked more closely into the data and
14 came up with this functional clustering algorithm.
15 And these next two slides are the ones where I am
16 happiest that Dick is here so that if there are
17 questions later, he can go over exactly how this
18 was done.
19 We still, as you can see, had 60 percent who
20 were in that stable group, but we had 20 percent
21 who were improving and about 20 percent who were
22 worsening over time. We did this for both the pain

Page 34

1 and the urinary symptoms. We have composite scores
2 using the GUPI questionnaire and the IC symptom
3 index to define the pain symptoms and the urinary
4 symptoms. Then once we had defined these
5 variables, then we could examine predictors of who
6 gets better, who gets worse.
7 Another editorial comment. This, Dick, was
8 about six months of work, right? It took a while.
9 When we do clinical trials, we prespecify an
10 outcome, and then we get to that point, and then we
11 look at it, and then we are done.
12 These types of cohort studies are much
13 different, and in my opinion much more difficult to
14 run because you are constantly reassessing as you
15 go. And it seems pretty simple that you ahead of
16 time say, well, these are some variables we
17 hypothesize will correlate with improvement.
18 You can even say we are going to measure
19 improvement one way or the other, but then as you
20 get into it and have all the data, you say, well,
21 there's probably, with all this data, a better way
22 to measure improvement or worsening. You don't

Page 35

1 necessarily want to publish a very simplistic paper
2 that concludes one thing, and then actually have a
3 more detailed analysis which you think is better
4 and concludes something else.
5 So then you kind of put the brakes on
6 things, spend six months or so to define what it
7 means to improve or get worse, which is kind of a
8 fundamental component, and then you can publish
9 your paper, and then move on using that variable
10 longitudinal data for other analyses.
11 This paper, as you can see, 2017, it just
12 came out about a month ago. We are seven or eight
13 years in. I don't think we have been resting our
14 feet the whole time. These things take a lot of
15 time.
16 The predictors of better outcomes
17 included -- and the most important one is the
18 higher baseline symptom severity. Other predictors
19 were less widespread; pain, less; non-urologic
20 symptoms based on the CMSI and body map; better
21 overall physical health and mental health; with the
22 measures you can see here, sleep and fatigue.

Page 36

1 The mental health particularly -- and this
2 has been shown before -- catastrophizing was
3 important and also perceived stress. Some of the
4 factors that were not important were age, sex,
5 symptom duration, and perhaps somewhat
6 surprisingly, anxiety and depression.
7 As we do more and more of these analyses, we
8 find that sex typically washes out. So we
9 certainly acknowledge that there are differences
10 between the sexes in the types of symptoms that
11 they often present with, but if you actually have
12 the same symptoms in a man and woman, the sex
13 doesn't matter, and that's what we've found
14 repeatedly.
15 That's one of the reasons for this rationale
16 or this UCPPS nomenclature because sex doesn't seem
17 to matter as much as perhaps was thought. And I've
18 already mentioned symptom duration has not really
19 panned out as being very important, at least as we
20 defined it as two years.
21 We talked about flares yesterday. This
22 every 2-week assessment included a question, have

Page 37

1 you had a flare in the last 2 weeks? Before we did
2 that, we did focus groups that showed that when we
3 asked about flares, the patients understand what
4 we're talking about, so that was reassuring.

5 There's one paper that's been published for
6 women, another that's in the works for men, with
7 the results of the focus group analyses. That's
8 where we learned that some patients have flares
9 that are minutes in length, et cetera.

10 Women have more flares than men.
11 Ninety-five percent of the cohort report at least
12 one flare, and you can see the distribution here
13 with 40 percent reporting 10 or more flares. This
14 was more common with individuals who had widespread
15 pain and those who had more severe bladder
16 symptoms.

17 The other interesting thing we did was when
18 they had a flare twice, it triggered a flare
19 supplemental questionnaire: In the last two weeks,
20 what foods have you eaten, what sexual activities,
21 what exercises, et cetera? Then there was also two
22 times when they said, no, I didn't have a flare,

Page 38

1 that same supplemental questionnaire was triggered.
2 So we had an internal control, if you will, within
3 the patients.

4 We didn't really identify dietary factors or
5 much in the way of activities that seemed to
6 trigger, using those methods. There were some
7 question of maybe having a preceding UTI. And one
8 of the things that's led us to do in MAPP II is to
9 look more closely using mobile apps at some of
10 these flares that may be more short term and see if
11 there's something we can learn from that since we
12 didn't identify clearly any risk factors across the
13 group for flares in MAPP I.

14 I mentioned that we had many, many
15 observations here, so one thing we looked at and
16 demonstrated, not surprisingly, is that there's a
17 significant regression to the mean effect.

18 In MAPP II, we're incorporating a four-week
19 run-in. And this doesn't really apply too much for
20 clinical trials, I suppose, but certainly for
21 cohort studies, having a run-in period and then
22 setting the baseline after 4 weeks, that's

Page 39

1 something we've incorporated in all of our data
2 analyses. You can see that if you don't account
3 for the run-in period, the number of people
4 assigned to different categories of improved,
5 worse, and change, it changes to some degree.

6 We also looked at variability. We have
7 every 2 weeks, and you can look at how their slope
8 is or how they do over time. You can also look at
9 the volatility of their symptoms, and we can assign
10 a high, low, or medium variability group.

11 We are looking at, for instance, healthcare
12 seeking. I don't have a slide on that, but every
13 2 weeks, we ask them did you go to the ER, did you
14 go to see your doctor for your symptoms. We can
15 look to quantify the degree of healthcare seeking
16 and correlate that with various things, including
17 symptom variability.

18 We concluded that the phenotyping should
19 focus on pain localization, pain outside of the
20 pelvis, the presence of chronic overlapping pain
21 conditions, and bladder hypersensitivity. We
22 should not use a total symptom score. We should

Page 40

1 have pain and urinary separate.

2 Very briefly, we talked a little bit about
3 pain testing. It is nothing like this. It uses a
4 device like this where there is pressure put on the
5 thumb bed, and then the subject basically says now
6 it's starting to hurt. And now we know this is
7 about as much as I can tolerate, and you can
8 generate curves and compare them across different
9 groups.

10 It has been demonstrated -- this is a
11 measure of global hypersensitivity. Our urologic
12 patients are just as sensitive as fibromyalgia
13 patients, et cetera, on the global level. It's
14 interesting, when you measure that as baseline,
15 that does seem to associate with some longitudinal
16 outcomes like number of flares and likelihood of
17 improvement.

18 Then the neural imaging, again, not
19 necessarily relevant for clinical trials, but very
20 briefly, we can see at least at 3 months, there are
21 certain resting state neuroimaging findings that
22 seem to correlate with 3-month outcomes, so that's

Page 41

1 interesting.

2 Other methods have shown that our patients
3 seem to have an increased signal in the area of the
4 pelvic floor, which is really cool because that
5 correlates with what we see clinically. What we're
6 wanting to do is in MAPP II, as I mentioned, we're
7 being more detailed about the pelvic-floor exam and
8 seeing if there's some correlation with those who
9 have pelvic tenderness that reproduces their
10 symptoms, do you get maybe even a better signal?

11 This just demonstrates that there is
12 similarities between our patients who have
13 widespread pain and fibromyalgia patients, who by
14 definition have widespread pain. So we're seeing
15 the same types of signals using these neuroimaging
16 techniques.

17 In the second phase, now a couple things
18 we're doing, we're following the patients for
19 3 years instead of 1 year. We're following them a
20 little less frequently. We're getting longitudinal
21 neuroimaging and sensory testing. In MAPP I, as I
22 mentioned, we only did it once. We're following up

Page 42

1 on some certain biomarkers. I didn't talk about
2 biomarkers here because that's not really
3 necessarily relevant to a clinical trial.

4 Very importantly, we're really focusing on
5 treatments. We're tracking their treatments
6 monthly, and we're really wanting to correlate our
7 phenotyping with treatment response, not by
8 assigning a treatment but by following them
9 closely, having them contact us when there's a
10 treatment change, again, prospectively following
11 them monthly.

12 Ultimately, the question here is can we
13 identify a signal that may be widespread pain
14 patients seem to do a little better with tricyclics
15 or something. That may help us then organize and
16 set up clinical trials on a small scale for the
17 next phase.

18 Here's the website. Thanks for your
19 attention.

20 (Applause.)

21 DR. SMITH: We're ahead of schedule
22 actually, so if there are any very specific

Page 43

1 questions that you'd like to ask Dr. Clemens, we
2 can do that now.

3 DR. KATZ: Hello.

4 DR. CLEMENS: Hi.

5 DR. KATZ: How did you define the
6 centralized phenotype exactly?

7 DR. CLEMENS: Well, the main way has been
8 with the body map using the number of sites
9 that -- and we're, again, continuing to improve
10 that definition, but that's the way though. Pain
11 in the pelvis only versus pelvic pain and beyond.

12 DR. KATZ: Was there a specific criteria?
13 How many sites, how many body sites did the
14 patients have to endorse before they were
15 considered centralized?

16 DR. CLEMENS: We've evaluated that in
17 different ways. I think Dick -- 3 or 4 sites
18 total, so we had to look at a gradient, but I think
19 it was not just one single site. I think it was
20 three total outside the pelvis.

21 DR. KATZ: What do you think is the best way
22 of determining --

Page 44

1 DR. LANDIS: I don't know if Henry is still
2 here or not, but the paper that just came out, we
3 had an intermediate group where they have one to
4 2 sites beyond the pelvis, and then 3 or more was
5 the basic gradient from none to intermediate to
6 widespread. That gradient tracked quite strikingly
7 with many different symptoms.

8 DR. CLEMENS: We are, in MAPP II, as I had
9 mentioned, looking at severity. I know John Farrar
10 has been involved with this quite a bit. Even
11 things like, well, if they have 2 sites outside,
12 but one of them is upper thigh and one is lower
13 thigh or something, then probably saying, well,
14 that probably is the same thing, so even looking
15 specifically to really try to incorporate not just
16 severity but also is it really one area or not.

17 The ultimate question is what is the least
18 detailed body map that we can get with, research
19 and clinical use. So what you do is you look at
20 all the data and be super complicated, and then do
21 a pretty simple one and see how much more you get
22 for the complicated one.

Page 45

1 So MAPP I was a fairly straightforward one,
2 and those are the data that I'm presenting. In a
3 year or so, we may have a little different
4 recommendation, but my goal ultimately is to have a
5 fairly straightforward body map for clinician use
6 that can maybe be part of the minimal dataset that
7 we propose for clinicians.
8 DR. KATZ: It seems to me that another
9 question is what is the validity of any cutoff that
10 you would choose. In other words, it could be
11 arbitrary; well, do 3 sections or 5 sections or
12 whatever, or you can say, well, what is the
13 definition that means something in terms of maybe
14 whatever.
15 DR. CLEMENS: Yes. So we've shown that when
16 we talk about validity, usually that means how does
17 it correlate with various clinical parameters. So
18 we've shown that it seems to be important for
19 longitudinal whether a patient gets better or
20 worse, if it's predictive of that.
21 MAPP II will have 3-year data and may be
22 able to similarly conclude that's what we'd like to

Page 46

1 be able to say is, yes, it matters. It will
2 correlate with how well in general patients do with
3 treatment. So I think that's where -- if it ends
4 up not correlating at all, then we probably
5 wouldn't propose it because, to your point, other
6 than for research purposes, it really has no
7 utility, perhaps.
8 John, anything?
9 DR. FARRAR: Nat, your question is very
10 reasonable. In MAPP I, there is very little QST
11 data, but in MAPP II, as Quentin was saying,
12 there's going to be a much higher correlation with
13 QST and these other symptoms. We'll be able to
14 answer that question more specifically, but we
15 don't have that data currently.
16 The definition of centralization, if you
17 like, is simply a clinical definition based on the
18 widespreadness of pain, and we understand that
19 that's not an appropriate definition of wind-up,
20 and centralization, and all of the things that we
21 would normally think about in the experimental
22 paradigm.

Page 47

1 What we hope is then -- well, what we will
2 be able to look at in MAPP II once we have all the
3 data is to look at the correlation between the
4 widespreadness and QST and neuroimaging studies in
5 a much more concise way to try and get at some of
6 those issues.
7 DR. SMITH: I think Ralf had one question.
8 DR. BARON: This was exactly my question, of
9 the correlation of QST and the body maps. But the
10 only QST measure you did was pressure pain
11 tolerance at the thumb; is that correct? Are there
12 any other QST measures planned in the next MAPP II
13 or something?
14 DR. CLEMENS: Yes. So we are doing auditory
15 and visual sensitivity in MAPP II at multiple time
16 points as well, but MAPP I was just the thumb
17 pressure.
18 The other point from validity I'd make is
19 that Bruce Naliboff did look at the correlation
20 between the body map findings and the CMSI, and
21 they correlated very highly when the CMSI was in
22 the last year.

Page 48

1 Also the CMSI asked in your lifetime, have
2 you had these. That didn't correlate at all. But
3 I think that was also reassuring that, A, you can
4 use either. They seem to be measuring the same
5 thing, and we're focusing on the body map because
6 it seems to be a more useful perhaps clinical tool,
7 quicker, too, for the patient to complete.
8 DR. SMITH: Chris and then we'll cut the
9 current questions unless anyone has something very
10 specific.
11 MS. VEASLEY: Chris Veasley. So we've
12 grappled with this idea of data analysis
13 understanding that cross-sectional studies are not
14 a great way to look at it, and then we obviously
15 need prospective.
16 The problem is, is that a person can be
17 categorized in year 1 as just having IC and just
18 having pain in the pelvis, but in year 3 or 4, they
19 could transition into another group.
20 So I guess my question is around data
21 analysis, is there a plan to go back and look at
22 those two time points to when a person may have

Page 49

1 transitioned from just IC to multiple conditions,
2 or changing their allocation in terms of what group
3 they fit into in the second data analysis?
4 DR. CLEMENS: Yes. So we are using the
5 run-in period to establish short-term stability in
6 working to get rid of perhaps background noise and
7 better identify the phenotype. Then for sure, in
8 MAPP II, they do the map at multiple time points
9 throughout the three years, so we can look at that.
10 And for those who have been in MAPP the whole -- so
11 not everyone has, but certainly, we can look all
12 the way back there and see.
13 There were some talk yesterday about this
14 progression. To date, this idea that pain for IC
15 starts in the pelvis and moves elsewhere hasn't
16 really panned out. People still talk about it. I
17 know Dan Clauw has this theory that it's really one
18 disease. In some people, it starts in the head and
19 moves to the pelvis, and others.
20 At least from the analyses we've done, that
21 seems to be somewhat true where it's semi-random
22 that the head is a little bit early; fibromyalgia,

Page 50

1 a little bit later. So I think it will be
2 interesting to examine that in more detail
3 throughout at least the three years.
4 DR. SMITH: Was your question very
5 specifically for Dr. Clemens about MAPP?
6 DR. WESSELMANN: Yes. My question was
7 actually in the same direction as what Chris asked.
8 For instance, Jack Warren has published a series of
9 papers on this topic specifically related to IC in
10 a prospective study where the symptoms often start
11 quite early on or can be triggered by surgical
12 interventions in the pelvic area and then move on
13 to widespread pain.
14 DR. SMITH: Next, I'd like to welcome
15 Dr. Stephen Coons. He's the executive director of
16 the Patient-Reported Outcome Consortium at the
17 Clinical Path Institute.
18 Presentation – Stephen Coons
19 DR. COONS: Good morning, and thank you for
20 inviting me. I appreciate the planning committee
21 extending an invitation. I'm honored to be a part
22 of this IMMPACT XX.

Page 51

1 I am going to talk about this journey that
2 we've been on, lessons learned along the path to
3 qualification of an IBS outcome measure. My
4 footnote is that we haven't reached the destination
5 yet. We do not have a qualified measure or
6 measures in this case for IBS.
7 I'm going to talk about qualitative research
8 that we have done in terms of concept elicitation
9 and cognitive interviews with our draft measures.
10 We have ongoing at the present time a quantitative
11 pilot study in 315 patients, and I don't have data.
12 I should have had data by now.
13 One of the problems that happens sometimes
14 is things don't go as planned, as you can imagine,
15 and we are deploying this instrument on an
16 electronic data capture device, essentially a
17 handheld device.
18 We should have had all of our data collected
19 by now, but some of the data collection was over
20 the period of time in which we changed to daylight
21 savings time. And it ended up that the devices
22 weren't programmed properly to take into

Page 52

1 consideration the fact that there was one less hour
2 in the day. So some of the instruments that we
3 were implementing to look at construct validity
4 didn't get administered. So I only, as I say, have
5 qualitative data to talk to you about today.
6 First, I want to talk about the context in
7 which we're doing this work, and that's the
8 Critical Path Institute. C-PATH was established in
9 2005 by the University of Arizona and FDA's Center
10 for Drug Evaluation and Research, and it's a
11 public-private partnership. It's an independent
12 nonprofit organization, and part of our funding
13 does still come from FDA. Most of my salary comes
14 from this grant, so I'm very appreciative of this.
15 C-PATH is dedicated to implementing FDA's
16 Critical Path Initiative by providing a neutral,
17 precompetitive venue for collaboration aimed at
18 accelerating development of safe and effective
19 medical products.
20 Then within C-PATH, the Patient Reported
21 Outcome Consortium was established. And we have
22 right now about 14 different consortia, and the PRO

Page 53

1 Consortium is one of them, formed in late 2008 by
2 C-PATH in cooperation with, again, FDA's Center for
3 Drug Evaluation and Research and the pharmaceutical
4 industry.
5 Our membership is pharmaceutical firms. We
6 have 26 members, and then we have other
7 participants, representatives of FDA, NIH, and at
8 times, EMA. Then we have other clinical
9 consultants, patients, academic researchers, and
10 CROs that partner with us in the development of PRO
11 measures and other clinical outcome assessment
12 tools. This is a list of our current 26 members.
13 The PRO Consortium mission is to establish
14 and maintain a collaborative framework with
15 appropriate stakeholders for the
16 qualification -- and I'm going to talk further
17 about qualification -- of patient-reported outcome
18 instruments and other clinical outcome assessment
19 tools that will be publicly available. That's part
20 of the process or part of the outcome of this is
21 that these instruments will be publicly available
22 for use in clinical trials where clinical outcome

Page 54

1 assessment-based endpoints are used to support
2 product labeling claims.
3 Our goals within the PRO Consortium are to
4 enable precompetitive collaboration that includes
5 FDA input along the way and expertise; develop and
6 obtain FDA qualification for PRO measures and other
7 COA tools; avoid development of multiple endpoint
8 measures for the same purpose.
9 That really is a major goal, and it's
10 certainly not -- we haven't achieved that in all
11 circumstances because a lot of individual companies
12 are still developing their own measures, but to
13 some extent, we have been able to avoid it within
14 the context of the working groups that I'll mention
15 just briefly.
16 Show the cost of developing new endpoint
17 measures. For those of you that have ever
18 developed a PRO measure or other clinical outcome
19 assessment tools, it can be very expensive, a
20 million to \$2 million to develop an instrument. So
21 we're able to share the costs across the sponsoring
22 firms.

Page 55

1 Then a major goal is to facilitate FDA's
2 review of medical products by standardizing
3 COA-based endpoint measures that will be, as I
4 said, publicly available. And we hope there will
5 be uptake within the industry to use those in their
6 trials.
7 Dr. Kovacs mentioned this briefly yesterday.
8 This is the DDT, drug development tool guidance.
9 This is talking about the qualification process for
10 drug development tools, COA tools, clinical outcome
11 assessment tools being one of those. The intent of
12 that is to expedite development of publicly
13 available drug development tools that can be widely
14 used in drug development.
15 The definition of qualification is that
16 qualification is based on an FDA review of evidence
17 that supports the conclusion that within the
18 specified or stated context of use, the drug
19 development tool can be relied upon to have a
20 specific interpretation or application in drug
21 development and regulatory review.
22 Our working groups, there are 10 of them,

Page 56

1 and you can see the irritable bowel syndrome
2 working group is one of them. We have an annual
3 membership fee, and then pharmaceutical firms can
4 opt into working groups. Indeed, then that subset
5 of the pharmaceutical firm members then sponsor the
6 activities that go on in those working groups. And
7 you can see that we have from 2 to 10 firms
8 sponsoring each of our 10 working groups.
9 The goal of the working groups is to produce
10 and/or compile the necessary evidence to enable new
11 or existing COAs to be qualified by the FDA. We
12 don't only want to develop new measures. We would
13 love to leverage measures that are out there and
14 either adapt them, modify them, or use them and see
15 what evidence is available for them, and ultimately
16 develop a qualification package that we can submit
17 to the FDA. But most of the instruments that we're
18 working on now were developed de novo within the
19 context of our working groups.
20 Then again, Dr. Kovacs mentioned this
21 yesterday, in terms of the different types of
22 clinical outcome assessment tools, and our working

Page 57

1 groups are working in all of these except right
2 now, clinician-reported outcome measures. We're
3 not moving forward right now with any ClinRO
4 measures for qualification.
5 The IBS working group was established in
6 March of 2009, so we've been working on this for
7 quite a while; three pharmaceutical industry
8 sponsors, Allergan, Ironwood, and Takeda.
9 RTI Health Solutions was selected as the
10 working group's contract research partner, and the
11 specific goal was to develop and obtain FDA
12 qualification of three patient-reported outcome
13 measures of the signs and symptoms of IBS-C, IBS-D,
14 and IBS-M for use in assessing primary endpoints in
15 clinical trials to establish treatment benefit.
16 Much of what I'm going to talk about today
17 is discussed in this article that appeared
18 relatively recently in Value in Health, development
19 of the diary for irritable bowel symptoms. And
20 that's the name of the instrument, and we have one
21 of these measures for each of the 3 subtypes.
22 This is the foundational qualitative

Page 58

1 research that I'll be talking about. In our
2 qualitative research, the participants were
3 recruited through GI clinics in 6 U.S. regions and
4 met the following criteria. You can see what they
5 are.
6 The bottom one, reported an average of
7 abdominal pain intensity score of 3 or more on a 0
8 to 10 scale over the 7 days before screening. So
9 we did want a symptomatic group and specifically a
10 symptomatic group related to abdominal pain.
11 One of the first things we did after doing
12 an extensive literature review and interacting with
13 experts in the field, we went out and did concept
14 elicitation interviews with 49 individuals. They
15 were designed to identify relevant signs and
16 symptoms of IBS and determine the way that these
17 signs and symptoms were experienced by patients and
18 how they spoke about them; the relationships
19 between them, the relationships between those signs
20 and symptoms; the most bothersome of the signs and
21 symptoms, the ways in which these signs and
22 symptoms interfere with daily life; and the 5 top

Page 59

1 signs and symptoms that each participant would want
2 a medication to improve. And you can see the
3 breakdown of participants into the 3 subtypes.
4 This gives you an indication of what we
5 found. These were the signs and symptoms that were
6 reported by at least 5 individuals, but each of the
7 49 individuals provided us a list of their top 5 in
8 terms of the signs and symptoms that are most
9 important in their lives to have treated and
10 improved.
11 You can see that abdominal pain is the first
12 one, and it's universal across the 3 subtypes. The
13 next bar is loose or watery stools, and you can
14 see, as expected, that only IBS-D and IBS-M
15 patients report that as is the case for urgency as
16 well.
17 We'll talk a little more about these later,
18 but you can see that these are the usual suspects;
19 and again, the types of things that we found in our
20 extensive, as I said, literature review of the
21 research that has already been done, qualitative
22 research with IBS patients.

Page 60

1 I'm going to only give you a very high level
2 in terms of some very selected findings. One of
3 the goals of this meeting was to talk about the
4 assessment of abdominal pain in IBS, and so I'm
5 focused primarily on abdominal pain.
6 Across the 3 subtypes, abdominal pain was
7 reported spontaneously by 43 of the 49
8 participants. Thirty-two of the 49 participants
9 included abdominal pain among the 5 symptoms most
10 important to treat, which is more than any other
11 IBS symptom, and 11 participants identified
12 abdominal pain as their single most bothersome
13 symptom.
14 In terms of ultimately we needed to then
15 decide, well, what are the signs and symptoms we're
16 going to assess in our measurement tools, in
17 conjunction with our clinical experts, we developed
18 these selection criteria directly attributable to
19 IBS experience and deemed important to treat by
20 most participants within each relevant subtype and
21 that have the potential to respond to treatment
22 within the context of the clinical trial, which is

Page 61

1 often a 12-week duration.
2 Note, it was decided that the signs and
3 symptoms included for IBS-M should be a combination
4 of those used for IBS-D and IBS-C.
5 In terms of the signs and symptoms that were
6 ultimately selected, again, based on the concept
7 elicitation interviews, a review of existing
8 qualitative literature, and clinical expert input,
9 the following signs and symptoms were selected for
10 the draft PRO measures.
11 They're broken into two areas: abdominal
12 symptoms, pain, discomfort, cramping, and bloating;
13 and then bowel movement-related signs and symptoms,
14 stool frequency, consistency, incomplete bowel
15 movements, urgency, recurrent bowel movements, and
16 straining.
17 For each subtype, you can see that this is
18 how it broke down in terms of all three of the
19 instruments contained most of the items. IBS-D and
20 IBS-M only have urgency, recurrent bowel movements,
21 and cramping, and then IBS-C and IBS-M are the two
22 tools that contain straining.

Page 62

1 Note, it's recognized that not all of the
2 signs and symptoms above will be used to derive
3 clinical trial endpoints. Dr. Hanes talked
4 yesterday about the fact that FDA has a concern
5 about urgency, the measurement of urgency, same
6 with straining, but these are symptoms that are
7 important to patients. So we feel that at this
8 point in time -- and again, the final instrument
9 will emerge from the quantitative pilot study.
10 Our quantitative pilot study will show us
11 how these items are performing psychometrically and
12 how much additional information each of the items
13 is giving us. So there may be some item reduction
14 that occurs. And some of these may go away if,
15 indeed, they're not providing useful information.
16 But we did feel that we needed to go out with this
17 item pool for our quantitative pilot study.
18 We go from the concepts or the signs and
19 symptoms, and then we have to generate items for
20 each of those signs and symptoms. So multiple
21 alternative items were generated for each of them.
22 The items were then used to assemble the draft PRO

Page 63

1 measures for further qualitative testing through
2 cognitive interviews, and then the three measures
3 were named, as I said earlier, the diary of
4 irritable bowel syndrome symptoms D, C, and M.
5 The format and mode of data collection, what
6 we decided upon, was we needed to deploy these on
7 handheld devices. As you will see, or as I
8 mentioned here, the format for entry of bowel
9 movement-related signs and symptoms responses is
10 event driven. So in this case, the event is a
11 bowel movement. So we want them to be able to have
12 a device nearby so that as soon as possible after
13 the event occurs, they can report on the bowel
14 movement-related signs that are part of the
15 instrument.
16 The format for responding to the abdominal
17 symptoms, pain, discomfort, et cetera, is a 24-hour
18 recall at the end of the day. At that point as
19 well, they would be able to report any bowel
20 movements that they hadn't reported earlier in the
21 day as it had occurred.
22 We then went out and did cognitive

Page 64

1 interviews, and so three rounds of cognitive
2 interviews were conducted to confirm the most
3 important signs and symptoms were addressed. We
4 wanted to make sure that we covered what patients
5 felt we needed to be covering and to optimize item
6 wording and response scales.
7 Some of you are certainly familiar with
8 cognitive interviews, but one of the things we do
9 is we ask people to read aloud the item, and as
10 they're doing it, we ask them to explain to us
11 their thought process as they consider what's being
12 asked of them and what they do, what their process
13 is when they decide what response to give.
14 We also explored the differences between
15 symptoms, primarily the ones that were talked about
16 yesterday in terms of how are people distinguishing
17 between abdominal pain, abdominal discomfort,
18 abdominal cramping. You can see that we had
19 43 subjects again broken down by the 3 subtypes.
20 Again, just some selected findings, although
21 often described as very related, the majority of
22 participants reported a distinction between each of

Page 65

1 the abdominal symptoms, specifically, the pain,
2 bloating, cramping, and discomfort. For instance,
3 abdominal pain was commonly described as a sharp,
4 tight, or shooting sensation, whereas abdominal
5 discomfort was often described as an irritation,
6 fullness, and/or ache. We have these sorts of
7 distinctions for each of the symptoms that we have
8 included in our instrument.

9 More selected findings, abdominal pain is a
10 highly salient and important symptom to patients,
11 regardless of IBS subtypes. That certainly was
12 expected. But how do we measure it?

13 I just want to say I certainly empathized
14 with Dennis when he was talking about herding cats
15 because one of the disadvantages of a consortium
16 approach to the development of a PRO measure is
17 that everyone has a very strong opinion about how
18 each item should be worded.

19 We have 10 items total across our 3
20 instruments, 3 measures, and you can't imagine how
21 excruciatingly painful it was for each of those 10
22 items. And I'm just going to give you an example

Page 66

1 of this.

2 During the cognitive interviews, we actually
3 tested 4 different versions of the abdominal pain
4 item, one of them being how would you rate your
5 abdominal pain at its worst in the last 24 hours.
6 We had proponents in the group of using a verbal
7 rating scale as opposed to an NRS, and they just
8 really wanted to see what patients thought about
9 that and whether that might be a better alternative
10 to a 0 to 10 numeric rating scale. That was one of
11 our options.

12 Then for the numeric rating scale options,
13 the stem was, on average, how would you rate any
14 abdominal pain you experienced in the last
15 24 hours. And then there were two different
16 essentially sets of descriptors that were used on
17 the extremes of the NRS. The first one was where
18 zero was no abdominal pain and then 10 worst
19 abdominal pain I can imagine, and the other option
20 here was again, zero was no abdominal pain but 10
21 was worst possible abdominal pain. And then option
22 4, how would you rate your abdominal pain at its

Page 67

1 worst in the last 24 hours, and again, this is
2 where we used at the extreme end of 10 worst
3 possible abdominal pain.

4 Just to give you a sense of how ultimately
5 we decided where we were going to land, one of the
6 things I didn't mention is that our items included
7 initially last 24 hours as opposed to past
8 24 hours. Again, that was a bone of contention
9 among the group, which should we use.

10 The words "last" and "past" can be
11 interpreted in different ways. The use of the word
12 "past" most commonly refers to the most recent
13 24 hours, and so that was confirmed in our
14 cognitive interviews. So the decision was to go
15 with the past 24 hours.

16 This issue was brought up yesterday as well,
17 on average versus worst. Participants described
18 different methods of averaging their pain over the
19 course of the day. That was one of the concerns,
20 and Dr. Lee Simon brought this up yesterday in
21 terms of in OMERACT, they found that average -- I
22 think you were saying, Lee, that average was what

Page 68

1 ultimately was landed upon as potentially the best
2 way to go.

3 We found the exact opposite in the sense
4 that our concern was that, cognitively, people are
5 using all sorts of different ways to decide on what
6 is average, whereas for the most part, we felt that
7 participants were consistently interpreting the
8 word "worst" as their most severe pain during the
9 past 24-hour period. Again, we had a small sample
10 size, 43 individuals, but that was our finding.

11 Then although participants were generally
12 able to articulate the difference between a symptom
13 at its worst and then on average, they responded
14 the same way or very similarly to both items.

15 So I think that's important as well, and I
16 think there's a large body of evidence that would
17 indicate that in some respects, it doesn't matter
18 whether you use average or worst because for the
19 most part, you get the same response. So we went
20 with using worst, and that is consistent with what
21 has been the FDA's preference in terms of a 0 to 10
22 numeric rating scale.

Page 69

1 Then the whole issue of a numeric rating
2 scale versus a verbal rating scale, so across
3 rounds, there was a slight preference for the NRS,
4 the numeric rating scale, as opposed to the verbal
5 rating scale. But in addition, the NRS is used
6 more often, it's used in clinical practice, and
7 certainly, the FDA IBS guidance used or recommended
8 the NRS. So the NRS was ultimately chosen.
9 Then this issue of worst abdominal pain I
10 can imagine versus worst possible abdominal pain,
11 although all participants were able to select a
12 response using either version of the numeric rating
13 scale, some participants stated that they could
14 imagine pain more severe than they ever
15 experienced, and thus they would not use the upper
16 end of the scale.
17 So that's a concern because we certainly
18 want a scale, a response scale for which people
19 will use the full continuum. So the decision was
20 to use worst possible to increase the probability
21 the respondents would use the entire response
22 scale.

Page 70

1 This was another issue, placement of worst
2 in the item stem, and two participants reported
3 that moving the word "worst" could improve question
4 clarity, and their recommendation was supported by
5 the translators.
6 For our instruments, we do a translatability
7 assessment. We don't do full translations, but we
8 have translation specialists review the wording of
9 our items and response sets. And in this case,
10 that individual recommended changing the sentence
11 structure to facilitate future translation for
12 multinational trials. So the decision was how
13 would you rate your worst abdominal pain rather
14 than how would you rate your abdominal pain at its
15 worst.
16 The final item -- and again, this is just
17 the abdominal pain item -- how would you rate your
18 worst abdominal pain in the past 24 hours with the
19 response scale of no abdominal to worst possible
20 abdominal pain.
21 But we essentially came full circle. This
22 is almost identical to the wording recommended in

Page 71

1 FDA's IBS guidance, which used an 11-point interest
2 to ask patients to rate their worst abdominal pain
3 over the past 24 hours. The only difference being
4 we used in the past 24 hours as opposed to over the
5 past 24 hours. And this is a general
6 representation of how it shows up on the handheld
7 device.
8 The limitations of what we've done so far,
9 and again, I've just given you a very high level
10 look at our qualitative research, but although the
11 study participants are reasonably representative of
12 IBS clinical trial population in terms of age, sex,
13 race, ethnicity, and education, 92 people recruited
14 from 6 U.S. clinics are unlikely to fully represent
15 this target population, and we recognize that.
16 The working group members, again, we were
17 appreciative for the financial support from
18 Allergan, Ironwood, and Takeda, and their
19 representatives that are mentioned here that were
20 very much a part of this process. Then I need to
21 acknowledge the folks at RTI Health Solutions,
22 Sheri Fehnel and Claire Ervin that were a part of

Page 72

1 this whole process in terms of collecting. The two
2 of them did the interviews, both the cognitive
3 interviews and the concept elicitation interviews,
4 and are now conducting the quantitative pilot
5 study.
6 Then you can see we have a number of
7 clinicians and other researchers that have helped
8 us with this, as well as many of you probably know
9 Nancy Norton from IFFGD, who was a patient
10 representative on our working group. And Dr. Chey,
11 who is not here right now, was very helpful early
12 on in this process as well.
13 With that, I will conclude my remarks.
14 (Applause.)
15 DR. SMITH: We have a long break for
16 checkout.
17 (Whereupon, at 9:57 a.m., a recess was
18 taken.)
19 Q&A and Panel Discussion
20 DR. SMITH: We're going to get started. I
21 just want to introduce the two members of our panel
22 who haven't spoken yet. Dr. Farrar is an associate

Page 73

1 professor of epidemiology at the University of
2 Pennsylvania, and Dr. Landis is the professor and
3 director of biostatistics of the Department of
4 Biostatistics, Epidemiology, and Informatics at the
5 University of Pennsylvania as well.
6 We're just waiting for John.
7 DR. TURK: It's been a stimulating day and a
8 half. Hopefully, all of you are feeling the same
9 way. Yesterday, there was an orientation to us to
10 think about moving out of our silos to making sure
11 we have a bit more understanding about some of
12 these different conditions that share some common
13 features but in fact are unique in many ways
14 themselves.
15 We started looking this morning in the
16 presentations at some efforts to tease some things
17 apart in more detail, lessons learned, things we're
18 learning from these different approaches. I think
19 that's been very helpful.
20 Remember what our objective is. There's
21 going to be a quiz. The objective that you should
22 be thinking about is we want to come up with some

Page 74

1 type of recommendation, suggestion, ideas about
2 what we want or think would be useful for people to
3 do when it comes to the assessment of outcomes in
4 clinical trials. Actually, it could be other kinds
5 of research as well, but I think clinical trials
6 predominantly in these particular conditions.
7 So that's what we are trying to get to, and
8 the idea is that we've used the presentations, and
9 more importantly the interactions that people have
10 had over the coffee breaks and over the meals to
11 try to get us to the point where we can move in
12 that direction.
13 We have moved from a little bit, the silo,
14 and now we're moving back to, okay, how are we
15 going to pull this together in one type of program?
16 We have a panel. It's nice to see we have a
17 few biostatisticians because we always need them to
18 keep us honest, so thank you for joining us, Dick
19 and John. I think of you as a combination of a
20 biostatistician and a neurologist.
21 DR. FARRAR: Yeah, I was going to say I
22 think I'm insulting my biostatistics colleagues --

Page 75

1 DR. TURK: You're the interdisciplinary team
2 all within yourself.
3 DR. FARRAR: I'm the epidemiologist in this
4 area.
5 DR. TURK: We want to see from the -- well,
6 first of all, what I want to do is before I ask for
7 your questions out there, comments from anybody on
8 the panel about each other's presentations or
9 anything that you've heard that you think would be
10 wise or useful for us to at least have on the table
11 for discussions and maybe even leading us toward
12 our endpoint.
13 Dick, you look like you're -- anything you
14 want to say to us, any wisdom for us, comments that
15 you want to make about the presentation -- okay.
16 John, okay.
17 DR. FARRAR: The one thing that struck me
18 about both presentations or the presentations this
19 morning is that there actually is a fair amount of
20 information available to think about with regards
21 to what the goal of this particular meeting is,
22 especially with regards to the IBS measures.

Page 76

1 There's work underway that is going to help inform
2 that process in a very specific and useful method.
3 The work that was done as part of the MAPP spent a
4 lot of time thinking about how measures work and
5 which parts, which measures should be put together
6 into an outcome.
7 I think that the process of trying to
8 summarize some of what we have heard today may in
9 fact be wait a little bit. There is a process
10 underway to try and help define that.
11 Then the second thing that was obvious is
12 that the diseases and the processes that we're
13 talking about, even though they all occur in the
14 same general region in the body, are distinct and
15 different. Even within IBS, I think the point has
16 been made very clearly that there are at least two
17 types, and then there's the type that has both, and
18 those are going to be different.
19 I think that what struck me really was the
20 need to be both general in measures that capture
21 some parts of this, and then more specific for
22 individual components of this.

Page 77

1 DR. TURK: Thanks, John.
2 Rick, any comment you want to make?
3 DR. LANDIS: I really appreciate the
4 opportunity to be here and felt that these
5 presentations this morning really captured the
6 complexity that we're dealing with really well.
7 What I'm as a statistician very interested
8 in is the fact that these syndromes have multiple
9 domains of symptoms, and the more we try to create
10 a global summary measure without paying attention
11 to the individual target sub-areas of symptoms, I
12 think the more we're missing opportunities to
13 identify the different subtypes of these conditions
14 and the fact that targeted measures for each of the
15 unique subdomains of data are critically important.
16 One of the things we're discovering in
17 MAPP II that Quentin summarized this morning in his
18 talk is that we have a run-in period with 5 weeks
19 in which there's a screening visit, and then the
20 participants in the next 3 weeks each week log in
21 and do a full battery of symptoms, plus they repeat
22 the body map.

Page 78

1 So at the fifth week when they come in for
2 the deep phenotyping with all the biomarkers and
3 the QST and the neuroimage scans, we have the
4 background of 5 weekly repeated measures of each of
5 these key features.
6 I think this will be really useful. We
7 haven't gotten very far because we're still
8 recruiting, but we're beginning to look at the
9 initial one-half of the participants. We now have
10 over 400 who are through the screening visit, and
11 one of the issues is how stable these subtypes are.
12 When you have a bladder phenotype, is it
13 repeatable, or does it vary from one week to the
14 next? When you have regions on the body map, are
15 they endorsing that same region every week for
16 5 weeks, or does it rove all over the body? We'll
17 be able to answer those questions now, and I'm
18 really looking forward to that.
19 But I think that's going to be the key to
20 identifying subtypes that are repeatedly endorsing
21 the same features.
22 DR. TURK: You want to respond r-- okay.

Page 79

1 Quentin.
2 DR. CLEMENS: I'm not responding. I had a
3 separate --
4 DR. TURK: Oh, okay.
5 DR. CLEMENS: What struck from Dr. Coons'
6 talk, and we had discussions yesterday, this idea
7 of average pain versus maximum pain or most pain.
8 And I think what you said was it really doesn't
9 matter, but it seems as though the maximum pain is
10 what has been decided upon.
11 I guess the point would be that if it
12 appears that this issue has come repeatedly in
13 various pain states, perhaps a statement that says,
14 listen, it doesn't really matter, just pick one,
15 and maybe worst pain is a little more
16 understandable.
17 That would help some of the rest of us,
18 let's say we're going through a similar process for
19 IC or chronic prostatitis, to maybe just have that
20 as the background in a statement from this group or
21 others so we can avoid the perhaps, how do I put
22 it -- shorten the process by a few days by not

Page 80

1 needing to go through the pain you described.
2 DR. TURK: Let me just comment that when we
3 developed the draft of the manuscript that comes
4 out of the discussions, that will be circulated to
5 all of you to look at. If for some reason, we've
6 missed any point that anyone feels that you felt
7 got short -- had a second thought about it, or
8 you've got more ideas, there will be an
9 opportunity -- and usually this goes through a
10 couple of iterations. So maybe you'll see it two
11 or three times before this is ready for submission
12 for publication.
13 So don't feel as if everything that you
14 thought about this and you're flying home on the
15 plane or a week from now when you see a
16 patient -- there will be opportunities to try to
17 bring other things up.
18 What we will do is there will be a draft
19 manuscript that Jen and Shannon will take the lead
20 on. They've been taking copious notes, minutes of
21 what's going on in the meeting, trying to get this
22 into an initial version. They'll probably

Page 81

1 circulate it to the steering committee for the
2 first round of comments, and then you'll see it
3 again, so you will have an opportunity.
4 I'll pull you before I take Dr. Coons'
5 comment, that is, if you look around the room, the
6 number of people are here, that for us to be able
7 to move this manuscript along -- even if you want
8 to say great job, at least let us know you've seen
9 it -- preferably, you'll give us comments on it so
10 we can improve it or clarify things or explain how
11 things are done.
12 Then there's an attempt to synthesize,
13 harmonize, if you will, the comments to come up
14 with the next version you're going to see, which
15 again you can then look at and then get back to us.
16 The more reasonable turnaround that we have, the
17 more you'll remember your comment and your
18 questions and why you said what you wanted to say.
19 If it ends up taking too long, you're going to
20 forget, or you may forget, some of the concerns you
21 had.
22 As a plea in advance when you get

Page 82

1 these -- and make sure we have -- if you change an
2 address or change an email, make sure we know about
3 that because it may be two or three or four months
4 before you see it the next time, but it really
5 means that we need to keep up with you.
6 I'm sorry, just editorializing that.
7 Dr. Coons?
8 DR. COONS: That's okay. I agree totally
9 with Dr. Clemens. It's a situation where this, I
10 would think this issue of average versus worst
11 would be settled science. And from my read -- and
12 it's a superficial read of the literature -- that
13 it appears, first of all, that they -- as long as
14 you're doing it consistently throughout the trial,
15 using average or worst, it's not a problem. But
16 for the most part, the literature that I'm seeing
17 is that they are almost the same score, if not the
18 same score for individuals, when asked at the same
19 time.
20 I think that an important part of this paper
21 could be just that, that there is a -- I don't know
22 if there's an opportunity to do a more extensive

Page 83

1 literature review that then there would be an
2 empirical basis for making that statement, that it
3 really doesn't matter which you use. And we'll see
4 if the literature shows that, indeed, people
5 cognitively are coming up with their answer related
6 to average pain very differently, and so maybe we
7 should be concerned about that.
8 DR. TURK: Shannon, I don't know if this is
9 premature, if you want to even comment, but Shannon
10 Smith has been involved in the process of doing a
11 detailed analysis using the FDA's database to
12 address exactly the issues.
13 Shannon, do you think it's premature, or do
14 you want to make any comment?
15 DR. SMITH: It is slightly premature, but I
16 will say what we've done. We did a systematic
17 review of pharmacologic treatments for low back
18 pain, osteoarthritis, fibromyalgia, postherpetic
19 neuralgia, and diabetic peripheral neuropathy -- so
20 from the literature -- that reported both average
21 pain intensity and worse pain intensity.
22 There are a few people in here who already

Page 84

1 read the draft. I regret to inform you that it's
2 going to be revised slightly because there were
3 some data issues. So we'll see what that turns up,
4 what in terms of like the greater assay sensitivity
5 of average pain intensity or worse pain intensity.
6 It is something that we're actually working
7 on right now.
8 DR. TURK: I misspoke. I said the FDA
9 database, but it was from the published literature,
10 so I apologize for that. There's so many different
11 projects going on that I'm losing track a little
12 bit. But the idea is that we may be able to at
13 least put some data to speak toward that issue
14 based on the analysis that Shannon and the group
15 are working on.
16 DR. COONS: Right. I think that is an
17 important point, which of them is more sensitive to
18 change within the context of a clinical trial. So
19 if there's empirical evidence there that can help
20 us determine that, then I think that's fantastic.
21 DR. LANDIS: Just following up on the
22 average versus worst, I noticed the 24-hour period

Page 85

1 was the reference time frame. I'm wondering if
2 you're asking patients to summarize their previous
3 week whether average and worst would potentially
4 separate.
5 MALE SPEAKER: No, that's a possibility, and
6 we're not doing that in our work in terms of we're
7 not asking them about their weekly worst or their
8 weekly average.
9 DR. COONS: There is actually data on that
10 topic. Mark Jensen 10 years ago, I guess, now,
11 maybe longer, did several studies, at least two
12 that I know of, where he asked every day and then
13 asked at the end of the week on average for the
14 week and worst and so on. So there is a published
15 literature. It makes a small difference, but it
16 doesn't make a huge difference.
17 DR. LANDIS: Even for a whole week?
18 DR. COONS: Yes. I don't think he went to a
19 month, if anybody knows, but I think a week
20 certainly works. Then there are concerns about
21 memory over a month or longer.
22 DR. TURK: There are some other studies,

Page 86

1 too, that have looked at that. We were involved,
2 let's see, a long time ago in which we looked at
3 pain at particular 24-hour period versus up to
4 three months, and we actually showed the
5 relationships were pretty close. They were much
6 better than some people who are into the electronic
7 momentary assessment would lead us to believe they
8 are. So there is a body of literature that
9 addresses that.
10 Jen, you wanted to comment on --
11 DR. GEWANDTER: Mine is a different topic,
12 so.
13 DR. TURK: Is there anything else on this
14 issue? Bob, you were interested in this or you
15 were not?
16 Lee Simon?
17 DR. SIMON: One question is not just what
18 the point estimate looks like but what the
19 variability looks like between the two. And in
20 addition, John, I wondered about the variability in
21 the context of how much recall changes that in the
22 context of episodic pain rather than constant pain.

Page 87

1 A gazillion years ago when I was in
2 Washington, one of the people in my division looked
3 at the question of recall versus 24-hour versus one
4 month and whatever, and it looked in our
5 hands -- all this was done by hand; nothing was
6 electronic in those days. It looked like it recall
7 was a problem, whereas more immediacy of the
8 24-hour or, at worst, 72 hours was the best
9 evidence that we could get at that time where
10 patients gave consistency with less variability.
11 It's the variability that worries me more so
12 than the point prevalence.
13 DR. TURK: John, respond?
14 MR. FARRAR: No, no.
15 DR. TURK: We're getting a little into
16 weeds.
17 DR. FARRAR: The weeds.
18 DR. TURK: But what it really shows me, if
19 not to all of you, is how complex what we think is
20 a very simple question. Physicians for hundreds of
21 years have asked people to rate your pain a 0 to 10
22 scale. Rate your pain on a 5-point scale. Is your

Page 88

1 pain mild or moderate?
2 We've been thinking that that's a simple
3 question, and the complex -- how many -- 2008 you
4 began working on this, Steve?
5 DR. COONS: 2009.
6 DR. TURK: 2009. To see how complex it is,
7 I think is a good reminder to us that when you ask
8 people a subjective response, you get huge range of
9 factors that influence that.
10 John?
11 DR. FARRAR: Just one very quick comment,
12 Lee and I talked about this briefly during the
13 break, which is that I think the conclusion of what
14 I've heard at least is that they all work, that
15 different disease processes, whether you have
16 constant up and down variation, as you might have I
17 think with IBS or other syndromes, versus a more
18 constant level of pain might help you decide
19 physiologically which one makes the most sense to
20 look at.
21 I would argue -- and I don't think we
22 probably want to spend much more time on this. But

Page 89

1 I would argue that if we understand that they all
2 work and that some decision can be made about which
3 one to use based on the physiology of what you're
4 studying, the combination of biology and
5 measurement science sounds like a good one to me.
6 DR. TURK: I think we should move from this
7 topic. Obviously, we could spend a lot of time on
8 it.
9 I think Jen had a comment, and then we'll
10 come to the audience.
11 DR. GEWANDTER: We can let them go first.
12 That's okay.
13 DR. TURK: Was yours a comment on anybody
14 else's?
15 DR. GEWANDTER: We can let them go first.
16 DR. TURK: She's deferring to you because
17 she wants to get the last word.
18 (Laughter.)
19 DR. TURK: Yes?
20 DR. WIEDERHORN: Roger Wiederhorn, FDA. I
21 spoke with Dr. Landis about this, and he alluded to
22 it in his comments, was the stability of

Page 90

1 phenotyping. Specifically, with the stability, do
2 patients migrate within and out certain groups only
3 or through all groups in terms of the phenotyping?
4 Also, this is a short-term study -- well,
5 another question, of course, migrating in and out
6 of phenotyping, is to my knowledge, people don't
7 migrate from no Hunner's ulcers to all Hunner's
8 ulcers once they develop symptoms or vice versa.
9 But that would be an important phenotype migration
10 to document, which I don't believe there's evidence
11 for at this point in time.
12 Also, there is the interstitial cystitis
13 database, which is a longitudinal prospective
14 cohort, if my epidemiology is correct. You can
15 correct me; I'm probably wrong. But the point is
16 that a lot of patients were studied for up to
17 10 years.
18 Do any of these findings help you in terms
19 of the relatively short-term study? I realize they
20 were different criteria and everything, but is
21 there any way you can relate them, glean something
22 from them that would be helpful in terms of symptom

Page 91

1 stability and subgroup and phenotype stability?
2 DR. LANDIS: Just continuing a little bit
3 further on this run-in period with the 5 repeated
4 weeks, the painful bladder criteria for filling,
5 the pain increases with filling and the urgency
6 that's the painful urgency component, as well as
7 some of these body map regions, there's quite a bit
8 of variability overall, but there's a subgroup of
9 40 percent who endorse the same feature every week
10 for 5 weeks in a row. And then there's another
11 30 percent who 3 out of 5 times endorse the
12 features.
13 So I think there's variability as a
14 characteristic of a subgroup, and then there's the
15 stability endorsing a every time feature of a
16 sizable subgroup. So another feature could
17 potentially be the persistent presence versus the
18 variable presence that would allow you to identify
19 potentially subgroup differences, but this is all
20 exploratory at this point.
21 DR. LAI: Roger -- this is Henry Lai. The
22 MAPP study similar to the IC database, is really a

Page 92

1 treated natural history study. Patients come in
2 and out of treatment within that one year or three
3 years that we're talking about. So you might
4 expect some change because they have multiple
5 things that are changing over time in a phenotype
6 in a classification. That's something important to
7 bear in mind, too.
8 DR. TURK: Does anybody want to comment
9 about this issue about the phenotype stability?
10 Steve?
11 DR. BRUEHL: I think this relates to the
12 phenotype stability issue. So if our goal is to
13 identify optimal outcome measures for clinical
14 trials, when you do a clinical trial, you have some
15 entry criteria, I think what I've heard over the
16 last couple of days is that the criteria that are
17 used to determine entry in the studies are not
18 necessarily well-conceived. They may change over
19 time.
20 If you take that as an issue plus the issue
21 of whether the people meeting those criteria are
22 stable or not and how many overlapping conditions

Page 93

1 there are, I think that has huge implications at
2 the 10,000-foot level for how we would measure
3 things in trials like this.
4 Let's say you've got -- pain seems to be
5 common to all of these, so clearly the pain
6 component has to be there. But we've also got the
7 component of some type of disease-specific measure,
8 and maybe it's a urinary urgency. Maybe it's
9 defecation issues. Across conditions, it may
10 differ some, but if these people are moving from
11 condition to condition or have multiple conditions,
12 I guess what I would wonder is whether taking a
13 very broad assessment approach would make sense in
14 order to capture everything that might be
15 informative in the future about what silo they fall
16 into.
17 Because what if five years from now in the
18 course of doing a study, we refine criteria based
19 on the MAPP study and decide that pelvic pain is
20 this rather than this? Well, now we want to make
21 sure we have information on symptoms to be able to
22 go back and reclassify those diagnostically using

Page 94

1 those new criteria.
2 I just wanted to throw that out because I
3 think it relates to this issue of whether there are
4 truly silos or whether these are illusory and
5 overlapping and changeable and what impact that
6 would have on the disease-specific measures you
7 might include.
8 DR. CLEMENS: I found your comments helpful
9 because focusing on the clinical trial
10 applicability, which is really the main focus of
11 the meeting, which is typically a 6-week to 12-week
12 time period. And while, yes, these phenotypes do
13 change, certainly, if we identify someone with
14 widespread pain, let's say, as an important
15 phenotype, we are not seeing in the short term
16 dramatic fluctuations where someone has widespread
17 pain and a couple weeks later has none.
18 I think keeping in the context that while,
19 yes, there is some degree of instability, in the
20 context of a 3-month time period, which I think is
21 what we're really talking about, perhaps out to a
22 year with the extended follow-up. But these are,

Page 95

1 at least from the IC and chronic prostatitis world,
2 pretty stable patients. Even in the ICDB long-term
3 study, only about 20 percent overall actually
4 changed and got better.
5 I think that that's just useful to keep in
6 mind. These are generally stable chronic patients
7 however we phenotype them. In fact, to some
8 degree, at times we've had to do a fairly
9 substantial amount of effort to be able to identify
10 change or identify a way to look at a variable
11 related to change that won't have everyone being
12 stable in it. So I think this may be useful to
13 keep in mind.
14 Dick, you can follow up with any comments,
15 but during run-in period, we see some changes, but
16 again, people aren't going from widespread pain to
17 none at all.
18 DR. LANDIS: Yes. I think it's going to be
19 more how variable they are at the threshold of
20 present or absent. But certainly, it's a challenge
21 to make sure, especially for a clinical trial, that
22 you have the correct baseline phenotype and you

Page 96

1 have something that captures the level of the
2 primary outcome in a way that when you do -- at
3 primary endpoint, that you can confirm that this
4 is, in fact, a real change or not.
5 DR. TURK: John?
6 DR. FARRAR: This conversation reminds me
7 that we need to keep, I think, quite clear and
8 probably separate, although they're related, the
9 difference between defining a phenotype and the
10 variability of the phenotype and then defining the
11 outcome measure.
12 In pain studies, we study knee pain and hip
13 pain and headache and diabetic neuropathy. We
14 enroll those patients into trials, but the outcome
15 measure is 0 to 10, how much does it hurt measure
16 or BRS or something else.
17 I would just argue that we are very clear
18 about this need to both have measures that define
19 the phenotypes specifically, but that those
20 definitions of phenotype may have nothing -- will
21 not dictate what the outcome measure necessarily
22 would be or the best outcome measure for that

Page 97

1 trial.

2 DR. TURK: Jen?

3 DR. GEWANDTER: In regards to what

4 Dr. Landis just said, based on the MAPP study and

5 Dr. Coons' experience with interviews, we usually

6 for diabetic neuropathy will do like a week-long

7 run-in, get their average pain on all the says, and

8 if they have a 4, they're in.

9 Do you think that, based on your experience,

10 you need, A, a longer run-in period for these

11 people, and B, would something that came up

12 yesterday, would it be -- if we want to have a

13 minimum pain severity, would it be on only the days

14 they have any pain or all the days?

15 DR. LANDIS: John, part of my answer is,

16 picking up on what John just said, classifying the

17 correct phenotype is different than their level of

18 pain. So in particular, we're looking at binary

19 features like do they endorse pain getting worse as

20 the bladder fills or not. That feature is a

21 repeated measure for 5 weeks, but it's not the same

22 as what is their baseline pain for the beginning of

Page 98

1 the study or their outcome at the end of a study.

2 So the variability that I'm really concerned

3 about is when you try to stratify patients for a

4 clinical trial and say this is a group that

5 endorses the bladder phenotype, or this is a group

6 that does not endorse the bladder phenotype

7 because, in fact, the therapy may be targeted for

8 the one group relative to the other.

9 It's that reliability that I'm really

10 talking about when I say the run-in period has

11 opened up some new understanding that there's a

12 group that endorses the bladder phenotype every

13 week, and then there's another group that varies

14 whether or not they believe their pain is getting

15 worse if the bladder fills or not, for example.

16 DR. GEWANDTER: Right. So I think that

17 maybe my question is a little bit separate then

18 because I think if we're going to make pain one of

19 the outcomes, we need to have a baseline level of

20 pain that's at least moderate in these patients.

21 I guess the question is if their pain is

22 variable and we only do a week-long run-in to

Page 99

1 evaluate their pain and they don't make it in the

2 study, are we going to be throwing out a lot of

3 people that we shouldn't be, and should we make the

4 baseline period longer because these conditions are

5 not as necessarily as consistent as, say, diabetic

6 neuropathy?

7 DR. TURK: Dr. Pontari has been trying to

8 get in for a while.

9 DR. PONTARI: One of the possible advantages

10 we have with at least prostatitis and IC is that

11 even within the pelvis, on the GUPI, there are 6 or

12 8 areas. You can get data for location and

13 severity and the pain.

14 Have there been other pain conditions that

15 looked at -- I don't know -- as opposed to just

16 headache or knee pain, where you've looked at

17 number of sites of pain as being an improvement in

18 addition to the frequency? You can get more

19 information out of that using it as a composite

20 score as opposed to just what's your average pain

21 or what's your worst pain?

22 DR. TURK: Anyone have an answer?

Page 100

1 DR. FARRAR: Not specifically, but there

2 have been some studies in acute and chronic pain

3 that have looked at patients' ability to

4 differentiate pain at different sites. If somebody

5 comes in with pain in three different sites,

6 they're able to say my knee pain is better this

7 week, but my headache still hurts.

8 That's confounded by the fact that if you

9 actually get rid of the knee pain, then the

10 headache might hurt more because it's the only

11 pain. But there is an ability to differentiate.

12 I think what you're asking, though, is

13 whether looking at the number of sites of pain

14 might be another way of assessing the degree of the

15 abnormality, and I don't know of any studies for

16 that.

17 DR. TURK: By the way, if I don't call you,

18 it's really hard to see because the lights are so

19 sensitive and the microphones, that you can't use

20 that. So try raising your hand. Yes?

21 DR. VINCENT: Kate Vincent. I've got two

22 points. The first is about the time scale that

Page 101

1 we're measuring, and I mentioned this a bit
2 yesterday. About at least 50 percent of our
3 patients are going to be female, and not all of
4 those are going to be on hormonal treatments that
5 will give them a stable hormone state across the
6 month. And we know that IBS, interstitial
7 cystitis, bladder pain syndrome, and any other
8 chronic pelvic pain pathologies often cycle in
9 their symptom severity across the month.
10 So if we're only going to ask about pain in
11 the last day or pain in the last week, then I think
12 we need some way in which we're controlling for
13 their time in their hormonal cycle to collect those
14 data points. We did a systematic review that we
15 haven't published yet but presented at IASP,
16 showing that about 5 percent of pelvic pain trials,
17 including endometriosis trials, where we should at
18 least be looking at that, actually considered
19 hormonal point and the hormonal cycle in the design
20 of that trial. I just think that's a point we need
21 to be considering.
22 My second point slightly adds to what you

Page 102

1 were just saying about pain symptoms. We've talked
2 here all the time about pelvic pain. Actually, to
3 me as a gynecologist, that's a composite of a
4 variety of different symptoms. It's noncyclic
5 pelvic pain. It's dyspareunia, dyschezia,
6 dysmenorrhea, dysuria, and though they may not be
7 part of the definition of IBS -- for example, in my
8 experience, lots of IBS patients will also complain
9 about dyspareunia. But the mechanisms generating
10 those pains might well be different, and they might
11 only respond to certain treatments.
12 I'm not saying they should be the primary
13 outcomes, but maybe we should be thinking about
14 collecting those as secondary outcomes as well.
15 DR. TURK: Comment?
16 DR. CLEMENS: The take-home point, I think,
17 is that we should limit our IC trials to
18 postmenopausal women.
19 (Laughter.)
20 DR. VINCENT: Then you have to ask whether
21 they're on HRT or not.
22 DR. TURK: That was Quentin Clemens.

Page 103

1 (Laughter.)
2 DR. TURK: John?
3 DR. FARRAR: I don't want to stop where
4 we're going, but I did want to make one further
5 comment about something that we've been playing
6 with in the MAPP, which is that you asked about
7 run-in periods. I think that we've found in this
8 observational trial is that a one-week run-in
9 period is probably way too short if you're thinking
10 about what happens to a placebo group treatment
11 because everyone enrolled in the MAPP gets better
12 over the first 4 weeks, everyone, almost without
13 exception. And there isn't any treatment
14 that's -- well, there are ongoing regular
15 treatments, but there's no change in treatment that
16 suddenly happens.
17 What Quentin presented earlier was that if
18 you ignore that fact, you actually get a different
19 answer to the question of who gets better and who
20 gets worse over time. So I think it raises the
21 question of how long people should be enrolled in
22 gathering data, i.e., getting the love that comes

Page 104

1 with being in a trial before you actually measure
2 their baseline, and then try and establish a
3 benefit over time. That's an interesting
4 question --
5 DR. TURK: Does that mean that they're all
6 going to feel better from having attended this
7 meeting? Everybody is going to leave feeling very
8 good because you've entered this project.
9 DR. LANDIS: I'm feeling better.
10 (Laughter.)
11 DR. TURK: It was successful.
12 DR. LANDIS: In fact, the first MAPP cohort,
13 we didn't have a run-in period, and yet we had
14 biweekly symptom assessment. And the regression to
15 the mean or the feeling better after having just
16 been at the beginning of starting a new trial, or
17 in this case, even an observational study that
18 wasn't a trial, we ended up eliminating the data
19 from baseline week 2, and we used week 4 as the
20 launch period for assessing longitudinal change.
21 So essentially, it's a pseudo run-in period of
22 4 weeks.

Page 105

1 In MAPP II, we're seeing the same pattern
2 that the first 4 weeks are basically a stabilizing
3 period where those who start out at higher levels
4 of symptoms are decreasing. There is a group at
5 the low end of the scale, though, who actually gets
6 worse during the run-in period. So it reinforces
7 the fact that probably in these cases I would argue
8 for a four-week run-in period for any clinical
9 trial.

10 DR. CLEMENS: But, of course, you're only
11 going to lose then from a clinical trial design
12 standpoint because you're not going to be running
13 into people who don't meet -- so if your numeric
14 scale value is 4, let's say you have to be a 4 or
15 more. Well, by definition, you're not going to
16 bring anyone in who's a 1 or 2. So you're going to
17 lose those people who might have worsened.

18 What's going to happen, all you're going to
19 do is -- in other words, you're not going to have
20 the opportunity to capture those people who started
21 below and worsened. So all you're going to do is
22 lose the people who started at a 4 or 5 and go down

Page 106

1 to 2.

2 It's just something that needs to be -- if
3 you're going to do the 4 week, you just have to
4 count on whatever would be a 20 percent attrition
5 rate probably during that time.

6 DR. TURK: Dr. Dworkin?

7 DR. DWORKIN: I completely agree that there
8 are all sorts of great reasons to think about a
9 4-week baseline run-in instead of what we typically
10 do, which is one-week. However, if we're waiting
11 4 weeks before randomization, patients are going to
12 be really unhappy that they're not getting any
13 treatment, placebo or active, for a month. I think
14 that's a real obstacle that I don't know how to
15 confront.

16 I think all the reasons everyone has said,
17 regression to the mean, placebo effects, et cetera,
18 is a great reason for a 4-week run-in, but the
19 logistic of doing that is, I think, impractical
20 because the patients are going to say I'm out of
21 here.

22 DR. TURK: We just tell people that you're

Page 107

1 getting 4 weeks of placebo while you're waiting for
2 the real treatment. So Ted Kaptchuk would say that
3 might be successful.

4 DR. CLEMENS: You have the control arm. I
5 don't necessarily view -- I'm not a statistician,
6 but I don't necessarily view the regression to the
7 mean as an issue for a randomized trial where you
8 have a control group, which likely will also
9 demonstrate a regression to the mean, right? So
10 this is more of an important thing for a cohort
11 study. Is that not true?

12 DR. FARRAR: It's the assay sensitivity.
13 The response to the placebo group has been blamed
14 for failed trials more than anything else, and the
15 response of the placebo group is going to be
16 much -- the MAPP data suggests that most of the
17 response to the placebo group would occur in the
18 first 4 weeks. So as a way of eliminating that
19 complaint about doing clinical trials, a longer
20 run-in.

21 How to conduct it is an interesting one, and
22 I like Quentin's point, which is that maybe the

Page 108

1 criteria for getting into the run-in period should
2 be much lower than the criteria for getting into
3 the trial because, in fact, there may be people
4 that get worse over time.

5 DR. TURK: Michel?

6 DR. PONTARI: I think what you just asked,
7 though -- what he's saying is that isn't there some
8 placebo effect also in the treatment group that
9 would make those equivalent, correct? So why can't
10 you put -- so in a cohort, yes, we understand that.

11 So what's the reason in a treatment trial
12 that they don't wash out; that they don't knock
13 each out?

14 DR. FARRAR: It does. You get the balance
15 in the two groups. It's not going to affect in
16 theory the outcome. You should be able to tell the
17 difference.

18 The problem is that differentiating between
19 groups depends on where they start, and if the
20 placebo group has a much larger response, then you
21 end up with having more statistical difficulty in
22 looking and finding a difference between treatment

Page 109

1 and placebo.
2 DR. DWORKIN: Michel, I'm not sure I believe
3 it, but I think the argument is if the placebo
4 group does so well, your active treatment doesn't
5 have a lot of room to do better. So it's depending
6 on the direction. It's either a floor effect or a
7 ceiling effect.
8 I don't know that I believe that argument,
9 but John is absolutely right, that that argument
10 has been said thousands of time in the literature
11 as an explanation for a negative clinical trial.
12 It's a kind of the placebo group has done so well
13 because of regression, because of placebo effects,
14 because of natural history, that your drug can't
15 differentiate. That's the argument.
16 We could have a whole other two-day meeting
17 about whether there's any merit to that one.
18 DR. TURK: Well, we have nothing else to do.
19 All those who want to stay for two days after this
20 meeting to meet with Bob, we will let you do that.
21 Quentin?
22 DR. CLEMENS: I just wanted to bring up the

Page 110

1 Hunner's lesion patients. The question reminded me
2 of a couple things. The first is that keep in mind
3 that this MAPP study is a one-year study of
4 patients who have already had 8 years of symptoms.
5 To be truly meaningful, we'd need to follow these
6 patients longer, see how they do over a longer
7 period of time, and even MAPP II at 3 years might
8 not be long enough to really answer the questions
9 as well as we want.
10 There's no question that the Hunner's
11 patients are different. In MAPP I -- but there is
12 some controversy about what exactly a Hunner's
13 lesion is. Some of the sites rely on community
14 physicians to refer patients into this more than
15 others. So for a variety of those reasons, the
16 group decided in MAPP I to not really track or
17 identify or look for whether or not the patients
18 were Hunner's lesion patients.
19 I think over time as there have been
20 different treatments identified such as
21 cyclosporine for Hunner's lesion patients, we've
22 realized that it's much more important to really

Page 111

1 identify those. So we are doing that in MAPP II to
2 the ability at least to identify those who we have
3 evidence they have Hunner's lesion patients,
4 understanding that there's going to be a group that
5 we don't know.
6 I think from a clinical trial standpoint,
7 the important point is that we should definitely
8 identify those as a separate phenotype, whether
9 it's deciding to exclude them or to at least
10 identify them prospectively as a different group
11 and track them differently from the clinical trial
12 because I think the urology world has recognized
13 they are a totally different phenotype, and they
14 may respond totally different to the treatments.
15 Henry is leading this. I don't know if you
16 have any comments about that.
17 DR. LAI: I think the MAPP II effort will be
18 really good because the number -- the papers that
19 compare Hunner's lesion to non-Hunner's lesions in
20 terms of the systemic manifestation and that kind
21 of comparisons, really most single center, single
22 investigator, very small number of people with

Page 112

1 Hunner's lesion, 40, 50 at most. It's very
2 difficult to reach statistical significance of any
3 kind of meaningful comparison.
4 I think that will be really useful. Our
5 anecdotal experience is that they behave very
6 differently and needs to be treated very
7 differently. The challenge is how to identify them
8 and see if they have a different type of physiology
9 or different phenotype.
10 DR. TURK: Question in the back. I forgot
11 to say this before. Say your name to make sure
12 that the transcriptionist can get it.
13 DR. JUGE: Dean Juge from Texas. I wanted
14 to make a point about the run-in periods on the low
15 end and also the high-end patients on the high end.
16 A couple years ago, I was doing studies on topical
17 pain creams, pharmaceutical compounds, and we did
18 patient-reported outcomes. We were using the Brief
19 Pain Inventory, and we were offering it as either a
20 paper copy at the time or they could call in and
21 talk to a nurse. The nurses then were trained in
22 how to take the questions and not lead answers and

Page 113

1 stuff.

2 What we found is those that were calling in,
3 where they would have to ask them a question to
4 explain it to them, is that people on the low end,
5 especially the elderly, and that could be 50 and
6 above, tended to under-report until they understood
7 because a lot of times they weren't complainers.
8 So they felt like this is the number I want to get.

9 Then a group at the very high end who had a
10 pain problem for years tended to run that way
11 because that was the only way as the squeaky wheel
12 that they could get access. But once they're in
13 and seen, after a period of time and they get
14 comfortable, then they got real with what the
15 numbers were to them.

16 So you're going to see that. That's what we
17 saw in the run-in period is that we started with
18 2 weeks, and they were constantly on pain meds.
19 Then we sent them pain creams and then started
20 tracking it every 2 weeks for 3 months, and then
21 went monthly after that. And we saw numbers that
22 went negative to what they were saying, and then

Page 114

1 when they would call up to verify that with the
2 patients, especially on a paper copy, we want to
3 validate this, the patient would say, well, it
4 really wasn't that bad the last time. So they're
5 getting better.

6 If you threw away the first month and looked
7 at it from second month forward as to how did I do,
8 then you saw some real numbers as opposed to in the
9 beginning.

10 So we thought about that run-in period or
11 whatever, but we had to keep it the way it was set
12 for the first year we did the data. But you'll see
13 that in the data, and I think that's what you're
14 explaining you're seeing now.

15 DR. TURK: I take umbrage to saying that
16 people over age 50, having just crossed that
17 threshold, would be in the elderly group.

18 (Laughter.)

19 DR. LEMBO: Can I comment on the -- just to
20 go back to the run-in period. So we've done a lot
21 of work in this area because I actually work with
22 Ted. We've been collaborators for about a decade.

Page 115

1 In one of our studies where we looked at
2 this run-in, accounting for that
3 practitioner-patient relationship, even after six
4 weeks, we still saw continued improvement. So
5 4 weeks may not be enough without any other
6 intervention. And in the IBS world, it's a lot of
7 the co-interventions that I was talking about
8 yesterday that probably occurs.

9 The other point is this point about the
10 placebo just washing out is actually not a proven
11 fact, and there is enough evidence now to suggest
12 that it may be other factors that are involved.
13 Not only are there genetic predispositions such as
14 dopamine, which is one of our areas of big
15 interest, where there are clear indicators of who
16 may respond better to a doctor-patient interaction
17 that we're not accounting for. But rarely are
18 these trials truly blinded, and particularly in the
19 GI world.

20 We talked yesterday about why is it IBS-C or
21 IBS-D that's mainly studied. If you're giving a
22 drug that has some effect on bowel, it's not really

Page 116

1 a blinded study. We can't really fool ourselves to
2 think that. And once you unblind somebody and you
3 add the placebo effect, you're going to have
4 different results. So the fact that these things
5 are additive has been a major assumption, and we're
6 not actually sure that that's always true.

7 I would argue for the run-in that we don't
8 actually know. A plain run-in of no intervention
9 of 4 weeks is clearly too long for our IBS
10 patients. We can't take them off drugs for that
11 long. Two weeks is too long.

12 As I argued yesterday, maybe a placebo
13 run-in might be a better thing to do. We just did
14 this with our rifaximin trial where at baseline, we
15 gave them all placebo. It does affect your
16 results. It does lower the efficacy, and we can't
17 tell if it changed the overall things. But that's
18 something to consider.

19 I'll leave it at that, but I'm not sure the
20 4 weeks is appropriate. That's my point.

21 DR. TURK: Other questions for our panel?
22 Again, the lights are deceiving, so I can't tell

Page 117

1 whether our voice is carrying and being picked up,
2 so you have to raise your hand in addition to the
3 light going on.
4 More questions for either this panel about
5 specifically what they -- or even bringing up
6 yesterday to try to again move us forward. Michel?
7 DR. PONTARI: Has DOOR ever been used in a
8 published trial?
9 DR. GEWANDTER: Yes, right. I think --
10 DR. DWORKIN: Yes, I think in antibiotics,
11 infectious disease, not for pain.
12 DR. GEWANDTER: They're doing AE -- they use
13 it a lot for risk-benefit. That's what they
14 originally developed it for.
15 DR. JUGE: I just want to make one more
16 comment about when we were doing the review of the
17 patient-reported outcomes and stuff that we had
18 found. We started moving the BPI from paper-based
19 to handheld-based in both platforms for iPhone or
20 for Android.
21 What we found is that -- I know there's
22 some -- I think OMERACT has some information out

Page 118

1 there about you almost have to requalify your
2 outcomes reporting when you take a paper-based tool
3 that's been used for years and now throw it out on
4 either the internet, especially an app.
5 I'll just go to the examples given about how
6 you had to play around with the wording, but also,
7 the information. The BPI asks 4 pain questions,
8 and if your first question is how is your worst
9 pain -- see, on an app, they're going each. They
10 don't sit there at a paper and decide what to read
11 first, and they move forward.
12 If you ask them their worst pain
13 first -- we're doing this in a testing group to see
14 about moving it forward, and we're working with
15 Academy of Integrated Pain Management, who
16 basically owns the BPI, in trying to qualify it for
17 an app.
18 If you ask them the worst pain first, then
19 that's their last thought and all the other pain
20 registries come off of that. If you ask them their
21 average first, then they've got a different view to
22 answer the next subsequent question.

Page 119

1 When you're using an app to ask questions,
2 it's almost like the old test that you had to ask a
3 question four different ways and 80 questions to
4 make sure they're not cheating it. You kind of
5 have to do that with the ones that you're rolling
6 through because you're not letting them go back,
7 and it gets their mind in a certain process.
8 You can lead your answers on that. It's
9 easy to lead answers to get the positive opinions
10 you want on those apps, too, for some of these
11 studies as it is to get the wrong answer because
12 that frame of mind. If you're looking at paper,
13 you can go up and down a list, but not when you're
14 clicking through and moving forward.
15 One of the things we played with, especially
16 with past answers, was to throw up on the app, if
17 you're asking for an average versus a past time,
18 give them what their past time was. Instead of
19 them clicking a number, it was a sliding bar. So
20 you gave them their old one, and they slid the bar
21 up or down.
22 By sliding that bar on that size on the

Page 120

1 app -- and we're doing like you said, you had to
2 make sure depending on the phones or whatever, the
3 size was right, it recalculated how they felt they
4 were doing, better or worse. So they were saying
5 better or worse by sliding a bar, and we used the
6 temperature bar. So they slid it. It went
7 sideways, not up and down. And we played with up,
8 down, or sideways in apps, and sideways is better.
9 The temperature bar got better results than
10 asking them to rate it against it, not knowing what
11 they did or asking them to rate a verbiage, not
12 knowing what they did, because they saw where it
13 was last time, oh, am I better than I was last
14 week? Oh, a little bit better, or a lot better.
15 We didn't tell them what to say. We just
16 said slide the bar to where you feel and gave the
17 two endpoints, and we got different results for
18 that. And I think you're going to see as we move
19 into this computerized age, there's a lot of
20 factors like that that go into doing this,
21 especially the younger crowd that's used to doing
22 apps for everything. They're going to slide that

Page 121

1 bar different than again, elderly, 55 and above,
2 whatever.
3 (Laughter.)
4 DR. JUGE: Whatever range you want to make
5 it, I don't -- we didn't stop at 65, but there's
6 a -- we stopped at the age of people that -- we
7 should have asked a question, and we didn't, how
8 computer literate are you? Do you use Facebook?
9 Do you use your phone? Do you just call with it?
10 Do you do things with it?
11 People that would do stuff with it would
12 give you different ratings than people that
13 wouldn't. They would all learn to use it, but they
14 would score differently because they're used to
15 those devices. They've got Fitbits. They're
16 tracking everything. They're going to score that
17 slider a lot better. So we expected better results
18 from that group.
19 DR. TURK: Stephen, from your vast
20 experience of working on these things, how do you
21 respond?
22 DR. COONS: Well, I think there are a number

Page 122

1 of issues that you've brought up. One of them,
2 just to say, the FDA wants ultimately all sourced
3 data to be collected electronically, so it's
4 inevitable that we're going to be using electronic
5 data capture devices.
6 The other issue, there are order effects,
7 you're absolutely right, with questionnaires, but
8 you can have an order effect even on a paper-based
9 questionnaire. But many times, order effects
10 aren't as big of a problem as one might think. But
11 if you're asking about different attributes of pain
12 in a series of questions that only show up one item
13 at a time on a screen-based device, I understand
14 that may be a problem.
15 There will also be more questionnaires that
16 are developed specifically for electronic data
17 capture, so you're not migrating an existing
18 instrument to an electronic data capture platform.
19 That's why all the instruments we're developing
20 within the PRO Consortium are being developed to be
21 deployed on electronic data capture devices, and
22 there are certain measurement rules that you need

Page 123

1 to think about as you're developing measures that
2 will only be collected electronically.
3 I do think that -- and a lot of the studies
4 have shown that older adults, of which I am one,
5 are very savvy, that they don't have necessarily
6 much more of a problem in using electronic data
7 capture devices as younger people.
8 If you have them sitting in front of a
9 computer and you have them clicking a mouse or
10 something like that, there may be a problem if
11 somebody has Parkinson's. There are things that
12 older adults may have, conditions or diseases that
13 they have that may impact their ability to even use
14 a touchscreen.
15 I think there are lots of things we need to
16 consider, but there are not insurmountable. This
17 is the future, and we just need to know what the
18 limitations are along the way to getting to the
19 point where we're capturing all of this data
20 electronically.
21 The fact that so many people have handheld
22 devices -- you're talking about using an app, but

Page 124

1 I'm assuming that these people went to the app
2 store and downloaded it to their own handheld
3 device?
4 DR. JUGE: Right.
5 DR. COONS: That's a very attractive
6 approach in the future as long as you know that to
7 get a representative sample, you may need to deploy
8 devices to people who don't necessarily have a
9 handheld device that can be used with that app.
10 I think again these are not insurmountable
11 issues, and we're going to get a lot better data
12 because of this issue of -- especially daily diary
13 data that people would fill out the day before they
14 needed to hand it in, even though it was a 24-hour
15 recall, whereas you have date and time stamps on
16 electronic data capture devices so you know exactly
17 when they completed it, and there's better
18 compliance.
19 DR. TURK: The priming issue is a really
20 fascinating issue. I know there are several
21 questions. But from some of these batteries of
22 questionnaires that you're asking people, imagine

Page 125

1 that the first questionnaire is about your mood and
2 depression, and your next one is about pain versus
3 the opposite. What's the effect of the priming of
4 having to do that?
5 I think as we think -- I'll get you, John.
6 As we think of the batteries, the numbers of
7 questionnaires we're asking the people fill out,
8 it's not just the absolute number, but it's also
9 what's the impact of filling out -- in the case,
10 you said the worst pain before you do average pain
11 versus if you ask average versus worst. John?
12 DR. FARRAR: If I could ask for a specific
13 question, which was the best, worst first or
14 average first? Which gave you the right answer?
15 (Laughter.)
16 DR. JUGE: The more consistent answers
17 seemed to come from the average first, but we were
18 just playing with the app. We never got to full
19 development. But average first of a past
20 week -- because it asked for the past, it asked for
21 the last 24 hours, and it asked for now. The BPI
22 asked in multiple modes.

Page 126

1 So the past was getting them to think about
2 the whole week and getting them away from what
3 their current condition might be, good or bad, and
4 then bringing them to day, the now.
5 DR. FARRAR: The reason we're asking that is
6 that assuming that we don't use -- what should we
7 call it -- mindwashing or brainwashing to design
8 these apps so that we are leading people to the
9 answer we want, but assuming you don't do that, I
10 guess what I would argue is that one of them might
11 be more consistent than the other and that would be
12 an important thing to know.
13 Getting back to what we said before, as long
14 as it's consistently used by the same person on the
15 same phone for the entire process, it doesn't
16 really matter if it's slightly different for one
17 person versus another. As long as they both change
18 over time, you have a sense as to whether people
19 are getting better or not.
20 This argument comes up all the time with the
21 0 to 10 scale, which I think is a wonderful scale
22 for a clinical trial because it translates across

Page 127

1 cultures, everybody understands numbers, and it
2 works well. But it's a lousy scale if I want to
3 know whether a patient has a lot of pain after
4 their surgery because I don't know what a 7 is or a
5 5 is or a 7 or a 10. Is your 7 more than my 5 or
6 not?
7 The reason that it works is because I'm
8 making the assumption that if you start at 7 and I
9 start at 5 and we both go down with the treatment,
10 then I can say that we both got better. I think we
11 should worry about these things and make sure that
12 we're not misleading patients and giving them a
13 reason to give us the wrong answer. But if we're
14 consistent about it over time, I'm comfortable with
15 the fact that as long as they're using the same
16 method throughout the study, we're likely to get
17 valid answers.
18 DR. TURK: We're getting into a little bit
19 of the details, but for the last word on this, Bob
20 Dworkin, you want to comment?
21 Then I think we've heard the complexity
22 DR. DWORKIN: I have technophobia, so I want

Page 128

1 to change the subject. Is that okay?
2 DR. TURK: But just to say we're going to
3 close down this, but I think the point that you've
4 heard a lot of is how complex this is. Every
5 nuance from the wording to the anchors to the
6 order, all can have an effect. John's point is as
7 long as the patient uses it the same way may be
8 less of a concern than looking across patients.
9 Bob, next, you have a different question?
10 DR. DWORKIN: I will apologize to Quentin if
11 he showed this data, and I didn't process it. This
12 is a question for Dr. Landis as well.
13 In the MAPP data, I guess I want to know
14 about three percentages. What is the percentage of
15 these patients who have what could be considered
16 clinically meaningful pain and clinically
17 meaningful urinary abnormalities that concern them?
18 I don't know how we define clinically meaningful.
19 For pain, it might be 3 or greater, and I don't
20 know what it would be for urinary abnormalities.
21 What is the percentage -- so it's one
22 percentage because they've got both, and then of

Page 129

1 course, the two other percentages are the
2 percentage of patients that have clinically
3 meaningful abdominal pain but have no urinary
4 abnormalities, and correspondingly, the percentage
5 with clinically meaningful urinary abnormalities
6 but trivial or no pain.
7 Because it seems to me that those three
8 percentages become important for this afternoon's
9 discussion when we're going to be talking about
10 composite scales like the GUPI versus co-primary
11 endpoints of pain and urination versus complex
12 composite responder analyses like we see in the IBS
13 guidance. Those three percentages, I think, would
14 inform a discussion about what are the optimal
15 endpoints, outcomes in a clinical trial.
16 I'm sorry if you presented those three
17 percentages.
18 DR. LANDIS: That's very interesting,
19 especially in these syndromes that have several
20 really correlated but different outcomes. The data
21 that Quentin showed for the functional clusters
22 over one year, the improver group, if you noticed,

Page 130

1 with the baseline reference of 0 after the run-in
2 period was subtracted, I think the clinically
3 meaningful improvement was clearly there because it
4 was 6 to 8 units of change for that subgroup that
5 was, quote, improver.
6 But if you look at those who improved on the
7 pain severity and then those who improved on the
8 urinary severity, and you cross-classify those two,
9 only about half of them improved on both at that
10 level. So there's a group that improved on the one
11 but not the other or the other and not the one.
12 One of the things that I think any clinical
13 trial in this chronic pelvic pain is going to have
14 to deal with is the fact that we're going to need
15 multiple outcomes, and the drug or the therapy may
16 actually target the one and not the other. So the
17 stratification, I think, is also going to
18 be -- this may be an afternoon topic. But it's
19 only about half of them who were in that clinically
20 meaningful change level within the first three
21 months, and they stayed down for the entire year.
22 Half of them tracked that way on both of those

Page 131

1 outcomes. The other half were one or the other but
2 not both.
3 DR. TURK: Your numbers are getting pretty
4 small. If I remember, in your improved group, it
5 was like 20 percent of the population or something
6 in that range. Then if you then split that in
7 half, so you're getting pretty thin.
8 DR. LANDIS: It's interesting because it's
9 about 60 percent in the middle who just vary but
10 neither improve or get worse, and then it's
11 20 percent in each end that were getting worse and
12 staying worse or getting better and staying better.
13 DR. TURK: Does that suggest that at
14 baseline, you have these three groups of patients
15 with both and then patients with one or the other?
16 DR. CLEMENS: I think that the way we could
17 do this, which we haven't yet, is you could
18 define -- so first, you have to define what is a
19 clinically meaningful level of symptoms, and
20 generally, we have numeric rating scales. Usually,
21 the value is 4.
22 We could propose looking at those with a

Page 132

1 pain score of 4 or above, those with a urinary
2 score, which we have frequency and urgency. We
3 could look at both, and then those in between.
4 I think from this discussion standpoint is
5 that would be a surrogate definition for those who
6 would be eligible for a clinical trial, and we
7 would then be able to look at the pain and the
8 urinary phenotype in the degree of overlap. So
9 conceptually, you could set up a trial where they
10 did numeric rating scale of 4 above for pain or
11 urinary and look at that.
12 I think that's what you're asking. We
13 haven't done that. We have the data, but we
14 haven't done that analysis.
15 DR. DWORKIN: In a month of you seeing
16 patients, what would you say those three
17 percentages are, the patients in your practice that
18 have clinically meaningful both and the percentage
19 with clinically meaningful pain and no urination,
20 vice versa?
21 DR. CLEMENS: It varies based on sex, but
22 for the women with IC, the majority are going to be

Page 133

1 mixed. I would say probably 25, 20 percent would
2 be the urinary only. Virtually all are going to
3 have pain.
4 I don't know what your thought is, Mike,
5 about that.
6 DR. PONTARI: Urinary only isn't IC, though.
7 That's OAB and things -- are we talking about -- so
8 if we see someone come in with no pain, we're not
9 considering that this, or do you mean --
10 DR. CLEMENS: There are philosophical
11 differences. If someone urinates every 20 minutes
12 and they don't have any incontinence, I don't know
13 that that's OAB, but --
14 DR. PONTARI: No, that's -- what about
15 serious symptoms without pain, isn't that really
16 what we're -- conceptually we consider --
17 DR. DWORKIN: But their pain is 2 --
18 DR. PONTARI: Low grade pain, okay.
19 DR. DWORKIN: That's clinically meaningful.
20 DR. CLEMENS: But we should do that soon.
21 DR. TURK: You'll have a lot of data, and
22 you'll be having a lot of fun with these data for a

Page 134

1 long time.
2 I was thinking about in the IBS world, has
3 there been any longitudinal study that has that
4 much data that you could begin looking at some of
5 these same things to see if, in fact, one thing,
6 they can learn from the MAPP is not just about your
7 outcomes but the kinds of things that they may want
8 to look back at, at those existing databases. I
9 don't know if we want to go there.
10 From the IBS world, is there any equivalent
11 kinds of projects there?
12 DR. LEMBO: Not that I'm aware of, not that
13 follows people for a year without treatment.
14 There's lots of placebo treatment data but --
15 DR. TURK: That are that extensive
16 evaluations?
17 DR. LEMBO: Yes, not that extensive, yes.
18 DR. TURK: Quentin?
19 DR. CLEMENS: Following up a little bit on
20 the outcome discussion, it seems to me that one of
21 the reasons we're perseverating so much about these
22 numeric rating scales is it's just a single

Page 135

1 question. The FDA has -- so it's a question for
2 the FDA, and I'm going to be intentionally
3 provocative, so don't get mad at me.
4 The advantage of a PRO is it has multiple
5 dimensions. It's more than just a single question,
6 and it seems to me that the FDA has highlighted how
7 important developing a PRO is, and then set the bar
8 so high that it's impossible to actually do.
9 At least within our field, I don't think
10 that a PRO has been developed, and there were
11 comments made during the FDA talks that none of the
12 instruments we use really measure up.
13 My question is are there examples from other
14 fields, pain fields or otherwise, where they have
15 successfully developed PROs that meet your
16 criteria, and what degree of effort and resources
17 were needed in order to meet that bar?
18 DR. TURK: Anybody from the FDA want to
19 comment?
20 DR. WIEDERHORN: Yes. I was involved with
21 the approval of collagenase histolyticum product
22 for Peyronie's disease. We had one endpoint, which

Page 136

1 was degree of curvature, but we had a PRO that was
2 approved. It was developed. It was an iterative
3 process. It took -- I don't know.
4 Were you involved in that, sir?
5 It took four or five years, but we ended up
6 using the Peyronie's disease Bother Scale as one of
7 the endpoints. So we have. You're right. It's
8 extremely difficult, and I know we were involved
9 with MAPP because you had approached about doing a
10 PRO. But I think the problem is it takes a long
11 time, a lot of development. It's not simple.
12 Kevin Weinfurt and I talked back and forth.
13 He's on the MAPP committee. In fact, I sent him
14 one of Sarrit's slides, the whole approach to this.
15 I think he agreed with us that we -- now, it's not
16 a light undertaking. I think Sarrit showed you
17 this yesterday, because we have to be exact. We
18 have to make sure it's reliable and accurate.
19 I'm not defending it, but I am saying yes,
20 we have been successful in doing PROs.
21 DR. COONS: But there have been a lot of
22 drugs approved based on patient-reported outcome

Page 137

1 measures. I don't want anybody to leave here
2 thinking that that hasn't happened. You think of
3 erectile dysfunction, itching. There are all sorts
4 of pain, obviously. There are all sorts of things
5 that are patient reported that there are no
6 biomarkers for.
7 The issue is -- and you mentioned they have
8 been approved. Well, they have been accepted as
9 endpoint measures. Qualification is a very
10 different step.
11 DR. WIEDERHORN: I think again that the
12 problem gets into -- and Dr. Lai alluded to it, is
13 that within IC various gradations, there are a
14 whole bunch of different entities, maybe. That
15 makes it very difficult to establish a PRO because
16 you have to define who you're studying. If it's
17 just like anything else, if it's too broad, you
18 can't focus on it. Peyronie's disease was easy
19 because it's fairly obvious what the disease is.
20 DR. HERTZ: There have been other situations
21 where PROs and other novel end measures have been
22 developed, and the reason why we have set up

Page 138

1 the -- or why this whole entire team has developed
2 for these qualifications is because this is not an
3 unusual thing. We have a number of instruments
4 that come in that happened that are novel to the
5 FDA even if not brand-new.
6 In general, I think when a new instrument is
7 developed, the work that we're asking for is the
8 work that is done to develop a new instrument.
9 There's not something novel about the qualification
10 process that FDA has introduced into the concept.
11 It's just we have, because of the need,
12 developed guidance and a team of qualified
13 individuals with this kind of background. You
14 don't want me reviewing this. I'm a neurologist.
15 What the heck do I know?
16 I understand that it's burdensome, and I
17 understand that it's expensive and time consuming.
18 But it's not an FDA process. It's just creating
19 the environment in which we can help to some
20 extent.
21 Now, I've been involved in some of the
22 meetings for a couple of things that are going on,

Page 139

1 and I got to say, I was a little surprised in some
2 of them about the questions my colleagues were
3 asking during internal questions. But totally open
4 to hearing about the clinical need, the setting,
5 willing to put it in perspective once they have the
6 information that somebody with the background was
7 able to provide.
8 I want to push back with the concept that
9 there is something uniquely burdensome about
10 qualification in the context of drug development in
11 the U.S. The good news is once you get there, it
12 just opens it up for use.
13 Now, some of these programs that are
14 developed and instruments are proprietary. Some of
15 them are open. If you can get to the stage where
16 we've got something that's been adequately
17 qualified, I've been taught, perhaps beaten, into
18 using the word "qualification" over validation, but
19 then getting that work done really does create an
20 opportunity to move forward. And the good news
21 then is everyone has confidence that the instrument
22 is doing what it claims to do.

Page 140

1 DR. TURK: Jacobs? Kovacs. Sorry.
2 DR. KOVACS: Sarrit Kovacs, FDA clinical
3 outcome assessments. Drugs are approved based on
4 PRO diaries all the time, and we have approvals on
5 nocturia, for example. Patients are reporting on
6 their nocturnal voids. That's a primary endpoint
7 or co-primary endpoint.
8 Also, with IBS, CIC, IBS-C, with CSBMs,
9 complete spontaneous bowel movements, abdominal
10 pain. There are approvals. Those are still PROs.
11 Another example is the Kybella example for
12 submental fat. It was a co-primary with a patient-
13 reported outcome tool as well as a clinician-
14 reported outcome tool looking at the reduction in
15 submental fat, where it was a 2-point grade, I
16 think, improvement that you had to win on both.
17 So there's some flexibility there. Even if
18 we don't necessarily think that a one-grade
19 improvement is necessarily clinically meaningful,
20 there are some ways where you can use a two-grade
21 improvement, but you could still use the PRO or the
22 CLINRO.

Page 141

1 DR. TURK: Let me end this session now
2 because we've reached the noontime, and I know for
3 people wanting to check out, this is obviously a
4 prime time. So if you can save your comment and we
5 can start off the noon with your comment. I'm
6 sorry to shut you off, but I just want to make sure
7 that for those who haven't checked out, that you
8 have an opportunity.
9 I believe that we have now started getting
10 to some ideas about what this manuscript is going
11 to look like, and the fun is over, and then we're
12 going to start herding.
13 Lunch is back where we had it yesterday. We
14 should be back here promptly at 1:00.
15 (Whereupon, at 12:00 p.m., a lunch recess
16 was taken.)
17
18
19
20
21
22

Page 142

1 AFTERNOON SESSION
2 (1:10 p.m.)
3 Group Discussion
4 DR. GEWANDTER: If everyone can please take
5 their seats, we're going to get started.
6 Thank you, everyone, for your participation
7 so far and for coming here today. I think that
8 we've had some really great talks and really
9 productive discussion, and we hope that we're going
10 to be able to make some progress on a consensus for
11 these goals we have here.
12 What we're hoping that we're going to
13 achieve by the end of this meeting is a consensus
14 on types of primary endpoints we should use in
15 these trials as well as secondary and exploratory
16 endpoints that we think should be included in these
17 trials to try to get some consistency across the
18 trials.
19 Shannon along with help from Dennis and Bob
20 and I came up with a framework for how to structure
21 the discussion today after listening to what we've
22 heard from you all over the past two days.

Page 143

1 It seems like vulvodynia is a little bit
2 separate from the other conditions in the
3 challenges, so I think the challenge for the
4 primary endpoints for vulvodynia is what type of
5 provocation might be useful in terms of the primary
6 endpoint and would it be something where we just
7 ask patients about it or experimental, those kinds
8 of questions, versus with the other conditions,
9 although when we asked the speakers to talk in our
10 first -- how we were envisioning the meeting
11 focused mainly on pain, it became very clear
12 throughout the discussion that, obviously, we have
13 to be able to assess these symptoms simultaneously.
14 So the question is how do we assess pain,
15 and how do we combine that with other symptoms,
16 what are the best methods to do that in order to
17 control type 1 error but still have it be
18 clinically meaningful.
19 Also, another question that we'd like to
20 address is the time frame of the analysis,
21 considering these conditions are potentially
22 cyclical or have flares. Although generally in

Page 144

1 other chronic pain conditions, we do a landmark
2 analysis of the last week, is that sufficient for
3 these trials or what should that be?
4 Then, as I mentioned, secondary endpoints.
5 And then if we have still time, discussion of entry
6 criteria surrounding the endpoint. Just for an
7 example, if we're going to be measuring pain, we
8 need to have a minimum pain intensity or we should
9 all agree that we should have a minimum pain
10 intensity.
11 That's what we're hoping to cover today.
12 Yes, Lee?
13 DR. SIMON: I'm just wondering, in your
14 construct that you just created, is it not
15 possible -- and I don't know; I'm not in this
16 field. But is it not possible that you could have
17 a drug for IBS that might be developed that only
18 does pain, only does pain?
19 DR. GEWANDTER: Yes. Thank you for bringing
20 that up. I think that that's definitely true. You
21 could do that. So if you were going to do
22 pregabalin for IBS, then pain might be your

Page 145

1 primary, and I think that we could definitely
2 acknowledge that in the paper. But for today's
3 purposes, I think that's kind of -- well, after the
4 discussion this afternoon, probably not
5 straightforward, but compared to everything else
6 we're talking about, maybe a little bit more
7 straightforward.
8 Of course, we'll acknowledge that in the
9 paper, but I think we want to focus the discussion
10 on for those conditions, if drug affects both or
11 multiple symptoms, how are we going to handle that?
12 Do you have anything to add?
13 DR. SMITH: I was just going to say so I
14 think what you're saying is we already kind of
15 agree that if your drug, the mechanism of action is
16 to help treat the pain, pain is the primary
17 endpoint.
18 DR. SIMON: But it's important to
19 understand, though, that from the creation of a
20 development program to target your pain as the
21 primary outcome, that's great. But you don't have
22 the choice up there in your box of the possibility

Page 146

1 of having secondary outcomes being all these other
2 things, because we don't know, we really don't
3 know, that if you change pain, you might change
4 other aspects that you would then consider them
5 secondary.
6 The other question is do you want to protect
7 those secondary outcomes from a labeling point of
8 view to be able to be expressed if, in fact,
9 they're important and they're protected and all the
10 other issues.
11 I actually think that you've only given two
12 alternatives, methods to combine pain and other
13 symptoms in the context of a primary outcome, but I
14 think that there should be a second box of pain as
15 the primary outcome, and then how you would do all
16 the rest of the stuff. Because that may be
17 important, and you may want to decide to do it in a
18 certain way to protect them to be able to have the
19 FDA consider them important enough to inform and
20 label for.
21 So we need to be more inclusive than
22 exclusive in the context of structured boxes, I

Page 147

1 think, up there.
2 DR. GEWANDTER: I think that's great. Does
3 anyone disagree with that? I think we could put
4 that down as something that we would say is a
5 consensus pretty easily.
6 DR. DWORKIN: A related question, does the
7 flip of this apply? Is there a box for a drug that
8 improves defecation or urination but has no effect
9 on pain?
10 DR. SIMON: Absolutely. It should be
11 considered.
12 DR. GEWANDTER: I think actually I was
13 talking to Dr. Pontari about this at the break,
14 that one way to do this is if you think pain is
15 your most important symptom that your drug is going
16 to affect, you make that your primary, and then you
17 do a gatekeeping type strategy where the next one
18 is a defecation or whatever. And that way, I'm
19 assuming that that means you can put it on the
20 label because you have protected type 1 error. So
21 that would be a strategy in which we could do that.
22 DR. SMITH: Great. Thank you.

Page 148

1 DR. HERTZ: I would say that when we're
2 talking about outcomes, it might be safest to
3 discuss what's important and how to structure the
4 study, and not worry quite what goes in labeling
5 because that's probably going to vary depending on
6 standards in the divisions and other factors.
7 DR. GEWANDTER: That's great. So for the
8 paper, we won't talk about it that way, but I think
9 we could still bring up this concept of doing
10 things hierarchically or identifying -- not just
11 tailoring the outcome to the condition but also
12 what you think the drug is going to affect. I
13 think that we can talk about it in those terms but
14 convey the same information.
15 Anyone has a question pertaining to this
16 subject?
17 DR. SIMON: Since I'm not an expert in
18 vulvodinia or IBS, I wonder whether or not the
19 experts could tell us whether or not it is
20 inappropriate to develop a drug that might only
21 deal with pain, or might only deal with dysuria, or
22 might only deal with numbers of defecations, and

Page 149

1 not have something that covers what we've talked
2 about, which is all of this complex symptomology.
3 This comes up periodically in the kind of work I
4 do, and I wonder whether or not they care about
5 that.
6 DR. GEWANDTER: You mean like clinically
7 meaningful to patients to do that?
8 DR. SIMON: No. I think do they want a drug
9 that might only deal with pain, or might only deal
10 with dysuria, or might only deal with the numbers
11 of bowel movements a day as opposed to dealing with
12 the construct of all symptoms and signs that we've
13 talked about that are the domains of measurement
14 that are considered part and parcel to that disease
15 state or syndrome.
16 DR. GEWANDTER: Yes, Quentin?
17 DR. CLEMENS: I think the answer for UCPPS
18 is yes, and there are examples that exist already.
19 One would be stakeholder modulation, which is
20 thought to have much more of an impact on urinary
21 frequency than on pain. And we have many, many
22 patients who agreed to undergo that therapy even

Page 150

1 though we tell them that we're not sure how much of
2 an impact it will have on your pain.
3 DR. LEMBOW: For IBS, the answer is yes as
4 well. So we have lots of examples of laxatives.
5 Those are drugs that help only bowel habits;
6 antidiarrheals, loperamide, only works on bowel, no
7 effect on pain; and several examples of pain
8 predominant. Antispasmodics mainly affect pain,
9 anecdotally at least. Lyrica has been studied in
10 IBS, has predominant pain effect. So the answer is
11 yes, we'd love a pain drug.
12 DR. GEWANDTER: Great. Thank you.
13 DR. SMITH: Is it about this?
14 DR. BRUEHL: Just another comment on this
15 same issue. So it sounds like in the box up there
16 for IC, UCPPS, IBS, there really would be primary
17 endpoint box 1 pain, box 2 disease-specific
18 symptoms. They could be co-primary, or they could
19 be exclusively one or the other, or they could be
20 sequential.
21 DR. GEWANDTER: Yes. So we do want to talk
22 a little bit about how to combine symptoms, and I

Page 151

1 think what you're saying is potentially different
2 methods to do that. But I do want to just take a
3 step back because what we were hoping to do was go
4 to vulvodynia first for the consensus because we've
5 talked so much less about it at this meeting.
6 Maybe I could open the floor to some of the
7 gynecologists in the room or our people who
8 specialize in vulvodynia to ask what their thoughts
9 are in terms of suggesting things for what good
10 primary endpoints would be for vulvodynia. So we
11 know we have Foster's tampon test. So something
12 like that, how do you think about, what else might
13 be good.
14 I'm looking at you because you're -- anyone
15 who wants -- or Chris has her hand raised.
16 MS. VEASLEY: Yes. Chris Veasley. Just to
17 mention that, we did only talk about provoked
18 vulvodynia yesterday, but there really is a need to
19 also develop primary and secondary endpoints for
20 women who have generalized vulvodynia, which I
21 think is going to be a lot easier for this group
22 because they have spontaneous 24-hour pain. And

Page 152

1 it's not as complicated as having to provoke it.
2 But that population of women with vulvodynia has
3 been largely ignored, both in basic science as well
4 as clinical. And I think there's really a need to
5 do that. I would hate to come away from this
6 process and just do this for provoked vulvodynia
7 and not do it for generalized.
8 DR. GEWANDTER: Just to clarify that, do you
9 think that there's anything that we could talk
10 about as a group in reference to consistent,
11 all-the-time vulvodynia pain that would be any
12 different from issues that we would talk
13 about -- the things that came up earlier about
14 worst versus average and all these things, anything
15 specific that you would like the group to cover
16 other than acknowledging in the manuscript that
17 this is important --
18 MS. VEASLEY: And different.
19 DR. GEWANDTER: -- and different condition
20 and the ways we measure pain now would apply to
21 that?
22 MS. VEASLEY: I don't think there's

Page 153

1 anything -- I think it generally mimics some of the
2 other conditions that we've talked about in terms
3 of worst, average, and those types of methods.
4 DR. GEWANDTER: Perfect. Katy?
5 DR. VINCENT: That was one of the things
6 that I want to say, maybe not so much about
7 vulvodynia, but I wanted to clarify. Is your
8 chronic pelvic pain syndrome meaning with no
9 associated pathology?
10 Are we considering things like
11 endometriosis-associated pain where we know the
12 amount of pain is completely disproportionate to
13 the disease we find, and therefore, most of the
14 things we discuss here are just as relevant to that
15 condition?
16 DR. GEWANDTER: Let me see if I understand
17 what you're saying. Are you saying is are our
18 consensus guidelines only going to focus on the
19 conditions that we spoke about today, or are we
20 hoping that they will be more generalizable to
21 other conditions as well?
22 DR. VINCENT: Are we thinking about chronic

Page 154

1 pelvic pain as a symptom, or are we thinking about
2 chronic pelvic pain syndrome where we're saying
3 we've excluded all identifiable types of pathology,
4 which therefore means if you're a woman, you have
5 to have a laparoscopy as part of your entry
6 criteria?
7 DR. GEWANDTER: My read on what I was
8 hearing yesterday -- and I think this is definitely
9 open for discussion -- is that it would be
10 impossible to exclude all other types of pain
11 because there just wouldn't be any patients, and
12 also, practically, doing a laparoscopy on everybody
13 would maybe not be practical.
14 I got the feeling that recommending an
15 exclusion criteria based on not being able to have
16 any comorbid pain conditions in the lower abdominal
17 area was not something we wanted to do. Do I have
18 any dissent from that?
19 DR. TU: Sorry. Can you repeat that again?
20 DR. GEWANDTER: I got the feeling that from
21 all of our discussions and based on a
22 generalizability and a feasibility standpoint that

Page 155

1 trying to eliminate all other comorbid pain
2 conditions that could affect the abdominal area
3 would not be something we would recommend in this
4 paper.
5 DR. VINCENT: I think maybe that's two
6 separate things. I think maybe we're saying if
7 you're doing a study on IBS, you don't want to
8 exclude everyone who's had endometriosis. That's
9 one way of looking at it. The way I was thinking
10 about it is are we actually saying that these
11 recommendations will also apply to trials of
12 endometriosis-associated pain, for example.
13 DR. GEWANDTER: Yes. Okay. So I think we'd
14 have to ask you guys as the experts. We're coming
15 up with these concepts of how to put two types of
16 symptoms together, and then for vulvodynia, what
17 type of provocation for evoked vulvodynia. If
18 there's place where those recommendations might
19 overlap, we could highlight them in the consensus
20 manuscript, but if there are places where the
21 things that we're seeing are really specific for
22 the conditions we've decided to cover, then they

Page 156

1 probably wouldn't apply to those areas.
2 DR. VINCENT: I think studying the
3 populations I see, they don't have clear organ-
4 based symptoms. So lots of my patients will have
5 dysuria, dyschezia, which might be cyclical or
6 might be constant throughout the month. Lots of
7 them will have dyspareunia. So I think that
8 they're just as applicable to any of the chronic
9 pelvic pain syndromes.
10 DR. GEWANDTER: I think when you say that,
11 one thing that I think about is, well, then what
12 kind of symptoms are you interested in treating and
13 throw it back to what is the mechanism of the drug
14 you're looking at.
15 So you say a lot of people I see have all
16 these overlapping symptoms. Does that mean you
17 want to do a trial to try to shift on all of these
18 things or -- so I think it kind of depends on the
19 context of the trial that you're doing, how many of
20 the things will apply to any given trial.
21 DR. VINCENT: Then if we're saying that
22 we're doing trials where the outcome is pain, does

Page 157

1 it matter what the mechanism of the drug we're
2 looking at is? Because that's going to be affected
3 by all sorts of different drugs.
4 DR. GEWANDTER: Well, I think -- oh, sorry.
5 Bob, do you want to --
6 DR. DWORKIN: Katy, I want to make sure I
7 understood. Are you suggesting that there really
8 should be three arrows up there, which is the two
9 we have now, vulvodynia with provoked pain, and
10 then these conditions where there's typically a
11 major component of abnormal urination or
12 defecation. And then there'd be a third arrow to
13 chronic pelvic pain.
14 We just have, unfortunately, neglected
15 chronic endometriosis-associated pain and maybe
16 some other conditions like that, but that they fit
17 in this article. Is that what you're suggesting?
18 DR. VINCENT: I want to clarify what I was
19 saying. These recommendations are only for
20 conditions where they have a symptom of pelvic pain
21 but no underlying pathology, or whether we think
22 these recommendations should apply to any trials

Page 158

1 where pelvic pain is the predominant symptom.
2 DR. DWORKIN: As an expert, it sounds like
3 you're suggesting they could.
4 DR. VINCENT: In my view, I think it would
5 be great for the endometriosis world to have some
6 advice from the pain world on how these things
7 should be done.
8 DR. DWORKIN: So if what we've been talking
9 about for the last two days also applies to those
10 conditions --
11 DR. VINCENT: In my view, do you agree --
12 DR. DWORKIN: -- let's add them.
13 DR. AS-SANIE: I'm sorry. I didn't mean to
14 cut off Frank. Go ahead.
15 DR. TU: Frank Tu from NorthShore Health.
16 Katy's point's an excellent one, but the list gets
17 longer and longer and longer. It's very
18 problematic. So it's easy to advocate for
19 endometriosis because there are strong patient
20 advocacy groups for it, but adenomyosis,
21 leiomyomas, there are a whole variety of other
22 syndromes.

Page 159

1 Suzie and I wrote a commentary in the
2 British Journal recently about the fact that you
3 really need a third category of visceral pain when
4 you -- well, certainly a fourth because if there's
5 prostatitis, which is really just male
6 undifferentiated pain somewhere in that hinterland
7 region, bowel and you have bladder. You have to
8 have a uterine category as well, which those four
9 cover everything between men and women.
10 The easier thing to do, I would argue, would
11 be to follow -- maybe the guys from NeuPSIG can
12 talk about this, something where you're saying we
13 have a probability of what you -- basically say we
14 think we've reasonably excluded other pathology
15 versus we don't think we've excluded reasonable
16 other pathology, which allows you the right size of
17 the trial based on your budget. Because if you
18 can't afford to do ultrasounds and laparoscopies on
19 everyone, but the population is simply too complex
20 to do that on, you actually need to be able to
21 adjust for the fact that you have a certain degree
22 of uncertainty with the data.

Page 160

1 I don't know exactly how NeuPSIG has
2 adjusted, but they seem to have this interesting
3 idea where they will assign a relative degree of
4 certainty to the diagnosis of neuropathic pain,
5 which I think could be used analogously in this
6 broad CPP category.
7 DR. RICE: Do you want me to comment from
8 the NeuPSIG or -- it came from that we developed a
9 relatively robust definition, but there are a
10 number of conditions. You can never have a
11 complete certainty about that diagnosis, and there
12 are a number of conditions around that that may or
13 may not be neuropathic depending -- CRPS being the
14 most obvious one.
15 Because we couldn't really resolve that,
16 that's why the grading system was developed. It
17 was only published a year or so ago, so it'd be
18 interesting to see how much it is actually used for
19 trials and practice.
20 DR. GEWANDTER: Can I just try to -- do you
21 want to say something, Ursula?
22 DR. WESSELMANN: I would just leave it

Page 161

1 really with the pain syndromes that we have and not
2 move on to more complex ones because once these
3 consensus goals are implemented for clinical
4 trials, we can probably learn a lot from it that
5 can then be applied to those pain conditions in the
6 pelvic area that are more complex or require more
7 diagnostic methods really to evaluate them, what
8 exactly it is.

9 It's kind of like headache because the
10 majority of patients who have headache don't have
11 migraine of headaches. But migraine-type headaches
12 are more easy to diagnose because they have certain
13 characteristics.

14 So a lot of the research of the clinical
15 trials have focused on those very specific
16 headaches and then the medications that are used.
17 So the treatment approaches that are used are
18 sometimes also implicated for those more diffuse
19 headaches that don't really have a name except for
20 headache.

21 DR. GEWANDTER: I think maybe we can table
22 this a little bit for now, and we can work it out

Page 162

1 in the draft. People can make some suggestions. I
2 think we could easily have a statement that says
3 some of these recommendations could easily apply to
4 assessing pain in other pelvic pain conditions
5 without actually getting in detail about how we
6 might apply them.

7 Yes?

8 DR. CLEMENS: This will be quick. I just
9 agree. The title of the document is Pelvic Pain,
10 though, and so I think maybe an explicit statement
11 that states that we did not address what might be
12 called gynecologic pelvic pain and maybe list
13 those. Because a gynecologist who reads this is
14 going to say, wait a minute, they've ignored
15 99 percent of the pelvic pain patients I see in a
16 document that says pelvic pain.

17 Then there might be opportunity for another
18 potential meeting where we hash out the exclusion
19 criteria for endometriosis and all these others,
20 which is complicated.

21 DR. SMITH: I think that's a great
22 suggestion. Instead, though, do you think there's

Page 163

1 a better title that we could use instead of calling
2 it pelvic pain? Would you recommend something else
3 that encompasses -- or should we just say IC, CPPS,
4 IBS, and vulvodynia? I see some agreement with
5 that idea.

6 DR. TURK: It seemed like that one way to
7 deal with, very interestingly, is to be very clear
8 in your introduction about what this is targeting
9 and acknowledging, as Quentin was saying, that
10 these are these other conditions. Certain
11 circumstances, many of the things we talked about
12 could be relevant, but it was specifically focused
13 on these populations.

14 Number one, acknowledge it so your
15 gynecologists who look at it don't feel left out,
16 but also imply that some of these may be relevant
17 factors for them to be considering in their
18 studies.

19 DR. GEWANDTER: Sounds great. Yes?

20 DR. POLESHUK: This is Ellen Poleshuk. I
21 would also make a plug for acknowledging the
22 discovery you've already made, that there's not

Page 164

1 enough work that's been done in the area of pelvic
2 pain specifically. You discovered so few trials in
3 your review, and so this would be a good place to
4 point out the need for more work in the area, too.

5 DR. GEWANDTER: Great. Okay. If there are
6 no more comments on that, maybe we can bring it
7 back to the provoked vulvodynia discussion. You
8 guys want to make some comments?

9 DR. RAPKIN: The tampon test is a reasonably
10 good provocation method. Obviously, it would be
11 better if you could have intercourse, but so many
12 patients no longer have partners or for various
13 reasons are not able to do that. The adherence and
14 the fact that it has been validated makes it a
15 useful test.

16 We were just talking about the fact that a
17 certain group of patients with provoked
18 vestibulodynia don't have pain with a tampon, and
19 so that's a fairly small number. Most do, and you
20 said that you got around it by making that an
21 entrance criteria, that they had to have pain with
22 the tampon as opposed to saying, okay, we're going

Page 165

1 to use a large enough tampon that everyone's going
2 to have pain with this tampon because then your
3 adherence is going to go down, as it would with
4 intercourse.
5 So I think that, as it's been validated,
6 that would be a reasonable method of provocation.
7 DR. GEWANDTER: Does anyone have any
8 alternate views or ideas?
9 (No response.)
10 DR. GEWANDTER: Okay. I think we could go
11 back then. Maybe we could go to secondary
12 endpoints then in vulvodynia. I think obviously,
13 maybe intercourse in the subset of people who want
14 to be having it would be good, and maybe pain with
15 intercourse, number of times that you have
16 intercourse.
17 I don't know if there's others that you
18 think -- anyone else thinks we should be collecting
19 for secondaries for vulvodynia. Maybe Chris has an
20 idea? Nat?
21 DR. KATZ: Sorry, Jen. I just wanted to
22 point out that we seem to have established

Page 166

1 consensus on the tampon test, and I've also heard
2 that that's a useful test. But none of us have or
3 most of us have not reviewed the performance of
4 that test. So on what basis are we arriving at
5 consensus without actually having reviewed any data
6 on the performance of the test itself?
7 DR. GEWANDTER: Andrea, do you know how it's
8 been validated?
9 DR. RAPKIN: There was one paper that was
10 published by Foster's group. I don't
11 remember -- do you remember how many subjects
12 were --
13 DR. WESSELMANN: I don't know. It's 2009,
14 and it was used also in a clinical trial, but it
15 has been validated.
16 DR. DWORKIN: I'm an author on that paper,
17 and it was a long time ago. I don't remember a
18 whole lot of details about it.
19 (Laughter.)
20 DR. DWORKIN: But to Nat's point, I assume
21 we're kind of considering this as a surrogate
22 endpoint, right, for intercourse? It's hard to

Page 167

1 imagine that it isn't a surrogate. Sarrit doesn't
2 seem to be here, but if Sarrit was here, I'd ask
3 her what the FDA's criteria are for a surrogate
4 endpoint. Clearly, that would be something that
5 needs to be considered.
6 I would doubt that -- and I know you're
7 going to say that we shouldn't, but I would doubt
8 that whatever was in our paper back in 2009 is
9 going to satisfy anyone who has a rigorous
10 definition of surrogacy.
11 DR. KATZ: I'm not disagreeing with the
12 recommendation, maybe as a process. Maybe some
13 information, maybe that paper or some information
14 about the performance of the test could be
15 circulated to the group afterwards just in case
16 anybody has any additional thoughts on it.
17 DR. GEWANDTER: That sounds like a great
18 idea. Of course, we will always -- if we think
19 that that's not -- that's the best we have right
20 now, but future research in other areas, we could
21 suggest areas for future research if you have some
22 other ideas that you think would be better -- if

Page 168

1 they were also validated in a certain population
2 would be better, we could also make recommendations
3 for research in those areas as well.
4 DR. HERTZ: I just want to say not
5 everything is on the same standard as a brand-new
6 PRO. So if you're talking about a surrogate, a
7 surrogate means there's no direct way to assess
8 something, so you need to have something else.
9 Blood pressure is a -- who cares what a
10 blood pressure is. The problem with blood pressure
11 is that longstanding untreated hypertension results
12 in downstream problems, but we don't make companies
13 with any hypertensive drugs measure downstream
14 problems because we know that measuring the blood
15 pressure serves suitably to anticipate all that.
16 With something like a tampon test, if that
17 elicits symptoms that you're directly trying to
18 influence, I'm not sure I would even consider it a
19 surrogate. It's a provocative test of a symptom
20 that requires provocation.
21 If you were going to use that as an outcome
22 for a constellation of symptoms in a syndrome, one

Page 169

1 would want to know the relatedness of that
2 provocative test to the rest of the syndrome, but
3 if you're targeting that pain, then you're
4 targeting that pain.
5 Much in the way when we evaluate topical
6 NSAIDs for ankle sprain, we allow the pain to be
7 measured when somebody is standing because that's
8 when they have the pain. I don't consider that a
9 surrogate or a provocative test. That's how they
10 have pain.
11 I think we need to be very clear on our use
12 of the terms because we don't want to create an
13 undue burden where -- imagine that, FDA doesn't
14 want to create undue burden.
15 (Laughter.)
16 DR. HERTZ: But we want to limit the burden
17 to where it's justified.
18 DR. DWORKIN: I withdraw my use of the word
19 "surrogate."
20 (Laughter.)
21 DR. BRUEHL: Quick question that just
22 occurred to me. So are we treating this pain of

Page 170

1 provocation like allodynia, where it's a yes or no
2 phenomenon, and normal is no and yes is abnormal,
3 or is it something where you'd actually be
4 assessing intensity as an outcome?
5 DR. WESSELMANN: Intensity.
6 DR. GEWANDTER: Intensity during the
7 activity. Yes, Rob?
8 DR. EDWARDS: Sorry. I was just about to
9 ask the same question Steve did. But now that it
10 has been answered, I'll assume we want to be
11 specific about how and with what scale we're
12 measuring the intensity of pain that women in these
13 trials experience with the tampon test. I'm also
14 assuming that if that's a primary endpoint, we'll
15 be setting an entry criterion, an inclusion
16 criterion for the trial on the basis of that.
17 DR. GEWANDTER: Thank you for bringing that
18 up. We are definitely going to -- well, I hope
19 that everyone will agree that we should have a
20 recommendation that whatever your primary endpoint
21 is going to be, that there should be a minimum
22 severity of that or those symptoms at baseline.

Page 171

1 If our primary endpoint is going to be the
2 tampon test, then someone has to have a minimum
3 severity while doing the tampon test to get into
4 the trial, which would solve the issue of people
5 who don't have that problem.
6 As far as standardizing the pain intensity
7 measure, I don't know if that's already been done.
8 DR. RAPKIN: We're trying to remember
9 whether it's a VRS or an NRS that was used, but it
10 may very well have been a VRS. I think it'd have
11 to be decided.
12 DR. GEWANDTER: Right. So if it's been -- I
13 don't want to say validated either. Laurie's not
14 here, but I can feel her over my shoulder. Yes,
15 that's an issue, right, like if we're going to
16 suggest the tampon test but we as a group prefer an
17 NRS, I don't know how that work or what we -- Bob,
18 do you have any comments on that?
19 DR. DWORKIN: My fallible memory is that we
20 used 0 to 10, and then used it in the desipramine
21 lidocaine combination trial. So the tampon test
22 was also used in a 2 by 2 factorial clinical trial.

Page 172

1 I think it's -- do you remember if it's 0 to 10?
2 Because Ellen was involved in all this, too.
3 DR. GEWANDTER: I think that brings up a
4 good point. So let's say it was 0 to 10, and in
5 that trial or in the validation study used
6 worst -- or I guess it would be pain right now if
7 it's a tampon test probably, right? So then you
8 don't have to worry about that issue.
9 DR. TURK: It would seem to me like anything
10 that we recommend that's based on some validated
11 measure, to use the protocol for the assessment, as
12 was the validation, because if they validated on a
13 0 to 10 scale and we said, no, it should be on a 0
14 to 5 scale or should be something else, then the
15 validation no longer is applicable.
16 So whatever we recommend, even with the
17 limitations of it, we have to say it should be
18 performed in whatever the accepted protocol is.
19 DR. GEWANDTER: It looks like it was done
20 with an NRS.
21 Frank -- or is it related to this specific
22 thing, Rob?

Page 173

1 DR. DWORKIN: Yes, but Frank's might be,
2 too.
3 DR. GEWANDTER: Is yours related to this
4 specific thing, or is this --
5 DR. TU: Yes, it is.
6 DR. GEWANDTER: Go ahead.
7 DR. TU: Frank Tu again from NorthShore. So
8 the 2017 article that's authored by Wesselmann and
9 Pukall is available at Open Access. Why don't we
10 just throw it up on the screen? It's got
11 recommended co-outcome measures and secondary
12 outcomes. I'm looking at the table right now.
13 These are all published from August.
14 DR. SMITH: Is that something that all of
15 the OB/GYN experts here in the room would agree
16 with? Because if that's the case, why do we need
17 to put it up? We can just reference --
18 DR. TU: I've seen it for the first time --
19 DR. SMITH: Oh, I see.
20 DR. TU: It's already written up by experts.
21 Why don't we start by taking a swing at it? It may
22 be perfectly acceptable.

Page 174

1 DR. GEWANDTER: Maybe, Ursula, do you have
2 it? Could you give to Valorie? She could put it
3 up on the slide.
4 FEMALE SPEAKER: I don't think a specific
5 recommendation was made over that.
6 DR. WESSELMANN: We made a recommendation
7 for the tampon test in there. It was mentioned but
8 not recommended.
9 DR. GEWANDTER: But there were mentioned
10 outcomes that we could consider and decide if we
11 should recommend them? So maybe like a useful
12 place --
13 (Crosstalk.)
14 DR. WESSELMANN: I'll send the paper to
15 Valorie.
16 DR. DWORKIN: Obviously, this paper that
17 Frank just referred to was distributed. So I guess
18 a reasonable question is, assuming most of us have
19 read the paper, does anyone have any objections to
20 what the recommendations are?
21 (Crosstalk.)
22 DR. TU: There's a core table. You can

Page 175

1 really throw it up on the screen right now. If
2 someone can just get on the internet, I'll send you
3 the link.
4 DR. GEWANDTER: Send it to Valorie.
5 (Crosstalk.)
6 DR. GEWANDTER: Yes, Rob, why don't we talk
7 about yours -- yes.
8 DR. EDWARDS: One more quick question. At
9 the risk of interfering with the magical consensus
10 building process of day 2 IMMPACT meetings --
11 MALE SPEAKER: Stifle yourself.
12 DR. EDWARDS: I probably should, but it's
13 too late now. I'll certainly defer to the real
14 experts in the room and to whatever everyone's
15 recommendation is.
16 It strikes me that one tricky thing about
17 the tampon test will be likely that the time frame
18 for people's recall of the amount of pain with
19 tampon insertion will differ potentially
20 substantially across women. For some people,
21 they'll be rating pain from that day. Others may
22 be rating their tampon-related pain from several

Page 176

1 weeks previous.
2 (Crosstalk.)
3 DR. EDWARDS: Outstanding.
4 DR. DWORKIN: Ursula, I'm looking at table 2
5 now in your article, and the recommendation, unless
6 I'm missing something, isn't for the tampon test.
7 It's for a 0 to 10 scale of vulvovaginal pain
8 during sexual activities in the past month.
9 DR. WESSELMANN: Right. I'm looking at it
10 right now, too, and they discuss the tampon test a
11 lot. So this paper is slightly different than what
12 we are discussing here in the way that here we want
13 to have a consensus, what might be useful to use as
14 the outcome measures for the FDA, whereas what was
15 written there was also for clinical research. So
16 not for every patient population a tampon test is
17 useful or practical actually to do.
18 DR. GEWANDTER: When you say not for every
19 population, what do you mean by that? Who wouldn't
20 it be practical for?
21 DR. SMITH: I think what she's saying that
22 they don't give them a box of tampons and say go

Page 177

1 home and insert these in a clinical setting or
2 would do that in a clinical trial.
3 DR. GEWANDTER: Got you. Thank you. I
4 wasn't clear. I think that's a good secondary
5 outcome to have, but I think we all talked about
6 the fact that -- and I'm sure you agree that some
7 people don't have sex. And if they are having
8 pain, they might avoid having sex. So that's not
9 really for a clinical trial probably going to be
10 that great for a primary.
11 DR. WESSELMANN: I forgot to introduce
12 myself again. Ursula Wesselmann. To measure the
13 pain with sexual intercourse, even if somebody has
14 a sexual partner, is difficult because it's so
15 situationally dependent, and also depending on the
16 lubrication, so you could get potentially very
17 varying results. So a tampon test would be much
18 more standardized.
19 DR. GEWANDTER: Andrew?
20 DR. RICE: I know nothing about this topic,
21 but there's something -- there's a little alarm
22 bell just ringing about this tampon test. So one

Page 178

1 thing I'm personally interested in is the
2 developing world and how these kinds of things
3 translate to other cultures. And I have no idea
4 how this test would translate to a lady living in
5 Afghanistan or South Africa or wherever. It seems
6 very Western orientated is I guess what I'm trying
7 to say.
8 DR. GEWANDTER: Chris?
9 MS. VEASLEY: Chris Veasley. The gold
10 standard for assessing provoked vestibulodynia is a
11 cotton swab test, and that's done obviously in a
12 clinical population. I think we'd be remiss not to
13 include that. The idea of doing the tampon test
14 that David Foster included was how are we going to
15 measure this pain in between clinical visits, and
16 that was kind of the best case scenario.
17 I have two concerns with it. I don't know.
18 I haven't followed the literature as to whether
19 this has been studied since then, but it was only
20 done with one type of tampon, and I'm wondering if
21 it's different between like cardboard applicator
22 and a plastic one, it would be different.

Page 179

1 The other issue is -- I don't know if David
2 looked at this or not, but one of the therapies in
3 terms of using dilators and other things in women's
4 vulvodynia is the idea of desensitization, that the
5 more you do it, the less fear you have, the less
6 anxiety you have over it, therefore the less pain.
7 And I don't know if you looked at that in the trial
8 or not, or if anyone else has looked at that, but
9 that's certainly an issue to bring up.
10 DR. GEWANDTER: I think that sounds
11 potentially like we could say recommended primaries
12 would be either the cotton swab test or the tampon
13 test. Do you guys think that -- or do you have
14 a -- no?
15 DR. RAPKIN: The cotton swab test is really,
16 I think, a surrogate in a way, but it's something
17 that -- there have been some more papers recently
18 suggesting it isn't as well correlated with
19 treatment outcome and improvement and a lot of
20 false positives. Of course, it has been studied
21 more than the tampon test.
22 I think cotton swab test is a good secondary

Page 180

1 endpoint. I think it would be nice to have
2 something more similar to the natural situation,
3 either intercourse ideal, but we know that isn't
4 practical or a tampon, and could certainly try to
5 standardize the type of tampon that's used,
6 cardboard or plastic.
7 DR. GEWANDTER: I think bringing up these
8 considerations, and Shannon and I will take a good
9 look -- or Shannon really is the one who's writing
10 the paper -- will take a good look at the tampon
11 test validation and talk about these
12 considerations. Yes?
13 DR. WESSELMANN: As far as sensitization is
14 concerned, it could go either way. So it could
15 either be daily dilatation of the vagina or it
16 could be that the vagina is getting more sensitized
17 due to the repeated provocation. But as far as I
18 recall, and that would be something we would have
19 to check, when the test was validated by David
20 Foster, that didn't seem to play a role.
21 DR. GEWANDTER: As we've talked about, we
22 want to minimize the nonspecific responses in a

Page 181

1 randomized trial that would be balanced, so
2 hopefully, so maybe not as bad of a thing
3 necessarily.
4 Valorie, do you have the slide? Oh, you're
5 working on it. Sorry.
6 While we're waiting for the slide, are there
7 any secondary outcomes other than the things we've
8 talked -- do you want to read what we have?
9 DR. SMITH: I have intercourse, number of
10 times having intercourse, the cotton swab test as a
11 secondary endpoint. Those are the things I have.
12 DR. GEWANDTER: I think maybe rating your
13 pain during sex for people who are having --
14 DR. AS-SANIE: There are standardized
15 measures of sexual function that have to do -- that
16 incorporate arousal, satisfaction, partner
17 relationships, those certainly, I think, I wouldn't
18 consider them primary but secondary could be very
19 useful. Lubrication is part of those measures.
20 I believe the most widely used is one called
21 the FSFI, and it's been validated, but PROMIS now
22 has multiple measures. All of them are fairly

Page 182

1 burdensome. The FSFI has, I think, 18 or 20
2 questions, so they're not super simple, but if you
3 wanted to capture all of the domains using PROMIS,
4 you pretty have to use a similar number of
5 questions.
6 DR. TU: You want me to read them to you as
7 a -- go through the core outcomes or the
8 secondary --
9 (Crosstalk.)
10 DR. RAPKIN: I think while you're waiting,
11 the caveat with the FSFI is not to include a total
12 score because you're dragged down by the fact that
13 if you're not having intercourse when it asks about
14 intercourse pain in the last month.
15 DR. GEWANDTER: That's great. Thank you.
16 Yes, Katy?
17 DR. VINCENT: Just while we're doing this as
18 well, we've just looked at the tampon test, and one
19 of the issues that I would have about it -- I don't
20 know how much the validation work has been
21 done -- is that it says no lubrication and a
22 cardboard applicator.

Page 183

1 So the cardboard applicator is going to be
2 standard, but if the woman is bleeding, for
3 example, she will find it much easier to put in and
4 take out a tampon, whereas if she's not bleeding,
5 she won't and therefore will generate more pain.
6 I'm not sure that is going to give you a
7 standard response throughout the month.
8 DR. GEWANDTER: Would a way to address that
9 issue would be to standardize like when in a cycle
10 you enroll people and when they would hit their
11 endpoint, so we could say the caveat would be that
12 be a necessary part of the trial, or is that not
13 sufficient for --
14 DR. VINCENT: I think you would have to say
15 that you were inserting on a day without bleeding
16 if you wanted to have a valid measure.
17 DR. GEWANDTER: Great. Thank you for that.
18 That's a great suggestion.
19 Here we go. So can people see this?
20 DR. SMITH: Here we go. Hopefully, people
21 can read it. If you have your copy in front of
22 you, that also would be helpful. Pain intensity,

Page 184

1 pain quality, and affect, so the short form McGill
2 Pain Questionnaire, the VPAQ Pain Descriptor Scale,
3 the 4 VRSs related to pain unpleasantness and
4 distress. Those are the recommended core outcomes.
5 And then pain temporality.
6 DR. RAPKIN: Core outcome doesn't mean --
7 DR. GEWANDTER: I guess the question would
8 be -- go ahead.
9 DR. RAPKIN: Core outcome is not
10 specifically a primary outcome.
11 DR. GEWANDTER: Right. So I guess the
12 question would be, after looking at this, does
13 anyone have anything else they'd like to nominate
14 for a potential primary? And if not, are there any
15 things on this list that you would say would be
16 like -- you would say they're less of a priority to
17 include as a secondary so we can try to -- I think
18 they're a lot there, so maybe we want to try to be
19 a little bit cognizant of recommending the most
20 important ones.
21 DR. DWORKIN: If I'm hearing correctly,
22 perhaps the strongest recommendation we could make

Page 185

1 is that if someone was designing a clinical trial
2 of vulvodynia, we recommend they consider either
3 the tampon test or this measure of provoked
4 intercourse vulvovaginal pain, and that we really
5 don't have an evidence base for recommending this
6 or the tampon test. But we can certainly recommend
7 that these are the two contenders --
8 DR. GEWANDTER: Sorry. Which one did you
9 say besides the tampon test?
10 DR. DWORKIN: This item is not tampon test.
11 DR. GEWANDTER: No. Which one did -- what
12 did you say, the provocation one?
13 DR. DWORKIN: The first one up here, pain
14 intensity, so that our recommendation would be that
15 someone designing a clinical trial of provoked
16 vestibulodynia should consider either of these two
17 as a primary endpoint.
18 DR. GEWANDTER: But if you consider this as
19 the primary endpoint, you have to exclude people
20 who aren't having sex.
21 DR. DWORKIN: The investigator would have to
22 figure that out, exactly.

Page 186

1 DR. GEWANDTER: Frank?
2 DR. TU: I would agree with that, but the
3 obvious thing to address Chris' concern about
4 handling generalizable vulvodynia is to have some
5 sort of a simple like it's a -- what do you call
6 like a -- the yes/no sort of like -- you branch
7 your logic out. If the person doesn't have logic
8 that makes sense to evaluate them on the 11-point
9 NRS, you'd go to 2 VPAQ scales and look at worse
10 vulvovaginal and average vulvovaginal pain in a
11 typical month.
12 This seems to capture all of the things
13 we've talked about in the last couple days. It
14 looks very well done for the pain intensity as a
15 primary endpoint.
16 DR. GEWANDTER: I think then maybe unless
17 anyone has anything else to bring up, that in terms
18 of primary and secondary vulvodynia, we are good.
19 Of course, obviously, we're going to make a
20 draft, and we hope as the eminent Dr. Turk
21 mentioned, that you'll all comment on the draft and
22 give us feedback. And if there's anything that we

Page 187

1 don't cover that you think is really important, you
2 can let us know, and we can try to incorporate
3 that. Ursula?
4 DR. WESSELMANN: Ursula Wesselmann.
5 Vulvodynia in some ways is different for a clinical
6 trial design than the other two or three pain
7 syndromes in that there are a lot of possibilities
8 actually for topical applications, which is not the
9 case in the others. That's why I think the tampon
10 test might be useful, especially if a topical
11 application is used, and there might be other
12 options if an RO [ph] application is used to
13 measure the primary outcome.
14 DR. SMITH: Can we go back to the other one?
15 Thank you.
16 DR. GEWANDTER: Then the only thing I wanted
17 to say because we --
18 (Crosstalk.)
19 DR. GEWANDTER: There it is. Also, Nat had
20 put this together for us. Thank you, Nat. And he
21 also had the VQOLs. I think maybe we could add
22 that, too. I don't know if it was up with the

Page 188

1 other one. I just wanted to check to make sure
2 there weren't any more on there.
3 Now we want to move back to the more left
4 part of the screen and talk about issues of primary
5 endpoints in the other three conditions. Really, I
6 think it became obvious, as I mentioned before,
7 that as Lee brought up, there will be situations
8 where your drug will target pain, and you want to
9 make that the primary endpoint.
10 But in situations where either you don't
11 know or you think it might combine both, and you
12 want to have your outcome measure be both, we were
13 thinking for the manuscript that we would summarize
14 the pros and cons of the different methods to do
15 that. So things like using co-primary endpoints;
16 hierarchical gatekeeping; DOOR; using a component
17 composite responder I think is what Laura Lee
18 called it, which is like the IBS guidance, what
19 they recommend right now. Then we would just
20 outline the pros and cons of each because we didn't
21 feel like we really as the group have an evidence
22 base to suggest one over the other.

Page 189

1 So is that a reasonable thing to do in the
2 consensus manuscript as far as everyone's
3 concerned? Do I have any dissent on that or any
4 comments anyone would like to make?
5 The only thing I guess I wanted to bring up
6 was a lot of the trials that I reviewed used this
7 composite endpoint, and I think based on what I
8 heard in the past couple days, using a composite
9 where you just make one score out of a bunch of
10 different symptoms or two different symptoms
11 probably wasn't the best way to go.
12 Does anyone disagree with that statement in
13 that you would want that as one of the options that
14 we think might be recommended?
15 (No response.)
16 DR. GEWANDTER: No? Okay.
17 DR. DWORKIN: That's actually a very strong
18 recommendation, that we're basically saying that
19 total scores like the total score on the GUPI that
20 combines pain and urination, or a total score that
21 would combine pain and defecation abnormalities, we
22 are recommending against.

Page 190

1 DR. GEWANDTER: Everyone's cool with that?
2 DR. BUTTERFIELD: I think that's consistent
3 with a lot of what we've heard as well, that there
4 isn't necessarily -- they don't track with each
5 other, and putting them together isn't going to be
6 helpful actually. It's not saying that looking at
7 pain and looking at urinary symptoms are not
8 important. It just means don't put them as a
9 composite.
10 DR. GEWANDTER: That's great.
11 DR. DIMITRAKOFF: I would support that
12 statement. I think it's important to keep that as
13 a caveat and probably say that, depending on the
14 findings from the MAPP and the emerging studies,
15 it's important to keep that in mind that the two
16 scores don't --
17 DR. GEWANDTER: Based on our best evidence
18 right now --
19 DR. DIMITRAKOFF: -- or best evidence at the
20 time, yes.
21 DR. TURK: We have a plea from our
22 transcriber to please say your name for everybody.

Page 191

1 Now, if you've said the same thing several times,
2 very quickly --
3 DR. LEMBO: This is Tony. I guess the one
4 caveat to this is that, as we heard earlier, not
5 everybody has pain. So it does exclude a
6 significant portion of the population in other
7 diseases.
8 Now, that would have been the case in IBS,
9 but now with Rome IV, we've made it our entry
10 criteria, made it a requirement to have pain. It
11 actually wouldn't affect IBS, but I just wanted to
12 make sure the other groups didn't feel like it was
13 excluding a large subset of their population.
14 DR. GEWANDTER: Can we just wait one minute?
15 So that's going to be -- we want to get to this
16 idea of what our entry criteria related to our
17 outcome is going to be. I think that what you're
18 saying is very true, For instance, in IC, if you
19 want to include people who don't have pain and
20 would call it discomfort, then I think the outcome
21 has to be discomfort. It can't be pain, right?
22 You can't put people in the trial who don't have

Page 192

1 pain and then make pain one of your main outcomes.
2 So I think that's probably something
3 important for us to discuss, on how we would handle
4 that. But I just want to get to one other thing.
5 Maybe I'm being a little rigid with the boxes.
6 Sorry if I am.
7 We're going to talk about how we would
8 combine these symptoms, and then I want to talk a
9 little bit about this time frame of analysis thing.
10 Generally, for things like DPN or CIPN -- well,
11 CIPN has nothing for -- I just think of it because
12 it's my thing. But we do a landmark analysis of
13 one week out of 12.
14 I guess the question for you
15 guys -- obviously, this wouldn't apply for provoked
16 allodynia -- is, is one week enough time when these
17 conditions have a little bit of recurrent pain?
18 Obviously, right now, the way the FDA IBS guidance
19 is they say you want to have a responder on 6 out
20 of 12 weeks because they just don't want to do an
21 endpoint analysis, like a landmark 1-week analysis.
22 I want to open it up to the floor of what do

Page 193

1 we think about this, what recommendations we can
2 make, or at least considerations in terms of not
3 making it a landmark of only one week. And maybe
4 Sharon can comment on what she thinks about that.
5 Sharon?
6 DR. HERTZ: This area is new in terms of the
7 clinical implications. Obviously, it's different
8 than what we do with landmark analysis in other
9 settings. So I'm actually not going to say
10 anything.
11 DR. GEWANDTER: Do you guys want to comment
12 on what you think about that in terms of how
13 variable the pain would be or the other symptoms,
14 and if 1-week landmark analysis is sufficient or if
15 we should be thinking of other things?
16 DR. CLEMENS: If I understand correctly,
17 this is the time frame. During the past week,
18 please rate your symptoms. Is that what you're
19 asking?
20 DR. GEWANDTER: Or you do a diary over a
21 week, and then you just use that last week in the
22 analysis versus the last, say, 4 weeks maybe, to

Page 194

1 get a better view of the person's experience.
2 DR. SMITH: Or the area under the curve
3 where you look at what's happening across the
4 entire time period.
5 DR. CLEMENS: I guess my feeling would be
6 that we're -- while there's a lot of ongoing
7 analyses, and maybe this change, right now, I think
8 a week time frame has been the standard for IC and
9 prostatitis research. And until there's compelling
10 data to suggest we should do it differently, that
11 would probably be the current suggestion.
12 DR. GEWANDTER: Mike.
13 DR. PONTARI: I really like the idea of the
14 area under the curve. Has that been used in other
15 studies, and does it correlate with a JRA, a
16 quality of life? What do we know about that in
17 terms of using that as an endpoint?
18 DR. GEWANDTER: Bob, do you want to comment?
19 You know a lot more about previous studies than I
20 do.
21 DR. DWORKIN: I'm sure people have taken an
22 area-under-the-curve approach. My understanding is

Page 195

1 that the concern about that, for example, for a
2 3-month trial, would be that you could get a
3 significant difference between treatment and
4 placebo that's driven by, say, the first 4 or
5 5 weeks and that the difference between treatment
6 and placebo disappears by week 12. And therefore,
7 you've got a treatment that apparently shows
8 efficacy but has no durability.
9 I think Sharon could comment on this.
10 (Laughter.)
11 DR. DWORKIN: So the question is if you look
12 at week 12, you've demonstrated durability, whereas
13 with an area under the curve analysis, there's at
14 least the potential that you don't have durability,
15 but you have a significant difference. But I think
16 Dr. Landis is going to clarify this.
17 DR. LANDIS: That's actually one of the
18 benefits of the functional clustering profile that
19 Quentin shared this morning, and that is, those who
20 improved in that early phase, in order to be in
21 that group, they had to stay at that improved level
22 the entire rest of the follow-up period. There

Page 196

1 were other patients in there who went on a lower
2 profile early and then went back up again.
3 So when you do functional clustering, you
4 capture the level, but you also capture the
5 distance they have to travel at the improved level
6 as well. So if you do something of that order,
7 then basically, you have the amount of improvement
8 but also the persistence of the improvement the
9 whole way to the end.
10 DR. GEWANDTER: Do you want to comment?
11 DR. AS-SANIE: This is Suzie As-Sanie. I
12 think, though, regardless of what we decide, I
13 think the paper needs to recognize that this is an
14 incredibly under-studied problem in reproductive
15 age women, because while things like one week have
16 been shown to be sufficient, I think we just simply
17 don't ask.
18 I think any one of the clinicians here that
19 primarily takes care of women of reproductive age
20 when we ask them clinically, there's huge
21 variability according to where they are in their
22 menstrual cycle. And many women, regardless of

Page 197

1 whether it's bladder symptoms, GI symptoms, or
2 dysmenorrhea, or chronic daily pelvic pain, their
3 symptoms flare right before and during their
4 menses. And if we don't acknowledge that, we are
5 just missing that problem because we simply haven't
6 asked patients, and then we won't be able to move
7 forward.

8 I would say that while the evidence that's
9 published might suggest a week is sufficient,
10 clinically, it's probably insufficient and would
11 just at minimum encourage more data collection in
12 women that aren't menstrually suppressed or
13 postmenopausal.

14 DR. GEWANDTER: Sharon?

15 DR. HERTZ: That's my point. These are the
16 kinds of things that you need subject matter
17 experts to opine on because the standard that we
18 use for general pain in most of the indications
19 that we get, that last week of 12 weeks is
20 generally okay. But it sounds like here that a
21 reasonable case can be made not just for that we
22 don't know, but that it could really be totally

Page 198

1 wrong. The generalities are the assessment period
2 and the method of evaluation have to be tailored to
3 the clinical syndrome.

4 Are 12 weeks enough? That's a standard
5 that's been used and has come under huge criticism
6 for a variety of reasons, but what is a 12-week
7 period in the context of somebody who has cyclic
8 changes? What's the interplay there?

9 I don't know if there's enough to make a
10 recommendation. It sounds like there's enough to
11 raise the issues for further study.

12 DR. GEWANDTER: Suzie and then Hanna.

13 DR. AS-SANIE: Suzie As-Sanie again. And I
14 would just probably go one step further and say
15 that not only should it be tailored to the clinical
16 syndrome, it should be tailored to the population.
17 This should be considered in reproductive age women
18 with any pain condition because when we see these
19 patients, whether or not it's pelvic pain or vulvar
20 pain or chronic abdominal pain, their symptoms
21 often fluctuate. And it's not because it's
22 endometriosis or whatnot. Their symptoms just

Page 199

1 change over the menstrual cycle.

2 DR. GEWANDTER: Mike and then Hanna.

3 DR. PONTARI: It would be helpful if the
4 gynecologists or someone talking about this, could
5 give whatever the best questions to assess that,
6 the best method to make sure you're getting that
7 accurately. I think it would help people who don't
8 do this a lot.

9 DR. GEWANDTER: Hanna?

10 DR. GROL-PROKOPCZYK: That's what I was
11 wondering, too. If we don't know enough yet to say
12 start the one week of key measurements 7 days after
13 the period ends, or if we aren't at a point where
14 we can suggest where in the cycle we should be
15 focusing the measurement, then what would you want
16 measured? Would you want just people to keep track
17 of how many days since their last period began?

18 DR. VINCENT: You can answer that two ways.
19 I think that there's plenty of published data. You
20 can cite Linda LeResche papers, for example,
21 showing that there was a clear cyclicity to lots of
22 different pain symptoms, including fibromyalgia,

Page 200

1 temporomandibular joint dysfunction. There's an
2 increasing body of literature showing that
3 endogenous hormonal fluctuation and exogenous
4 hormones alter the experience of pain and central
5 processing as well as the symptoms of a clinical
6 pain condition. So we know that there are
7 influences of these factors.

8 As far as what people's pain does, most
9 chronic pain conditions flare at times of falling
10 or low estrogen, so in the week before the period
11 and as the period starts. But I think if you want
12 to get a full spectrum of what's really going on
13 and what the interaction between hormones and bowel
14 function and hormones and bladder function is, for
15 example, you really have to be collecting a full
16 cycle of data rather than choosing a time that you
17 think is interesting.

18 DR. DWORKIN: Just to be teeny bit
19 provocative, could we say that for many, if not all
20 of these conditions, what should be considered is
21 if it's a 3-month trial, the endpoint is the last
22 month. So not an area under the curve of 3 months,

Page 201

1 but last month rather than the last week of a
2 3-month trial, and that would be mean pain or
3 whatever our measure is.
4 DR. GROL-PROKOPCZYK: What's your baseline
5 measure then, the first month?
6 DR. DWORKIN: The baseline measure has to be
7 before patients are randomized, and it's the
8 issue -- in the perfect ideal world, yes, it would
9 be nice to have a baseline of a month. But I think
10 we talked this morning about the practical issues
11 of keeping a patient on no treatment for a month,
12 and that's going to be a struggle.
13 So realistically, it might be the baseline
14 would be 2 weeks with careful attention to where in
15 the cycle women are. It's going to be --
16 DR. VINCENT: As long as your outcome is at
17 exactly the same point as your baseline measure and
18 you can time that with days from your last cycle
19 and the length of your last cycle. And at least
20 you've got some form of control for that.
21 I think ideally and what we do in the trial
22 we're running at the moment is get a weekly rating

Page 202

1 for the first 4 weeks before they're randomized,
2 and that helps to see who's going to stay in the
3 trial and actually give us the data we want anyway.
4 And patients aren't complaining about it.
5 DR. WIEDERHORN: Given the argument that
6 also during the first four weeks, you get the
7 inclusion in the trial effect, I would argue that
8 the paper ought to say 4 weeks should be considered
9 and that shorter could be chosen for practical
10 reasons.
11 I don't think we should obviate the need for
12 it by saying that we think it won't work, because I
13 actually think that in certain circumstances,
14 4 weeks might work reasonably well. It's just that
15 the issue is trying to figure out how to do it, and
16 I think that's real.
17 DR. DWORKIN: Four weeks is a
18 pre-randomization baseline. So now you've made a
19 3-month phase 3 trial 4 months.
20 DR. WIEDERHORN: Yes.
21 DR. JUGE: I just want to give another
22 example of following your endpoints. We had a

Page 203

1 product that was first in its area, if you will,
2 and they came up with a dual endpoint to the study.
3 And how that worked is you're looking at not only
4 early efficacy but does it maintain it over time.
5 So this was 6 months, but you could scale it any
6 way.
7 At month 3 and month 6, you had to hit
8 80 percent of that endpoint, and then at month 6,
9 the same thing. So you're really looking at two
10 time points. You got a middle time point. Are
11 they going to meet efficacy, and you have an end.
12 And the people that met that were considered the
13 responder group. So it was fail, not fail. We
14 called it a responder point.
15 I think it answers a lot of the questions
16 going around here is that that's another option
17 that could be used, but it would give you both the
18 early time point on getting success. If that's a
19 severe pain or whatever, that would be good. But
20 if it's symptoms, they might not only want success,
21 but they want maintenance of that success over
22 time. So it gives you two endpoints instead of

Page 204

1 that one endpoint there.
2 So however you span it out, if you want
3 6 weeks, 8 weeks, 2 months, then you can have two
4 time points. And if there are cyclical
5 involvement, if you did a month period, then you
6 have month 3 and month 6.
7 So you monitor it through the whole time,
8 but month 3 and 6, you did all of your extensive
9 testing. So they would come in weekly for 4 weeks
10 or whatever it took, but you're getting through
11 whatever their cycle is. You don't have to say you
12 got to start on an off or on day of your cycle. If
13 I'm getting a full month in there, I'll catch that
14 and all that data.
15 DR. GEWANDTER: Dr. Landis, do you want to
16 comment on that? It looked like you might -- you
17 looked like you wanted to maybe say something. No?
18 Dr. Landis, no? Did you want to say
19 something? It looked like you did.
20 DR. LANDIS: No. I think that's consistent
21 with the earlier comment I made about the improver
22 early phase persisting.

Page 205

1 DR. GEWANDTER: Is your method one that does
2 something similar to what -- I'm sorry; I forget
3 your name -- I think Dean was saying --
4 DR. JUGE: Dean, yes.
5 DR. GEWANDTER: -- but more like
6 incorporates the whole time.
7 DR. JUGE: Well, if you are in the responder
8 or the completer group, if you maintain in both
9 sets --
10 DR. GEWANDTER: No, I'm asking Dr. Landis.
11 DR. JUGE: Oh.
12 DR. GEWANDTER: For instance, depending on
13 the week you pick, it might be different, but if
14 he's looking at using a method that looks at the
15 response and duration over the whole period, that
16 might take a little bit more this whole issue of
17 recurrence and not knowing exactly when the pain is
18 going to be the worst and flares and stuff into
19 account.
20 DR. LANDIS: It complicates the criteria of
21 it that you could imagine saying in the example you
22 raised about the 3, 6, and 12 months if 12 months

Page 206

1 happens to be -- or 12 weeks happens to be the
2 primary endpoint, then you would have these
3 intermediate measures where they have to reach
4 criteria and stay below those during those key
5 measurement points.
6 DR. GEWANDTER: One thing I just wanted to
7 ask -- go ahead.
8 DR. HERTZ: But that doesn't get to the
9 point that seems to be very specific to a condition
10 that may cycle based on a month's hormonal changes.
11 So there are two questions here. One is
12 when does it make sense to figure out if something
13 is working and if the effect is sustained for what
14 would be considered a reasonable surrogate for
15 long-term benefit, and then, but how do you measure
16 this particular condition, which is different from
17 low back pain?
18 What's done in more general settings,
19 acknowledging that chronic pain fluctuates in most
20 conditions; different things will exacerbate it; a
21 lot of those are not well-quantified in clinical
22 studies; and day to day, pain scores vary.

Page 207

1 So one of the methods applied in this other
2 setting is to take the last week, get daily
3 assessments and average them, and try and cut down
4 some of the noise that way, right?
5 So that works in that setting. That could
6 completely miss the boat in this setting, so here
7 are some ideas. These are research questions, but
8 some ways to start approaching it to come up with
9 an answer would be to see if there are trends in
10 pain based on where in the cycle a woman is.
11 Hopefully, for the clinical trialists that
12 are going to be doing these studies, a consistent
13 finding may show up. For instance, the third week
14 of a cycle seems to be traditionally within the
15 worst range, even if it's bad for -- you could
16 identify in the course of a 4-week period if
17 there's consistently one of those weeks that tends
18 to be indicative of worst pain consistently across
19 the population. Even if there may be some
20 individual variability, you could then designate
21 that would be the baseline week, and that would be
22 the efficacy week at the end of the period if the

Page 208

1 data -- or maybe it's a 2-week period or whatever
2 it is.
3 Then you would basically enroll subjects and
4 begin their study participation in a synchronized
5 way for that. That could get to reducing some of
6 that variability if there is behavior of the pain
7 that is conducive.
8 In terms of the durability of effect, you
9 can check multiple times, but you don't have to.
10 You can just pick the distance out, the duration
11 out that you think is adequately predictive of a
12 long-term effect and just do that.
13 I never recommend just doing the beginning
14 and the end and not doing anything in the middle
15 because of course, that's highly informative. But
16 you don't have to do multiple checks per se unless
17 you have concerns.
18 So for instance, 3 months is hard enough to
19 keep people in a placebo-controlled study. I won't
20 go into a lot of those issues in this crowd, but we
21 have other conditions that we work on in the
22 division where 2 years is a standard outcome.

Page 209

1 Well, hello? How easy is that to keep people in
2 study?
3 So what we'll sometimes do is create a
4 series of assessments, and we'll come up with the
5 shortest period of time we think is reasonable to
6 evaluate efficacy that would both satisfy both some
7 measure of durability of effect and feasibility of
8 keeping your people in the study long enough to not
9 have a major missing data problem.
10 Then you can, with proper statistical input,
11 use additional longer-term assessments,
12 calculations. So for instance, you can do your
13 primary 3 months, and then if you really want to
14 try and see if the durability makes it to 6 months,
15 you can make that secondary to the 3-month
16 assessment.
17 So if you lose your population and you lose
18 your power, you're not going to be penalized with a
19 failed study by prioritizing the 6th month. And
20 then you can have a 9-month or a 12, whatever
21 you're interested, and those questions can all be
22 asked. But what you can do is start off with

Page 210

1 something that is at least conceptually feasible
2 once you've got the other details worked out, and
3 then if you want to have statistical evaluation of
4 the ongoing effect, you can do that in that stepped
5 approach.
6 DR. GEWANDTER: Is it really quick?
7 DR. CLEMENS: Real quick. Yes. Maybe this
8 doesn't make sense, but for this cyclical aspect
9 related to menstrual cycle, at a minimum to suggest
10 that subjects when they're measured, that
11 premenopausal women let us know when was their last
12 menstrual cycle, when did it start and the
13 duration, whatever the appropriate variables are.
14 That might allow for that aspect to be
15 examined or controlled for in a study, and it may
16 not be perfect but may be more feasible than trying
17 to follow someone for a month.
18 Is that maybe a reasonable suggestion,
19 somewhere in between?
20 DR. GEWANDTER: Yes. Thank you. That's a
21 very good intro to my summary.
22 I think what the best going forward going

Page 211

1 forward will be is that Shannon and I and Bob and
2 Dennis can discuss all of the options that we've
3 talked about, and in the paper, just bring this up
4 as an issue in these set of conditions. It might
5 not be as straightforward as just one baseline
6 week, one endpoint week like we often do in some
7 other conditions.
8 Then offer some of these alternatives we've
9 talked about as things to consider and things that
10 require future research to validate, and we'll
11 include that in the draft that we send to you. And
12 everyone will have an opportunity, as we keep
13 repeating, to give comments and add things and be
14 constructively critical of and provide feedback on.
15 I think this is a good place to break for
16 coffee and to use the rest room, and be back at
17 2:45. Sound good?
18 DR. TURK: You'll all be invited back in
19 five years when all the things we recommend, all
20 the data come in, and we're going to redo these
21 guidelines.
22 (Whereupon, at 2:22 p.m., a recess was

Page 212

1 taken.)
2 DR. GEWANDTER: That was very good progress.
3 In the interest of keeping it going in time, for
4 secondary endpoints for the three non-vulvodynia
5 conditions, Nat again made this for us. So these
6 are things that could be considered as pain-related
7 secondaries for these conditions. We just wanted
8 to see if anyone objects to recommending any of
9 these.
10 Then for non-pain-related symptoms, we
11 thought instead of trying to come up with a list
12 here, the experts, urologists and
13 gastroenterologists, could just send us the
14 non-pain secondary endpoints that you would like to
15 see in trials instead of -- yes, Nat?
16 DR. KATZ: Just in terms of this slide, I
17 just put those up there as random examples. I have
18 no opinion about whether those measures are good or
19 not, or just to provide a framework.
20 DR. GEWANDTER: Okay. Well, I like a lot of
21 them. Of course, we'll say QST would be based on
22 resources and whatever, or if there's any that

Page 213

1 people would like to add that they think also
2 should be on this. Nat, yes?
3 DR. KATZ: Just to provide a little bit more
4 context, the concept here was that, as we were
5 discussing yesterday, all these disorders seem to
6 be specific examples of more general phenomenon,
7 which is some kind of general visceral
8 hypersensitivity. We know that these patients
9 have -- many of them -- most of them have these
10 other more general findings.
11 So the concept is are there any other
12 patient-reported outcome measures that we should
13 consider in general across these syndromes that
14 might capture the more general phenomenon. Then
15 there's patient-reported outcome measures that
16 could be considered, and then there's sensory
17 testing or evoked pain tests that could be
18 considered.
19 Then once you're done with that, then you
20 could talk about the specific disorders and what
21 measures might be relevant there. So it's just a
22 framework for discussion.

Page 214

1 DR. GEWANDTER: Yes. I think that as long
2 as no one objects, I think we could have a section
3 of the paper where we talk about including these
4 secondary endpoints for that purpose of trying to
5 better define this potential phenotype of patients
6 who have more of a central component, and maybe we
7 could add a couple of sentences about how the
8 future might look like where we could potentially
9 move trials to a place where we are doing
10 mechanism-based recruitment and not recruiting
11 based on end-organ disease, and how that might be
12 the future of that area. And by including these
13 things in a lot of trials, we can try to get there
14 even though we're not really there yet.
15 I think that we can have a section on that
16 because I do think that came up quite a bit in the
17 meeting, and just leaving it out might do a
18 disservice, even though we don't feel like we're
19 all the way there to recommend it as a method now.
20 Does anyone have any objections to that or
21 any other comments they'd like to add to that?
22 (No response.)

Page 215

1 DR. GEWANDTER: No? Okay. Great.
2 The last thing is this issue of entry
3 criteria, and actually, Shannon and I were talking,
4 and we realized that Lee's point at the very
5 beginning, we were remiss in making this
6 potentially a symmetrical diagram, that it's not
7 just places where drugs of mechanisms that we think
8 pain should be the primary, but also potentially
9 defecation only or urination only might be also a
10 situation where you wouldn't expect your drug to
11 help pain but you would expect it to help these
12 other symptoms.
13 We proposed to put in the manuscript to make
14 our modified figure symmetrical and add how that
15 sometimes you might consider those endpoints only
16 in a trial. Do you guys as experts disagree with
17 that?
18 Yes, you're shaking your head yes. Can you
19 comment on why you might?
20 DR. PONTARI: I'm not sure that we would do
21 an IC trial or prostatitis trial just for the
22 urinary symptoms. I know these people have pain;

Page 216

1 we talked about that. But there's been so many
2 other drugs studied for urinary symptoms, for
3 frequency, urgency, things like that, that I'm not
4 sure -- you can disagree if you want, Henry, but I
5 don't think we'd ever set out for a drug just for
6 urination.
7 Now, there was a drug that was tested for
8 prostatitis that was an alpha blocker that helped
9 urination. It also helped pain.
10 DR. LAI: I agree with you. I think it's
11 purely urinary symptoms. It shouldn't be IC or CP.
12 The question becomes the discomfort part and the
13 pressure part. You say pain, pressure, discomfort,
14 plus urinary symptoms, I think it's okay.
15 DR. GEWANDTER: Okay. So that leads us to
16 our next topic. I think I've said a couple of
17 times how I think if your pain is going to be an
18 outcome, you need to have a minimum pain severity
19 in your trial. I think what Dr. Lembo brought up a
20 little while ago, that I tabled now, is this issue
21 of but we'll be excluding a lot of patients and
22 what do we with that.

Page 217

1 That's why we were thinking maybe you would
2 only have your outcome be urination or defecation.
3 Maybe that would take care of that group. But it
4 seems that another way to handle that would be
5 instead of making pain an outcome, a co-primary or
6 however you decide to do hierarchical, whatever,
7 discomfort or something else as the primary.
8 I think we don't necessarily know how to
9 measure discomfort yet. I think yesterday it
10 seemed like everyone was in agreement that that is
11 still elusive. Maybe we could have a section of
12 the manuscript that says something -- oh, Sharon,
13 why don't you go ahead.
14 DR. HERTZ: I'm not sure I understand how
15 this would work. If you have a population with a
16 condition, and there's these different
17 subpopulations, and some have pain and others
18 don't, you have a drug that's targeting pain, why
19 would you include people without pain? If you did,
20 how could you possibly hope to win? If you have
21 people with discomfort and people with pain, and
22 you have something that targets everything, then

Page 218

1 you would come up with a discomfort scale.
2 Now, if your patients with pain don't
3 acknowledge the presence of discomfort, the
4 populations are not necessarily amenable or are
5 they, and if so, how, to being included in the same
6 clinical study. At the end of the day, you need a
7 primary endpoint that is appropriate for your whole
8 population even if you're going to do some
9 subpopulation analyses.
10 So I'm not sure how you can solve this
11 problem without somebody describing what is the
12 right outcome that the whole population can be
13 assessed on.
14 DR. GEWANDTER: This is the CIPN problem I
15 have, right, like the same issue. Some people have
16 pain, some people have numbness, some people have
17 tingling, overlap, and how do we handle that,
18 right?
19 I think what you're saying is are they
20 distinct people, could they be the same people, and
21 could we somehow come up with a single primary
22 endpoint that would incorporate all of them?

Page 219

1 Yes?
2 DR. PONTARI: I think from what we had
3 talked -- so we say urinary -- all these people for
4 us have pain. What the category -- what
5 Dr. Dworkin and I talked about were people have low
6 pain. I kind of agree that, thinking about it,
7 there may be people with, let's say, a pain score
8 of 2 with a lot of urinary symptoms. They're not
9 getting into trials is what you're saying. That's
10 like the pain group.
11 Another thing is what's interesting for
12 us -- and we can comment -- we don't distinguish
13 pain and discomfort. Should we be doing that? Do
14 we have -- our symptoms scores, it's all pain and
15 discomfort. We have no just discomfort and just
16 pain. Is that something that we need to --
17 DR. GEWANDTER: Change that.
18 DR. HERTZ: In people who are coming in with
19 a pain score of 1 or 2, they're just going to kill
20 your study. You're never going to show efficacy if
21 that's your primary because they're not getting
22 enough movement.

Page 220

1 DR. PONTARI: Right, we're not going to do
2 pain in them. I think you were talking about there
3 could be patients with --
4 DR. GEWANDTER: What I was bringing up was
5 this issue that has come up a couple times that if
6 we -- that some people describe it as discomfort
7 and not pain, and that we're not aiming to create
8 drugs for those people if we just ignore them.
9 They would be excluded in all of the trials if our
10 endpoint is pain.
11 I think the question is do we as a
12 group -- maybe the question is -- maybe the answer
13 is we know. We just ignore it, and we don't do
14 that, like you have to have pain to get in the
15 trials we're talking about. Or do we want to have
16 a section about how future studies -- looking at
17 how to measure this lower level, something that
18 patients don't describe as pain but is discomfort?
19 DR. DIMITRAKOFF: I think part of the
20 discussion yesterday was that we simply don't have
21 a way of measuring discomfort at this time. So I
22 don't think we can just say these people should be

Page 221

1 excluded unless we think discomfort is a different
2 degree of pain.
3 DR. GEWANDTER: I think that might be true.
4 DR. HERTZ: Right. I'm not saying that
5 people should be discarded, and I'm not saying that
6 it's not important to consider how to develop
7 therapeutics for them. But at the end of the day
8 in the context of a clinical study, you have to
9 have a primary endpoint, and you have to have
10 people who come into the study with enough of
11 something that can then be changed over time so
12 that you can demonstrate a difference from placebo
13 or whatever your control is.
14 Given everything that's been said about the
15 placebo effect, regression to mean, and everything
16 else, if you allow people who have on a 10-point
17 scale 1 and 2 symptom ratings in, and that's your
18 primary, you might as well give up because the
19 power to show a change is going to be -- you're
20 going to need thousands of patients.
21 What is the priority then?
22 DR. GEWANDTER: So maybe I opened a can of

Page 222

1 worms that was totally unnecessary by bringing this
2 up. Hanna?
3 DR. GROKOPCZYK: Hanna Grol-Prokopczyk.
4 From what I've heard in the last two days, it seems
5 like it's not necessarily clear when discomfort
6 means that someone has low level pain that they're
7 too stoical to refer to as pain. It's really along
8 the same unidimensional scale, but they prefer a
9 different word and when it's measuring something
10 qualitatively different.
11 If I'm right that that's not always clear,
12 then it seems the best our group could do is
13 mention that that might be an area for future
14 research.
15 DR. GEWANDTER: I think that sounds like a
16 great plan. I think we're going to be saying that
17 the focus of these research studies that we are
18 talking about is pain, so you need to have a
19 minimum entry of pain to get in the study, and that
20 future research could look into these other
21 symptoms that are similar to pain but may be a
22 little different if that's a different population.

Page 223

1 DR. HERTZ: Or specifically perhaps, people
2 who have low levels of pain along with the other
3 symptoms, that the research agenda include how does
4 one study them.
5 DR. GEWANDTER: Actually, following up with
6 that, just to be clear because you
7 guys -- actually, you didn't comment on the issue
8 of would you want to design a drug only for
9 defecation and not -- you guys said you wouldn't
10 want to be focusing -- on drugs only for urination.
11 So you think you don't want that to be in the paper
12 at all, that concept?
13 No? Well, you can comment later.
14 DR. TU: This is a pain meeting. Is that
15 not implicit, what we're doing here? Sorry. This
16 is Frank Tu.
17 DR. GEWANDTER: Let's save that for the
18 paper, and you guys can comment.
19 (Laughter.)
20 DR. GEWANDTER: Sorry. Ian, you were going
21 to say something. Moving on.
22 DR. GILRON: I was just trying to suggest

Page 224

1 that maybe there should be a caveat in the paper
2 that could say if someone has a therapeutic agent
3 that the mechanism is likely to address only one of
4 multiple symptoms, that that should be encouraged
5 if that's a possibility, and that will affect the
6 trial design. We're not necessarily
7 looking -- people may not necessarily only have
8 agents that are going to cover the whole spectrum.
9 DR. GEWANDTER: Yes, we could be a little
10 more general with that explanation and then use
11 pain as a good example of that. Sounds great.
12 Yes, Stephen?
13 DR. COONS: This is Stephen Coons from the
14 Critical Path Institute. But we still need to
15 assess the other symptoms.
16 DR. GEWANDTER: Yes, of course.
17 DR. SMITH: To the degree we can.
18 Discomfort is still going to be one of those things
19 that there's going to be a research agenda.
20 DR. GEWANDTER: I think he means like
21 urination.
22 DR. SMITH: Oh, right. You mean other

Page 225

1 symptoms specific --
2 DR. COONS: So we can prove that we haven't
3 made anything else worse.
4 DR. SMITH: Oh, yes.
5 DR. GEWANDTER: Ursula?
6 DR. WESSELMANN: I was going to say the same
7 thing. We focus on pain, but some patients have
8 pain and discomfort. So it's really two different
9 things and not discomfort being the lower level
10 pain, so it will be important to measure that as
11 well. I don't think that has been really done
12 systematically.
13 I forgot to introduce myself, Ursula
14 Wesselmann.
15 DR. GEWANDTER: I think people can recognize
16 your accent.
17 How to measure discomfort is an area of
18 future research, I think we can all agree on that.
19 Any dissent?
20 (No response.)
21 DR. GEWANDTER: No? Okay.
22 DR. SMITH: I think really the last thing is

Page 226

1 to ask if there are other ideas that people have
2 for research agendas relevant to the things that
3 we've been talking about here today. We were
4 talking about this need to figure out discomfort,
5 bloating, cramping, and using some of the outcomes
6 that were on the slide that Nat had made. A lot of
7 that would probably be very exploratory as well.
8 Other thoughts about things that we should
9 put in? Again, you'll get to see the manuscript a
10 number of times, and you'd be able to provide your
11 input along the way. But if there are thoughts you
12 have now about things that we might want to
13 consider for a research agenda as we're crafting
14 the manuscript, that would be helpful. Ian?
15 DR. GILRON: Ian Gilron. I just wonder
16 whether -- there are a lot of issues that we can
17 learn from previous IMPACT and ACTTION
18 recommendations and meetings. One of the biggest
19 concerns that comes to my mind with multiple
20 outcomes is the question of assay sensitivity that
21 we really worry about.
22 I wonder whether we can revisit our table 1

Page 227

1 from our 2012 assay sensitivity paper and see
2 whether any of those levels of evidence -- we had
3 various levels of evidence for different
4 recommendations like extremes of pain on entry; see
5 whether there's any new evidence to upgrade or
6 downgrade those, and also try to see how they're
7 relevant to these multi-symptom conditions.
8 DR. GEWANDTER: I think that's a really good
9 suggestion. I think Shannon and I can go through
10 the table together and see if any seem particularly
11 relevant to this condition, and we can put that in
12 the paper if we find things, and you guys can all
13 comment on that, too. I think that's a great
14 suggestion. Thank you.
15 Yes, Tara.
16 DR. ALTEPETER: I wanted to come back to a
17 comment that was made yesterday when someone had
18 asked if there were creative ways in which you can
19 assess if multiple people in the trial have more
20 than one symptom that's most important to them. I
21 didn't get a chance to comment at the time, but we
22 have seen really creative strategies to approach

Page 228

1 that.
2 I wonder when people were asking the
3 question about how could you broaden your
4 enrollment population to be more representative of
5 the ultimate patient population and wanting to
6 include some of these people who have only low
7 level pain but may be more bothered by their other
8 symptom, I think that if you truly had a drug and
9 you understood the biologic mechanism of the
10 disease that you're talking about, and you know
11 that your drug has a reasonable chance of affecting
12 both of these things, then I think it is possible
13 to potentially broaden your population to maybe
14 some of those people who have less severe pain, but
15 their success or failure is going to be assessed
16 based on what they identified as the most
17 bothersome symptom.
18 You could potentially have a more
19 heterogeneous population that's enrolled and then
20 say, okay, everybody is going to decide at the
21 beginning which of these symptoms is most
22 bothersome to you, and that would be the way that

Page 229

1 your individual responder status would be
2 determined.
3 We have seen at least some proposals for
4 strategies like that. I think it's something at
5 least people could consider if you want to maybe
6 think about how you could get at the idea of having
7 a more representative sample rather than trying to
8 be really homogenous and just take the most severe
9 part of your population.
10 DR. HERTZ: What is your conclusion at the
11 end of a study, that the drug treats the syndrome
12 regard -- I'm just wondering how one would
13 interpret that outcome if it affects pain in some,
14 urinary symptoms in another, some other distant
15 pain in another, but not -- I'm having a hard time
16 wrapping my head around it.
17 DR. ALTEPETER: I think it would probably be
18 most appropriate to a symptomatic condition, and
19 you could say that patients had a reduction in
20 their most bothersome symptoms.
21 DR. GEWANDTER: Yes?
22 DR. BROWN: Yes. This is Cole,

Page 230

1 Philadelphia. Just to add on to what she was
2 saying, I think in evaluation of migraine, you see
3 where you evaluate to pain freedom, and then you
4 can also look at the most bothersome symptom,
5 whether that be nausea, vomiting, photophobia. And
6 you're really thinking of it from a syndrome sense,
7 right, as a complex. We've seen that in the
8 migraine space.
9 DR. GEWANDTER: Is that part of the primary
10 in the migraine space?
11 DR. BROWN: Yes. So you can have
12 several -- you'll have co-primaries.
13 DR. HERTZ: Co-primaries are an end
14 phenomenon, so that doesn't quite get at what
15 happens when some people don't have some of the
16 symptoms. There's way to handle multiple aspects
17 of a syndrome and create this paradigm where you
18 have to really get at the critical aspects of the
19 syndrome.
20 The part here that I'm having trouble
21 picturing is when the manifestations are
22 sufficiently different so that different people

Page 231

1 actually have non-overlapping symptoms.
2 DR. ALTEPETER: I guess I wasn't trying to
3 say that they were not overlapping. I was trying
4 to say that if you have some who are much more
5 bothered by symptom A versus symptom B, that you
6 could primarily assess based on improvement in the
7 part that was most bothersome to them.
8 DR. HERTZ: Isn't that still
9 non-overlapping? If 10 people are being assessed
10 for the urinary frequency and that's their most
11 bothersome, and 10 people are being assessed for
12 pain because that's their most bothersome, if these
13 people don't have a change in their urinary
14 frequency and these people don't have a change in
15 their mild pain, what am I actually measuring at
16 the end of the study? What is the drug doing?
17 DR. ALTEPETER: I would envision that you
18 could say that the drug is improving the aspect of
19 the syndrome that is most bothersome to them. You
20 would have to believe that your drug has the
21 biological effect on both, and it's just that for
22 your people who are primarily bothered by frequency

Page 232

1 and have low level of pain, you're not able to
2 detect much change there because it was already at
3 a minimal level where the measurement problem
4 exists there.
5 DR. GEWANDTER: Maybe Dr. Landis can comment
6 on this and Dr. Coons.
7 DR. LANDIS: I don't want to complicate the
8 answer to your question by saying the subgroup
9 phenotyping at the beginning of this topic has to
10 also be done in a precise enough way that we have
11 subgroups that are enriched for higher probability
12 of success on a particular drug.
13 I'm thinking back more than 10 years ago to
14 the IC trial where it was a combination trial for
15 both hydroxyzine and Flomax. We had a primary
16 outcome that failed, but if we now take everything
17 we learned in recent years, you would want to have
18 primary endpoints for those who are going to get
19 better on pain different from those who are going
20 to get better on their urinary symptoms. But you
21 also have to know who those patients are at
22 baseline and stratify them in a way that you enrich

Page 233

1 so that you don't have the pain subgroup only on
2 the drug that doesn't even target pain.
3 I think this is going to require the
4 subtyping and stratification at baseline before
5 randomization so that you're enriching for the
6 outcome for the drug class that's being tested.
7 DR. LAI: Henry Lai. I think we know as
8 clinical experience, there are treatments that are
9 being commonly utilized to treat IC that doesn't
10 improve pain but improves the urinary symptoms a
11 lot. People will go for that, and it's done
12 routinely. These people come in with pain and
13 urinary symptoms, but the pain doesn't get any
14 better with that treatment.
15 DR. HERTZ: So your primary are the urinary
16 symptoms. That seems pretty clear.
17 DR. LANDIS: We would need a primary for
18 each.
19 DR. LAI: You would need a primary for each
20 but not in the N sense and not in the composite way
21 because you would wash out anything that you would
22 detect, because there are mechanisms like

Page 234

1 neuromodulation that will improve frequency and
2 urgency tremendously without doing much for pain.
3 DR. GEWANDTER: I think Dr. Coons wanted to
4 say something, too, about this.
5 DR. COONS: Stephen Coons, Critical Path
6 Institute. I just wanted to follow up on what Cole
7 had.
8 Sharon, was the migraine guidance out of
9 your group?
10 DR. HERTZ: Yes.
11 DR. COONS: Okay. Because that is an
12 important document in the sense that this is a
13 situation where headache is a given. It's
14 essentially combining headache and then the most
15 bothersome of three symptoms: photophobia,
16 phonophobia, and nausea. And the patient at the
17 beginning of the trial would pick one of those
18 three because they're likely to have one of them
19 that is the most predominant and bothersome to
20 them. That is what the guidance recommends.
21 The only other thing, Ospheña was another
22 drug, which is for painful intercourse

Page 235

1 post-menopause. So there was a biomarker, but then
2 there was also a situation where the patient picked
3 one of three symptoms that was most bothersome to
4 them. So it has been done.
5 DR. HERTZ: Right, but it sounds like the
6 primary has one common element and then the other
7 manifestations in addition. What I'm hearing is,
8 conceptually, there might be two different
9 primaries based on that prespecification, and I
10 guess the devil's in the details of how one would
11 structure that kind of clinical study.
12 DR. COONS: I assumed it ended up being a
13 composite endpoint --
14 DR. GEWANDTER: Maybe we can look at the
15 headache guidance and look at the details and see
16 what kind of example we can get from that.
17 Also, maybe, Tara, if you could send us some
18 of the examples. I don't know if they're
19 proprietary things, but if there's something that
20 you could send us that we could look at the
21 details, maybe we can try to incorporate some
22 example like that in the paper after talking about

Page 236

1 it with our steering committee and then everyone
2 can comment. I think that would be a good way to
3 move forward with that subject.
4 DR. BUTTERFIELD: Just a quick comment.
5 It's Noam Butterfield. It's actually in the
6 pre-read that we got for this meeting. It's in the
7 multiple endpoints document where they give the
8 example of the migraines.
9 DR. GEWANDTER: Migraine, great.
10 DR. BUTTERFIELD: Line 521.
11 DR. GEWANDTER: Thank you.
12 DR. BUTTERFIELD: So you can get it quick.
13 I think the point was just not necessarily -- it
14 may not be that we're looking at two different
15 primary endpoints, just are there methods to look
16 at a primary endpoint and additional ways to look
17 at those additional symptoms.
18 One way to do it may be not just choosing
19 one because maybe that one urinary symptom, for
20 example, is not the same or not the most bothersome
21 to all patients. So some patients maybe it's
22 nocturia; other patients, it's frequency. Maybe

Page 237

1 what's the most bothersome to that particular
2 patient is one of those secondary variables, and
3 ranking them by most bothersome is a method of
4 doing it.
5 DR. GEWANDTER: Yes. You hit on something
6 that we intentionally glossed over. We didn't even
7 get into how we should recommend measuring
8 urination abnormalities and defecation
9 abnormalities. But I think because of the focus of
10 our group and this meeting, that we're going to
11 leave that as not -- we're not going to define that
12 in this paper. But I think that your point is well
13 taken that maybe that can be a helpful way to do
14 that half of the symptoms as well.
15 Does anyone have anything else they'd like
16 to bring up? Yes?
17 DR. TU: Can I bring up one last thought
18 related to some of these measures? Frank Tu again
19 from NorthShore. There was a presentation by Bill
20 Chey, who I don't see here unfortunately today,
21 about some rather interesting app where you can
22 grab a lot of these secondary measures that was for

Page 238

1 GI specifically.
2 Quentin didn't mention this, but MAPP has an
3 app as well that grabs urological measures.
4 There's actually two different forms of that being
5 used on MAPP. There's a group out of Medical
6 College of Wisconsin that's built another symptom
7 tracker.
8 Is it within the scope of this
9 recommendation to talk about the idea of trying to
10 get more patient-facing data collection where a
11 patient could do it on their own and come into
12 trial having already phenotyped themselves as a
13 next generation strategy trying to minimize cost
14 burden of these trials?
15 One of the problems of this group of people,
16 as we've talked about a lot, is that there's too
17 many things packed into the pelvis and abdomen.
18 One solution that we might propose is that future
19 groups need to just fundamentally change the game
20 and have the patients get the data themselves and
21 essentially free themselves up from the research
22 teams.

Page 239

1 DR. GEWANDTER: Are you saying, in essence,
2 patients fill out PROs on an app before they come
3 to their first visit?
4 DR. TU: They can do it through their whole
5 life if they're really that -- especially like the
6 ones that we talked about, the true comorbid
7 conditions, there might be a call to action that we
8 could put as part of this, to say it's so
9 complicated to study this group of patients that
10 one potential novel avenue that we would propose
11 needs to be an area of significant inquiry is how
12 to create an infrastructure that severs patients
13 from clinical research in order to track their own
14 symptoms and to make that in some sort of universal
15 code that can be pulled into trials subsequently.
16 DR. GEWANDTER: I think that maybe what
17 you're saying is it's kind of like -- what is that
18 term? They do it a lot in other countries where
19 they have an infrastructure set up where it's a
20 registry trial. They already have a registry, and
21 then they randomize within it.
22 I think that might be a little outside the

Page 240

1 scope of this paper, but I think it's a very
2 interesting point. But I think that's something
3 we'd have to think about, how it might fit in the
4 paper. But I think it's well taken, especially if
5 we're thinking about baseline of 4 weeks, maybe
6 that would fit in there.
7 DR. DWORKIN: One of the things we're going
8 to have to say in this paper is that we're focusing
9 on outcomes and that there are all sorts of
10 research design questions that were beyond the
11 scope of this effort, but that could be the focus
12 of a subsequent effort.
13 Yesterday, I think Sharon mentioned enriched
14 enrollment randomized withdrawal trials. That's
15 the kind of thing we didn't talk about at all at
16 this meeting, but would be worth considering at
17 another meeting.
18 DR. GEWANDTER: All right. Well, thanks,
19 everyone.
20 Oh, sorry. One more thing.
21 DR. JUGE: I just wanted to make one more
22 comment, and it's about the PROs. It was a comment

Page 241

1 I was going to make before we broke for lunch, so
2 I'm sorry for keeping you guys now because we're
3 about to leave.
4 But the PRO issue I think changed in around
5 2008-2009 when the FDA allowed that to be part of
6 the indications. Because what happened is you got
7 a drug approved, and then you did the outcome
8 studies and added data like that afterward. But it
9 took a couple of years to get the data. And I
10 believe it was in 2008 they allowed the
11 combination.
12 So if you're doing that at the same time as
13 you're doing your phase 3 indication, you can
14 include that info into the label. So companies
15 started looking at putting that info in the label,
16 and they started designing these PROs for studies.
17 But once the study is done, what do you use out in
18 the field? If it's so cumbersome, nobody is going
19 to touch it.
20 From my perspective, the data that we did is
21 we took the useful tool that could be used in the
22 field and build it backward, and see how I can wrap

Page 242

1 it up for a study but make it a useful tool. So my
2 pitch is if we're going to make a statement about
3 coming up with guidelines, then we should also
4 develop a tool that can be used forward because
5 manufacturers want two things out of the PRO. They
6 want the information in the label from an outcomes
7 basis because that's where everything is going,
8 what's helpful to the patient.
9 They also would love a tool that would then
10 allow them to fight with managed care plans that
11 are doing prior auths to say I have a tool that if
12 I'm doing that will show the benefit of this drug.
13 So when you come to me in a year and want to
14 approve for the refill, I can give you that data to
15 continue the use of that versus patients not
16 getting benefit, I should drop them.
17 That stuff will help out on both ends for
18 them doing that. It gives us a tool for the study
19 and gives the tool to be used by the patient, and
20 it goes to what they were saying about having that
21 tool in the field for patients to track themselves.
22 The research stuff is usually far beyond what a

Page 243

1 patient really wants. They really want this
2 information ahead of time, and they're prescreening
3 themselves with it.
4 DR. GEWANDTER: I think we could mention
5 that more simplistic measures are better in terms
6 of their -- things that could be applied in the
7 clinic as well as research so we can have some
8 crosstalk is a good thing, and maybe incorporating
9 it using technology so people can do it in their
10 everyday lives as well.
11 We could consider mentioning that in the
12 paper, that advocating for that in the future is a
13 good thing. I don't see any reason why not to do
14 that.
15 Does anyone have any other comments related
16 to that or in general?
17 (No response.)
18 DR. GEWANDTER: Okay. Well, thank you-all
19 so much for coming and for participating so well in
20 the meeting. We want to again thank Valorie and
21 Andrea for putting this together because, of
22 course, we could not do any of it without their

Page 244

1 help. Thank you.
2 (Applause.)
3 Adjournment
4 DR. GEWANDTER: I also wanted to just thank
5 Bob and Dennis for helping organize -- they're not
6 listening at all.
7 (Laughter.)
8 DR. GEWANDTER: Thank you.
9 (Applause.)
10 (Whereupon, at 3:20 p.m., the meeting was
11 adjourned.)
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	14 (2) 1:12;52:22	29:4;40:20;41:19; 43:17;44:4;45:11;48:18; 57:21;58:7;59:3,12; 60:6;64:19;65:19,20; 77:20;91:11;110:7; 113:20;128:19;200:22; 202:19;203:7;204:6,8; 205:22;208:18;209:13; 241:13	101:2;112:1;113:5; 114:16 521 (1) 236:10 54 (1) 9:2 55 (1) 121:1 57 (1) 13:1 5-point (1) 87:22	92 (1) 71:13 99 (1) 162:15 9-month (1) 209:20	
\$	18 (1) 182:1 1-week (2) 192:21;193:14				
\$2 (1) 54:20					
\$5 (1) 27:15	2			A	
[2 (27) 24:14;25:15;28:2; 37:1;39:7,13;44:4,11; 56:7;104:19;105:16; 106:1;113:18,20; 133:17;150:17;171:22, 22;175:10;176:4;186:9; 201:14;204:3;208:22; 219:8,19;221:17	3:20 (2) 1:13;244:10 30 (3) 9:5;31:1;91:11 30,000-foot (1) 15:20 315 (1) 51:11 3-hour (1) 25:15 3-month (7) 40:22;94:20;195:2; 200:21;201:2;202:19; 209:15 3-year (1) 45:21	6		
[ph] (2) 17:20;187:12	2:22 (1) 211:22 2:45 (1) 211:17 20 (10) 16:15;33:20,21;95:3; 106:4;131:5,11;133:1, 11;182:1	4	6 (15) 10:22;27:10;58:3; 71:14;99:11;130:4; 192:19;203:5,7,8;204:3, 6,8;205:22;209:14 60 (2) 33:19;131:9 65 (1) 121:5 67 (1) 9:2 69 (1) 8:19 6th (1) 209:19 6-week (1) 94:11	abdomen (2) 29:17;238:17 abdominal (44) 4:5;7:22;8:7,9:17; 58:7,10;59:11;60:4,5,6, 9,12;61:11;63:16;64:17, 17,18;65:1,3,4,9;66:3,5, 14,18,19,20,21,22;67:3; 69:9,10;70:13,14,17,18, 19,20;71:2;129:3;140:9; 154:16;155:2;198:20 ability (4) 100:3,11;111:2; 123:13 able (30) 31:20;45:22;46:1,13; 47:2;54:13,21;63:11,19; 68:12;69:11;78:17;81:6; 84:12;93:21;95:9;100:6; 108:16;132:7;139:7; 142:10;143:13;146:8, 18;154:15;159:20; 164:13;197:6;226:10; 232:1	
0				abnormal (2) 157:11;170:2 abnormalities (7) 128:17,20;129:4,5; 189:21;237:8,9 abnormality (1) 100:15 above (5) 62:2;113:6;121:1; 132:1,10 absent (1) 95:20 absolute (1) 125:8 absolutely (3) 109:9;122:7;147:10 abstract (1) 5:16 academic (1) 53:9 Academy (1) 118:15 accelerating (1) 52:18 accent (1) 225:16 acceptable (1) 173:22 accepted (2) 137:8;172:18	
0 (14) 8:22;58:7;66:10; 68:21;87:21;96:15; 126:21;130:1;171:20; 172:1,4,13,13;176:7					
0.025 (3) 14:1,3;15:12					
0.05 (3) 13:18;15:4,12					
1	200 (1) 28:14 2000 (1) 6:7 2005 (1) 52:9 2008 (3) 53:1;88:3;241:10 2008-2009 (1) 241:5 2009 (5) 57:6;88:5,6;166:13; 167:8 2012 (1) 227:1 2017 (3) 1:12;35:11;173:8 24 (12) 66:5,15;67:1,7,8,13, 15;70:18;71:3,4,5; 125:21 24-hour (8) 63:17;68:9;84:22; 86:3;87:3,8;124:14; 151:22 25 (2) 6:8;133:1 26 (3) 29:4;53:6,12 2-point (1) 140:15 2-week (2) 36:22;208:1	4 (33) 38:22;43:17;48:18; 66:3,22;97:8;103:12; 104:19,22;105:2,14,14, 22;106:3,11;107:1,18; 115:5;116:9,20;118:7; 131:21;132:1,10;184:3; 193:22;195:4;202:1,8, 14,19;204:9;240:5 40 (4) 30:22;37:13;91:9; 112:1 400 (1) 78:10 415 (1) 28:14 424 (1) 28:13 43 (3) 60:7;64:19;68:10 49 (4) 58:14;59:7;60:7,8 4-week (3) 106:9,18;207:16	7		
1 (10) 12:20;41:19;48:17; 105:16;143:17;147:20; 150:17;219:19;221:17; 226:22					
1:00 (1) 141:14					
1:10 (1) 142:2					
10 (27) 8:22;37:13;55:22; 56:7,8;58:8;65:19,21; 66:10,18,20;67:2;68:21; 85:10;87:21;90:17; 96:15;126:21;127:5; 171:20;172:1,4,13; 176:7;231:9,11;232:13					
10,000-foot (1) 93:2					
10-point (1) 221:16					
11 (1) 60:11					
11-point (2) 71:1;186:8					
12 (12) 10:22;27:10;192:13, 20;195:6,12;197:19; 198:4;205:22,22;206:1; 209:20					
12:00 (1) 141:15					
121 (1) 5:17	3				
12-week (3) 61:1;94:11;198:6	3 (29)	50 (9) 16:11,13,17,19;18:7;	8		
			8 (5) 28:21;99:12;110:4; 130:4;204:3 8:35 (2) 1:13;3:2 80 (2) 119:3;203:8 83 (1) 29:3 86 (1) 8:19		
			9		
			9 (2) 13:8;28:21 9:57 (1) 72:17		

access (2) 113:12;173:9	23:18	advice (1) 158:6	87:1;112:16;160:17; 166:17;216:20;232:13	alternative (2) 62:21;66:9
according (1) 196:21	adapt (1) 56:14	advocacy (1) 158:20	agree (15) 16:22;26:13;82:8; 106:7;144:9;145:15; 158:11;162:9;170:19; 173:15;177:6;186:2; 216:10;219:6;225:18	alternatives (2) 146:12;211:8
account (2) 39:2;205:19	add (11) 31:3;116:3;145:12; 158:12;187:21;211:13; 213:1;214:7,21;215:14; 230:1	advocate (1) 158:18	agreed (2) 136:15;149:22	although (7) 64:20;68:11;69:11; 71:10;96:8;143:9,22
accounting (2) 115:2,17	added (1) 241:8	advocating (1) 243:12	agreement (2) 163:4;217:10	always (8) 7:6;19:18,21;26:11; 74:17;116:6;167:18; 222:11
accurate (1) 136:18	addition (5) 69:5;86:20;99:18; 117:2;235:7	AE (1) 117:12	ahead (8) 34:15;42:21;158:14; 173:6;184:8;206:7; 217:13;243:2	amenable (1) 218:4
accurately (1) 199:7	additional (6) 5:18;62:12;167:16; 209:11;236:16,17	affect (9) 108:15;116:15; 147:16;148:12;150:8; 155:2;184:1;191:11; 224:5	aimed (1) 52:17	among (2) 60:9;67:9
ache (1) 65:6	additive (1) 116:5	affected (3) 4:3;30:16;157:2	aiming (1) 220:7	amount (6) 27:17;75:19;95:9; 153:12;175:18;196:7
achieve (1) 142:13	add-ons (1) 27:21	affecting (1) 228:11	alarm (1) 177:21	analgesics (1) 8:14
achieved (1) 54:10	address (9) 23:12;31:16;82:2; 83:12;143:20;162:11; 183:8;186:3;224:3	affects (2) 145:10;229:13	alcohol (1) 8:7	analogously (1) 160:5
acknowledge (8) 4:18;36:9;71:21; 145:2,8;163:14;197:4; 218:3	addressed (1) 64:3	afford (1) 159:18	algorithm (1) 33:14	analyses (17) 13:8,18;14:1,2,8;15:2; 19:17,22;24:17;35:10; 36:7;37:7;39:2;49:20; 129:12;194:7;218:9
acknowledging (4) 152:16;163:9,21; 206:19	addresses (1) 86:9	Afghanistan (1) 178:5	Allergan (2) 57:8;71:18	analysis (33) 13:2,5,7,15,16;15:2,3, 10;16:3,8;17:4,12;18:4, 5,9;32:4;35:3;48:12,21; 49:3;83:11;84:14; 132:14;143:20;144:2; 192:9,12,21,21;193:8, 14,22;195:13
across (18) 24:9;38:12;40:8; 54:21;59:12;60:6;65:19; 69:2;93:9;101:5,9; 126:22;128:8;142:17; 175:20;194:3;207:18; 213:13	adds (1) 101:22	Africa (1) 178:5	allocation (1) 49:2	analyze (2) 17:9,10
action (2) 145:15;239:7	adenomyosis (1) 158:20	afternoon (3) 14:18;130:18;145:4	allodynia (2) 170:1;192:16	anchors (1) 128:5
active (2) 106:13;109:4	adequate (7) 11:1,3,4,8,12,13,15	afternoon's (1) 129:8	allow (5) 91:18;169:6;210:14; 221:16;242:10	ancillary (1) 22:21
activities (4) 37:20;38:5;56:6;176:8	adequately (2) 139:16;208:11	afterward (1) 241:8	allowances (1) 23:18	and/or (2) 56:10;65:6
activity (2) 32:16;170:7	adherence (2) 164:13;165:3	afterwards (1) 167:15	allowed (3) 28:1;241:5,10	Andrea (2) 166:7;243:21
activity-specific (1) 4:4	adjourned (1) 244:11	again (39) 11:22;12:5;14:11; 17:21;18:21;40:18; 42:10;43:9;53:2;56:20; 59:19;61:6;62:8;64:19; 20;66:20;67:1,8;68:9; 70:16;71:9,16;81:3,15; 95:16;116:22;117:6; 121:1;124:10;137:11; 154:19;173:7;177:12; 196:2;198:13;212:5; 226:9;237:18;243:20	allows (1) 159:16	Andrew (1) 177:19
ACTTION (2) 1:1;226:17	Adjournment (1) 244:3	against (2) 120:10;189:22	all-the-time (1) 152:11	Android (1) 117:20
actually (50) 21:5;26:19;29:17; 35:2;36:11;42:22;50:7; 66:2;74:4;75:19;84:6; 85:9;86:4;95:3;100:9; 101:18;102:2;103:18; 104:1;105:5;114:21; 115:10;116:6,8;130:16; 135:8;146:11;147:12; 155:10;159:20;160:18; 162:5;166:5;170:3; 176:17;187:8;189:17; 190:6;191:11;193:9; 195:17;202:3,13;215:3; 223:5,7;231:1,15;236:5; 238:4	adjust (5) 4:17;12:16;14:11,19; 159:21	age (8) 36:4;71:12;114:16; 120:19;121:6;196:15, 19;198:17	alluded (2) 89:21;137:12	anecdotal (1) 112:5
acute (1) 100:2	adjusted (2) 13:8;160:2	agenda (3) 223:3;224:19;226:13	almost (5) 70:22;82:17;103:12; 118:1;119:2	anecdotaly (1) 150:9
ad (1)	adjusting (2) 12:21;14:8	agendas (1) 226:2	along (9) 24:3;51:2;54:5;81:7; 123:18;142:19;222:7; 223:2;226:11	Anesthesiology (1) 3:9
	administered (2) 25:16;52:4	agent (1) 224:2	alpha (2) 13:22;216:8	ankle (1) 169:6
	adults (2) 123:4,12	agents (2) 6:12;224:8	ALTEPETER (4) 227:16;229:17;231:2, 17	annual (1) 56:2
	advance (1) 81:22	ago (9) 35:12;85:10;86:2;	alter (1) 200:4	ANOVA (1) 12:10
	advances (1) 27:2		alternate (1) 165:8	answered (1) 170:10
	advantage (1) 135:4			
	advantages (3) 16:2;17:8;99:9			
	advertise (1) 24:4			

antibiotics (1) 117:10	50:20;77:3	arriving (1) 166:4	235:12	49:12;74:14;81:15; 83:17;93:22;112:10;
anticipate (1) 168:15	appreciative (2) 52:14;71:17	arrow (1) 157:12	assuming (6) 124:1;126:6,9;147:19; 170:14;174:18	114:20;119:6;126:13; 134:8;136:12;139:8;
anticonstipation (1) 6:12	Approach (8) 20:3;65:16;93:13; 124:6;136:14;194:22;	arrows (1) 157:8	assumption (2) 116:5;127:8	141:13,14;151:3; 156:13;164:7;165:11;
anticonvulsants (2) 6:10;8:15	210:5;227:22	article (5) 15:17;57:17;157:17; 173:8;176:5	attempt (1) 81:12	167:8;187:14;188:3; 196:2;206:17;211:16, 18;227:16;232:13
antidepressants (2) 6:11;8:13	approached (1) 136:9	articles (7) 5:17,18;6:1;10:13; 13:1,6;14:9	attended (1) 104:6	background (5) 49:6;78:4;79:20; 138:13;139:6
antidiarrheal (1) 6:12	approaches (3) 14:16;73:18;161:17	articulate (1) 68:12	attention (4) 31:13;42:19;77:10; 201:14	backward (1) 241:22
antidiarrheals (1) 150:6	approaching (1) 207:8	aspect (3) 210:8,14;231:18	attractive (1) 124:5	backwards (1) 29:8
anti-inflammatories (1) 8:13	appropriate (6) 46:19;53:15;116:20; 210:13;218:7;229:18	aspects (3) 146:4;230:16,18	attributable (1) 60:18	bad (4) 114:4;126:3;181:2; 207:15
Antispasmodics (1) 150:8	approval (1) 135:21	AS-SANIE (6) 158:13;181:14; 196:11,11;198:13,13	attributes (1) 122:11	balance (1) 108:14
anxiety (3) 10:10;36:6;179:6	approvals (2) 140:4,10	assay (4) 84:4;107:12;226:20; 227:1	attrition (1) 106:4	balanced (1) 181:1
apart (1) 73:17	approve (1) 242:14	assemble (1) 62:22	audience (2) 4:20;89:10	bar (13) 6:17,18;59:13;119:19, 20,22;120:5,6,9,16; 121:1;135:7,17
apologize (2) 84:10;128:10	approved (6) 5:5;136:2,22;137:8; 140:3;241:7	assess (8) 60:16;143:13,14; 168:7;199:5;224:15; 227:19;231:6	audiences (1) 25:12	BARON (1) 47:8
app (13) 118:4,9,17;119:1,16; 120:1;123:22;124:1,9; 125:18;237:21;238:3; 239:2	apps (5) 38:9;119:10;120:8,22; 126:8	assessed (5) 28:2;218:13;228:15; 231:9,11	auditory (1) 47:14	base (2) 185:5;188:22
apparently (1) 195:7	arbitrary (1) 45:11	assessing (6) 57:14;100:14;104:20; 162:4;170:4;178:10	August (1) 173:13	based (32) 10:20;11:11;15:15; 17:3;27:21;28:11;35:20; 46:17;55:16;61:6;84:14; 89:3;93:18;97:4,9; 132:21;136:22;140:3; 154:15,21;156:4; 159:17;172:10;189:7; 190:17;206:10;207:10; 212:21;214:11;228:16; 231:6;235:9
appealing (1) 17:18	area (21) 29:15;41:3;44:16; 50:12;75:4;114:21; 154:17;155:2;161:6; 164:1,4;193:6;194:2,14; 195:13;200:22;203:1; 214:12;222:13;225:17; 239:11	ASSESSMENT (18) 1:4,7;27:11;36:22; 53:11,18;54:19;55:11; 56:22;60:4;70:7;74:3; 86:7;93:13;104:14; 172:11;198:1;209:16	author (1) 166:16	baseline (36) 11:20,21;14:12;27:6, 12;28:19;30:2,8;31:22; 32:4,9;35:18;38:22; 40:14;95:22;97:22; 98:19;99:4;104:2,19; 106:9;116:14;130:1; 131:14;170:22;201:4,6, 9,13,17;202:18;207:21; 211:5;232:22;233:4; 240:5
appeared (1) 57:17	area-under-the-curve (1) 194:22	assessment-based (1) 54:1	authored (1) 173:8	basic (2) 44:5;152:3
appears (2) 79:12;82:13	argue (8) 88:21;89:1;96:17; 105:7;116:7;126:10; 159:10;202:7	assessments (5) 27:14;140:3;207:3; 209:4,11	auths (1) 242:11	basically (8) 32:3;40:5;105:2; 118:16;159:13;189:18; 196:7;208:3
Applause (5) 19:3;42:20;72:14; 244:2,9	areas (8) 3:15;61:11;99:12; 115:14;156:1;167:20, 21;168:3	assign (2) 39:9;160:3	available (7) 53:19,21;55:4,13; 56:15;75:20;173:9	basis (5) 7:6;83:2;166:4; 170:16;242:7
apples (1) 21:18	argued (1) 116:12	assigned (1) 39:4	avenue (1) 239:10	batteries (2)
applicability (1) 94:10	argument (6) 109:3,8,9,15;126:20; 202:5	assigning (1) 42:8	average (31) 58:6;66:13;67:17,21, 22;68:6,13,18;79:7; 82:10,15;83:6,20;84:5, 22;85:3,8,13;97:7; 99:20;118:21;119:17; 125:10,11,14,17,19; 152:14;153:3;186:10; 207:3	
applicable (2) 156:8;172:15	Arizona (1) 52:9	assistant (1) 3:8	averaging (1) 67:18	
application (3) 55:20;187:11,12	arm (3) 17:6,7;107:4	associate (2) 40:15;72:22	avoid (4) 54:7,13;79:21;177:8	
applications (1) 187:8	around (8) 48:20;81:5;118:6; 160:12;164:20;203:16; 229:16;241:4	associated (5) 7:22;20:16;21:8; 31:21;153:9	aware (1) 134:12	
applicator (3) 178:21;182:22;183:1	arousal (1) 181:16	assume (2) 166:20;170:10	away (4) 62:14;114:6;126:2; 152:5	
applied (3) 161:5;207:1;243:6		assumed (1)	B	
applies (1) 158:9			back (30) 27:9;32:18;48:21;	
apply (10) 38:19;147:7;152:20; 155:11;156:1,20; 157:22;162:3,6;192:15				
appointment (1) 23:22				
appreciate (2)				

124:21;125:6 battery (2) 25:15;77:21 bear (1) 92:7 beaten (1) 139:17 became (2) 143:11;188:6 become (1) 129:8 becomes (1) 216:12 bed (1) 40:5 began (2) 88:4;199:17 begin (2) 134:4;208:4 beginning (9) 78:8;97:22;104:16; 114:9;208:13;215:5; 228:21;232:9;234:17 behave (1) 112:5 behavior (1) 208:6 bell (1) 177:22 below (2) 105:21;206:4 bend (1) 29:7 benefit (5) 57:15;104:3;206:15; 242:12,16 benefits (1) 195:18 besides (1) 185:9 best (20) 16:12;20:1;22:16; 24:6;32:19;43:21;68:1; 87:8;96:22;125:13; 143:16;167:19;178:16; 189:11;190:17,19;199:5; 6;210:22;222:12 better (58) 16:5,6;18:2;22:6,8; 23:8;28:11,11;29:7; 30:8;33:7;34:6,21;35:3, 16,20,41:10;42:14; 45:19;49:7;66:9;86:6; 95:4;100:6;103:11,19; 104:6,9,15;109:5;114:5; 115:16;116:13;120:4,5, 8,9,13,14,14;121:17,17; 124:11,17;126:19; 127:10;131:12,12; 163:1;164:11;167:22; 168:2;194:1;214:5; 232:19,20;233:14;243:5 beyond (5)	30:12;43:11;44:4; 240:10;242:22 big (2) 115:14;122:10 biggest (1) 226:18 Bill (1) 237:19 binary (1) 97:18 bio (1) 26:5 biologic (1) 228:9 biological (1) 231:21 biology (1) 89:4 biomarker (2) 12:4;235:1 biomarkers (4) 42:1,2;78:2;137:6 biostatistician (1) 74:20 biostatisticians (1) 74:17 biostatistics (3) 73:3,4;74:22 bit (34) 10:15;15:8;21:18; 24:1,8;26:7;30:16; 32:10;40:2;44:10;49:22; 50:1;73:11;74:13;76:9; 84:12;91:2,7;98:17; 101:1;120:14;127:18; 134:19;143:1;145:6; 150:22;161:22;184:19; 192:9,17;200:18; 205:16;213:3;214:16 biweekly (2) 27:14;104:14 bladder (22) 21:1,8,12,16;31:8,11, 16,18,20;37:15;39:21; 78:12;91:4;97:20;98:5, 6,12,15;101:7;159:7; 197:1;200:14 blamed (1) 107:13 blanking (1) 7:7 bleeding (3) 183:2,4,15 blinded (2) 115:18;116:1 bloating (3) 61:12;65:2;226:5 blocker (1) 216:8 Blood (4) 168:9,10,10,14 boat (1) 207:6	Bob (10) 86:14;109:20;127:19; 128:9;142:19;157:5; 171:17;194:18;211:1; 244:5 body (18) 25:19;29:12;35:20; 43:8,13;44:18;45:5; 47:9,20;48:5;68:16; 76:14;77:22;78:14,16; 86:8;91:7;200:2 bone (1) 67:8 Bonferroni (3) 13:21;14:16;15:8 boring (1) 13:11 both (38) 7:2;13:18;14:1;15:4, 10;20:12;33:22;68:14; 72:2;75:18;76:17,20; 83:20;96:18;117:19; 126:17;127:9,10; 128:22;130:9,22;131:2, 15;132:3,18;140:16; 145:10;152:3;188:11, 12;203:17;205:8;209:6, 6;228:12;231:21; 232:15;242:17 Bother (1) 136:6 bothered (3) 228:7;231:5,22 bothersome (16) 58:20;60:12;228:17, 22;229:20;230:4;231:7, 11,12,19;234:15,19; 235:3;236:20;237:1,3 bottom (1) 58:6 Bowel (23) 1:9;6:1;11:5;20:16; 29:20;56:1;57:19;61:13, 14,15,20;63:4,8,11,13, 19;115:22;140:9; 149:11;150:5,6;159:7; 200:13 box (7) 145:22;146:14;147:7; 150:15,17,17;176:22 boxes (2) 146:22;192:5 BPI (4) 117:18;118:7,16; 125:21 brainwashing (1) 126:7 brakes (1) 35:5 branch (1) 186:6 brand-new (2) 138:5;168:5	break (4) 72:15;88:13;147:13; 211:15 breakdown (2) 5:21;59:3 breaks (1) 74:10 Brief (1) 112:18 briefly (6) 31:9;40:2,20;54:15; 55:7;88:12 bring (12) 19:11;80:17;105:16; 109:22;148:9;164:6; 179:9;186:17;189:5; 211:3;237:16,17 bringing (7) 117:5;126:4;144:19; 170:17;180:7;220:4; 222:1 brings (2) 22:16;172:3 British (1) 159:2 broad (5) 6:5;23:15;93:13; 137:17;160:6 broaden (2) 228:3,13 broke (2) 61:18;241:1 broken (2) 61:11;64:19 brought (5) 67:16,20;122:1;188:7; 216:19 BROWN (2) 229:22;230:11 BRS (1) 96:16 Bruce (1) 47:19 BRUEHL (3) 92:11;150:14;169:21 Buchwald (1) 22:14 budget (1) 159:17 build (1) 241:22 building (1) 175:10 built (1) 238:6 bunch (4) 12:8;16:20;137:14; 189:9 burden (4) 169:13,14,16;238:14 burdensome (3) 138:16;139:9;182:1 BUTTERFIELD (5)	190:2;236:4,5,10,12 <hr/> C <hr/> calculations (1) 209:12 call (10) 22:10;31:8;100:17; 112:20;114:1;121:9; 126:7;186:5;191:20; 239:7 called (4) 162:12;181:20; 188:18;203:14 calling (2) 113:2;163:1 came (12) 23:21;27:9;33:14; 35:12;44:2;70:21;97:11; 142:20;152:13;160:8; 203:2;214:16 can (177) 3:4;7:16;12:18,21; 13:16;14:3,19;15:12,13; 16:3,21;23:11;27:3; 28:15;30:1;32:19;33:1, 2,17,19;34:18;35:8,11, 22;37:12;38:11;39:2,7,8, 9,14;40:7,7,20;42:12; 43:2;44:18;45:6,12; 48:3,16;49:9,11;50:11; 51:14;54:19;55:13,19; 56:1,3,7,16;58:4;59:2, 11,13,18;61:17;63:13; 64:18;66:19;67:10; 69:10;72:6;74:11;79:21; 81:10,15;84:19;89:2,11, 15;90:14,21;95:14;96:3; 99:12,18;112:12; 114:19;119:8,13;122:8; 124:9;127:10;128:6; 134:6;138:19;139:15; 140:20;141:4,5;142:4; 147:19;148:13;154:19; 159:11;160:10,20;161:4, 5,21,22;162:1;164:6; 171:14;173:17;174:22; 175:2;183:19,21; 184:17;185:6;187:2,2, 14;191:14;193:1,4; 197:21;199:14,18,20; 201:18;204:3;208:9,10; 209:10,12,15,20,21,22; 210:4;211:2;214:13,15; 215:18;216:4;218:10, 12;219:12;220:22; 221:11,12,22;223:13,18; 224:17;225:2,15,18; 226:16,22;227:9,11,12, 18;230:4,11;232:5; 235:14,16,21;236:2,12; 237:13,17,21;239:4,15; 241:13,22;242:4,14;
--	---	--	---	--

243:7,9 Canada (1) 23:7 cancer (1) 8:2 capture (15) 51:16;76:20;93:14; 105:20;122:5,17,18,21; 123:7;124:16;182:3; 186:12;196:4,4;213:14 captured (1) 77:5 captures (1) 96:1 capturing (1) 123:19 cardboard (4) 178:21;180:6;182:22; 183:1 care (5) 25:12;149:4;196:19; 217:3;242:10 careful (1) 201:14 cares (1) 168:9 carrying (1) 117:1 case (12) 51:6;59:15;63:10; 70:9;104:17;125:9; 167:15;173:16;178:16; 187:9;191:8;197:21 cases (1) 105:7 catastrophizing (2) 25:14;36:2 catch (1) 204:13 categories (1) 39:4 categorized (1) 48:17 category (4) 159:3,8;160:6;219:4 cats (1) 65:14 causes (1) 4:5 caveat (5) 182:11;183:11; 190:13;191:4;224:1 ceiling (1) 109:7 Center (6) 1:17;19:6;22:22;52:9; 53:2;111:21 central (2) 200:4;214:6 centralization (2) 46:16,20 centralized (2) 43:6,15	certain (19) 8:5;10:20;11:2,3,5,9; 40:21;42:1;90:2;102:11; 119:7;122:22;146:18; 159:21;161:12;163:10; 164:17;168:1;202:13 certainly (18) 36:9;38:20;49:11; 54:10;64:7;65:11,13; 69:7,17;85:20;94:13; 95:20;159:4;175:13; 179:9;180:4;181:17; 185:6 certainty (2) 160:4,11 cetera (12) 22:14,14;25:14,15; 26:15;27:18;30:19;37:9, 21;40:13;63:17;106:17 challenge (3) 95:20;112:7;143:3 challenges (2) 17:2;143:3 chance (2) 227:21;228:11 change (33) 8:16;11:20,21;12:11; 18:17;33:10;39:5;42:10; 82:1,2;84:18;92:4,18; 94:13;95:10,11;96:4; 103:15;104:20;126:17; 128:1;130:4,20;146:3,3; 194:7;199:1;219:17; 221:19;231:13,14; 232:2;238:19 changeable (1) 94:5 changed (6) 18:19;51:20;95:4; 116:17;221:11;241:4 changes (5) 39:5;86:21;95:15; 198:8;206:10 changing (3) 49:2;70:10;92:5 characteristic (1) 91:14 characteristics (2) 4:11;161:13 chase (1) 24:16 cheating (1) 119:4 check (4) 141:3;180:19;188:1; 208:9 checked (1) 141:7 checkout (1) 72:16 checks (1) 208:16 Chey (2)	72:10;237:20 choice (1) 145:22 choose (1) 45:10 choosing (2) 200:16;236:18 chosen (2) 69:8;202:9 Chris (8) 48:8,11;50:7;151:15, 16;165:19;178:8,9 Chris' (1) 186:3 Chronic (31) 1:8;5:3,12;6:3;20:4, 10,11,18,18;25:3,8; 30:17,19;39:20;79:19; 95:1,6;100:2;101:8; 130:13;144:1;153:8,22; 154:2;156:8;157:13,15; 197:2;198:20;200:9; 206:19 CIC (1) 140:8 CIPN (3) 192:10,11;218:14 circle (1) 70:21 circulate (1) 81:1 circulated (2) 80:4;167:15 circumstances (3) 54:11;163:11;202:13 cite (1) 199:20 City (1) 1:17 claims (2) 54:2;139:22 Claire (1) 71:22 clarify (5) 81:10;152:8;153:7; 157:18;195:16 clarity (1) 70:4 class (1) 233:6 classification (1) 92:6 classifying (1) 97:16 Clauw (2) 22:13;49:17 clear (13) 96:7,17;115:15; 143:11;156:3;163:7; 169:11;177:4;199:21; 222:5,11;223:6;233:16 clearly (6) 38:12;76:16;93:5;	116:9;130:3;167:4 Clemens (32) 19:5;7,8,16;43:1,4,7, 16;44:8;45:15;47:14; 49:4;50:5;79:2,5;82:9; 94:8;102:16,22;105:10; 107:4;109:22;131:16; 132:21;133:10,20; 134:19;149:17;162:8; 193:16;194:5;210:7 clicking (3) 119:14,19;123:9 clinic (1) 243:7 CLINICAL (79) 1:4,8;3:15;23:9,12,15, 21;32:18;34:9;38:20; 40:19;42:3,16;44:19; 45:17;46:17;48:6;50:17; 53:8,11,18,22,22;54:18; 55:10;56:22;57:15; 60:17,22;61:8;62:3; 69:6;71:12;74:4,5; 84:18;92:13,14;94:9; 95:21;98:4;105:8,11; 107:19;109:11;111:6, 11;126:22;129:15; 130:12;132:6;139:4; 140:2,19;152:4;161:3, 14;166:14;171:22; 176:15;177:1,2,9; 178:12,15;185:1,15; 187:5;193:7;198:3,15; 200:5;206:21;207:11; 218:6;221:8;233:8; 235:11;239:13 clinically (16) 41:5;128:16,16,18; 129:2,5;130:2,19; 131:19;132:18,19; 133:19;143:18;149:6; 196:20;197:10 clinician (3) 7:12;23:22;45:5 clinician- (1) 140:13 clinician-reported (1) 57:2 clinicians (3) 45:7;72:7;196:18 clinics (2) 58:3;71:14 ClinRO (2) 57:3;140:22 close (2) 86:5;128:3 closely (6) 22:1;28:5;31:6;33:13; 38:9;42:9 club (1) 19:14 clustering (3) 33:14;195:18;196:3	clusters (1) 129:21 CMSI (5) 29:19;35:20;47:20,21; 48:1 COA (2) 54:7;55:10 COA-based (1) 55:3 COAs (1) 56:11 code (1) 239:15 coding (1) 3:21 coffee (2) 74:10;211:16 cognitive (8) 51:9;63:2,22;64:1,8; 66:2;67:14;72:2 cognitively (2) 68:4;83:5 cognizant (1) 184:19 cohort (7) 34:12;37:11;38:21; 90:14;104:12;107:10; 108:10 coined (1) 20:11 co-interventions (1) 115:7 Cole (2) 229:22;234:6 collaboration (2) 52:17;54:4 collaborative (1) 53:14 collaborators (1) 114:22 collagenase (1) 135:21 colleagues (2) 74:22;139:2 collect (1) 101:13 collected (3) 51:18;122:3;123:2 collecting (4) 72:1;102:14;165:18; 200:15 collection (4) 51:19;63:5;197:11; 238:10 College (1) 238:6 Colorado (1) 23:1 combination (6) 61:3;74:19;89:4; 171:21;232:14;241:11 combine (10) 12:18;14:10,20,21;
--	---	---	---	--

143:15;146:12;150:22; 188:11;189:21;192:8 combined (1) 15:16 combines (1) 189:20 combining (2) 21:4;234:14 comfortable (2) 113:14;127:14 coming (6) 83:5;142:7;155:14; 219:18;242:3;243:19 comment (43) 34:7;77:2;80:2;81:5, 17;83:9,14;86:10;88:11; 89:9,13;92:8;102:15; 103:5;114:19;117:16; 127:20;135:19;141:4,5; 150:14;160:7;186:21; 193:4,11;194:18;195:9; 196:10;204:16,21; 215:19;219:12;223:7,13, 18;227:13,17,21;232:5; 236:2,4;240:22,22 commentary (1) 159:1 comments (17) 75:7,14;81:2,9,13; 89:22;94:8;95:14; 111:16;135:11;164:6,8; 171:18;189:4;211:13; 214:21;243:15 committee (5) 23:3;50:20;81:1; 136:13;236:1 common (15) 6:3,19,20;7:14,20;8:2; 9:9,18,18,21;10:5;37:14; 73:12;93:5;235:6 commonalities (1) 9:11 commonality (1) 10:17 commonly (5) 8:10;28:17;65:3; 67:12;233:9 community (1) 110:13 comorbid (4) 7:21;154:16;155:1; 239:6 companies (3) 54:11;168:12;241:14 compare (3) 21:11;40:8;111:19 compared (2) 29:1;145:5 comparing (2) 11:18,19 comparison (1) 112:3 comparisons (1)	111:21 compelling (1) 194:9 competing (2) 16:4;17:21 compile (1) 56:10 complain (1) 102:8 complainers (1) 113:7 complaining (1) 202:4 complaint (1) 107:19 complete (3) 48:7;140:9;160:11 completed (1) 124:17 completely (4) 17:15;106:7;153:12; 207:6 completer (1) 205:8 completion (1) 12:14 complex (10) 87:19;88:3,6;128:4; 129:11;149:2;159:19; 161:2,6;230:7 complexity (2) 77:6;127:21 compliance (1) 124:18 compliant (1) 27:16 complicate (1) 232:7 complicated (5) 44:20,22;152:1; 162:20;239:9 complicates (1) 205:20 component (7) 35:8;91:6;93:6,7; 157:11;188:16;214:6 components (1) 76:22 composite (21) 7:8,9;9:12;11:14,22; 14:14;18:4,14,20;32:12; 34:1;99:19;102:3; 129:10,12;188:17;189:7, 8;190:9;233:20;235:13 compounds (1) 112:17 computer (2) 121:8;123:9 computerized (1) 120:19 concept (12) 33:2,8;51:8;58:13; 61:6;72:3;138:10;139:8;	148:9;213:4,11;223:12 concepts (2) 62:18;155:15 conceptually (4) 132:9;133:16;210:1; 235:8 concern (7) 62:4;68:4;69:17; 128:8,17;186:3;195:1 concerned (4) 83:7;98:2;180:14; 189:3 concerns (6) 67:19;81:20;85:20; 178:17;208:17;226:19 concise (1) 47:5 conclude (2) 45:22;72:13 concluded (1) 39:18 concludes (2) 35:2,4 conclusion (5) 14:4;32:13;55:17; 88:13;229:10 condition (17) 5:4;7:21;8:11;25:8; 93:11,11;126:3;148:11; 152:19;153:15;198:18; 200:6;206:9,16;217:16; 227:11;229:18 conditions (58) 4:8;5:1,6,11,22;7:5; 8:8;14:6;20:13;21:4; 25:4,5,7;28:17;31:4; 39:21;49:1;73:12;74:6; 77:13;92:22;93:9,11; 99:4,14;123:12;143:2,8, 21;144:1;145:10;153:2, 19,21;154:16;155:2,22; 157:10,16,20;158:10; 160:10,12;161:5;162:4; 163:10;188:5;192:17; 200:9,20;206:20; 208:21;211:4,7;212:5,7; 227:7;239:7 conductive (1) 208:7 conduct (2) 22:20;107:21 conducted (1) 64:2 conducting (1) 72:4 confidence (1) 139:21 confirm (2) 64:2;96:3 confirmed (1) 67:13 confounded (1) 100:8	confront (1) 106:15 conjunction (1) 60:17 cons (2) 188:14,20 consensus (12) 142:10,13;147:5; 151:4;153:18;155:19; 161:3;166:1,5;175:9; 176:13;189:2 consider (22) 6:9;15:13;64:11; 116:18;123:16;133:16; 146:4,19;168:18;169:8; 174:10;181:18;185:2,16, 18;211:9;213:13; 215:15;221:6;226:13; 229:5;243:11 consideration (1) 52:1 considerations (3) 180:8,12;193:2 considered (16) 14:2;15:5;43:15; 101:18;128:15;147:11; 149:14;167:5;198:17; 200:20;202:8;203:12; 206:14;212:6;213:16,18 considering (7) 101:21;133:9;143:21; 153:10;163:17;166:21; 240:16 consistency (7) 11:9,15;12:1;18:8; 61:14;87:10;142:17 consistent (9) 68:20;99:5;125:16; 126:11;127:14;152:10; 190:2;204:20;207:12 consistently (5) 68:7;82:14;126:14; 207:17,18 consortia (1) 52:22 Consortium (7) 50:16;52:21;53:1,13; 54:3;65:15;122:20 constant (4) 86:22;88:16,18;156:6 constantly (2) 34:14;113:18 constellation (1) 168:22 constipation (8) 12:1;13:17;15:3; 17:14,16;18:7,17,19 construct (3) 52:3;144:14;149:12 constructively (1) 211:14 consultants (1) 53:9	consuming (1) 138:17 contact (1) 42:9 contacts (1) 29:4 contain (1) 61:22 contained (1) 61:19 contenders (1) 185:7 contention (1) 67:8 context (17) 52:6;54:14;55:18; 56:19;60:22;84:18; 86:21,22;94:18,20; 139:10;146:13,22; 156:19;198:7;213:4; 221:8 continue (1) 242:15 continued (1) 115:4 continuing (3) 27:3;43:9;91:2 continuous (1) 11:19 continuum (1) 69:19 contract (1) 57:10 control (10) 4:2;17:7;24:22;25:9; 38:2;107:4,8;143:17; 201:20;221:13 controlled (1) 210:15 controlling (1) 101:12 controls (5) 27:6,8;28:14,15,15 controversy (1) 110:12 conversation (1) 96:6 convey (1) 148:14 cool (2) 41:4;190:1 Coons (21) 50:15,18,19;82:7,8; 84:16;85:9,18;88:5; 121:22;124:5;136:21; 224:13,13;225:2;232:6; 234:3,5,5,11;235:12 Coons' (3) 79:5;81:4;97:5 cooperation (1) 53:2 coordinating (1) 22:21
--	---	--	---	---

co-outcome (1) 173:11	224:8	176:2;182:9;187:18; 243:8	19;52:5;63:5;77:15; 84:3,13;85:9;99:12; 101:14;103:22;104:18; 107:16;114:12,13;122:3, 5,16,18,21;123:6,19; 124:11,13,16;128:11,13; 129:20;132:13;133:21, 22;134:4,14;159:22; 166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	118:10;146:17;174:10; 196:12;217:6;228:20
co-PI (1) 22:13	4:1;14:21;64:4	crowd (2) 120:21;208:20	107:16;114:12,13;122:3, 5,16,18,21;123:6,19; 124:11,13,16;128:11,13; 129:20;132:13;133:21, 22;134:4,14;159:22; 166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	decided (7) 61:2;63:6;67:5;79:10; 110:16;155:22;171:11
copious (1) 80:20	5:12;64:5	CRPS (1) 160:13	124:11,13,16;128:11,13; 129:20;132:13;133:21, 22;134:4,14;159:22; 166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	deciding (1) 111:9
co-primaries (2) 230:12,13	149:1	CSBMs (1) 140:8	129:20;132:13;133:21, 22;134:4,14;159:22; 166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	decision (4) 67:14;69:19;70:12; 89:2
co-primary (8) 15:2;17:11;129:10; 140:7,12;150:18; 188:15;217:5	23:16;24:7;216:11	cultures (2) 127:1;178:3	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	decreasing (1) 105:4
copy (3) 112:20;114:2;183:21	C-PATH (4) 52:8,15,20;53:2	cumbersome (1) 241:18	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	dedicated (2) 20:10;52:15
core (6) 23:1;174:22;182:7; 184:4,6,9	CPP (1) 160:6	current (4) 48:9;53:12;126:3; 194:11	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	Dedra (1) 22:14
correction (2) 13:21;15:8	CPPS (1) 163:3	currently (2) 28:3;46:15	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	deemed (1) 60:19
correctly (2) 184:21;193:16	crafting (1) 226:13	curvature (1) 136:1	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	deep (1) 78:2
correlate (9) 31:15;34:17;39:16; 40:22;42:6;45:17;46:2; 48:2;194:15	cramping (5) 61:12,21;64:18;65:2; 226:5	curve (4) 194:2,14;195:13; 200:22	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	defecation (9) 93:9;147:8,18;157:12; 189:21;215:9;217:2; 223:9;237:8
correlated (3) 47:21;129:20;179:18	creams (2) 112:17;113:19	curves (1) 40:8	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	defecations (2) 10:7;148:22
correlates (1) 41:5	create (8) 77:9;139:19;169:12, 14;209:3;220:7;230:17; 239:12	cut (4) 24:16;48:8;158:14; 207:3	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	defending (1) 136:19
correlating (1) 46:4	created (1) 144:14	cutoff (1) 45:9	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	defer (1) 175:13
correlation (5) 41:8;46:12;47:3,9,19	creating (1) 138:18	cycle (18) 101:8,13,19;183:9; 196:22;199:1,14; 200:16;201:15,18,19; 204:11,12;206:10; 207:10,14;210:9,12	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	deferring (1) 89:16
correspondingly (1) 129:4	creation (1) 145:19	cyclic (1) 198:7	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	deficiencies (1) 14:7
cost (2) 54:16;238:13	creative (2) 227:18,22	cyclical (4) 143:22;156:5;204:4; 210:8	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	define (14) 23:10;29:13;30:7; 34:3;35:6;43:5;76:10; 96:18;128:18;131:18, 18;137:16;214:5;237:11
costs (1) 54:21	criteria (39) 3:18;4:13;5:8;6:15,17, 19,21,22;7:10,20,21; 17:3;21:11;23:14;29:22; 43:12;58:4;60:18;90:20; 91:4;92:15,16,21;93:18; 94:1;108:1,2;135:16; 144:6;154:6,15;162:19; 164:21;167:3;191:10, 16;205:20;206:4;215:3	cytic (1) 198:7	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	defined (4) 9:4;24:15;34:4;36:20
cotton (5) 178:11;179:12,15,22; 181:10	critical (6) 52:8,16;211:14; 224:14;230:18;234:5	cytology (1) 199:21	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	defining (3) 11:1;96:9,10
count (1) 106:4	critically (1) 77:15	cyctosporine (1) 110:21	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	definitely (5) 111:7;144:20;145:1; 154:8;170:18
countries (1) 239:18	criticism (1) 198:5	cystitis (4) 6:2;7:15;90:12;101:7	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	definition (15) 7:12;11:6;21:13; 41:14;43:10;45:13; 46:16,17,19;55:15; 102:7;105:15;132:5; 160:9;167:10
couple (18) 12:2,7,10;19:13;29:9; 41:17;80:10;92:16; 94:17;110:2;112:16; 138:22;186:13;189:8; 214:7;216:16;220:5; 241:9	CROs (1) 53:10	D	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	definitions (2) 14:12;96:20
course (18) 23:2;25:17;27:6;31:2; 67:19;90:5;93:18; 105:10;129:1;145:8; 167:18;179:20;186:19; 207:16;208:15;212:21; 224:16;243:22	cross-classify (1) 130:8	daily (6) 7:5;58:22;124:12; 180:15;197:2;207:2	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	degree (14) 28:2;29:10;39:5,15; 94:19;95:8;100:14; 132:8;135:16;136:1; 159:21;160:3;221:2; 224:17
cover (7) 10:13;144:11;152:15; 155:22;159:9;187:1;	crossed (1) 114:16	Dan (1) 49:17	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	demonstrate (2) 107:9;221:12
	cross-sectional (1) 48:13	darker (1) 6:17	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	demonstrated (3)
	Crosstalk (7) 174:13,21;175:5;	data (77) 19:17;22:21;26:17; 27:17;28:19;29:22;31:6; 33:1,3,6,13;34:20,21; 35:10;39:1;44:20;45:2, 21;46:11,15;47:3;48:12, 20;49:3;51:11,12,16,18,	166:5;194:10;197:11; 199:19;200:16;202:3; 204:14;208:1;209:9; 211:20;238:10,20;241:8, 9,20;242:14	

38:16;40:10;195:12 demonstrates (1) 41:11 Dennis (4) 65:14;142:19;211:2; 244:5 denominator (2) 8:18;9:7 Department (2) 3:8;73:3 dependent (1) 177:15 depending (7) 109:5;120:2;148:5; 160:13;177:15;190:13; 205:12 depends (2) 108:19;156:18 deploy (2) 63:6;124:7 deployed (1) 122:21 deploying (1) 51:15 depression (3) 10:10;36:6;125:2 depth (2) 30:13,14 derive (2) 33:1;62:2 describe (2) 220:6,18 described (6) 27:7;64:21;65:3,5; 67:17;80:1 describing (3) 4:15;13:4;218:11 Descriptor (1) 184:2 descriptors (1) 66:16 desensitization (1) 179:4 design (7) 101:19;105:11;126:7; 187:6;223:8;224:6; 240:10 designate (1) 207:20 designed (1) 58:15 designing (4) 3:21;185:1,15;241:16 desipramine (1) 171:20 desirable (1) 17:6 desperate (1) 29:6 destination (1) 51:4 detail (5) 13:5;26:4;50:2;73:17;	162:5 detailed (5) 26:1;35:3;41:7;44:18; 83:11 details (7) 25:17;127:19;166:18; 210:2;235:10,15,21 detect (2) 232:2;233:22 determine (3) 58:16;84:20;92:17 determined (1) 229:2 determining (1) 43:22 develop (11) 54:5,20;56:12,16; 57:11;90:8;138:8; 148:20;151:19;221:6; 242:4 deployed (18) 54:18;56:18;60:17; 80:3;117:14;122:16,20; 135:10,15;136:2; 137:22;138:1,7,12; 139:14;144:17;160:8,16 developing (7) 18:11;54:12,16; 122:19;123:1;135:7; 178:2 development (16) 52:18;53:10;54:7; 55:8,10,12,13,14,19,21; 57:18;65:16;125:19; 136:11;139:10;145:20 device (8) 40:4;51:16,17;63:12; 71:7;122:13;124:3,9 devices (9) 51:21;63:7;121:15; 122:5,21;123:7,22; 124:8,16 devil's (1) 235:10 diabetic (4) 83:19;96:13;97:6;99:5 diagnose (1) 161:12 diagnosed (4) 20:18;21:3;23:19;25:2 diagnoses (1) 31:2 diagnosis (4) 7:11;23:15;160:4,11 diagnostic (3) 6:21;29:22;161:7 diagnostically (1) 93:22 diagram (2) 26:19;215:6 diaries (2) 10:6;140:4 diary (4)	57:19;63:3;124:12; 193:20 dichotomous (2) 18:3,9 Dick (7) 22:22;33:16;34:7; 43:17;74:18;75:13; 95:14 dictate (1) 96:21 dietary (1) 38:4 differ (2) 93:10;175:19 difference (12) 4:15;68:12;71:3; 85:15,16;96:9;108:17, 22;195:3,5,15;221:12 differences (5) 18:15;36:9;64:14; 91:19;133:11 different (91) 8:6;12:9;14:12,13; 17:15;20:21;22:4;24:12, 21;25:13;28:9;29:18; 32:8;34:13;39:4;40:8; 43:17;44:7;45:3,5,22; 56:21;66:3,15;67:11,18; 68:5;73:12,18;76:15,18; 77:13;84:10;86:11; 88:15;90:20;97:17; 100:4,5;102:4,10; 103:18;110:11,20; 111:10,13,14;112:8,9; 116:4;118:21;119:3; 120:17;121:1,12; 122:11;126:16;128:9; 129:20;137:10,14; 151:1;152:12,18,19; 157:3;176:11;178:21, 22;187:5;188:14; 189:10,10;193:7; 199:22;205:13;206:16, 20;217:16;221:1;222:9, 10,22,22;225:8;227:3; 230:22,22;232:19; 235:8;236:14;238:4 differentiate (3) 100:4,11;109:15 differentiating (1) 108:18 differently (8) 10:15;32:9;83:6; 111:11;112:6,7;121:14; 194:10 difficult (5) 34:13;112:2;136:8; 137:15;177:14 difficulty (1) 108:21 diffuse (1) 161:18 dilatation (1)	180:15 dilators (1) 179:3 dimensions (1) 135:5 DIMITRAKOFF (3) 190:11,19;220:19 direct (1) 168:7 direction (3) 50:7;74:12;109:6 directly (2) 60:18;168:17 director (2) 50:15;73:3 disadvantages (1) 65:15 disagree (4) 147:3;189:12;215:16; 216:4 disagreeing (1) 167:11 disappears (1) 195:6 discarded (1) 221:5 discomfort (29) 5:16;9:17;61:12; 63:17;64:17;65:2,5; 191:20,21;216:12,13; 217:7,9,21;218:1,3; 219:13,15,15;220:6,18, 21;221:1;222:5;224:18; 225:8,9,17;226:4 discovered (2) 31:8;164:2 discovering (1) 77:16 discovery (3) 22:10,19;163:22 discuss (5) 148:3;153:14;176:10; 192:3;211:2 discussed (1) 57:17 discussing (2) 176:12;213:5 discussion (20) 3:20;14:17;19:9; 32:10;72:19;129:9,14; 132:4;134:20;142:3,9, 21;143:12;144:5;145:4, 9;154:9;164:7;213:22; 220:20 discussions (4) 75:11;79:6;80:4; 154:21 disease (16) 9:15;10:1,9,11;23:12; 49:18;88:15;117:11; 135:22;136:6;137:18, 19;149:14;153:13; 214:11;228:10	diseases (3) 76:12;123:12;191:7 disease-specific (3) 93:7;94:6;150:17 disorders (2) 213:5,20 disproportionate (1) 153:12 dissent (3) 154:18;189:3;225:19 disservice (1) 214:18 distance (2) 196:5;208:10 distant (1) 229:14 distinct (2) 76:14;218:20 distinction (1) 64:22 distinctions (1) 65:7 distinguish (1) 219:12 distinguishing (1) 64:16 distress (1) 184:4 distributed (2) 15:17;174:17 distribution (1) 37:12 divided (1) 29:17 division (2) 87:2;208:22 divisions (1) 148:6 doctor (1) 39:14 doctor-patient (1) 115:16 document (5) 90:10;162:9,16; 234:12;236:7 domains (3) 77:9;149:13;182:3 Don (1) 22:13 done (40) 10:18;23:21;24:17; 26:10,21;27:8,12,20; 31:19;33:18;34:11; 49:20;51:8;59:21;71:8; 76:3;81:11;83:16;87:5; 109:12;114:20;132:13, 14;138:8;139:19;158:7; 164:1;171:7;172:19; 178:11,20;182:21; 186:14;206:18;213:19; 225:11;232:10;233:11; 235:4;241:17 DOOR (4)
---	--	--	--	--

<p>15:17;17:3;117:7; 188:16 dopamine (1) 115:14 dose (1) 12:12 dot (3) 7:7,7,8 double-blind (1) 5:14 doubt (2) 167:6,7 down (15) 61:18;64:19;88:16; 105:22;119:13,21;120:7, 8;127:9;128:3;130:21; 147:4;165:3;182:12; 207:3 downgrade (1) 227:6 downloaded (1) 124:2 downstream (2) 168:12,13 DPN (1) 192:10 DR (485) 3:3,7,11;4:14;7:15,19; 19:1,4,5,8,16;42:21; 43:1,3,4,5,7,12,16,21; 44:1,8;45:8,15;46:9; 47:7,8,14;48:8;49:4; 50:4,5,6,14,15,19;55:7; 56:20;62:3;67:20;72:10, 15,20,22;73:2,7;74:21; 75:1,3,5,17;77:1,3; 78:22;79:2,4,5,5;80:2; 81:4;82:7,8,9;83:8,15; 84:8,16,21;85:9,17,18, 22;86:11,13,17;87:13, 15,17,18;88:5,6,11;89:6, 11,13,15,16,19,20,21; 91:2,21;92:8,11;94:8; 95:18;96:5,6;97:2,3,4,5, 15;98:16;99:7,7,9,22; 100:1,17,21;102:15,16, 20,22;103:2,3;104:5,9, 11,12;105:10;106:6,6,7, 22;107:4,12;108:5,6,14; 109:2,18,22;111:17; 112:10,13;114:15,19; 116:21;117:7,9,10,12, 15;121:4,19,22;124:4,5, 19;125:12,16;126:5; 127:18,22;128:2,10,12; 129:18;131:3,8,13,16; 132:15,21;133:6,10,14, 17,18,19,20,21;134:12, 15,17,18,19;135:18,20; 136:21;137:11,12,20; 140:1,2;141:1;142:4; 144:13,19;145:13,18; 147:2,6,10,12,13,22;</p>	<p>148:1,7,17;149:6,8,16, 17;150:3,12,13,14,21; 152:8,19;153:4,5,16,22; 154:7,19,20;155:5,13; 156:2,10,21;157:4,6,18; 158:2,4,8,11,12,13,15; 160:7,20,22;161:21; 162:8,21;163:6,19,20; 164:5,9;165:7,10,21; 166:7,9,13,16,20; 167:11,17;168:4;169:16, 18,21;170:5,6,8,17; 171:8,12,19;172:3,9,19; 173:1,3,5,6,7,14,18,19, 20;174:1,6,9,14,16,22; 175:4,6,8,12;176:3,4,9, 18,21;177:3,11,19,20; 178:8;179:10,15;180:7, 13,21;181:9,12,14; 182:6,10,15,17;183:8, 14,17,20;184:6,7,9,11, 21;185:8,10,11,13,18, 21;186:1,2,16,20;187:4, 14,16,19;189:16,17; 190:1,2,10,11,17,19,21; 191:3,14;193:6,11,16, 20;194:2,5,12,13,18,21; 195:11,16,17;196:10,11; 197:14,15;198:12,13; 199:2,3,9,10,18;200:18; 201:4,6,16;202:5,17,20, 21;204:15,15,18,20; 205:1,4,5,7,10,10,11,12, 20;206:6,8;210:6,7,20; 211:18;212:2,16,20; 213:3;214:1;215:1,20; 216:10,15,19;217:14; 218:14;219:2,5,17,18; 220:1,4,19;221:3,4,22; 222:3,15;223:1,5,14,17, 20,22;224:9,13,16,17,20, 22;225:2,4,5,6,15,21,22; 226:15;227:8,16;229:10, 17,21,22;230:9,11,13; 231:2,8,17;232:5,5,6,7; 233:7,15,17,19;234:3,3, 5,10,11;235:5,12,14; 236:4,9,10,11,12;237:5, 17;239:1,4,16;240:7,18, 21;243:4,18;244:4,8 draft (10) 51:9;61:10;62:22; 80:3,18;84:1;162:1; 186:20,21;211:11 dragged (1) 182:12 dramatic (1) 94:16 driven (5) 18:15,16,18;63:10; 195:4 drop (1) 242:16</p>	<p>drug (43) 8:7;18:1;52:10;53:3; 55:8,10,13,14,18,20; 109:14;115:22;130:15; 139:10;144:17;145:10, 15;147:7,15;148:12,20; 149:8;150:11;156:13; 157:1;188:8;215:10; 216:5,7;217:18;223:8; 228:8,11;229:11;231:16, 18,20;232:12;233:2,6; 234:22;241:7;242:12 drugs (14) 5:5;6:8;8:6,9;116:10; 136:22;140:3;150:5; 157:3;168:13;215:7; 216:2;220:8;223:10 dual (1) 203:2 due (1) 180:17 durability (6) 195:8,12,14;208:8; 209:7,14 duration (10) 6:19;24:12,21;28:21; 36:5,18;61:1;205:15; 208:10;210:13 durations (1) 24:19 during (16) 30:6;66:2;68:8;88:12; 95:15;105:6;106:5; 135:11;139:3;170:6; 176:8;181:13;193:17; 197:3;202:6;206:4 Dworkin (34) 106:6,7;109:2;117:10; 127:20,22;128:10; 132:15;133:17,19; 147:6;157:6;158:2,8,12; 166:16,20;169:18; 171:19;173:1;174:16; 176:4;184:21;185:10,13, 21;189:17;194:21; 195:11;200:18;201:6; 202:17;219:5;240:7 dyschezia (2) 102:5;156:5 dysfunction (2) 137:3;200:1 dysmenorrhea (2) 102:6;197:2 dyspareunia (3) 102:5,9;156:7 dysuria (4) 102:6;148:21;149:10; 156:5</p>	<p>152:13;191:4;204:21 early (9) 24:15;49:22;50:11; 72:11;195:20;196:2; 203:4,18;204:22 easier (3) 151:21;159:10;183:3 easily (3) 147:5;162:2,3 easy (5) 119:9;137:18;158:18; 161:12;209:1 eaten (1) 37:20 editorial (1) 34:7 editorializing (2) 20:14;82:6 education (1) 71:13 EDWARDS (4) 170:8;175:8,12;176:3 effect (20) 38:17;108:8;109:6,7; 115:22;116:3;122:8; 125:3;128:6;147:8; 150:7,10;202:7;206:13; 208:8,12;209:7;210:4; 221:15;231:21 effective (2) 15:6;52:18 effects (4) 106:17;109:13;122:6, 9 efficacy (7) 116:16;195:8;203:4, 11;207:22;209:6;219:20 effort (6) 4:19;95:9;111:17; 135:16;240:11,12 efforts (1) 73:16 eight (1) 35:12 either (18) 5:10;10:6;14:3;48:4; 56:14;69:12;109:6; 112:19;117:4;118:4; 171:13;179:12;180:3,14, 15;185:2,16;188:10 elderly (3) 113:5;114:17;121:1 electronic (9) 51:16;86:6;87:6; 122:4,16,18,21;123:6; 124:16 electronically (3) 122:3;123:2,20 element (1) 235:6 elicitation (4) 51:8;58:14;61:7;72:3 elicits (1)</p>	<p>168:17 eligibility (1) 3:18 eligible (2) 27:20;132:6 eliminate (1) 155:1 eliminating (2) 104:18;107:18 Ellen (2) 163:20;172:2 else (20) 6:11;35:4;86:13; 96:16;107:14;109:18; 137:17;145:5;151:12; 163:2;165:18;168:8; 172:14;179:8;184:13; 186:17;217:7;221:16; 225:3;237:15 else's (1) 89:14 elsewhere (1) 49:15 elusive (1) 217:11 EMA (2) 5:6;53:8 email (1) 82:2 embarrassing (1) 19:2 Emeran (1) 22:13 emerge (1) 62:9 emerged (2) 29:9;32:5 emerging (1) 190:14 eminent (1) 186:20 empathized (1) 65:13 empirical (2) 83:2;84:19 enable (2) 54:4;56:10 encapsulate (1) 20:12 encompasses (1) 163:3 encourage (1) 197:11 encouraged (1) 224:4 end (25) 26:7;63:18;67:2; 69:16;85:13;98:1;105:5; 108:21;112:15,15;113:4, 9;131:11;137:21;141:1; 142:13;196:9;203:11; 207:22;208:14;218:6; 221:7;229:11;230:13;</p>
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<p>231:16 ended (5) 33:12;51:21;104:18; 136:5;235:12 endogenous (1) 200:3 endometriosis (8) 21:7;24:2;101:17; 155:8;158:5,19;162:19; 198:22 endometriosis-associated (3) 153:11;155:12;157:15 end-organ (2) 14:6;214:11 endorse (5) 43:14;91:9,11;97:19; 98:6 endorses (2) 98:5,12 endorsing (3) 78:15,20;91:15 endpoint (54) 9:3,6;11:12,13,14,16, 20,22;12:1,4;13:3; 14:14;15:22;17:11;54:7, 16;55:3;75:12;96:3; 135:22;137:9;140:6,7; 143:6;144:6;145:17; 150:17;166:22;167:4; 170:14,20;171:1;180:1; 181:11;183:11;185:17, 19;186:15;188:9;189:7; 192:21;194:17;200:21; 203:2,8;204:1;206:2; 211:6;218:7,22;220:10; 221:9;235:13;236:16 endpoints (35) 4:13;8:17;10:14,19; 11:10,17;12:6,17;14:11, 21;54:1;57:14;62:3; 120:17;129:11,15; 136:7;142:14,16;143:4; 144:4;151:10,19; 165:12;188:5,15; 202:22;203:22;212:4, 14;214:4;215:15; 232:18;236:7,15 ends (4) 46:3;81:19;199:13; 242:17 energy (1) 22:17 enjoyed (1) 19:9 enough (16) 110:8;115:5,11; 146:19;164:1;165:1; 192:16;198:4,9,10; 199:11;208:18;209:8; 219:22;221:10;232:10 enrich (1) 232:22 enriched (2)</p>	<p>232:11;240:13 enriching (1) 233:5 enroll (3) 96:14;183:10;208:3 enrolled (3) 103:11,21;228:19 enrollment (2) 228:4;240:14 entered (1) 104:8 entire (6) 69:21;126:15;130:21; 138:1;194:4;195:22 entities (1) 137:14 entrance (1) 164:21 entry (12) 14:5;63:8;92:15,17; 144:5;154:5;170:15; 191:9,16;215:2;222:19; 227:4 environment (1) 138:19 envision (1) 231:17 envisioning (1) 143:10 epidemiologist (1) 75:3 epidemiology (3) 73:1,4;90:14 episodic (1) 86:22 equally (1) 26:15 equilibrated (1) 26:15 equivalent (2) 108:9;134:10 ER (1) 39:13 erectile (1) 137:3 error (3) 12:20;143:17;147:20 Ervin (1) 71:22 especially (12) 75:22;95:21;113:5; 114:2;118:4;119:15; 120:21;124:12;129:19; 187:10;239:5;240:4 essence (1) 239:1 essentially (8) 20:15;30:2;51:16; 66:16;70:21;104:21; 234:14;238:21 establish (5) 49:5;53:13;57:15; 104:2;137:15</p>	<p>established (5) 6:21;52:8,21;57:5; 165:22 estimate (1) 86:18 estrogen (1) 200:10 et (12) 22:14,14;25:14,15; 26:15;27:18;30:19;37:9, 21;40:13;63:17;106:17 ethnicity (1) 71:13 etiologies (2) 5:14;22:4 evaluate (6) 99:1;161:7;169:5; 186:8;209:6;230:3 evaluated (1) 43:16 evaluation (6) 23:21;52:10;53:3; 198:2;210:3;230:2 evaluations (1) 134:16 Evans (2) 15:18;19:1 even (34) 14:6;20:6;34:18; 41:10;44:10,14;75:11; 76:13,15;81:7;83:9; 85:17;95:2;99:11; 104:17;110:7;115:3; 117:5;122:8;123:13; 124:14;138:5;140:17; 149:22;168:18;172:16; 177:13;207:15,19; 214:14,18;218:8;233:2; 237:6 evening (1) 20:5 event (3) 63:10,10,13 Everybody (6) 104:7;127:1;154:12; 190:22;191:5;228:20 everyday (1) 243:10 everyone (22) 3:3,11;18:21;19:11; 26:13;33:12;49:11; 65:17;95:11;103:11,12; 106:16;139:21;142:4,6; 155:8;159:19;170:19; 211:12;217:10;236:1; 240:19 everyone's (4) 165:1;175:14;189:2; 190:1 evidence (17) 55:16;56:10,15;68:16; 84:19;87:9;90:10;111:3; 115:11;185:5;188:21;</p>	<p>190:17,19;197:8;227:2, 3,5 evoked (2) 155:17;213:17 exacerbate (1) 206:20 exact (2) 68:3;136:17 exactly (11) 33:17;43:6;47:8; 83:12;110:12;124:16; 160:1;161:8;185:22; 201:17;205:17 exam (4) 8:3;25:20;26:3;41:7 examine (4) 24:11;33:2;34:5;50:2 examined (1) 210:15 examining (1) 31:6 example (27) 8:21;10:22;11:11; 15:9,17,21;16:9;27:2; 65:22;98:15;102:7; 140:5,11,11;144:7; 155:12;183:3;195:1; 199:20;200:15;202:22; 205:21;224:11;235:16, 22;236:8,20 examples (9) 14:10;118:5;135:13; 149:18;150:4,7;212:17; 213:6;235:18 excellent (1) 158:16 except (3) 27:11;57:1;161:19 exception (1) 103:13 exclude (6) 30:11;111:9;154:10; 155:8;185:19;191:5 excluded (7) 8:14,15;154:3;159:14, 15;220:9;221:1 excluding (2) 191:13;216:21 exclusion (6) 4:12;6:15;7:20,21; 154:15;162:18 exclusions (1) 24:8 exclusive (1) 146:22 exclusively (1) 150:19 excruciatingly (1) 65:21 executive (2) 23:3;50:15 exercises (1) 37:21</p>	<p>exist (1) 149:18 existing (6) 32:18;33:2;56:11; 61:7;122:17;134:8 exists (1) 232:4 exogenous (1) 200:3 expect (5) 21:10;30:18;92:4; 215:10,11 expected (3) 59:14;65:12;121:17 expedite (1) 55:12 expensive (2) 54:19;138:17 experience (12) 17:10,17;60:19;97:5, 9;102:8;112:5;121:20; 170:13;194:1;200:4; 233:8 experienced (3) 58:17;66:14;69:15 experiences (1) 22:16 experimental (2) 46:21;143:7 expert (3) 61:8;148:17;158:2 expertise (1) 54:5 experts (10) 58:13;60:17;148:19; 155:14;173:15,20; 175:14;197:17;212:12; 215:16 explain (4) 15:19;64:10;81:10; 113:4 explaining (1) 114:14 explanation (2) 109:11;224:10 explicit (1) 162:10 exploratory (3) 91:20;142:15;226:7 explored (1) 64:14 expressed (1) 146:8 extended (1) 94:22 extending (1) 50:21 extensive (6) 58:12;59:20;82:22; 134:15,17;204:8 extent (2) 54:13;138:20 extreme (1)</p>
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67:2 extremely (1) 136:8 extremes (2) 66:17;227:4	Farrar (17) 32:16;44:9;46:9; 72:22;74:21;75:3,17; 87:14,17;88:11;96:6; 100:1;103:3;107:12; 108:14;125:12;126:5	7:2 fibromyalgia (7) 25:2;30:17;40:12; 41:13;49:22;83:18; 199:22	121:15 five (3) 93:17;136:5;211:19 flare (7) 37:1,12,18,18,22; 197:3;200:9	51:4 forget (3) 81:20,20;205:2 Forgive (1) 13:11 forgot (3) 112:10;177:11;225:13
F	fascinating (1) 124:20	field (6) 58:13;135:9;144:16; 241:18,22;242:21	flares (10) 36:21;37:3,8,10,13; 38:10,13;40:16;143:22; 205:18	form (2) 184:1;201:20 format (3) 63:5,8,16 formed (1) 53:1
Facebook (1) 121:8	fat (2) 140:12,15	fields (2) 135:14,14	flexibility (1) 140:17	forms (1) 238:4
facilitate (2) 55:1;70:11	fatigue (4) 25:3;30:17,19;35:22	fifth (1) 78:1	flip (1) 147:7	forth (1) 136:12
fact (29) 32:16;52:1;62:4; 73:13;76:9;77:8,14; 95:7;96:4;98:7;100:8; 103:18;104:12;105:7; 108:3;115:11;116:4; 123:21;127:15;130:14; 134:5;136:13;146:8; 159:2,21;164:14,16; 177:6;182:12	FDA (30) 5:5;11:7,7;52:13;53:7; 54:5,6;55:16;56:11,17; 57:11;62:4;69:7;84:8; 89:20;122:2;135:1,2,6, 11,18;138:5,10,18; 140:2;146:19;169:13; 176:14;192:18;241:5	fight (1) 242:10	Flomax (1) 232:15	forward (14) 13:19;57:3;78:18; 114:7;117:6;118:11,14; 119:14;139:20;197:7; 210:22;211:1;236:3; 242:4
factor (1) 32:4	FDA's (8) 52:9,15;53:2,55:1; 68:21;71:1;83:11;167:3	figure (5) 185:22;202:15; 206:12;215:14;226:4	floor (4) 41:4;109:6;151:6; 192:22	Foster (2) 178:14;180:20
factorial (1) 171:22	fear (1) 179:5	fill (3) 124:13;125:7;239:2	flow (1) 27:4	Foster's (2) 151:11;166:10
factors (12) 23:10;26:8;32:5;36:4; 38:4,12;88:9;115:12; 120:20;148:6;163:17; 200:7	feasibility (2) 154:22;209:7	filling (3) 91:4,5;125:9	fluctuate (1) 198:21	found (22) 3:16;4:11;5:21;19:21; 20:1;21:14;23:17;28:18; 30:3,22;32:5,8;36:13; 59:5,19;67:21;68:3; 94:8;103:7;113:2; 117:18,21
fail (2) 203:13,13	feasible (2) 210:1,16	fills (2) 97:20;98:15	fluctuates (1) 206:19	foundational (1) 57:22
failed (3) 107:14;209:19;232:16	feature (4) 91:9,15,16;97:20	final (2) 62:8;70:16	fluctuation (1) 200:3	four (6) 82:3;119:3;136:5; 159:8;202:6,17
failure (1) 228:15	features (5) 73:13;78:5,21;91:12; 97:19	finally (2) 15:14;16:18	fluctuations (1) 94:16	fourth (1) 159:4
fair (1) 75:19	fee (1) 56:3	financial (1) 71:17	fly (1) 80:14	four-week (2) 38:18;105:8
fairly (8) 23:6;25:20;45:1,5; 95:8;137:19;164:19; 181:22	feedback (3) 4:21;186:22;211:14	find (8) 5:6;6:4;21:2;29:6; 36:8;153:13;183:3; 227:12	focus (11) 37:2,7;39:19;94:10; 137:18;145:9;153:18; 222:17;225:7;237:9; 240:11	frame (7) 85:1;119:12;143:20; 175:17;192:9;193:17; 194:8
fall (1) 93:15	feel (11) 19:18;62:7,16;80:13; 104:6;120:16;163:15; 171:14;188:21;191:12; 214:18	finding (4) 29:12;68:10;108:22; 207:13	focusing (6) 42:4;48:5;94:9; 199:15;223:10;240:8	frames (1) 14:13
fallible (1) 171:19	feeling (8) 22:2;73:8;104:7,9,15; 154:14,20;194:5	findings (10) 19:12;20:2;40:21; 47:20;60:2;64:20;65:9; 90:18;190:14;213:10	follow (5) 95:14;110:5;159:11; 210:17;234:6	framework (4) 53:14;142:20;212:19; 213:22
falling (1) 200:9	feels (1) 80:6	finer (1) 16:21	followed (3) 24:18;27:9;178:18	Frank (8) 158:14,15;172:21; 173:7;174:17;186:1; 223:16;237:18
false (3) 4:2;12:20;179:20	feet (1) 35:14	firm (1) 56:5	following (12) 28:5;41:18,19,22; 42:8,10;58:4,6,9; 84:21;134:19;202:22; 223:5	Frank's (1) 173:1
familiar (1) 64:7	Fehnel (1) 71:22	firms (4) 53:5;54:22;56:3,7	follows (1) 134:13	free (1) 238:21
families (1) 10:18	felt (6) 64:5;68:6;77:4;80:6; 113:8;120:3	first (48) 3:6;4:18;5:18,20; 10:19;13:14;28:18; 31:10;33:7;52:6;58:11; 59:11;66:17;75:6;81:2; 82:13;89:11,15;100:22; 103:12;104:12;105:2; 107:18;110:2;114:6,12; 118:8,11,13,18,21; 125:1,13,14,17,19; 130:20;131:18;143:10; 151:4;173:18;185:13; 195:4;201:5;202:1,6; 203:1;239:3	follow-up (2) 94:22;195:22	freedom (1) 230:3
family (1) 10:19	female (2) 101:3;174:4	fit (4) 49:3;157:16;240:3,6	foods (1) 37:20	frequency (10)
fantastic (1) 84:20	females (1) 30:22	Fitbits (1)	fool (1) 116:1	
far (10) 19:9;71:8;78:7;142:7; 171:6;180:13,17;189:2; 200:8;242:22	few (5) 3:22;74:17;79:22; 83:22;164:2		footnote (1)	

61:14;99:18;132:2; 149:21;216:3;231:10,14, 22:234:1;236:22 frequent (1) 17:20 frequently (2) 10:9;41:20 Friday (2) 1:12;20:5 front (2) 123:8;183:21 FSFI (3) 181:21;182:1,11 full (8) 69:19;70:7,21;77:21; 125:18;200:12,15; 204:13 fullness (1) 65:6 fully (1) 71:14 fun (2) 133:22;141:11 function (3) 181:15;200:14,14 functional (4) 33:14;129:21;195:18; 196:3 fundamental (1) 35:8 fundamentally (1) 238:19 funded (1) 20:9 funding (1) 52:12 further (6) 53:16;63:1;91:3; 103:4;198:11,14 future (17) 3:20;23:11;70:11; 93:15;123:17;124:6; 167:20,21;211:10;214:8, 12;220:16;222:13,20; 225:18;238:18;243:12	10:2;25:18;46:2;71:5; 76:14,20;138:6;197:18; 206:18;213:6,7,10,13, 14;224:10;243:16 generalities (1) 198:1 generalizability (1) 154:22 generalizable (2) 153:20;186:4 generalized (2) 151:20;152:7 generally (7) 68:11;95:6;131:20; 143:22;153:1;192:10; 197:20 generate (3) 40:8;62:19;183:5 generated (1) 62:21 generating (1) 102:9 generation (1) 238:13 genetic (1) 115:13 geographical (1) 23:6 gets (10) 34:6,6;45:19;103:11, 19,20;105:5;119:7; 137:12;158:16 Gewandter (126) 3:7,10,11;7:19;86:11; 89:11,15;97:3;98:16; 117:9,12;142:4;144:19; 147:2,12;148:7;149:6, 16;150:12,21;152:8,19; 153:4,16;154:7,20; 155:13;156:10;157:4; 160:20;161:21;163:19; 164:5;165:7,10;166:7; 167:17;170:6,17; 171:12;172:3,19;173:3, 6;174:1,9;175:4,6; 176:18;177:3,19;178:8; 179:10;180:7,21; 181:12;182:15;183:8, 17;184:7,11;185:8,11, 18;186:1,16;187:16,19; 189:16;190:1,10,17; 191:14;193:11,20; 194:12,18;196:10; 197:14;198:12;199:2,9; 204:15;205:1,5,10,12; 206:6;210:6,20;212:2, 20;214:1;215:1;216:15; 218:14;219:17;220:4; 221:3,22;222:15;223:5, 17,20;224:9,16,20; 225:5,15,21;227:8; 229:21;230:9;232:5; 234:3;235:14;236:9,11;	237:5;239:1,16;240:18; 243:4,18;244:4,8 GI (4) 58:3;115:19;197:1; 238:1 GILRON (3) 223:22;226:15,15 given (7) 71:9;118:5;146:11; 156:20;202:5;221:14; 234:13 gives (5) 18:5;59:4;203:22; 242:18,19 giving (3) 62:13;115:21;127:12 glean (1) 90:21 global (3) 40:11,13;77:10 glossed (1) 237:6 goal (7) 45:4;54:9;55:1;56:9; 57:11;75:21;92:12 goals (5) 23:8;54:3;60:3; 142:11;161:3 goes (4) 31:2;80:9;148:4; 242:20 gold (1) 178:9 Good (35) 3:3,11;4:14;22:18; 32:10;50:19;88:7;89:5; 104:8;111:18;126:3; 139:11,20;151:9,13; 164:3,10;165:14;172:4; 177:4;179:22;180:8,10; 186:18;203:19;210:21; 211:15,17;212:2,18; 224:11;227:8;236:2; 243:8,13 grab (1) 237:22 grabs (1) 238:3 gradation (1) 16:21 gradations (1) 137:13 grade (2) 133:18;140:15 gradient (3) 43:18;44:5,6 grading (1) 160:16 grant (2) 32:17;52:14 grappled (1) 48:12 great (25)	48:14;81:8;106:8,18; 142:8;145:21;147:2,22; 148:7;150:12;158:5; 162:21;163:19;164:5; 167:17;177:10;182:15; 183:17,18;190:10; 215:1;222:16;224:11; 227:13;236:9 greater (4) 16:10,14;84:4;128:19 Griffith (1) 32:2 GROL-PROKOPCZYK (4) 199:10;201:4;222:3,3 group (70) 4:19;7:3;10:18;25:9,9; 26:9;33:9,20;37:7; 38:13;39:10;44:3;48:19; 49:2;56:2;57:5;58:9,10; 66:6;67:9;71:16;72:10; 79:20;84:14;98:4,5,8,12, 13;103:10;105:4;107:8, 13,15,17;108:8,20; 109:4,12;110:16;111:4, 10;113:9;114:17; 118:13;121:18;129:22; 130:10;131:4;142:3; 151:21;152:10,15; 164:17;166:10;167:15; 171:16;188:21;195:21; 203:13;205:8;217:3; 219:10;220:12;222:12; 234:9;237:10;238:5,15; 239:9 groups (19) 24:22;37:2;40:9; 54:14;55:22;56:4,6,8,9, 19;57:1;90:2,3;108:15, 19;131:14;158:20; 191:12;238:19 group's (1) 57:10 guess (19) 31:17;48:20;79:11; 85:10;93:12;98:21; 126:10;128:13;172:6; 174:17;178:6;184:7,11; 189:5;191:3;192:14; 194:5;231:2;235:10 guidance (12) 11:7;18:5;55:8;69:7; 71:1;129:13;138:12; 188:18;192:18;234:8, 20;235:15 guidelines (3) 153:18;211:21;242:3 GUPI (4) 34:2;99:11;129:10; 189:19 guys (12) 155:14;159:11;164:8; 179:13;192:15;193:11; 215:16;223:7,9,18;	227:12;241:2 gynecologic (1) 162:12 gynecologist (3) 20:22;102:3;162:13 gynecologists (3) 151:7;163:15;199:4
H				
			habits (1) 150:5 half (9) 6:13;7:2;73:8;130:9, 19,22;131:1,7;237:14 halfway (1) 26:21 hand (5) 87:5;100:20;117:2; 124:14;151:15 handheld (6) 51:17;63:7;71:6; 123:21;124:2,9 handheld-based (1) 117:19 handle (5) 145:11;192:3;217:4; 218:17;230:16 handling (1) 186:4 hands (1) 87:5 Hanes (1) 62:3 Hanna (5) 198:12;199:2,9;222:2, 3 happen (1) 105:18 happened (3) 137:2;138:4;241:6 happening (1) 194:3 happens (6) 51:13;103:10,16; 206:1,1;230:15 happiest (1) 33:16 hard (4) 100:18;166:22; 208:18;229:15 harmonize (1) 81:13 hash (1) 162:18 hate (1) 152:5 head (5) 30:11;49:18,22; 215:18;229:16 headache (10) 96:13;99:16;100:7,10; 161:9,10,20;234:13,14;	
G				
game (1) 238:19 gastroenterologists (1) 212:13 gatekeeping (5) 13:11,12;14:15; 147:17;188:16 gathering (1) 103:22 gave (5) 87:10;116:15;119:20; 120:16;125:14 gazillion (1) 87:1 general (16)				

235:15 headaches (4) 161:11,11,16,19 health (7) 35:21,21;36:1;57:9, 18;71:21;158:15 healthcare (2) 39:11,15 healthy (1) 28:14 heard (12) 75:9;76:8;88:14; 92:15;127:21;128:4; 142:22;166:1;189:8; 190:3;191:4;222:4 hearing (4) 139:4;154:8;184:21; 235:7 heck (2) 33:11;138:15 Hello (2) 43:3;209:1 help (20) 29:8,18;30:7;31:20; 42:15;76:1,10;79:17; 84:19;88:18;90:18; 138:19;142:19;145:16; 150:5;199:7;215:11,11; 242:17;244:1 helped (4) 31:16;72:7;216:8,9 helpful (11) 3:5;72:11;73:19; 90:22;94:8;183:22; 190:6;199:3;226:14; 237:13;242:8 helping (2) 21:21;244:5 helps (1) 202:2 Henry (5) 44:1;91:21;111:15; 216:4;233:7 herding (2) 65:14;141:12 Here's (1) 42:18 HERTZ (17) 137:20;148:1;168:4; 169:16;193:6;197:15; 206:8;217:14;219:18; 221:4;223:1;229:10; 230:13;231:8;233:15; 234:10;235:5 heterogeneous (1) 228:19 Hi (1) 43:4 hierarchical (2) 188:16;217:6 hierarchically (1) 148:10 high (7)	14:5;39:10;60:1;71:9; 112:15;113:9;135:8 high-end (1) 112:15 higher (4) 35:18;46:12;105:3; 232:11 highlight (1) 155:19 highlighted (1) 135:6 highly (3) 47:21;65:10;208:15 hinterland (1) 159:6 hip (1) 96:12 histolyticum (1) 135:21 history (4) 23:9;28:6;92:1;109:14 hit (6) 14:3;15:4,12;183:10; 203:7;237:5 hits (1) 15:11 Holm (1) 15:9 home (2) 80:14;177:1 homogenous (2) 4:7;229:8 honest (1) 74:18 honored (1) 50:21 hope (6) 47:1;55:4;142:9; 170:18;186:20;217:20 hopefully (7) 19:1;22:6;23:10;73:8; 181:2;183:20;207:11 hoping (4) 142:12;144:11;151:3; 153:20 hormonal (6) 101:4,13,19,19;200:3; 206:10 hormone (1) 101:5 Hormones (4) 8:14;200:4,13,14 hour (1) 52:1 hours (13) 66:5,15;67:1,7,8,13, 15;70:18;71:3,4,5;87:8; 125:21 HRT (1) 102:21 huge (6) 27:17;85:16;88:8; 93:1;196:20;198:5	hundreds (1) 87:20 Hunner's (10) 90:7,7;110:1,10,12,18, 21;111:3,19;112:1 hurt (3) 40:6;96:15;100:10 hurts (1) 100:7 hydroxyzine (1) 232:15 hypersensitivity (4) 31:21;39:21;40:11; 213:8 hypertension (1) 168:11 hypertensive (1) 168:13 hypothesize (1) 34:17 I Ian (3) 223:20;226:14,15 IASP (1) 101:15 IBS (47) 6:17,21;7:2;9:16,17; 11:3;18:5;25:3;29:14, 20;30:17;51:3,6;57:5; 58:16;59:22;60:4,11,19; 65:11;69:7;71:1,12; 75:22;76:15;88:17; 101:6;102:7,8;115:6; 116:9;129:12;134:2,10; 140:8;144:17,22; 148:18;150:3,10,16; 155:7;163:4;188:18; 191:8,11;192:18 IBS-C (5) 57:13;61:4,21;115:20; 140:8 IBS-D (5) 57:13;59:14;61:4,19; 115:21 IBS-M (5) 57:14;59:14;61:3,20, 21 IC (29) 9:13;20:10;21:3,13; 23:15,19;24:6;31:12; 34:2;48:17;49:1,14; 50:9;79:19;91:22;95:1; 99:10;102:17;132:22; 133:6;137:13;150:16; 163:3;191:18;194:8; 215:21;216:11;232:14; 233:9 ICDB (1) 95:2 idea (21) 4:7,9;14;15:2;24:3;	28:4;48:12;49:14;74:8; 79:6;84:12;160:3;163:5; 165:20;167:18;178:3, 13;179:4;191:16; 194:13;229:6;238:9 ideal (2) 180:3;201:8 ideally (1) 201:21 ideas (7) 74:1;80:8;141:10; 165:8;167:22;207:7; 226:1 identical (1) 70:22 identifiable (1) 154:3 identified (9) 8:19;9:3,19;13:6,7; 14:4;60:11;110:20; 228:16 identify (23) 5:19;8:3,21;13:2;23:9; 38:4,12;42:13;49:7; 58:15;77:13;91:18; 92:13;94:13;95:9,10; 110:17;111:1,2,8,10; 112:7;207:16 identifying (4) 13:3;14:7;78:20; 148:10 ie (1) 103:22 IFFGD (1) 72:9 ignore (4) 31:18;103:18;220:8, 13 ignored (2) 152:3;162:14 II (20) 24:18;25:22;26:21; 29:17;30:5;38:8,18; 41:6;44:8;45:21;46:11; 47:2,12,15;49:8;77:17; 105:1;110:7;111:1,17 illusory (1) 94:4 imagine (9) 51:14;65:20;66:19; 69:10,14;124:22;167:1; 169:13;205:21 imaging (3) 7:13;8:2;40:18 immediacy (1) 87:7 IMMPACT (3) 50:22;175:10;226:17 IMMPACT-XX (1) 1:4 impact (5) 94:5;123:13;125:9; 149:20;150:2	implemented (1) 161:3 implementing (2) 52:3,15 implicated (1) 161:18 implications (2) 93:1;193:7 implicit (1) 223:15 imply (1) 163:16 important (44) 23:16;29:10,11;35:17; 36:3,4,19;45:18;59:9; 60:10,19;62:7;64:3; 65:10;68:15;77:15; 82:20;84:17;90:9;92:6; 94:14;107:10;110:22; 111:7;126:12;129:8; 135:7;145:18;146:9,17, 19;147:15;148:3; 152:17;184:20;187:1; 190:8,12,15;192:3; 221:6;225:10;227:20; 234:12 importantly (4) 26:2;27:22;42:4;74:9 impossible (2) 135:8;154:10 impractical (1) 106:19 improve (11) 16:10,13;18:6;35:7; 43:9;59:2;70:3;81:10; 131:10;233:10;234:1 improved (15) 11:5;17:13,13,14,16; 39:4;59:10;130:6,7,9,10; 131:4;195:20,21;196:5 improvement (20) 9:5;11:8,13,15;16:17, 19;34:17,19,22;40:17; 99:17;115:4;130:3; 140:16,19,21;179:19; 196:7,8;231:6 improver (3) 129:22;130:5;204:21 improves (2) 147:8;233:10 improving (2) 33:21;231:18 inappropriate (2) 20:19;148:20 include (14) 4:3;5:16;7:6;11:6; 94:7;178:13;182:11; 184:17;191:19;211:11; 217:19;223:3;228:6; 241:14 included (16) 5:1,12;6:4;7:3;10:9; 11:7;12:4;35:17;36:22;
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60:9;61:3;65:8;67:6; 142:16;178:14;218:5 includes (1) 54:4 including (8) 23:7;27:5;30:6;39:16; 101:17;199:22;214:3,12 inclusion (9) 4:12;5:8;6:14,16,19; 7:10;23:14;170:15; 202:7 inclusive (1) 146:21 incomplete (1) 61:14 incontinence (1) 133:12 incorporate (8) 12:19;15:22;16:3; 44:15;181:16;187:2; 218:22;235:21 incorporated (1) 39:1 incorporates (2) 12:8;205:6 incorporating (2) 38:18;243:8 increase (1) 69:20 increased (1) 41:3 increases (1) 91:5 increasing (1) 200:2 increasingly (1) 29:12 incredibly (1) 196:14 Indeed (3) 56:4;62:15;83:4 independent (1) 52:11 index (1) 34:3 indicate (1) 68:17 indication (3) 6:5;59:4;241:13 indications (2) 197:18;241:6 indicative (1) 207:18 indicators (1) 115:15 individual (7) 17:11;54:11;70:10; 76:22;77:11;207:20; 229:1 individuals (7) 37:14;58:14;59:6,7; 68:10;82:18;138:13 industry (4)	6:13;53:4;55:5;57:7 inevitable (1) 122:4 infection (1) 8:4 infectious (1) 117:11 inflating (1) 12:19 influence (2) 88:9;168:18 influences (1) 200:7 info (2) 241:14,15 inform (6) 3:19;23:11;76:1;84:1; 129:14;146:19 Informatics (1) 73:4 information (13) 62:12,15;75:20;93:21; 99:19;117:22;118:7; 139:6;148:14;167:13, 13;242:6;243:2 informative (2) 93:15;208:15 infrastructure (2) 239:12,19 initial (3) 23:22;78:9;80:22 initially (1) 67:7 INITIATIVE (2) 1:3;52:16 input (5) 18:12;54:5;61:8; 209:10;226:11 inquiry (1) 239:11 insert (1) 177:1 inserting (1) 183:15 insertion (1) 175:19 insight (1) 22:17 instability (1) 94:19 instance (10) 21:10;30:12;39:11; 50:8;65:2;191:18; 205:12;207:13;208:18; 209:12 instead (10) 10:18;41:19;106:9; 119:18;162:22;163:1; 203:22;212:11,15;217:5 Institute (4) 50:17;52:8;224:14; 234:6 instrument (11)	29:19;51:15;54:20; 57:20;62:8;63:15;65:8; 122:18;138:6,8;139:21 instruments (11) 52:2;53:18,21;56:17; 61:19;65:20;70:6; 122:19;135:12;138:3; 139:14 insufficient (1) 197:10 insulting (1) 74:22 insurmountable (2) 123:16;124:10 Integrated (1) 118:15 intensity (20) 9:5,19,21;10:4;12:12; 58:7;83:21,21;84:5,5; 144:8,10;170:4,5,6,12; 171:6;183:22;185:14; 186:14 intent (1) 55:11 intentionally (3) 25:6;135:2;237:6 interacting (1) 58:12 interaction (2) 115:16;200:13 interactions (1) 74:9 intercourse (14) 164:11;165:4,13,15, 16;166:22;177:13; 180:3;181:9,10;182:13, 14;185:4;234:22 interdisciplinary (1) 75:1 interest (4) 27:21;71:1;115:15; 212:3 interested (6) 25:10;77:7;86:14; 156:12;178:1;209:21 interesting (16) 7:1;12:5;37:17;40:14; 41:1;50:2;104:3;107:21; 129:18;131:8;160:2,18; 200:17;219:11;237:21; 240:2 interestingly (3) 6:7;10:4;163:7 interests (1) 16:4 interfere (1) 58:22 interfering (1) 175:9 intermediate (3) 44:3,5;206:3 internal (2) 38:2;139:3	internet (3) 27:14;118:4;175:2 interplay (1) 198:8 interpret (1) 229:13 interpretation (2) 17:19;55:20 interpreted (1) 67:11 interpreting (1) 68:7 interstitial (4) 6:2;7:14;90:12;101:6 intervention (2) 115:6;116:8 interventions (1) 50:12 interviews (13) 51:9;58:14;61:7;63:2; 64:1,2,8;66:2;67:14; 72:2,3,3;97:5 into (43) 10:14,18;12:18;14:10; 29:16,17;30:13;32:20; 33:13;34:20;48:19;49:3; 51:22;56:4;59:3;61:11; 76:6;80:22;86:6;87:15; 93:16;96:14;105:13; 108:1,2;110:14;120:19, 20;127:18;137:12; 138:10;139:17;171:3; 205:18;208:20;219:9; 221:10;222:20;237:7; 238:11,17;239:15; 241:14 intro (1) 210:21 introduce (3) 72:21;177:11;225:13 introduced (1) 138:10 introduction (1) 163:8 Inventory (1) 112:19 investigated (1) 6:8 investigator (3) 22:12;111:22;185:21 invitation (1) 50:21 invited (1) 211:18 inviting (1) 50:20 involved (12) 4:20;18:22;19:17; 44:10;83:10;86:1; 115:12;135:20;136:4,8; 138:21;172:2 involvement (1) 204:5	iPhone (1) 117:19 IPIP (1) 25:14 Ironwood (2) 57:8;71:18 Irritable (5) 1:9;6:1;56:1;57:19; 63:4 irritation (1) 65:5 issue (37) 17:21;67:16;69:1,9; 70:1;79:12;82:10;84:13; 86:14;92:9,12,20,20; 94:3;107:7;122:6; 124:12,19,20;137:7; 150:15;171:4,15;172:8; 179:1,9;183:9;201:8; 202:15;205:16;211:4; 215:2;216:20;218:15; 220:5;223:7;241:4 issues (15) 47:6;78:11;83:12; 84:3;93:9;122:1;124:11; 146:10;152:12;182:19; 188:4;198:11;201:10; 208:20;226:16 itching (1) 137:3 item (11) 62:13,17;64:5,9; 65:18;66:4;70:2,16,17; 122:12;185:10 items (11) 61:19;62:11,12,19,21, 22;65:19,22;67:6;68:14; 70:9 iterations (1) 80:10 iterative (1) 136:2 IV (1) 191:9
J				
				Jack (1) 50:8 Jacobs (1) 140:1 Jamie (1) 32:2 Jen (5) 80:19;86:10;89:9; 97:2;165:21 Jennifer (2) 3:7,10 Jensen (1) 85:10 job (2) 4:14;81:8 John (17)

32:16;44:9;46:8;73:6; 74:19;75:16;77:1;86:20; 87:13;88:10;96:5;97:15, 16;103:2;109:9;125:5, 11 John's (1) 128:6 Johnson (1) 4:14 joining (1) 74:18 joint (1) 200:1 Journal (1) 159:2 journey (1) 51:1 JRA (1) 194:15 Juge (11) 112:13,13;117:15; 121:4;124:4;125:16; 202:21;205:4,7,11; 240:21 July (1) 1:12 justified (1) 169:17	149:3;156:12,18;161:9; 166:21;178:16;213:7; 219:6;235:11,16; 239:17;240:15 kinds (7) 25:13;74:4;134:7,11; 143:7;178:2;197:16 knee (4) 96:12;99:16;100:6,9 knees (1) 20:15 knock (1) 108:12 knowing (3) 120:10,12;205:17 knowledge (1) 90:6 knows (1) 85:19 Kovacs (5) 55:7;56:20;140:1,2,2 Kybella (1) 140:11	108:20 last (37) 37:1,19;47:22;66:5, 14;67:1,7,10;89:17; 92:16;101:11,11;114:4; 118:19;120:13,13; 125:21;127:19;144:2; 158:9;182:14;186:13; 193:21,22;197:19; 199:17;200:21;201:1,1, 18,19;207:2;210:11; 215:2;222:4;225:22; 237:17 late (2) 53:1;175:13 later (6) 14:17;33:17;50:1; 59:17;94:17;223:13 Laughter (14) 19:15;89:18;102:19; 103:1;104:10;114:18; 121:3;125:15;166:19; 169:15,20;195:10; 223:19;244:7 launch (1) 104:20 Laura (1) 188:17 Laurie's (1) 171:13 laxatives (1) 150:4 lead (6) 22:7;80:19;86:7; 112:22;119:8,9 leading (3) 75:11;111:15;126:8 leads (2) 32:13;216:15 learn (5) 38:11;121:13;134:6; 161:4;226:17 learned (5) 19:20;37:8;51:2; 73:17;232:17 learning (1) 73:18 least (30) 5:15;26:3;36:19; 37:11;40:20;44:17; 49:20;50:3;59:6;75:10; 76:16;81:8;84:13;85:11; 88:14;95:1;98:20;99:10; 101:2,18;111:2,9;135:9; 150:9;193:2;195:14; 201:19;210:1;229:3,5 leave (6) 104:7;116:19;137:1; 160:22;237:11;241:3 leaving (1) 214:17 led (3) 32:3,16;38:8	Lee (7) 67:20,22;86:16;88:12; 144:12;188:7,17 Lee's (1) 215:4 left (2) 163:15;188:3 leiomyomas (1) 158:21 LEMBO (5) 114:19;134:12,17; 191:3;216:19 LEMBOW (1) 150:3 length (2) 37:9;201:19 LeResche (1) 199:20 lesion (7) 110:1,13,18,21;111:3, 19;112:1 lesions (1) 111:19 less (17) 9:18;15:9;16:16,19; 24:14;35:19,19;41:20; 52:1;87:10;128:8;151:5; 179:5,5,6;184:16;228:14 lessons (3) 19:19;51:2;73:17 letting (1) 119:6 level (21) 13:18;40:13;60:1; 71:9;88:18;93:2;96:1; 97:17;98:19;130:10,20; 131:19;195:21;196:4,5; 220:17;222:6;225:9; 228:7;232:1,3 levels (4) 105:3;223:2;227:2,3 leverage (1) 56:13 lidocaine (1) 171:21 life (7) 10:11;30:21;31:15,22; 58:22;194:16;239:5 lifetime (1) 48:1 light (2) 117:3;136:16 lights (2) 100:18;116:22 likelihood (1) 40:16 likely (5) 107:8;127:16;175:17; 224:3;234:18 limit (2) 102:17;169:16 limitations (4) 18:11;71:8;123:18;	172:17 Linda (1) 199:20 Line (1) 236:10 lines (1) 24:3 link (1) 175:3 list (8) 25:11;53:12;59:7; 119:13;158:16;162:12; 184:15;212:11 listed (2) 5:11;22:10 listen (1) 79:14 listening (2) 142:21;244:6 literate (1) 121:8 literature (15) 28:21;58:12;59:20; 61:8;82:12,16;83:1,4,20; 84:9;85:15;86:8;109:10; 178:18;200:2 little (41) 6:13;10:15;15:8; 20:14;21:15,18;26:4; 40:2;41:20;42:14;45:3; 46:10;49:22;50:1;59:17; 74:13;76:9;79:15;84:11; 87:15;91:2;98:17; 120:14;127:18;134:19; 139:1;143:1;145:6; 150:22;161:22;177:21; 184:19;192:5,9,17; 205:16;213:3;216:20; 222:22;224:9;239:22 lives (2) 59:9;243:10 living (1) 178:4 localization (1) 39:19 location (1) 99:12 log (1) 77:20 logic (2) 186:7,7 logistic (1) 106:19 long (21) 15:11;72:15;81:19; 82:13;86:2;103:21; 110:8;116:9,11,11; 124:6;126:13,17; 127:15;128:7;134:1; 136:10;166:17;201:16; 209:8;214:1 longer (14) 24:13,21;85:11,21;
K	L			
Kaptchuk (1) 107:2 Kate (1) 100:21 Katy (3) 153:4;157:6;182:16 Katy's (1) 158:16 KATZ (9) 43:3,5,12,21;45:8; 165:21;167:11;212:16; 213:3 keep (13) 74:18;82:5;95:5,13; 96:7;110:2;114:11; 190:12,15;199:16; 208:19;209:1;211:12 keeping (6) 21:17;94:18;201:11; 209:8;212:3;241:2 Kevin (1) 136:12 key (4) 78:5,19;199:12;206:4 kidney (1) 8:1 kill (1) 219:19 kind (24) 7:12,13;27:20;35:5,7; 109:12;111:20;112:3; 119:4;138:13;145:3,14;	lab (1) 8:3 label (5) 146:20;147:20; 241:14,15;242:6 labeling (3) 54:2;146:7;148:4 lady (1) 178:4 Lai (9) 7:15;91:21,21;111:17; 137:12;216:10;233:7,7, 19 land (1) 67:5 landed (1) 68:1 Landis (26) 22:22;44:1;73:2;77:3; 84:21;85:17;89:21;91:2; 95:18;97:4,15;104:9,12; 128:12;129:18;131:8; 195:16,17;204:15,18,20; 205:10,20;232:5,7; 233:17 landmark (6) 144:1;192:12,21; 193:3,8,14 laparoscopies (1) 159:18 laparoscopy (2) 154:5,12 large (3) 68:16;165:1;191:13 largely (1) 152:3 larger (1)	lab (1) 8:3 Laura (1) 188:17 Laurie's (1) 171:13 laxatives (1) 150:4 lead (6) 22:7;80:19;86:7; 112:22;119:8,9 leading (3) 75:11;111:15;126:8 leads (2) 32:13;216:15 learn (5) 38:11;121:13;134:6; 161:4;226:17 learned (5) 19:20;37:8;51:2; 73:17;232:17 learning (1) 73:18 least (30) 5:15;26:3;36:19; 37:11;40:20;44:17; 49:20;50:3;59:6;75:10; 76:16;81:8;84:13;85:11; 88:14;95:1;98:20;99:10; 101:2,18;111:2,9;135:9; 150:9;193:2;195:14; 201:19;210:1;229:3,5 leave (6) 104:7;116:19;137:1; 160:22;237:11;241:3 leaving (1) 214:17 led (3) 32:3,16;38:8	Lee (7) 67:20,22;86:16;88:12; 144:12;188:7,17 Lee's (1) 215:4 left (2) 163:15;188:3 leiomyomas (1) 158:21 LEMBO (5) 114:19;134:12,17; 191:3;216:19 LEMBOW (1) 150:3 length (2) 37:9;201:19 LeResche (1) 199:20 lesion (7) 110:1,13,18,21;111:3, 19;112:1 lesions (1) 111:19 less (17) 9:18;15:9;16:16,19; 24:14;35:19,19;41:20; 52:1;87:10;128:8;151:5; 179:5,5,6;184:16;228:14 lessons (3) 19:19;51:2;73:17 letting (1) 119:6 level (21) 13:18;40:13;60:1; 71:9;88:18;93:2;96:1; 97:17;98:19;130:10,20; 131:19;195:21;196:4,5; 220:17;222:6;225:9; 228:7;232:1,3 levels (4) 105:3;223:2;227:2,3 leverage (1) 56:13 lidocaine (1) 171:21 life (7) 10:11;30:21;31:15,22; 58:22;194:16;239:5 lifetime (1) 48:1 light (2) 117:3;136:16 lights (2) 100:18;116:22 likelihood (1) 40:16 likely (5) 107:8;127:16;175:17; 224:3;234:18 limit (2) 102:17;169:16 limitations (4) 18:11;71:8;123:18;	

<p>97:10;99:4;107:19; 110:6,6;158:17,17,17; 164:12;172:15 longer-term (1) 209:11 longitudinal (8) 33:6;35:10;40:15; 41:20;45:19;90:13; 104:20;134:3 longitudinally (1) 32:7 longstanding (1) 168:11 long-term (3) 95:2;206:15;208:12 look (56) 10:16;16:5;24:20; 28:19;30:1,6,13;32:8,18, 20;33:4,8;34:11;38:9; 39:7,8,15;43:18;44:19; 47:2,3,19;48:14,21;49:9, 11;52:3;71:10;75:13; 78:8;80:5;81:5,15; 88:20;95:10;110:17; 130:6;132:3,7,11;134:8; 141:11;163:15;180:9, 10;186:9;194:3;195:11; 214:8;222:20;230:4; 235:14,15,20;236:15,16 looked (25) 6:11;29:1;32:3,7;33:6, 13;38:15;39:6;86:1,2; 87:2,4,6;99:15,16;100:3; 114:6;115:1;179:2,7,8; 182:18;204:16,17,19 looking (35) 3:14;29:16;30:13; 33:12;39:11;44:9,14; 73:15;78:18;97:18; 100:13;101:18;108:22; 119:12;128:8;131:22; 134:4;140:14;151:14; 155:9;156:14;157:2; 173:12;176:4,9;184:12; 190:6,7;203:3,9;205:14; 220:16;224:7;236:14; 241:15 looks (5) 86:18,19;172:19; 186:14;205:14 loose (1) 59:13 loperamide (1) 150:6 lose (5) 105:11,17,22;209:17, 17 losing (1) 84:11 lot (59) 4:19;6:4;8:5;9:13; 10:17;19:10;25:16; 27:17;32:11;33:11;</p>	<p>35:14;54:11;76:4;89:7; 90:16;99:2;109:5;113:7; 114:20;115:6;117:13; 120:14,19;121:17; 123:3;124:11;127:3; 128:4;133:21,22;136:11, 21;151:21;156:15; 161:4,14;166:18; 176:11;179:19;184:18; 187:7;189:6;190:3; 194:6,19;199:8;203:15; 206:21;208:20;212:20; 214:13;216:21;219:8; 226:6,16;233:11; 237:22;238:16;239:18 lots (7) 102:8;123:15;134:14; 150:4;156:4,6;199:21 lousy (1) 127:2 love (4) 56:13;103:22;150:11; 242:9 low (13) 39:10;83:17;105:5; 112:14;113:4;133:18; 200:10;206:17;219:5; 222:6;223:2;228:6; 232:1 lower (9) 4:5;17:22;44:12; 108:2;116:16;154:16; 196:1;220:17;225:9 lubrication (3) 177:16;181:19;182:21 Lunch (3) 141:13,15;241:1 Lyrica (1) 150:9</p>	<p>85:15;88:19;137:15; 164:14;186:8;209:14 making (7) 73:10;83:2;127:8; 164:20;193:3;215:5; 217:5 male (4) 31:1;85:5;159:5; 175:11 man (2) 20:14;36:12 managed (1) 242:10 Management (1) 118:15 manifestation (1) 111:20 manifestations (2) 230:21;235:7 manual (1) 3:21 manufacturers (1) 242:5 manuscript (13) 4:21;80:3,19;81:7; 141:10;152:16;155:20; 188:13;189:2;215:13; 217:12;226:9,14 many (27) 4:5;9:10;21:15;38:14, 14;43:13,13;44:7;72:8; 73:13;84:10;88:3;92:22; 122:9;123:21;149:21, 21;156:19;163:11; 164:11;166:11;196:22; 199:17;200:19;213:9; 216:1;238:17 map (12) 23:5;25:19;35:20; 43:8;44:18;45:5;47:20; 48:5;49:8;77:22;78:14; 91:7 MAPP (57) 19:10,19;20:3,5,8; 21:20,22;24:18;25:21, 22;26:20,21;27:1,28:19; 29:17;30:5;33:5;38:8, 13,18;41:6,21;44:8;45:1, 21;46:10,11;47:2,12,15, 16;49:8,10;50:5;76:3; 77:17;91:22;93:19;97:4; 103:6,11;104:12;105:1; 107:16;110:3,7,11,16; 111:1,17;128:13;134:6; 136:9,13;190:14;238:2,5 maps (2) 29:12;47:9 March (1) 57:6 Mark (1) 85:10 matter (10) 24:17;36:13,17;68:17;</p>	<p>79:9,14;83:3;126:16; 157:1;197:16 matters (1) 46:1 maximum (2) 79:7,9 may (52) 18:3;38:10;42:13,15; 45:3,21;48:22;62:13,14; 76:8;81:20;82:3;84:12; 92:18;93:9;95:12;96:20; 98:7;102:6;108:3; 111:14;115:5,12,16; 122:14;123:10,12,13; 124:7;128:7;130:15,18; 134:7;146:16,17;160:12, 13;163:16;171:10; 173:21;175:21;206:10; 207:13,19;210:15,16; 219:7;222:21;224:7; 228:7;236:14,18 maybe (75) 23:17;30:7,10;38:7; 41:10;45:6,13;75:11; 79:15,19;80:10;83:6; 85:11;93:8,8;98:17; 102:13;107:22;116:12; 137:14;145:6;151:6; 153:6;154:13;155:5,6; 157:15;159:11;161:21; 162:10,12;164:6;165:11, 13,14,19;167:12,12,13; 174:1,11;181:2,12; 184:18;186:16;187:21; 192:5;193:3,22;194:7; 204:17;208:1;210:7,18; 214:6;217:1,3,11; 220:12,12;221:22; 224:1;228:13;229:5; 232:5;235:14,17,21; 236:19,21,22;237:13; 239:16;240:5;243:8 Mayer (1) 22:14 McGill (1) 184:1 meals (1) 74:10 mean (21) 9:3;16:6;18:1;28:21; 31:12,13;38:17;104:5, 15;106:17;107:7,9; 133:9;149:6;156:16; 158:13;176:19;184:6; 201:2;221:15;224:22 meaning (1) 153:8 meaningful (16) 110:5;112:3;128:16, 17,18;129:3,5;130:3,20; 131:19;132:18,19; 133:19;140:19;143:18; 149:7</p>	<p>means (10) 35:7;45:13,16;82:5; 147:19;154:4;168:7; 190:8;222:6;224:20 meant (1) 8:12 measure (52) 7:8;8:21;9:1,10,13,18; 10:5;11:14;18:15,16; 30:9;34:18,22;40:11,14; 47:10;51:3,5;54:18; 65:12,16;77:10;93:2,7; 96:11,15,15,21,22; 97:21;104:1;135:12; 152:20;168:13;171:7; 172:11;177:12;178:15; 183:16;185:3;187:13; 188:12;201:3,5,6,17; 206:15;209:7;217:9; 220:17;225:10,17 measured (3) 169:7;199:16;210:10 MEASUREMENT (9) 1:3;60:16;62:5;89:5; 122:22;149:13;199:15; 206:5;232:3 measurements (1) 199:12 measures (64) 3:19;4:13;8:17,20; 9:20;10:4,8,10,14;11:19; 12:10;13:13;14:6,15,20; 27:17;30:5;35:22;47:12; 51:6,9;53:11;54:6,8,12, 17;55:3;56:12,13;57:2,4, 13,21;61:10;63:1,2; 65:20;75:22;76:4,5,20; 77:14;78:4;92:13;94:6; 96:18;123:1;137:1,9,21; 173:11;176:14;181:15, 19,22;206:3;212:18; 213:12,15,21;237:18,22; 238:3;243:5 measuring (9) 48:4;101:1;144:7; 168:14;170:12;220:21; 222:9;231:15;237:7 mechanism (6) 6:9;145:15;156:13; 157:1;224:3;228:9 mechanism-based (1) 214:10 mechanisms (3) 102:9;215:7;233:22 Medical (4) 19:6;52:19;55:2;238:5 medication (8) 16:2,5,7,12,14,18,20; 59:2 medications (1) 161:16 medium (1) 39:10</p>
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<p>meds (1) 113:18</p> <p>meet (5) 105:13;109:20; 135:15,17;203:11</p> <p>meeting (21) 19:9;60:3;75:21; 80:21;92:21;94:11; 104:7;109:16,20; 142:13;143:10;151:5; 162:18;214:17;223:14; 236:6;237:10;240:16, 17;243:20;244:10</p> <p>meetings (3) 138:22;175:10;226:18</p> <p>member (1) 23:3</p> <p>members (5) 53:6,12;56:5;71:16; 72:21</p> <p>membership (2) 53:5;56:3</p> <p>memory (2) 85:21;171:19</p> <p>men (11) 21:11,16;31:5,7,10,12; 32:6,19;37:6,10;159:9</p> <p>menses (1) 197:4</p> <p>menstrual (4) 196:22;199:1;210:9, 12</p> <p>menstrually (1) 197:12</p> <p>mental (2) 35:21;36:1</p> <p>mention (7) 14:18;54:14;67:6; 151:17;222:13;238:2; 243:4</p> <p>mentioned (21) 4:8;15:1;27:5;31:10; 36:18;38:14;41:6,22; 44:9;55:7;56:20;63:8; 71:19;101:1;137:7; 144:4;174:7,9;186:21; 188:6;240:13</p> <p>mentioning (1) 243:11</p> <p>merit (1) 109:17</p> <p>met (2) 58:4;203:12</p> <p>method (12) 17:2,8;76:2;127:16; 164:10;165:6;198:2; 199:6;205:1,14;214:19; 237:3</p> <p>methodology (1) 4:10</p> <p>METHODS (18) 1:3;4:16;12:16;13:10; 14:10,19;15:15;38:6;</p>	<p>41:2;67:18;143:16; 146:12;151:2;153:3; 161:7;188:14;207:1; 236:15</p> <p>Michel (3) 108:5;109:2;117:6</p> <p>Michigan (1) 19:6</p> <p>microphones (1) 100:19</p> <p>middle (3) 131:9;203:10;208:14</p> <p>might (78) 16:5,6,9,22;17:12; 18:9;30:11,18;33:4; 66:9;88:16,18;92:3; 93:14;94:7;100:10,14; 102:10,10;105:17; 107:3;110:7;116:13; 122:10;126:3,10; 128:19;143:5;144:17, 22;146:3;148:2,20,21, 22;149:9,9,10;151:12; 155:18;156:5,6;162:6, 11,17;173:1;176:13; 177:8;187:10,11; 188:11;189:14;197:9; 201:13;202:14;203:20; 204:16;205:13,16; 210:14;211:4;213:14, 21;214:8,11,17;215:9, 15,19;221:3,18;222:13; 226:12;235:8;238:18; 239:7,22;240:3</p> <p>migraine (8) 25:7;31:3;161:11; 230:2,8,10;234:8;236:9</p> <p>migraines (1) 236:8</p> <p>migraine-type (1) 161:11</p> <p>migrate (2) 90:2,7</p> <p>migrating (2) 90:5;122:17</p> <p>migration (1) 90:9</p> <p>Mike (4) 23:3;133:4;194:12; 199:2</p> <p>mild (2) 88:1;231:15</p> <p>million (2) 54:20,20</p> <p>mimics (1) 153:1</p> <p>mind (9) 21:18;92:7;95:6,13; 110:2;119:7,12;190:15; 226:19</p> <p>mindwashing (1) 126:7</p> <p>Mine (1)</p>	<p>86:11</p> <p>minimal (3) 25:20;45:6;232:3</p> <p>minimize (2) 180:22;238:13</p> <p>minimum (12) 6:19;7:3,8;97:13; 144:8,9;170:21;171:2; 197:11;210:9;216:18; 222:19</p> <p>minute (4) 8:7;29:15;162:14; 191:14</p> <p>minutes (3) 37:9;80:20;133:11</p> <p>miscellaneous (1) 12:7</p> <p>misleading (1) 127:12</p> <p>miss (1) 207:6</p> <p>missed (2) 29:3;80:6</p> <p>missing (4) 77:12;176:6;197:5; 209:9</p> <p>mission (1) 53:13</p> <p>misspoke (1) 84:8</p> <p>mixed (1) 133:1</p> <p>mobile (1) 38:9</p> <p>mode (1) 63:5</p> <p>model (2) 12:8;29:21</p> <p>moderate (2) 88:1;98:20</p> <p>modes (1) 125:22</p> <p>modified (1) 215:14</p> <p>modify (1) 56:14</p> <p>modulation (1) 149:19</p> <p>module (1) 29:19</p> <p>moment (1) 201:22</p> <p>momentary (1) 86:7</p> <p>monitor (1) 204:7</p> <p>month (30) 35:12;85:19,21;87:4; 101:6,9;106:13;114:6,7; 132:15;156:6;176:8; 182:14;183:7;186:11; 200:22;201:1,5,9,11; 203:7,7,8;204:5,6,6,8,</p>	<p>13;209:19;210:17</p> <p>monthly (3) 42:6,11;113:21</p> <p>months (19) 27:10,10;28:2;34:8; 35:6;40:20;82:3;86:4; 113:20;130:21;200:22; 202:19;203:5;204:3; 205:22,22;208:18; 209:13,14</p> <p>month's (1) 206:10</p> <p>mood (1) 125:1</p> <p>more (123) 17:6,22;18:3,10; 21:12;22:2,2,7,16,17; 26:1,4,22;28:17;29:3,16; 30:3,13,14,20;31:11,22; 33:13;34:13;35:3;36:7; 7:37:10,13,14,15;38:9, 10;41:7;44:4,21;46:14; 47:5;48:6;50:2;58:7; 59:17;60:10;65:9;69:6, 14;73:11,17;74:9;76:21; 77:9,12;79:15;80:8; 81:16,17;82:22;84:17; 87:7,11;88:17,22;95:19; 99:18;100:10;105:15; 107:10,14;108:21; 110:14,22;117:4,15; 122:15;123:6;125:16; 126:11;127:5;135:5; 145:6;146:21;149:20; 153:20;161:2,6,6,12,18; 164:4,6;175:8;177:18; 179:5,17,21;180:2,16; 183:5;188:2,3;194:19; 197:11;205:5,16; 206:18;210:16;213:3,6, 10,14;214:6;224:10; 227:19;228:4,7,18; 229:7;231:4;232:13; 238:10;240:20,21;243:5</p> <p>morning (11) 3:3,7,11,13;50:19; 73:15;75:19;77:5,17; 195:19;201:10</p> <p>most (59) 6:3,18,20;7:20;8:2; 9:9,21;25:11;33:11; 35:17;52:13;56:17; 58:20;59:8;60:9,12,20; 61:19;64:2;67:12,12; 68:6,8,19;79:7;82:16; 88:19;107:16;111:21; 112:1;147:15;153:13; 160:14;164:19;166:3; 174:18;181:20;184:19; 197:18;200:8;206:19; 213:9;227:20;228:16, 21;229:8,18,20;230:4, 231:7,10,12,19;234:14,</p>	<p>19;235:3;236:20;237:1, 3</p> <p>mostly (1) 28:16</p> <p>mouse (1) 123:9</p> <p>move (15) 13:19;35:9;50:12; 74:11;81:7;89:6;117:6; 118:11;120:18;139:20; 161:2;188:3;197:6; 214:9;236:3</p> <p>moved (1) 74:13</p> <p>movement (2) 63:11;219:22</p> <p>movement-related (3) 61:13;63:9,14</p> <p>movements (8) 11:5;20:16;61:15,15, 20;63:20;140:9;149:11</p> <p>moves (2) 49:15,19</p> <p>moving (9) 57:3;70:3;73:10; 74:14;93:10;117:18; 118:14;119:14;223:21</p> <p>much (45) 18:12;21:21;24:17,18, 20;25:12;27:10;31:5,20; 34:12,13;36:17;38:5,19; 40:7;44:21;46:12;47:5; 57:16;62:12;71:20;86:5, 21;88:22;96:15;107:16; 108:2,20;110:22;123:6; 134:4,21;149:20;150:1; 151:5;153:6;160:18; 169:5;177:17;182:20; 183:3;231:4;232:2; 234:2;243:19</p> <p>Multidisciplinary (1) 20:3</p> <p>multi-institutional (1) 26:9</p> <p>multinational (1) 70:12</p> <p>multiple (26) 4:1,8;19:9;20:13,7; 14:9;15:16;47:15;49:1, 8;54:7;62:20;77:8;92:4; 93:11;125:22;130:15; 135:4;145:11;181:22; 208:9,16;224:4;226:19; 227:19;230:16;236:7</p> <p>multiplicity (8) 4:17;12:16,22;13:9; 14:8,11,20;22:4</p> <p>multi-symptom (1) 227:7</p> <p>muscle (1) 25:22</p> <p>muscles (1) 26:2</p>
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<p>myself (3) 19:2;177:12;225:13</p> <hr/> <p style="text-align: center;">N</p> <hr/> <p>Naliboff (1) 47:19</p> <p>name (5) 57:20;112:11;161:19; 190:22;205:3</p> <p>named (1) 63:3</p> <p>names (1) 5:4</p> <p>Nancy (1) 72:9</p> <p>Nat (8) 46:9;165:20;187:19, 20;212:5,15;213:2; 226:6</p> <p>Nat's (1) 166:20</p> <p>natural (5) 23:9;28:6;92:1; 109:14;180:2</p> <p>nausea (2) 230:5;234:16</p> <p>nearby (1) 63:12</p> <p>necessarily (25) 16:6,22;18:1;20:20; 21:7;35:1;40:19;42:3; 92:18;96:21;99:5;107:5, 6;123:5;124:8;140:18, 19;181:3;190:4;217:8; 218:4;222:5;224:6,7; 236:13</p> <p>necessary (2) 56:10;183:12</p> <p>need (44) 18:13;21:20;22:5; 48:15;71:20;74:17; 76:20;82:5;96:7,18; 97:10;98:19;101:12,20; 110:5;122:22;123:15, 17;124:7;130:14; 138:11;139:4;144:8; 146:21;151:18;152:4; 159:3,20;164:4;168:8; 169:11;173:16;197:16; 202:11;216:18;218:6; 219:16;221:20;222:18; 224:14;226:4;233:17, 19;238:19</p> <p>needed (6) 60:14;62:16;63:6; 64:5;124:14;135:17</p> <p>needing (1) 80:1</p> <p>needs (5) 106:2;112:6;167:5; 196:13;239:11</p> <p>negative (3)</p>	<p>33:4;109:11;113:22</p> <p>neglected (1) 157:14</p> <p>neither (1) 131:10</p> <p>NeuPSIG (3) 159:11;160:1,8</p> <p>neural (1) 40:18</p> <p>neuralgia (1) 83:19</p> <p>neuroimage (1) 78:3</p> <p>neuroimaging (8) 26:6,10,18;27:11; 40:21;41:15,21;47:4</p> <p>neurologist (2) 74:20;138:14</p> <p>neuromodulation (1) 234:1</p> <p>neuropathic (2) 160:4,13</p> <p>neuropathy (4) 83:19;96:13;97:6;99:6</p> <p>neutral (1) 52:16</p> <p>new (11) 15:14;54:16;56:10,12; 94:1;98:11;104:16; 138:6,8;193:6;227:5</p> <p>news (2) 139:11,20</p> <p>next (23) 8:2;9:7,21;15:12; 16:12,16;19:4,22;33:15; 42:17;47:12;50:14; 59:13;77:20;78:14; 81:14;82:4;118:22; 125:2;128:9;147:17; 216:16;238:13</p> <p>nice (5) 3:12;23:5;74:16; 180:1;201:9</p> <p>NIDDK (3) 20:9;22:11;23:2</p> <p>NIH (1) 53:7</p> <p>Ninety-five (1) 37:11</p> <p>nipples (1) 20:15</p> <p>Noam (1) 236:5</p> <p>nobody (1) 241:18</p> <p>nocturia (2) 140:5;236:22</p> <p>nocturnal (1) 140:6</p> <p>noise (2) 49:6;207:4</p> <p>nomenclature (1) 36:16</p>	<p>nominate (1) 184:13</p> <p>non- (1) 11:13</p> <p>noncyclic (1) 102:4</p> <p>none (5) 44:5;94:17;95:17; 135:11;166:2</p> <p>non-Hunner's (1) 111:19</p> <p>non-overlapping (2) 231:1,9</p> <p>non-pain (4) 9:12;10:6;11:22; 212:14</p> <p>non-pain-related (1) 212:10</p> <p>non-primary (2) 10:3,5</p> <p>nonprofit (1) 52:12</p> <p>nonspecific (1) 180:22</p> <p>non-urologic (1) 35:19</p> <p>non-urology (1) 22:12</p> <p>non-vulvodynia (1) 212:4</p> <p>noon (1) 141:5</p> <p>noontime (1) 141:2</p> <p>normal (1) 170:2</p> <p>normally (1) 46:21</p> <p>NorthShore (3) 158:15;173:7;237:19</p> <p>Northwestern (1) 32:3</p> <p>Norton (1) 72:9</p> <p>note (3) 15:5;61:2;62:1</p> <p>noted (1) 7:1</p> <p>notes (1) 80:20</p> <p>noticed (3) 21:14;84:22;129:22</p> <p>novel (5) 31:5;137:21;138:4,9; 239:10</p> <p>novo (1) 56:18</p> <p>NRS (10) 66:7,17;69:3,5,8,8; 171:9,17;172:20;186:9</p> <p>NSAIDs (1) 169:6</p> <p>nuance (1)</p>	<p>128:5</p> <p>number (25) 10:7,7;26:16;39:3; 40:16;43:8;72:6;81:6; 99:17;100:13;111:18, 22;113:8;119:19; 121:22;125:8;138:3; 160:10,12;163:14; 164:19;165:15;181:9; 182:4;226:10</p> <p>numbers (10) 9:6;10:16;113:15,21; 114:8;125:6;127:1; 131:3;148:22;149:10</p> <p>numbness (1) 218:16</p> <p>numeric (10) 66:10,12;68:22;69:1, 4,12;105:13;131:20; 132:10;134:22</p> <p>numerical (1) 8:22</p> <p>nurse (1) 112:21</p> <p>nurses (1) 112:21</p>	<p>62:14;63:13;115:8</p> <p>off (9) 30:20,20;116:10; 118:20;141:5,6;158:14; 204:12;209:22</p> <p>offer (1) 211:8</p> <p>offering (1) 112:19</p> <p>official (1) 20:7</p> <p>often (11) 8:10;20:17;36:11; 50:10;61:1;64:21;65:5; 69:6;101:8;198:21; 211:6</p> <p>old (2) 119:2,20</p> <p>older (3) 29:1;123:4,12</p> <p>OMERACT (2) 67:21;117:22</p> <p>once (12) 34:4;41:22;47:2;90:8; 113:12;116:2;139:5,11; 161:2;210:2;213:19; 241:17</p> <p>one (179) 5:10,15;7:1,11,13; 8:19,21;9:11,20;12:14, 18;13:6,14,21;14:3;15:1, 11,12;16:2;17:1;22:10; 24:22;26:11;29:10;31:1; 34:19;35:2,17;36:15; 37:5,12;38:7,15;43:19; 44:3,12,12,16,21,22; 45:1;47:7;49:17;51:13; 52:1;53:1;55:11;56:2; 57:20;58:6,11;59:12; 60:2;64:8;65:15;66:4, 10,17;67:5,19;74:15; 75:17;77:16;78:11,13; 79:14;86:17;87:2,3; 88:11,19;89:3,5;92:2; 98:8,18;99:9;103:4; 107:21;109:17;115:1, 14;117:15;119:15,20; 122:1,10,12;123:4; 125:2;126:10,16; 128:21;129:22;130:10, 11,12,16;131:1,15; 134:5,20;135:22;136:6, 14;147:14,17;149:19; 150:19;153:5;155:9; 156:11;158:16;160:14; 163:6,14;166:9;168:22; 175:8,16;177:22;178:20, 22;179:2;180:9;181:20; 182:18;185:8,11,12,13; 187:14;188:1,22;189:9, 13;191:3,14;192:1,4,13, 16;193:3;195:17; 196:15,18;198:14;</p>
		O		
		<p>OAB (2) 133:7,13</p> <p>OB/GYN (1) 173:15</p> <p>objections (2) 174:19;214:20</p> <p>objective (3) 3:17;73:20,21</p> <p>objects (2) 212:8;214:2</p> <p>observational (2) 103:8;104:17</p> <p>observations (1) 38:15</p> <p>obstacle (1) 106:14</p> <p>obtain (3) 26:5;54:6;57:11</p> <p>obviate (1) 202:11</p> <p>obvious (6) 24:2;76:11;137:19; 160:14;186:3;188:6</p> <p>obviously (14) 16:21;48:14;89:7; 137:4;141:3;143:12; 164:10;165:12;174:16; 178:11;186:19;192:15, 18;193:7</p> <p>occur (2) 76:13;107:17</p> <p>occurred (3) 12:14;63:21;169:22</p> <p>occurs (3)</p>		

<p>199:12;204:1;205:1; 206:6,11;207:1,17; 211:5,6;214:2;223:4; 224:3,18;226:18; 227:20;229:12;234:17, 18;235:3,6,10;236:18, 19,19;237:2,17;238:15, 18;239:10;240:7,20,21</p> <p>one-grade (1) 140:18</p> <p>one-half (1) 78:9</p> <p>one-off (1) 26:11</p> <p>ones (6) 33:15;64:15;119:5; 161:2;184:20;239:6</p> <p>one-week (2) 103:8;106:10</p> <p>one-year (1) 110:3</p> <p>ongoing (4) 51:10;103:14;194:6; 210:4</p> <p>only (63) 6:7;12:14;13:3;29:13; 32:8;41:22;43:11;47:10; 52:4;56:12;59:14;60:1; 61:20;71:3;90:2;95:3; 97:13;98:22;100:10; 101:10;102:11;105:10; 113:11;115:13;122:12; 123:2;130:9,19;133:2,6; 144:17,18;146:11; 148:20,21,22;149:9,9, 10;150:5,6;151:17; 153:18;157:19;160:17; 178:19;187:16;189:5; 193:3;198:15;203:3,20; 215:9,15;217:2;223:8, 10;224:3,7;228:6;233:1; 234:21</p> <p>open (6) 139:3,15;151:6;154:9; 173:9;192:22</p> <p>opened (2) 98:11;221:22</p> <p>opens (1) 139:12</p> <p>opine (1) 197:17</p> <p>opinion (3) 34:13;65:17;212:18</p> <p>opinions (1) 119:9</p> <p>opioids (2) 6:10;8:9</p> <p>opportunities (2) 77:12;80:16</p> <p>opportunity (9) 77:4;80:9;81:3;82:22; 105:20;139:20;141:8; 162:17;211:12</p>	<p>opposed (10) 24:3;66:7;67:7;69:4; 71:4;99:15,20;114:8; 149:11;164:22</p> <p>opposite (2) 68:3;125:3</p> <p>opt (1) 56:4</p> <p>optimal (2) 92:13;129:14</p> <p>optimize (1) 64:5</p> <p>option (3) 66:19,21;203:16</p> <p>options (5) 66:11,12;187:12; 189:13;211:2</p> <p>oranges (1) 21:18</p> <p>order (15) 3:19;12:18;13:14; 16:8;17:1;93:14;122:6, 8,9;128:6;135:17; 143:16;195:20;196:6; 239:13</p> <p>organ- (1) 156:3</p> <p>organization (2) 19:12;52:12</p> <p>organize (2) 42:15;244:5</p> <p>organized (1) 22:9</p> <p>orientated (1) 178:6</p> <p>orientation (1) 73:9</p> <p>originally (1) 117:14</p> <p>Osphena (1) 234:21</p> <p>osteoarthritis (1) 83:18</p> <p>others (9) 8:20;49:19;79:21; 110:15;162:19;165:17; 175:21;187:9;217:17</p> <p>other's (1) 75:8</p> <p>otherwise (1) 135:14</p> <p>ought (1) 202:8</p> <p>ourselves (1) 116:1</p> <p>out (64) 4:6;10:22;21:6;24:19; 33:3;35:12;36:8,19; 44:2;49:16;56:13;58:13; 62:16;63:22;73:10;75:7; 80:4;90:2,5;91:11;92:2; 94:2,21;99:2,19;105:3; 106:20;108:12,13;</p>	<p>115:10;117:22;118:3; 124:13;125:7,9;141:3,7; 161:22;162:18;163:15; 164:4;165:22;183:4; 185:22;186:7;189:9; 192:13,19;202:15; 204:2;206:12;208:10, 11;210:2;214:17;216:5; 226:4;233:21;234:8; 238:5;239:2;241:17; 242:5,17</p> <p>outcome (80) 3:18;5:15;8:16,20,21; 9:9,12,20;10:3,5;11:14, 19;12:18;13:13,15,17, 19;14:5,15,20;16:12,13; 17:6;34:10;50:16;51:3; 52:21;53:11,17,18,20, 22;54:18;55:10;56:22; 57:2,12;76:6;92:13; 96:2,11,14,21,22;98:1; 108:16;134:20;136:22; 140:3,13,14;145:21; 146:13,15;148:11; 156:22;168:21;170:4; 176:14;177:5;179:19; 184:6,9,10;187:13; 188:12;191:17,20; 201:16;208:22;213:12, 15;216:18;217:2,5; 218:12;229:13;232:16; 233:6;241:7</p> <p>Outcomes (40) 1:8;4:13;15:10,11,16; 17:9,21;22:8;32:11,14, 15;33:1;35:16;40:16,22; 74:3;98:19;102:13,14; 112:18;117:17;118:2; 129:15,20;130:15; 131:1;134:7;146:1,7; 148:2;173:12;174:10; 181:7;182:7;184:4; 192:1;226:5,20;240:9; 242:6</p> <p>outline (2) 4:10;188:20</p> <p>outside (4) 39:19;43:20;44:11; 239:22</p> <p>Outstanding (1) 176:3</p> <p>over (47) 6:13;10:20;11:9;12:9; 14:13;29:8;33:11,17,22; 39:8;51:19;58:8;67:18; 71:3,4;74:10,10;78:10, 16;85:21;92:5,15,18; 103:12,20;104:3;108:4; 110:6,19;114:16; 126:18;127:14;129:22; 139:18;141:11;142:22; 171:14;174:5;179:6; 188:22;193:20;199:1;</p>	<p>203:4,21;205:15; 221:11;237:6</p> <p>overall (11) 9:14;17:9,12,13,17; 28:13;32:1;35:21;91:8; 95:3;116:17</p> <p>overlap (3) 132:8;155:19;218:17</p> <p>overlapping (8) 4:8;25:8;31:3;39:20; 92:22;94:5;156:16; 231:3</p> <p>oversampled (1) 24:13</p> <p>oversight (1) 23:2</p> <p>own (4) 54:12;124:2;238:11; 239:13</p> <p>owns (1) 118:16</p>	<p>11,16;102:1,2,5;112:17, 19;113:10,18,19;117:11; 118:7,9,12,15,18,19; 122:11;125:2,10,10; 127:3;128:16,19;129:3, 6,11;130:7,13;132:1,7, 10,19;133:3,8,15,17,18; 135:14;137:4;140:10; 143:11,14;144:1,7,8,9, 18,18,22;145:16,16,20, 146:3,12,14;147:9,14; 148:21;149:9,21;150:2, 7,7,8,10,11,17;151:22; 152:11,20;153:8,11,12; 154:1,2,10,16;155:1,12; 156:9,22;157:9,13,15, 20;158:1,6;159:3,6; 160:4;161:1,5;162:4,4,9, 12,15,16;163:2;164:2, 18,21;165:2,14;169:3,4, 6,8,10,22;170:12;171:6; 172:6;175:18,21,22; 176:7;177:8,13;178:15; 179:6;181:13;182:14; 183:5,22;184:1,2,2,3,5; 185:4,13;186:10,14; 187:6;188:8;189:20,21; 190:7;191:5,10,19,21; 192:1,1,17;193:13; 197:2,18;198:18,19,20, 20;199:22;200:4,6,8,9; 201:2;203:19;205:17; 206:17,19,22;207:10,18; 208:6;213:17;215:8,11, 22;216:9,13,17,18; 217:5,17,18,19,21; 218:2,16;219:4,6,7,10, 13,14,16,19;220:2,7,10, 14,18;221:2;222:6,7,18, 19,21;223:2,14;224:11; 225:7,8,10;227:4;228:7, 14;229:13,15;230:3; 231:12,15;232:1,19; 233:1,2,10,12,13;234:2</p> <p>painful (4) 65:21;91:4,6;234:22</p> <p>pain-related (2) 5:15;212:6</p> <p>pains (1) 102:10</p> <p>Panel (6) 72:19,21;74:16;75:8; 116:21;117:4</p> <p>panned (2) 36:19;49:16</p> <p>pans (1) 33:3</p> <p>paper (38) 35:1,9,11;37:5;44:2; 82:20;112:20;114:2; 118:10;119:12;145:2,9; 148:8;155:4;166:9,16; 167:8,13;174:14,16,19;</p>
		P		
		<p>package (1) 56:16</p> <p>packed (1) 238:17</p> <p>page (1) 8:18</p> <p>paid (1) 27:14</p> <p>PAIN (403) 1:3,7,9;4:3,3,5,5;5:3,4, 13;6:5,9,18,20;7:3,4,5, 10,22;8:22;9:5,12,17,19, 21;10:4;11:2,4,13,14,20, 21;12:4,11;13:15,15,19; 15:3;16:1,5,11,17,19; 17:13,15,22;18:7,17,18; 20:4,12,15,19,22,22; 21:7;25:8,18;29:11,13; 30:4,11,12,31;32:5,13, 14,20,22;33:22;34:3; 35:19;37:15;39:19,19, 20;40:1,3;41:13,14; 42:13;43:10,11;46:18; 47:10;48:18;49:14; 50:13;58:7,10;59:11; 60:4,5,6,9,12;61:12; 63:17;64:17;65:1,3,9; 66:3,5,14,18,19,20,21, 22;67:3,18;68:8;69:9,10, 14;70:13,14,17,18,20; 71:2;79:7,7,9,13,15; 80:1;83:6,18,21,21;84:5, 5;86:3,22,22;87:21,22; 88:1,18;91:5;93:4,5,19; 94:14,17;95:16;96:12, 12,13;97:7,13,14,18,19, 22;98:14,18,20,21;99:1, 13,14,16,17,20,21;100:2, 4,5,6,9,11,13;101:7,8,10,</p>		

176:11;180:10;196:13; 202:8;211:3;214:3; 223:11,18;224:1;227:1, 12;235:22;237:12; 240:1,4,8;243:12	pathologies (1) 101:8	77:10	91:9,11;95:3;101:2,16; 106:4;131:5,9,11;133:1; 162:15;203:8	Peyronie's (3) 135:22;136:6;137:18
paper-based (3) 117:18;118:2;122:8	pathology (5) 153:9;154:3;157:21; 159:14,16	Pelvic (46) 1:9;5:3,13;6:5,18;7:3, 10;12:4;20:4,11,18,21; 21:6;25:21,22;26:1; 29:13;30:4,11;41:4,9; 43:11;50:12;93:19; 101:8,16;102:2,5; 130:13;153:8;154:1,2; 156:9;157:13,20;158:1; 161:6;162:4,9,12,15,16; 163:2;164:1;197:2; 198:19	percentage (12) 6:16;10:20;11:2,4,5,9; 128:14,21,22;129:2,4; 132:18	pharmaceutical (6) 53:3,5;56:3,5;57:7; 112:17
papers (4) 50:9;111:18;179:17; 199:20	pathophysiology (1) 23:13	pelvic-floor (1) 41:7	percentages (7) 9:7;128:14;129:1,8, 13,17;132:17	pharmacologic (2) 5:10;83:17
paradigm (2) 46:22;230:17	patience (1) 7:19	pelvis (9) 39:20;43:11,20;44:4; 48:18;49:15,19;99:11; 238:17	Perfect (3) 153:4;201:8;210:16	phase (6) 41:17;42:17;195:20; 202:19;204:22;241:13
parameters (1) 45:17	patient (24) 10:21;17:5,6,9;45:19; 48:7;52:20;72:9;80:16; 114:3;127:3;128:7; 137:5;158:19;176:16; 201:11;228:5;234:16; 235:2;237:2;238:11; 242:8,19;243:1	penalized (1) 209:18	perfectly (1) 173:22	phenomenon (4) 170:2;213:6,14; 230:14
parcel (1) 149:14	patient-facing (1) 238:10	Pennsylvania (2) 73:2,5	performance (3) 166:3,6;167:14	phenotype (26) 30:7;31:9;32:20;43:6; 49:7;78:12;90:9;91:1; 92:5,9,12;94:15;95:7,22; 96:9,10,20;97:17;98:5,6, 12;111:8,13;112:9; 132:8;214:5
Parkinson's (1) 123:11	patient-Reported (8) 50:16;53:17;57:12; 112:18;117:17;136:22; 213:12,15	people (116) 9:19;11:1;17:12,20; 22:1;25:6;27:19;29:14; 39:3;49:16,18;64:9,16; 68:4;69:18;71:13;74:2, 9;81:6;83:4,22;86:6; 87:2,21;88:8;90:6; 92:21;93:10,95:16; 97:11;99:3;103:21; 105:13,17,20,22;106:22; 108:3;111:22;113:4; 114:16;121:6,11,12; 123:7,21;124:1,8,13,22; 125:7;126:8,18;134:13; 141:3;151:7;156:15; 162:1;165:13;171:4; 175:20;177:7;181:13; 183:10,19,20;185:19; 191:19,22;194:21;199:7, 16;203:12;208:19; 209:1,8;213:1;215:22; 217:19,21,21;218:15,16, 16,20,20;219:3,5,7,18; 220:6,8,22;221:5,10,16; 223:1;224:7;225:15; 226:1;227:19;228:2,6, 14;229:5;230:15,22; 231:9,11,13,14,22; 233:11,12;238:15;243:9	performed (1) 172:18	phenotyped (1) 238:12
part (31) 19:14;25:8;45:6; 50:21;52:12;53:19,20; 63:14;68:6,19;71:20,22; 76:3;82:16,20;97:15; 102:7;149:14;154:5; 181:19;183:12;188:4; 216:12,13;220:19; 229:9;230:9,20;231:7; 239:8;241:5	patients (114) 5:12;15:22;16:10; 17:2,10,14,16;18:13; 21:21;22:3,20;23:17; 24:7,19;25:2;26:22; 27:8;28:13;29:5;30:16, 18;31:14;33:7,10;37:3, 8;38:3;40:12,13;41:2,12, 13,18;42:14;43:14;46:2; 51:11;53:9;58:17;59:15, 22;62:7;64:4;65:10; 66:8;71:2;85:2;87:10; 90:2,16;92:1;95:2,6; 96:14;98:3,20;101:3; 102:8;106:11,20;110:1, 4,6,11,14,17,18,21; 111:3;112:15;114:2; 116:10;127:12;128:8, 15;129:2;131:14,15; 132:16,17;140:5;143:7; 149:7,22;154:11;156:4; 161:10;162:15;164:12, 17;196:1;197:6;198:19; 201:7;202:4;213:8; 214:5;216:21;218:2; 220:3,18;221:20;225:7; 229:19;232:21;236:21, 21,22;238:20;239:2,9, 12;242:15,21	period (44) 30:6;38:21;39:3;49:5; 51:20;68:9;77:18;84:22; 86:3;91:3;94:12,20; 95:15;97:10;98:10;99:4; 103:9;104:13,20,21; 105:3,6,8;108:1;110:7; 113:13,17;114:10,20; 130:2;194:4;195:22; 198:1,7;199:13,17; 200:10,11;204:5; 205:15;207:16,22; 208:1;209:5	performing (1) 62:11	phenotyping (9) 22:5;27:7;39:18;42:7; 78:2;90:1,3,6;232:9
participant (1) 59:1	patients' (1) 100:3	periodically (1) 149:3	perhaps (13) 31:19;33:3;36:5,17; 46:7;48:6;49:6;79:13, 21;94:21;139:17; 184:22;223:1	Philadelphia (1) 230:1
participants (19) 15:15;16:9;53:7;58:2; 59:3;60:8,8,11,20;64:22; 67:17;68:7,11;69:11,13; 70:2;71:11;77:20;78:9	pattern (1) 105:1	peripheral (1) 83:19	periods (2) 103:7;112:14	philosophical (1) 133:10
participating (1) 243:19	Pause (1) 7:18	perseverating (1) 134:21	peripheral (1) 83:19	phone (2) 121:9;126:15
participation (2) 142:6;208:4	pay (1) 31:13	persistence (1) 196:8	persistently (1) 149:3	phones (1) 120:2
particular (7) 74:6;75:21;86:3; 97:18;206:16;232:12; 237:1	paying (1)	persistent (1) 91:17	periods (2) 103:7;112:14	phonophobia (1) 234:16
particularly (3) 36:1;115:18;227:10		persisting (1) 204:22	perish (1) 103:7;112:14	photophobia (2) 230:5;234:15
partner (4) 53:10;57:10;177:14; 181:16		person (5) 48:16,22;126:14,17; 186:7	perish (1) 83:19	phrase (1) 8:11
partners (1) 164:12		personally (1) 178:1	perish (1) 83:19	physical (2) 25:20;35:21
partnership (1) 52:11		person's (1) 194:1	perish (1) 83:19	Physicians (2) 87:20;110:14
parts (2) 76:5,21		perspective (2) 139:5;241:20	perish (1) 83:19	physiologically (1) 88:19
past (19) 67:7,10,12,15;68:9; 70:18;71:3,4,5;119:16, 17,18;125:19,20;126:1; 142:22;176:8;189:8; 193:17		pertaining (1) 148:15	perish (1) 83:19	physiology (2) 89:3;112:8
Path (6) 50:17;51:2;52:8,16; 224:14;234:5			perish (1) 83:19	pick (4) 79:14;205:13;208:10; 234:17

<p>155:18;164:3;174:12; 211:15;214:9 placebo (22) 103:10;106:13,17; 107:1,13,15,17;108:8, 20;109:1,3,12,13; 115:10;116:3,12,15; 134:14;195:4,6;221:12, 15 placebo-controlled (1) 208:19 placement (1) 70:1 places (2) 155:20;215:7 plain (1) 116:8 plan (2) 48:21;222:16 plane (1) 80:15 planned (3) 29:4;47:12;51:14 planning (2) 4:20;50:20 plans (1) 242:10 plastic (2) 178:22;180:6 platform (1) 122:18 platforms (1) 117:19 play (2) 118:6;180:20 played (2) 119:15;120:7 playing (2) 103:5;125:18 plea (2) 81:22;190:21 please (5) 9:16;10:1;142:4; 190:22;193:18 plenty (1) 199:19 plug (1) 163:21 plus (3) 77:21;92:20;216:14 pm (5) 1:13;141:15;142:2; 211:22;244:10 point (47) 11:11;28:18;31:10; 34:10;46:5;47:18;62:8; 63:18;74:11;76:15; 79:11;80:6;84:17;86:18; 87:12;90:11,15;91:20; 101:19,20,22;102:16; 107:22;111:7;112:14; 115:9,9;116:20;123:19; 128:3,6;146:7;164:4;</p>	<p>165:22;166:20;172:4; 197:15;199:13;201:17; 203:10,14,18;206:9; 215:4;236:13;237:12; 240:2 points (9) 19:13;47:16;48:22; 49:8;100:22;101:14; 203:10;204:4;206:5 point's (1) 158:16 Poleshuk (2) 163:20,20 Pontari (14) 23:3;99:7,9;108:6; 117:7;133:6,14,18; 147:13;194:13;199:3; 215:20;219:2;220:1 pool (1) 62:17 population (25) 4:7;21:6;71:12,15; 131:5;152:2;159:19; 168:1;176:16,19; 178:12;191:6,13; 198:16;207:19;209:17; 217:15;218:8,12; 222:22;228:4,5,13,19; 229:9 populations (3) 156:3;163:13;218:4 portion (1) 191:6 positive (12) 4:2;12:20;13:16,20; 14:3;15:5,13;25:9; 28:14,15;33:4;119:9 positives (1) 179:20 possibilities (1) 187:7 possibility (3) 85:5;145:22;224:5 possible (10) 63:12;66:21;67:3; 69:10,20;70:19;99:9; 144:15,16;228:12 possibly (1) 217:20 postherpetic (1) 83:18 postmenopausal (2) 102:18;197:13 post-menopause (1) 235:1 potential (7) 4:5;60:21;162:18; 184:14;195:14;214:5; 239:10 potentially (14) 68:1;85:3;91:17,19; 143:21;151:1;175:19; 177:16;179:11;214:8;</p>	<p>215:6,8;228:13,18 power (4) 18:3,10;209:18; 221:19 practical (6) 154:13;176:17,20; 180:4;201:10;202:9 practically (1) 154:12 practice (3) 69:6;132:17;160:19 practitioner-patient (1) 115:3 preceding (1) 38:7 precise (1) 232:10 precompetitive (2) 52:17;54:4 predictive (2) 45:20;208:11 predictors (3) 34:5;35:16,18 predispositions (1) 115:13 predominant (4) 150:8,10;158:1; 234:19 predominantly (1) 74:6 prefer (2) 171:16;222:8 preferably (1) 81:9 preference (2) 68:21;69:3 pregabalin (1) 144:22 premature (3) 83:9,13,15 premenopausal (1) 210:11 preparation (1) 4:22 pre-randomization (1) 202:18 pre-read (1) 236:6 prescreening (1) 243:2 prescribed (1) 28:10 presence (4) 39:20;91:17,18;218:3 present (3) 36:11;51:10;95:20 Presentation (6) 3:10;4:9;19:7;50:18; 75:15;237:19 presentations (6) 73:16;74:8;75:8,18, 18;77:5 presented (4)</p>	<p>10:14;101:15;103:17; 129:16 presenting (1) 45:2 prespecification (1) 235:9 prespecify (1) 34:9 pressure (9) 40:4;47:10,17;168:9, 10,10,15;216:13,13 pretty (13) 24:9;26:19;27:10; 33:9;34:15;44:21;86:5; 95:2;131:3,7;147:5; 182:4;233:16 prevalence (1) 87:12 preventing (1) 19:2 previous (5) 3:19;85:2;176:1; 194:19;226:17 previously (2) 28:20;31:4 primaries (2) 179:11;235:9 primarily (6) 13:10;60:5;64:15; 196:19;231:6,22 primary (61) 8:16,20;9:3,9,20;12:5; 13:2,3,7,8,13;14:8; 57:14;96:2,3;102:12; 140:6;142:14;143:4,5; 145:1,16,21;146:13,15; 147:16;150:16;151:10, 19;170:14,20;171:1; 177:10;181:18;184:10, 14;185:17,19;186:15,18; 187:13;188:4,9;206:2; 209:13;215:8;217:7; 218:7,21;219:21;221:9, 18;230:9;232:15,18; 233:15,17,19;235:6; 236:15,16 prime (1) 141:4 priming (2) 124:19;125:3 prior (1) 242:11 prioritizing (1) 209:19 priority (2) 184:16;221:21 PRO (21) 52:22;53:10,13;54:3, 6,18;61:10;62:22;65:16; 122:20;135:4,7,10; 136:1,10;137:15;140:4, 21;168:6;241:4;242:5 probability (7)</p>	<p>17:4,5,18;18:18; 69:20;159:13;232:11 probably (32) 22:3;28:11;32:14; 34:21;44:13,14;46:4; 72:8;80:22;88:22;90:15; 96:8;103:9;105:7;106:5; 115:8;133:1;145:4; 148:5;156:1;161:4; 172:7;175:12;177:9; 179:11;190:13;192:2; 194:11;197:10;198:14; 226:7;229:17 problem (19) 48:16;82:15;87:7; 108:18;113:10;122:10, 14;123:6,10;136:10; 137:12;168:10;171:5; 196:14;197:5;209:9; 218:11,14;232:3 problematic (1) 158:18 problems (4) 51:13;168:12,14; 238:15 procedures (1) 15:7 process (22) 53:20;55:9;64:11,12; 71:20;72:1,12;76:2,7,9; 79:18,22;83:10;119:7; 126:15;128:11;136:3; 138:10,18;152:6; 167:12;175:10 processes (2) 76:12;88:15 processing (1) 200:5 produce (1) 56:9 product (3) 54:2;135:21;203:1 productive (1) 142:9 products (2) 52:19;55:2 professor (4) 3:8;19:5;73:1,2 profile (2) 195:18;196:2 program (2) 74:15;145:20 programmed (1) 51:22 programs (1) 139:13 progress (3) 21:21;142:10;212:2 progression (1) 49:14 prohibited (3) 8:5,9,10 project (1)</p>
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104:8 projects (2) 84:11;134:11 PROMIS (2) 181:21;182:3 promptly (1) 141:14 proper (1) 209:10 properly (1) 51:22 proponents (1) 66:6 proposals (1) 229:3 propose (5) 45:7;46:5;131:22; 238:18;239:10 proposed (1) 215:13 proposing (1) 33:5 proprietary (2) 139:14;235:19 PROs (9) 135:15;136:20; 137:21;140:10;188:14, 20;239:2;240:22;241:16 prospective (3) 48:15;50:10;90:13 prospectively (2) 42:10;111:10 prostatitis (12) 6:3;7:9;9:14;20:10,18; 79:19;95:1;99:10;159:5; 194:9;215:21;216:8 protect (2) 146:6,18 protected (2) 146:9;147:20 protocol (3) 26:14;172:11,18 prove (1) 225:2 proven (1) 115:10 provide (5) 139:7;211:14;212:19; 213:3;226:10 provided (1) 59:7 providing (2) 52:16;62:15 provocation (8) 143:5;155:17;164:10; 165:6;168:20;170:1; 180:17;185:12 provocative (5) 135:3;168:19;169:2,9; 200:19 provoke (1) 152:1 provoked (9)	151:17;152:6;157:9; 164:7,17;178:10;185:3, 15;192:15 Ps (1) 19:14 pseudo (1) 104:21 psychiatric (1) 8:8 psychometrically (1) 62:11 psychometrician (1) 32:2 psychosocial (4) 25:13,18;30:15,21 publication (1) 80:12 publicly (4) 53:19,21;55:4,12 public-private (1) 52:11 publish (2) 35:1,8 published (12) 6:6;37:5;50:8;84:9; 85:14;101:15;117:8; 160:17;166:10;173:13; 197:9;199:19 Pukall (1) 173:9 pull (2) 74:15;81:4 pulled (1) 239:15 purely (1) 216:11 purpose (2) 54:8;214:4 purposes (3) 14:17;46:6;145:3 push (1) 139:8 put (26) 6:18;12:13;17:1; 19:18;20:6;35:5;40:4; 76:5;79:21;84:13; 108:10;139:5;147:3,19; 155:15;173:17;174:2; 183:3;187:20;190:8; 191:22;212:17;215:13; 226:9;227:11;239:8 putative (1) 6:9 putting (3) 190:5;241:15;243:21 p-value (2) 15:11,12 Q Q&A (1) 72:19 QST (11)	26:6,17;27:11;46:10, 13;47:4,9,10,12;78:3; 212:21 quadrants (1) 29:18 qualification (14) 51:3;53:16,17;54:6; 55:9,15,16;56:16;57:4, 12;137:9;138:9;139:10, 18 qualifications (1) 138:2 qualified (4) 51:5;56:11;138:12; 139:17 qualify (1) 118:16 qualitative (8) 51:7;52:5;57:22;58:2; 59:21;61:8;63:1;71:10 qualitatively (1) 222:10 quality (6) 10:10;30:21;31:15,22; 184:1;194:16 Quality-of-life (1) 10:8 quantify (1) 39:15 quantitative (5) 51:10;62:9,10,17;72:4 Quentin (15) 19:5,7;46:11;77:17; 79:1;102:22;103:17; 109:21;128:10;129:21; 134:18;149:16;163:9; 195:19;238:2 Quentin's (1) 107:22 questionnaire (8) 25:14;26:17;34:2; 37:19;38:1;122:9;125:1; 184:2 questionnaires (6) 25:11,16;122:7,15; 124:22;125:7 quick (9) 10:16;88:11;162:8; 169:21;175:8;210:6,7; 236:4,12 quicker (1) 48:7 quickly (2) 14:18;191:2 quite (10) 23:14;44:6,10;50:11; 57:7;91:7;96:7;148:4; 214:16;230:14 quiz (1) 73:21 quote (1) 130:5	R r- (1) 78:22 race (1) 71:13 raise (2) 117:2;198:11 raised (2) 151:15;205:22 raises (1) 103:20 raising (1) 100:20 Ralf (1) 47:7 random (1) 212:17 randomization (2) 106:11;233:5 randomize (1) 239:21 randomized (6) 5:9;107:7;181:1; 201:7;202:1;240:14 randomly (1) 17:5 range (4) 88:8;121:4;131:6; 207:15 ranged (1) 8:1 rank (3) 15:15;16:8;17:2 ranking (3) 16:9;18:11;237:3 ranks (1) 18:14 RAPKIN (7) 164:9;166:9;171:8; 179:15;182:10;184:6,9 rarely (2) 31:19;115:17 rate (17) 9:16;10:1;12:20,20; 66:4,13,22;70:13,14,17; 71:2;87:21,22;106:5; 120:10,11;193:18 rates (1) 4:2 rather (9) 17:10;19:19;70:13; 86:22;93:20;200:16; 201:1;229:7;237:21 rating (17) 8:22;66:7,10,12; 68:22;69:1,2,4,5,12; 131:20;132:10;134:22; 175:21,22;181:12; 201:22 ratings (2) 121:12;221:17	rationale (1) 36:15 RCTs (1) 3:19 reach (2) 112:2;206:3 reached (2) 51:4;141:2 read (10) 64:9;82:11,12;84:1; 118:10;154:7;174:19; 181:8;182:6;183:21 reads (1) 162:13 ready (1) 80:11 real (8) 96:4;106:14;107:2; 113:14;114:8;175:13; 202:16;210:7 realistically (1) 201:13 realize (1) 90:19 realized (2) 110:22;215:4 really (103) 7:12;9:10;17:17;19:8; 22:1,17;23:14;24:6,16, 20;27:16;29:5,21;36:18; 38:4,19;41:4;42:2,4,6; 44:15,16;46:6;49:16,17; 54:9;66:8;76:19;77:3,5, 6;78:6,18;79:8,14;82:4; 83:3;87:18;91:22;94:10, 21;98:2,9;100:18; 106:12;110:8,16,22; 111:18,21;112:4;114:4; 115:22;116:1;124:19; 126:16;129:20;133:15; 135:12;139:19;142:8,8; 146:2;150:16;151:18; 152:4;155:21;157:7; 159:3,5;160:15;161:1,7, 19;175:1;177:9;179:15; 180:9;185:4;187:1; 188:5,21;194:13; 197:22;200:12,15; 203:9;209:13;210:6; 214:14;222:7;225:8,11, 22;226:21;227:8,22; 229:8;230:6,18;239:5; 243:1,1 reason (8) 80:5;106:18;108:11; 126:5;127:7,13;137:22; 243:13 reasonable (11) 46:10;81:16;159:15; 165:6;174:18;189:1; 197:21;206:14;209:5; 210:18;228:11 reasonably (4)
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71:11;159:14;164:9; 202:14 reasons (8) 36:15;106:8,16; 110:15;134:21;164:13; 198:6;202:10 reassessing (1) 34:14 reassuring (2) 37:4;48:3 recalculated (1) 120:3 recall (7) 63:18;86:21;87:3,6; 124:15;175:18;180:18 received (1) 28:12 receiving (1) 12:12 recent (2) 67:12;232:17 recently (3) 57:18;159:2;179:17 recess (3) 72:17;141:15;211:22 reclassify (1) 93:22 recognize (3) 71:15;196:13;225:15 recognized (2) 62:1;111:12 recommend (12) 155:3;163:2;172:10, 16;174:11;185:2,6; 188:19;208:13;211:19; 214:19;237:7 recommendation (14) 45:4;70:4;74:1; 167:12;170:20;174:5,6; 175:15;176:5;184:22; 185:14;189:18;198:10; 238:9 Recommendations (12) 1:7;3:20;155:11,18; 157:19,22;162:3;168:2; 174:20;193:1;226:18; 227:4 recommended (8) 69:7;70:10,22;173:11; 174:8;179:11;184:4; 189:14 recommending (5) 154:14;184:19;185:5; 189:22;212:8 recommends (1) 234:20 recruit (2) 22:20;25:6 recruited (4) 27:5;28:13;58:3;71:13 recruiting (2) 78:8;214:10 recruitment (2)	26:22;214:10 recurrence (1) 205:17 recurrent (4) 4:3;61:15,20;192:17 redo (1) 211:20 reducing (1) 208:5 reduction (3) 62:13;140:14;229:19 refer (3) 20:8;110:14;222:7 reference (4) 85:1;130:1;152:10; 173:17 referred (1) 174:17 refers (1) 67:12 refill (1) 242:14 refine (1) 93:18 regard (2) 30:17;229:12 regardless (3) 65:11;196:12,22 regards (3) 75:20,22;97:3 region (3) 76:14;78:15;159:7 regions (4) 29:13;58:3;78:14;91:7 registries (1) 118:20 registry (2) 239:20,20 regression (7) 38:17;104:14;106:17; 107:6,9;109:13;221:15 regret (1) 84:1 regular (2) 28:1;103:14 regulatory (1) 55:21 reinforces (1) 105:6 relate (1) 90:21 related (14) 50:9;58:10;64:21; 83:5;95:11;96:8;147:6; 172:21;173:3;184:3; 191:16;210:9;237:18; 243:15 relatedness (1) 169:1 relates (2) 92:11;94:3 relationship (1) 115:3	relationships (4) 58:18,19;86:5;181:17 relative (2) 98:8;160:3 relatively (4) 15:14;57:18;90:19; 160:9 relevant (12) 23:11;40:19;42:3; 58:15;60:20;153:14; 163:12,16;213:21; 226:2;227:7,11 reliability (1) 98:9 reliable (1) 136:18 relied (1) 55:19 relief (9) 9:15,16,17,22;10:1; 11:2,3,4,12 rely (1) 110:13 remarks (1) 72:13 Remember (8) 73:20;81:17;131:4; 166:11,11,17;171:8; 172:1 reminded (1) 110:1 reminder (1) 88:7 reminds (1) 96:6 remiss (2) 178:12;215:5 repeat (3) 27:17;77:21;154:19 repeatable (1) 78:13 repeated (6) 12:9;30:5;78:4;91:3; 97:21;180:17 repeatedly (3) 36:14;78:20;79:12 repeating (1) 211:13 report (4) 37:11;59:15;63:13,19 reported (16) 5:15;6:1;28:20;29:20; 31:4;52:20;58:6;59:6; 60:7;63:20;64:22;70:2; 83:20;137:5;140:13,14 reporting (3) 37:13;118:2;140:5 represent (2) 22:3;71:14 representation (2) 23:6;71:6 representative (5) 71:11;72:10;124:7;	228:4;229:7 representatives (2) 53:7;71:19 reproduce (1) 26:3 reproduces (1) 41:9 reproductive (3) 196:14,19;198:17 requalify (1) 118:1 require (4) 5:13;161:6;211:10; 233:3 required (1) 22:11 requirement (1) 191:10 requires (1) 168:20 rescue (8) 16:1,4,7,11,14,18,20; 17:22 research (34) 23:10;44:18;46:6; 51:7;52:10;53:3;57:10; 58:1,2;59:21,22;71:10; 74:5;161:14;167:20,21; 168:3;176:15;194:9; 207:7;211:10;222:14,17, 20;223:3;224:19; 225:18;226:2,13; 238:21;239:13;240:10; 242:22;243:7 researchers (2) 53:9;72:7 resolve (1) 160:15 resources (2) 135:16;212:22 respects (1) 68:17 respond (8) 15:22;60:21;78:22; 87:13;102:11;111:14; 115:16;121:21 responded (1) 68:13 respondents (1) 69:21 responder (13) 10:19;14:12;16:7; 18:4,4,6;129:12;188:17; 192:19;203:13,14; 205:7;229:1 responding (3) 10:21;63:16;79:2 response (25) 9:4;11:1,10;15:16; 42:7;64:6,13;68:19; 69:12,18,21;70:9,19; 88:8;107:13,15,17; 108:20;165:9;183:7;	189:15;205:15;214:22; 225:20;243:17 responses (2) 63:9;180:22 rest (5) 79:17;146:16;169:2; 195:22;211:16 resting (2) 35:13;40:21 result (1) 26:16 resulted (1) 5:17 results (8) 37:7;116:4,16;120:9, 17;121:17;168:11; 177:17 retrospectively (1) 32:18 review (21) 3:14,17,21;4:10;5:1,8; 14:4,22;18:22;55:2,16, 21;58:12;59:20;61:7; 70:8;83:1,17;101:14; 117:16;164:3 reviewed (3) 166:3,5;189:6 reviewing (2) 19:1;138:14 revised (1) 84:2 revisit (1) 226:22 RFA (1) 25:3 RICE (2) 160:7;177:20 Rick (1) 77:2 rid (2) 49:6;100:9 rifaximin (1) 116:14 right (48) 19:4;24:4;27:22;34:8; 52:22;57:1,3;72:11; 84:7,16;98:16;107:9; 109:9;117:9;120:3; 122:7;124:4;125:14; 136:7;159:16;166:22; 167:19;171:12,15;172:6, 7;173:12;175:1;176:9, 10;184:11;188:19; 190:18;191:21;192:18; 194:7;197:3;207:4; 218:12,15,18;220:1; 221:4;222:11;224:22; 230:7;235:5;240:18 rigid (1) 192:5 rigorous (1) 167:9 ringing (1)
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177:22 risk (2) 38:12;175:9 risk-benefit (1) 117:13 RO (1) 187:12 Rob (3) 170:7;172:22;175:6 robust (1) 160:9 Rochester (1) 3:9 Roger (2) 89:20;91:21 role (1) 180:20 rolling (1) 119:5 Rome (2) 6:22;191:9 room (6) 81:5;109:5;151:7; 173:15;175:14;211:16 round (1) 81:2 rounds (2) 64:1;69:3 routinely (1) 233:12 rove (1) 78:16 row (1) 91:10 RTI (2) 57:9;71:21 rule (1) 4:6 rules (1) 122:22 run (2) 34:14;113:10 run-in (31) 30:6;38:19,21;39:3; 49:5;77:18;91:3;95:15; 97:7,10;98:10,22;103:7, 8;104:13,21;105:6,8; 106:9,18;107:20;108:1; 112:14;113:17;114:10, 20;115:2;116:7,8,13; 130:1 running (3) 26:8;105:12;201:22 runs (1) 22:22	52:13 salient (1) 65:10 same (42) 8:17;21:5;27:10; 36:12;38:1;41:15;44:14; 48:4;50:7;54:8;62:5; 68:14,19;73:8;76:14; 78:15,21;82:17,18,18; 91:9;97:21;105:1; 126:14,15;127:15; 128:7;134:5;148:14; 150:15;168:5;170:9; 191:1;201:17;203:9; 218:5,15,20;222:8; 225:6;236:20;241:12 sample (3) 68:9;124:7;229:7 Sarrit (4) 136:16;140:2;167:1,2 Sarrit's (1) 136:14 satisfaction (1) 181:16 satisfy (2) 167:9;209:6 save (2) 141:4;223:17 savings (1) 51:21 savvy (1) 123:5 saw (6) 23:17;113:17,21; 114:8;115:4;120:12 saying (39) 44:13;46:11;67:22; 102:1,12;108:7;113:22; 114:15;120:4;136:19; 145:14;151:1;153:17, 17;154:2;155:6,10; 156:21;157:19;159:12; 163:9;164:22;176:21; 189:18;190:6;191:18; 202:12;205:3,21; 218:19;219:9;221:4,5; 222:16;230:2;232:8; 239:1,17;242:20 scale (38) 8:22;18:8,8;42:16; 58:8;66:7,10,12;68:22; 69:2,2,4,5,13,16,18,18, 22;70:19;87:22,22; 100:22;105:5,14;126:21, 21;127:2;132:10;136:6; 170:11;172:13,14; 176:7;184:2;203:5; 218:1;221:17;222:8 scales (5) 64:6;129:10;131:20; 134:22;186:9 scanners (1) 26:14	scans (1) 78:3 scenario (1) 178:16 schedule (1) 42:21 scheme (2) 16:10;18:12 science (3) 82:11;89:5;152:3 scope (3) 238:8;240:1,11 score (17) 7:8,9;39:22;58:7; 82:17,18;99:20;121:14, 16;132:1,2;182:12; 189:9,19,20;219:7,19 scores (7) 28:22;32:12;34:1; 189:19;190:16;206:22; 219:14 Scott (1) 15:18 screen (3) 173:10;175:1;188:4 screen-based (1) 122:13 screening (3) 58:8;77:19;78:10 se (1) 208:16 search (4) 5:17,18,19,20 searched (2) 5:3,5 seats (2) 3:5;142:5 second (11) 5:19;6:3,20;7:16; 41:17;49:3;76:11;80:7; 101:22;114:7;146:14 secondaries (2) 165:19;212:7 secondary (23) 102:14;142:15;144:4; 146:1,5,7;151:19; 165:11;173:11;177:4; 179:22;181:7,11,18; 182:8;184:17;186:18; 209:15;212:4,14;214:4; 237:2,22 second-to-last (1) 7:11 section (4) 214:2,15;217:11; 220:16 sections (2) 45:11,11 seeing (10) 21:14;31:14;41:8,14; 82:16;94:15;105:1; 114:14;132:15;155:21 seeking (2)	39:12,15 seem (14) 31:14;36:16;40:15,22; 41:3;42:14;48:4;160:2; 165:22;167:2;172:9; 180:20;213:5;227:10 seemed (5) 31:21;38:5;125:17; 163:6;217:10 seems (19) 34:15;45:8,18;48:6; 49:21;79:9;93:4;129:7; 134:20;135:6;143:1; 178:5;186:12;206:9; 207:14;217:4;222:4,12; 233:16 select (1) 69:11 selected (7) 17:5;57:9;60:2;61:6,9; 64:20;65:9 selection (1) 60:18 semi-random (1) 49:21 send (7) 174:14;175:2,4; 211:11;212:13;235:17, 20 sensation (1) 65:4 sense (11) 67:4;68:3;88:19; 93:13;126:18;186:8; 206:12;210:8;230:6; 233:20;234:12 sensitive (3) 40:12;84:17;100:19 sensitivity (6) 31:9;47:15;84:4; 107:12;226:20;227:1 sensitization (1) 180:13 sensitized (1) 180:16 sensory (2) 41:21;213:16 sent (2) 113:19;136:13 sentence (1) 70:10 sentences (1) 214:7 separate (10) 29:21;32:19;40:1; 79:3;85:4;96:8;98:17; 111:8;143:2;155:6 separately (1) 32:15 sequential (1) 150:20 series (3) 50:8;122:12;209:4	serious (1) 133:15 serves (1) 168:15 session (1) 141:1 set (9) 9:7;42:16;114:11; 132:9;135:7;137:22; 211:4;216:5;239:19 sets (3) 66:16;70:9;205:9 setting (7) 38:22;139:4;170:15; 177:1;207:2,5,6 settings (2) 193:9;206:18 settled (1) 82:11 seven (1) 35:12 several (7) 85:11;124:20;129:19; 150:7;175:22;191:1; 230:12 severe (7) 31:22;37:15;68:8; 69:14;203:19;228:14; 229:8 severity (16) 7:4;11:17,19,21;30:8; 35:18;44:9,16;97:13; 99:13;101:9;130:7,8; 170:22;171:3;216:18 severs (1) 239:12 sex (10) 36:4,8,12,16;71:12; 132:21;177:7,8;181:13; 185:20 sexes (1) 36:10 sexual (5) 37:20;176:8;177:13, 14;181:15 SF-36 (1) 10:12 shaking (1) 215:18 Shannon (11) 80:19;83:8,9,13; 84:14;142:19;180:8,9; 211:1;215:3;227:9 share (2) 54:21;73:12 shared (1) 195:19 Sharon (7) 193:4,5;195:9;197:14; 217:12;234:8;240:13 sharp (1) 65:3 Sheri (1)
--	--	--	---	--

S

71:22 shift (1) 156:17 shooting (1) 65:4 short (7) 24:12,19;38:10;80:7; 94:15;103:9;184:1 shorten (1) 79:22 shorter (1) 202:9 shortest (1) 209:5 short-term (3) 49:5;90:4,19 shoulder (1) 171:14 show (9) 17:12;27:15;54:16; 62:10;122:12;207:13; 219:20;221:19;242:12 showed (5) 37:2;86:4;128:11; 129:21;136:16 showing (4) 6:15;101:16;199:21; 200:2 shown (6) 36:2;41:2;45:15,18; 123:4;196:16 shows (5) 23:5;71:6;83:4;87:18; 195:7 shut (1) 141:6 sideways (3) 120:7,8,8 signal (3) 41:3,10;42:13 signals (1) 41:15 significance (2) 13:17;112:2 significant (5) 38:17;191:6;195:3,15; 239:11 signs (22) 10:6;57:13;58:15,17, 19,20,21;59:1,5,8;60:15; 61:2,5,9,13;62:2,18,20; 63:9,14;64:3;149:12 silos (2) 74:13;93:15 silos (2) 73:10;94:4 similar (9) 28:19;29:2;32:6; 79:18;91:22;180:2; 182:4;205:2;222:21 similarities (1) 41:12 similarly (2)	45:22;68:14 Simon (8) 67:20;86:16,17; 144:13;145:18;147:10; 148:17;149:8 simple (7) 34:15;44:21;87:20; 88:2;136:11;182:2; 186:5 simplistic (2) 35:1;243:5 simply (5) 46:17;159:19;196:16; 197:5;220:20 simultaneously (1) 143:13 single (12) 9:3;11:11;14:7,10; 18:16;43:19;60:12; 111:21,21;134:22; 135:5;218:21 single-dose (1) 12:11 sit (1) 118:10 site (4) 22:12;26:11,12;43:19 sites (15) 22:10,20;27:22;28:7; 43:8,13,13,17;44:4,11; 99:17;100:4,5,13;110:13 site-specific (1) 27:20 sitting (1) 123:8 situation (5) 82:9;180:2;215:10; 234:13;235:2 situationally (1) 177:15 situations (3) 137:20;188:7,10 six (4) 22:9;34:8;35:6;115:3 sizable (1) 91:16 size (4) 68:10;119:22;120:3; 159:16 sleep (1) 35:22 slid (2) 119:20;120:6 slide (9) 19:13;39:12;120:16, 22;174:3;181:4,6; 212:16;226:6 slider (1) 121:17 slides (5) 9:8,12;19:1;33:15; 136:14 sliding (3)	119:19,22;120:5 slight (1) 69:3 slightly (5) 83:15;84:2;101:22; 126:16;176:11 slope (3) 33:8,11;39:7 small (7) 26:19;42:16;68:9; 85:15;111:22;131:4; 164:19 smart (1) 22:1 smartest (1) 22:11 SMITH (26) 3:3;19:4;42:21;47:7; 48:8;50:4,14;72:15,20; 83:10,15;145:13; 147:22;150:13;162:21; 173:14,19;176:21; 181:9;183:20;187:14; 194:2;224:17,22;225:4, 22 solution (1) 238:18 Solutions (2) 57:9;71:21 solve (2) 171:4;218:10 somebody (8) 100:4;116:2;123:11; 139:6;169:7;177:13; 198:7;218:11 somehow (1) 218:21 someone (16) 19:16;20:4;28:10; 94:13,16;133:8,11; 171:2;175:2;185:1,15; 199:4;210:17;222:6; 224:2;227:17 sometimes (8) 4:3;8:15;9:19;21:2; 51:13;161:18;209:3; 215:15 somewhat (4) 18:7;31:5;36:5;49:21 somewhere (2) 159:6;210:19 soon (2) 63:12;133:20 Sorry (20) 7:17;12:3;14:3;82:6; 129:16;140:1;141:6; 154:19;157:4;158:13; 165:21;170:8;181:5; 185:8;192:6;205:2; 223:15,20;240:20;241:2 sort (3) 186:5,6;239:14 sorts (7)	65:6;68:5;106:8; 137:3,4;157:3;240:9 Sound (1) 211:17 sounds (11) 89:5;150:15;158:2; 163:19;167:17;179:10; 197:20;198:10;222:15; 224:11;235:5 sourced (1) 122:2 South (1) 178:5 space (2) 230:8,10 span (1) 204:2 speak (1) 84:13 speaker (4) 3:6;85:5;174:4;175:11 speakers (1) 143:9 speaks (1) 29:6 specialists (1) 70:8 specialize (1) 151:8 specialized (1) 22:19 specific (25) 5:13;9:15,22;10:8,11; 12:12;42:22;43:12; 48:10;55:20;57:11;76:2, 21;125:12;152:15; 155:21;161:15;170:11; 172:21;173:4;174:4; 206:9;213:6,20;225:1 specifically (17) 25:3;44:15;46:14; 50:5,9;58:9;65:1;90:1; 96:19;100:1;117:5; 122:16;163:12;164:2; 184:10;223:1;238:1 specified (2) 8:12;55:18 specimens (1) 26:5 spectrum (2) 200:12;224:8 speed (1) 19:11 spend (3) 35:6;88:22;89:7 spent (1) 76:3 split (2) 13:22;131:6 spoke (3) 58:18;89:21;153:19 spoken (1) 72:22	sponsor (1) 56:5 sponsored (1) 6:13 sponsoring (2) 54:21;56:8 sponsors (1) 57:8 spontaneous (2) 140:9;151:22 spontaneously (1) 60:7 sprain (1) 169:6 squeaky (1) 113:11 stability (9) 30:7;49:5;89:22;90:1; 91:1,1,15;92:9,12 stabilizing (1) 105:2 stable (9) 33:9,12,20;78:11; 92:22;95:2,6,12;101:5 stage (2) 4:21;139:15 stakeholder (1) 149:19 stakeholders (1) 53:15 stamps (1) 124:15 stand (1) 20:5 standard (9) 24:9;168:5;178:10; 183:2,7;194:8;197:17; 198:4;208:22 standardize (2) 180:5;183:9 standardized (2) 177:18;181:14 standardizing (2) 55:2;171:6 standards (1) 148:6 standing (1) 169:7 standpoint (4) 105:12;111:6;132:4; 154:22 stands (1) 20:3 start (13) 50:10;105:3;108:19; 127:8,9;141:5,12; 173:21;199:12;204:12; 207:8;209:22;210:12 started (12) 3:4;72:20;73:15; 105:20,22;113:17,19; 117:18;141:9;142:5; 241:15,16
--	--	---	---	---

<p>starting (2) 40:6;104:16</p> <p>starts (3) 49:15,18;200:11</p> <p>state (3) 40:21;101:5;149:15</p> <p>stated (3) 8:14;55:18;69:13</p> <p>statement (8) 79:13,20;83:2;162:2, 10;189:12;190:12;242:2</p> <p>states (2) 79:13;162:11</p> <p>statistical (5) 13:5;108:21;112:2; 209:10;210:3</p> <p>statistically (1) 12:21</p> <p>statistician (3) 15:19;77:7;107:5</p> <p>statistics (1) 17:20</p> <p>status (1) 229:1</p> <p>stay (4) 109:19;195:21;202:2; 206:4</p> <p>stayed (1) 130:21</p> <p>staying (2) 131:12,12</p> <p>steering (2) 81:1;236:1</p> <p>stem (2) 66:13;70:2</p> <p>step (3) 137:10;151:3;198:14</p> <p>Stephen (6) 50:15,18;121:19; 224:12,13;234:5</p> <p>stepped (1) 210:4</p> <p>stepwise (1) 15:7</p> <p>Steve (3) 88:4;92:10;170:9</p> <p>Stifle (1) 175:11</p> <p>still (18) 15:13;33:19;44:1; 49:16;52:13;54:12;78:7; 100:7;115:4;140:10,21; 143:17;144:5;148:9; 217:11;224:14,18;231:8</p> <p>stimulating (1) 73:7</p> <p>stoical (1) 222:7</p> <p>stone (1) 8:1</p> <p>stool (5) 11:8,15,22;18:8;61:14</p> <p>stools (1)</p>	<p>59:13</p> <p>stop (3) 7:16;103:3;121:5</p> <p>stopped (1) 121:6</p> <p>store (1) 124:2</p> <p>straightforward (5) 45:1,5;145:5,7;211:5</p> <p>straining (3) 61:16,22;62:6</p> <p>strategies (2) 227:22;229:4</p> <p>strategy (4) 13:11;147:17,21; 238:13</p> <p>stratification (2) 130:17;233:4</p> <p>stratify (2) 98:3;232:22</p> <p>stress (1) 36:3</p> <p>strict (1) 15:9</p> <p>strikes (1) 175:16</p> <p>strikingly (1) 44:6</p> <p>strong (3) 65:17;158:19;189:17</p> <p>strongest (1) 184:22</p> <p>struck (3) 75:17;76:19;79:5</p> <p>structure (4) 70:11;142:20;148:3; 235:11</p> <p>structured (1) 146:22</p> <p>struggle (1) 201:12</p> <p>studied (6) 90:16;115:21;150:9; 178:19;179:20;216:2</p> <p>studies (31) 9:14;12:11;22:21; 24:10;27:20;29:1;33:4; 34:12;38:21;47:4;48:13; 85:11,22;92:17;96:12; 100:2,15;112:16;115:1; 119:11;123:3;163:18; 190:14;194:15,19; 206:22;207:12;220:16; 222:17;241:8,16</p> <p>study (54) 12:9;20:4;27:19;28:6; 50:10;51:11;62:9,10,17; 71:11;72:5;90:4,19; 91:22;92:1;93:18,19; 95:3;96:12;97:4;98:1,1; 99:2;104:17;107:11; 110:3,3;116:1;127:16; 134:3;148:4;155:7;</p>	<p>172:5;198:11;203:2; 208:4,19;209:2,8,19; 210:15;218:6;219:20; 221:8,10;222:19;223:4; 229:11;231:16;235:11; 239:9;241:17;242:1,18</p> <p>studying (6) 20:10;21:9,17;89:4; 137:16;156:2</p> <p>stuff (7) 113:1;117:17;121:11; 146:16;205:18;242:17, 22</p> <p>sub-areas (1) 77:11</p> <p>subcategorize (1) 33:5</p> <p>subdomains (1) 77:15</p> <p>subgroup (8) 91:1,8,14,16,19;130:4; 232:8;233:1</p> <p>subgroups (3) 22:7;23:11;232:11</p> <p>subject (6) 32:10;40:5;128:1; 148:16;197:16;236:3</p> <p>subjective (1) 88:8</p> <p>subjects (9) 24:13;26:16;27:4; 28:19;31:1;64:19; 166:11;208:3;210:10</p> <p>submental (2) 140:12,15</p> <p>submission (1) 80:11</p> <p>submit (1) 56:16</p> <p>subpopulation (1) 218:9</p> <p>subpopulations (1) 217:17</p> <p>subsequent (2) 118:22;240:12</p> <p>subsequently (1) 239:15</p> <p>subset (3) 56:4;165:13;191:13</p> <p>substantial (1) 95:9</p> <p>substantially (1) 175:20</p> <p>subtracted (1) 130:2</p> <p>subtype (2) 60:20;61:17</p> <p>subtypes (9) 57:21;59:3,12;60:6; 64:19;65:11;77:13; 78:11,20</p> <p>subtyping (1) 233:4</p>	<p>success (5) 203:18,20,21;228:15; 232:12</p> <p>successful (3) 104:11;107:3;136:20</p> <p>successfully (1) 135:15</p> <p>suddenly (1) 103:16</p> <p>sufficient (6) 13:5;144:2;183:13; 193:14;196:16;197:9</p> <p>sufficiently (1) 230:22</p> <p>suggest (11) 31:16;115:11;131:13; 167:21;171:16;188:22; 194:10;197:9;199:14; 210:9;223:22</p> <p>suggesting (5) 151:9;157:7,17;158:3; 179:18</p> <p>suggestion (7) 74:1;162:22;183:18; 194:11;210:18;227:9,14</p> <p>suggestions (1) 162:1</p> <p>suggests (1) 107:16</p> <p>suitably (1) 168:15</p> <p>summaries (1) 8:18</p> <p>summarize (8) 3:18;4:12,16;12:15; 20:1;76:8;85:2;188:13</p> <p>summarized (2) 10:3;77:17</p> <p>summary (3) 12:11;77:10;210:21</p> <p>super (3) 28:4;44:20;182:2</p> <p>superficial (1) 82:12</p> <p>supplemental (2) 37:19;38:1</p> <p>support (3) 54:1;71:17;190:11</p> <p>supported (1) 70:4</p> <p>supports (1) 55:17</p> <p>suppose (1) 38:20</p> <p>suppressed (1) 197:12</p> <p>sure (34) 23:20;24:1,6;25:10; 26:14;49:7;64:4;73:10; 82:1,2;93:21;95:21; 109:2;112:11;116:6,19; 119:4;120:2;127:11; 136:18;141:6;150:1;</p>	<p>157:6;168:18;177:6; 183:6;188:1;191:12; 194:21;199:6;215:20; 216:4;217:14;218:10</p> <p>surgery (2) 8:7;127:4</p> <p>surgical (1) 50:11</p> <p>surprised (2) 21:15;139:1</p> <p>surprisingly (2) 36:6;38:16</p> <p>surrogacy (1) 167:10</p> <p>surrogate (11) 132:5;166:21;167:1,3; 168:6,7,19;169:9,19; 179:16;206:14</p> <p>surrounding (1) 144:6</p> <p>suspects (1) 59:18</p> <p>sustained (1) 206:13</p> <p>Suzie (4) 159:1;196:11;198:12, 13</p> <p>swab (5) 178:11;179:12,15,22; 181:10</p> <p>swing (1) 173:21</p> <p>symmetrical (2) 215:6,14</p> <p>symptom (35) 9:15,16,22;10:1;11:3, 12;28:21,22;34:2;35:18; 36:5,18;39:17,22;60:11, 13;65:10;68:12;90:22; 101:9;104:14;147:15; 154:1;157:20;158:1; 168:19;221:17;227:20; 228:8,17;230:4;231:5,5; 236:19;238:6</p> <p>symptomatic (3) 58:9,10;229:18</p> <p>symptomology (1) 149:2</p> <p>symptoms (139) 4:1,4;10:6;12:18,19; 14:10;21:12,16;24:1,5, 12,14,20;25:1,13,17,18, 18;26:3;29:20;30:4,15, 19,21;31:11,17,18;32:1, 5,6;33:9,10;34:1,3,4; 35:20;36:10,12;37:16; 39:9,14;41:10;44:7; 46:13;50:10;57:13,19; 58:16,17,20,21,22;59:1, 5,8;60:9,15;61:3,5,9,12, 13;62:2,6,19,20;63:4,9, 17;64:3,15;65:1,7;77:9, 11,21;90:8;93:21;102:1,</p>
--	--	---	---	--

<p>4;105:4;110:4;131:19; 133:15;143:13,15; 145:11;146:13;149:12; 150:18,22;155:16;156:4, 12,16;168:17,22;170:22; 189:10,10;190:7;192:8; 193:13,18;197:1,1,3; 198:20,22;199:22; 200:5;203:20;212:10; 215:12,22;216:2,11,14; 219:8,14;222:21;223:3; 224:4,15;225:1;228:21; 229:14,20;230:16; 231:1;232:20;233:10,13, 16;234:15;235:3; 236:17;237:14;239:14</p> <p>synchronized (1) 208:4</p> <p>Syndrome (20) 1:9;6:2;20:12,19; 30:19;56:1;63:4;101:7; 149:15;153:8;154:2; 168:22;169:2;198:3,16; 229:11;230:6,17,19; 231:19</p> <p>syndromes (8) 77:8;88:17;129:19; 156:9;158:22;161:1; 187:7;213:13</p> <p>synthesize (1) 81:12</p> <p>system (1) 160:16</p> <p>systematic (8) 3:14,17;4:10;5:8; 14:22;18:22;83:16; 101:14</p> <p>systematically (1) 225:12</p> <p>systemic (1) 111:20</p> <hr/> <p style="text-align: center;">T</p> <hr/> <p>table (7) 75:10;161:21;173:12; 174:22;176:4;226:22; 227:10</p> <p>tabled (1) 216:20</p> <p>tailored (3) 198:2,15,16</p> <p>tailoring (1) 148:11</p> <p>takeaway (1) 9:11</p> <p>Takeda (2) 57:8;71:18</p> <p>take-home (1) 102:16</p> <p>talk (37) 6:14;8:6;19:10;26:6; 28:10;42:1,45;16;49;13,</p>	<p>16;51:1,7;52:5,6;53:16; 57:16;59:17;60:3;77:18; 79:6;112:21;143:9; 148:8,13;150:21; 151:17;152:9,12; 159:12;175:6;180:11; 188:4;192:7,8;213:20; 214:3;238:9;240:15</p> <p>talked (29) 7:15;12:17;23:22; 24:8;36:21;40:2;62:3; 64:15;88:12;102:1; 115:20;136:12;149:1, 13;151:5;153:2;163:11; 177:5;180:21;181:8; 186:13;201:10;211:3,9; 216:1;219:3,5;238:16; 239:6</p> <p>talking (31) 3:13,15;5:2;9:1;37:4; 55:9;58:1;65:14;76:13; 92:3;94:21;98:10;115:7; 123:22;129:9;133:7; 145:6;147:13;148:2; 158:8;164:16;168:6; 199:4;215:3;220:2,15; 222:18;226:3,4;228:10; 235:22</p> <p>talks (2) 135:11;142:8</p> <p>tampon (36) 151:11;164:9,18,22; 165:1,2;166:1;168:16; 170:13;171:2,3,16,21; 172:7;174:7;175:17,19; 176:6,10,16;177:17,22; 178:13,20;179:12,21; 180:4,5,10;182:18; 183:4;185:3,6,9,10; 187:9</p> <p>tampon-related (1) 175:22</p> <p>tampons (1) 176:22</p> <p>Tara (2) 227:15;235:17</p> <p>target (6) 71:15;77:11;130:16; 145:20;188:8;233:2</p> <p>targeted (3) 22:7;77:14;98:7</p> <p>targeting (4) 163:8;169:3,4;217:18</p> <p>targets (1) 217:22</p> <p>taught (1) 139:17</p> <p>team (3) 75:1;138:1,12</p> <p>teams (1) 238:22</p> <p>tease (1) 73:16</p>	<p>techniques (1) 41:16</p> <p>technology (2) 23:1;243:9</p> <p>technophobia (1) 127:22</p> <p>Ted (2) 107:2;114:22</p> <p>teeny (1) 200:18</p> <p>tells (1) 17:4</p> <p>temperature (2) 120:6,9</p> <p>temporality (1) 184:5</p> <p>temporomandibular (1) 200:1</p> <p>tempted (1) 19:18</p> <p>tempting (1) 19:20</p> <p>tend (3) 20:17;28:16;33:10</p> <p>tended (3) 24:20;113:6,10</p> <p>tender (1) 26:2</p> <p>tenderness (3) 25:21,22;41:9</p> <p>tends (2) 21:1;207:17</p> <p>term (5) 5:2;20:11;38:10; 94:15;239:18</p> <p>terms (37) 5:22;28:8;30:15; 45:13;49:2;51:8;56:21; 59:8;60:2,14;61:5,18; 64:16;67:21;68:21; 71:12;72:1;84:4;85:6; 90:3,18,22;111:20; 143:5;148:13;151:9; 153:2;169:12;179:3; 186:17;193:2,6,12; 194:17;208:8;212:16; 243:5</p> <p>test (44) 8:4;119:2;151:11; 164:9,15;166:1,2,4,6; 167:14;168:16,19;169:2, 9;170:13;171:2,3,16,21; 172:7;174:7;175:17; 176:6,10,16;177:17,22; 178:4,11,13;179:12,13, 15,21,22;180:11,19; 181:10;182:18;185:3,6, 9,10;187:10</p> <p>tested (3) 66:3;216:7;233:6</p> <p>testing (7) 8:3;40:3;41:21;63:1; 118:13;204:9;213:17</p>	<p>tests (1) 213:17</p> <p>Texas (1) 112:13</p> <p>Thanks (3) 42:18;77:1;240:18</p> <p>themes (1) 29:9</p> <p>theory (2) 49:17;108:16</p> <p>therapeutic (1) 224:2</p> <p>therapeutics (1) 221:7</p> <p>therapies (2) 22:8;179:2</p> <p>therapy (3) 98:7;130:15;149:22</p> <p>there'd (1) 157:12</p> <p>therefore (5) 153:13;154:4;179:6; 183:5;195:6</p> <p>thigh (2) 44:12,13</p> <p>thin (1) 131:7</p> <p>thinking (18) 19:21;73:22;76:4; 88:2;102:13;103:9; 134:2;137:2;153:22; 154:1;155:9;188:13; 193:15;217:1;219:6; 230:6;232:13;240:5</p> <p>third (4) 7:13;157:12;159:3; 207:13</p> <p>Thirty-five (1) 13:6</p> <p>Thirty-two (1) 60:8</p> <p>though (16) 43:10;76:13;79:9; 100:12;102:6;105:5; 108:7;124:14;133:6; 145:19;150:1;162:10, 22;196:12;214:14,18</p> <p>thought (13) 3:22;31:11;36:17; 64:11;66:8;80:7,14; 114:10;118:19;133:4; 149:20;212:11;237:17</p> <p>thoughts (4) 151:8;167:16;226:8, 11</p> <p>thousands (2) 109:10;221:20</p> <p>three (31) 25:4,5;27:1;29:13; 43:20;49:9;50:3;57:7, 12;61:18;63:2;64:1; 80:11;82:3;86:4;92:2; 100:5;128:14;129:7,13,</p>	<p>16;130:20;131:14; 132:16;157:8;187:6; 188:5;212:4;234:15,18; 235:3</p> <p>threshold (2) 95:19;114:17</p> <p>threw (1) 114:6</p> <p>throughout (9) 27:13;29:4;49:9;50:3; 82:14;127:16;143:12; 156:6;183:7</p> <p>throw (6) 94:2;118:3;119:16; 156:13;173:10;175:1</p> <p>throwing (1) 99:2</p> <p>thumb (3) 40:5;47:11,16</p> <p>thus (1) 69:15</p> <p>tight (1) 65:4</p> <p>times (16) 12:9;37:22;53:8; 80:11;91:11;95:8;113:7; 122:9;165:15;181:10; 191:1;200:9;208:9; 216:17;220:5;226:10</p> <p>tingling (1) 218:17</p> <p>tissue (1) 22:22</p> <p>title (5) 19:13,18;20:7;162:9; 163:1</p> <p>today (13) 3:16;4:1;5:2,12;52:5; 57:16;76:8;142:7,21; 144:11;153:19;226:3; 237:20</p> <p>today's (1) 145:2</p> <p>together (10) 6:18;26:13;27:1; 74:15;76:5;155:16; 187:20;190:5;227:10; 243:21</p> <p>tolerance (1) 47:11</p> <p>tolerate (1) 40:7</p> <p>Tony (1) 191:3</p> <p>took (9) 16:14;26:7,17;34:8; 136:3,5;204:10;241:9,21</p> <p>tool (15) 30:2;48:6;55:8,19; 118:2;140:13,14; 241:21;242:1,4,9,11,18, 19,21</p> <p>tools (11)</p>
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53:12,19;54:7,19; 55:10,10,11,13;56:22; 60:16;61:22 top (2) 58:22;59:7 topic (8) 50:9;85:10;86:11; 89:7;130:18;177:20; 216:16;232:9 topical (4) 112:16;169:5;187:8, 10 total (8) 39:22;43:18,20;65:19; 182:11;189:19,19,20 totally (6) 82:8;111:13,14;139:3; 197:22;222:1 touch (1) 241:19 touchscreen (1) 123:14 toward (2) 75:11;84:13 track (7) 84:11;110:16;111:11; 190:4;199:16;239:13; 242:21 tracked (4) 28:1;32:9;44:6;130:22 tracker (1) 238:7 tracking (3) 42:5;113:20;121:16 traditionally (1) 207:14 trained (1) 112:21 transcriber (1) 190:22 transcriptionist (1) 112:12 transition (1) 48:19 transitioned (1) 49:1 translatability (1) 70:6 translate (2) 178:3,4 translates (1) 126:22 translation (2) 70:8,11 translations (1) 70:7 translators (1) 70:5 travel (1) 196:5 treat (4) 60:10,19;145:16; 233:9	treated (6) 5:10;23:9;28:6;59:9; 92:1;112:6 treating (3) 28:8;156:12;169:22 treatment (30) 5:10;12:13;15:6,16; 42:7,8,10;46:3;57:15; 60:21;92:2;103:10,13, 15;106:13;107:2;108:8, 11,22;109:4;127:9; 134:13,14;161:17; 179:19;195:3,5,7; 201:11;233:14 treatments (17) 8:11;28:1,3,4,9,12; 29:7;32:21;42:5,5; 83:17;101:4;102:11; 103:15;110:20;111:14; 233:8 treats (1) 229:11 tremendously (1) 234:2 trends (1) 207:9 trial (80) 4:12;5:9;7:6;9:5; 12:14;13:21;14:13,14; 15:4,5,13;33:1;42:3; 60:22;62:3;71:12;82:14; 84:18;92:14;94:9;95:21; 97:1;98:4;101:20;103:8; 104:1,16,18;105:9,11; 107:7;108:3,11;109:11; 111:6,11;116:14;117:8; 126:22;129:15;130:13; 132:6,9;156:17,19,20; 159:17;166:14;170:16; 171:4,21,22;172:5; 177:2,9;179:7;181:1; 183:12;185:1,15;187:6; 191:22;195:2;200:21; 201:2,21;202:3,7,19; 215:16,21,21;216:19; 224:6;227:19;232:14, 14;234:17;238:12; 239:20 trialists (1) 207:11 TRIALS (66) 1:4,8;3:15,20;4:11,17; 5:7,14;6:1,4,6,16;7:2,10; 8:5,13,19;9:2;10:17; 12:2;14:2;23:12;24:9; 32:12,19;34:9;38:20; 40:19;42:16;53:22;55:6; 57:15;70:12;74:4,5; 92:14;93:3;96:14; 101:16,17;102:17; 107:14,19;115:18; 142:15,17,18;144:3; 155:11;156:22;157:22;	160:19;161:4,15;164:2; 170:13;189:6;212:15; 214:9,13;219:9;220:9, 15;238:14;239:15; 240:14 tribute (1) 29:5 tricky (1) 175:16 tricyclics (1) 42:14 trigger (1) 38:6 triggered (4) 29:21;37:18;38:1; 50:11 trivial (2) 30:10;129:6 trouble (1) 230:20 true (8) 18:20;49:21;107:11; 116:6;144:20;191:18; 221:3;239:6 truly (4) 94:4;110:5;115:18; 228:8 try (28) 8:3;15:18;26:4;29:18; 32:17,19;44:15;47:5; 74:11;76:10;77:9;80:16; 98:3;100:20;104:2; 117:6;142:17;156:17; 160:20;180:4;184:17, 18;187:2;207:3;209:14; 214:13;227:6;235:21 trying (20) 30:12;74:7;76:7; 80:21;99:7;118:16; 155:1;168:17;171:8; 178:6;202:15;210:16; 212:11;214:4;223:22; 229:7;231:2,3;238:9,13 T-test (1) 11:18 TU (16) 154:19;158:15,15; 173:5,7,7,18,20;174:22; 182:6;186:2;223:14,16; 237:17,18;239:4 TURK (54) 73:7;75:1,5;77:1; 78:22;79:4;80:2;83:8; 84:8;85:22;86:13;87:13, 15,18;88:6;89:6,13,16, 19;92:8;96:5;97:2;99:7, 22;100:17;102:15,22; 103:2;104:5,11;106:6, 22;108:5;109:18; 112:10;114:15;116:21; 121:19;124:19;127:18; 128:2;131:3,13;133:21; 134:15,18;135:18;	140:1;141:1;163:6; 172:9;186:20;190:21; 211:18 turnaround (1) 81:16 turned (1) 10:13 turns (2) 24:19;84:3 twice (1) 37:18 two (57) 4:15;5:18;12:18,19; 13:13,22;15:10;19:14; 21:4;24:22;32:5;33:15; 36:20;37:19,21;48:22; 61:11,21;66:15;70:2; 72:1,21;76:16;80:10; 82:3;85:11;86:19; 100:21;108:15;109:19; 116:11;120:17;129:1; 130:8;142:22;146:11; 155:5,15;157:8;158:9; 178:17;185:7,16;187:6; 189:10;190:15;199:18; 203:9,22;204:3;206:11; 222:4;225:8;235:8; 236:14;238:4;242:5 two-day (1) 109:16 two-grade (1) 140:20 type (14) 12:20;16:3;74:1,15; 76:17;93:7;112:8;143:4, 17;147:17,20;155:17; 178:20;180:5 types (15) 8:6;24:5;31:3;32:21; 34:12;36:10;41:15; 56:21;59:19;76:17; 142:14;153:3;154:3,10; 155:15 typical (1) 186:11 typically (5) 25:7;36:8;94:11; 106:9;157:10 typo (1) 12:3	21:2;30:10;42:12; 45:4;56:15;60:14;61:6; 67:4;68:1;69:8;122:2 ultrasounds (1) 159:18 umbrage (1) 114:15 unblind (1) 116:2 uncertainty (1) 159:22 under (5) 194:2,14;195:13; 198:5;200:22 undergo (1) 149:22 undergoing (1) 28:3 underlying (2) 23:12;157:21 under-report (1) 113:6 understandable (1) 79:16 understands (1) 127:1 understood (3) 113:6;157:7;228:9 under-studied (1) 196:14 undertaking (1) 136:16 underway (2) 76:1,10 underwent (1) 27:13 undifferentiated (1) 159:6 undue (2) 169:13,14 unearthed (1) 19:19 unfortunately (2) 157:14;237:20 unhappy (1) 106:12 unidimensional (1) 222:8 unique (2) 73:13;77:15 uniquely (1) 139:9 units (1) 130:4 universal (2) 59:12;239:14 University (7) 3:9;19:6;22:15;23:1; 52:9;73:1,5 unless (5) 48:9;176:5;186:16; 208:16;221:1 unlikely (1)
---	---	--	---	--

71:14 unnecessary (1) 222:1 unpleasantness (1) 184:3 unstructured (1) 32:4 untreated (1) 168:11 unusual (1) 138:3 up (100) 18:12;19:11;24:18; 26:8;31:2;32:17;33:12, 14;41:22;42:16;46:4; 51:21;67:16,20;71:6; 73:22;80:17;81:13,19; 82:5;83:5;84:3,21;86:3; 88:16;90:16;95:14; 97:11,16;98:11;104:18; 108:21;109:22;114:1; 117:1,5;119:13,16,21; 120:7,7;122:1,12; 126:20;132:9;134:19; 135:12;136:5;137:22; 139:12;142:20;144:20; 145:22;147:1;148:9; 149:3;150:15;152:13; 155:15;157:8;170:18; 172:3;173:10,17,20; 174:3;175:1;179:9; 180:7;185:13;186:17; 187:22;188:7;189:5; 192:22;196:2;203:2; 207:8,13;209:4;211:3; 212:11,17;214:16; 216:19;218:1,21;220:4, 5;221:18;222:2;223:5; 234:6;235:12;237:16, 17;238:21;239:19; 242:1,3 upgrade (1) 227:5 upon (4) 55:19;63:6;68:1;79:10 upper (2) 44:12;69:15 uptake (1) 55:5 urgency (11) 59:15;61:15,20;62:5, 5;91:5,6;93:8;132:2; 216:3;234:2 urinary (35) 32:6,12,15,20,22;34:1, 3;40:1;93:8;128:17,20; 129:3,5;130:8;132:1,8, 11;133:2,6;149:20; 190:7;215:22;216:2,11, 14;219:3,8;229:14; 231:10,13;232:20; 233:10,13,15;236:19 urinates (1)	133:11 urination (12) 129:11;132:19;147:8; 157:11;189:20;215:9; 216:6,9;217:2;223:10; 224:21;237:8 urinations (1) 10:7 urogynecology (1) 21:22 urologic (7) 20:6,11;25:1,17;30:4, 16;40:11 urological (1) 238:3 urologists (2) 21:2;212:12 urology (4) 19:5;20:17;21:22; 111:12 Ursula (8) 160:21;174:1;176:4; 177:12;187:3,4;225:5,13 use (50) 8:5,8;11:1;14:19; 16:21;39:22;44:19;45:5; 48:4;53:22;55:5,18; 56:14;57:14;67:9,11; 68:18;69:15,19,20,21; 83:3;89:3;100:19; 117:12;121:8,9,13; 123:13;126:6;135:12; 139:12;140:20,21; 142:14;163:1;165:1; 168:21;169:11,18; 172:11;176:13;182:4; 193:21;197:18;209:11; 211:16;224:10;241:17; 242:15 used (51) 4:17;9:6,13;13:10,21; 20:20;28:22;54:1;55:14; 61:4;62:2,22;66:16; 67:2;69:5,6,7;71:1,4; 74:8;92:17;104:19; 117:7;118:3;120:5,21; 121:14;124:9;126:14; 160:5,18;161:16,17; 166:14;171:9,20,20,22; 172:5;180:5;181:20; 187:11,12;189:6; 194:14;198:5;203:17; 238:5;241:21;242:4,19 useful (21) 21:19;29:12;48:6; 62:15;74:2;75:10;76:2; 78:6;95:5,12;112:4; 143:5;164:15;166:2; 174:11;176:13,17; 181:19;187:10;241:21; 242:1 uses (3) 17:9;40:3;128:7	using (37) 14:12;21:11;28:18; 33:2,11;34:2;35:9;38:6, 9;41:15;43:8;49:4;66:6; 68:5,20;69:12;82:15; 83:11;93:22;99:19; 112:18;119:1;122:4; 123:6,22;127:15;136:6; 139:18;179:3;182:3; 188:15,16;189:8; 194:17;205:14;226:5; 243:9 usual (1) 59:18 usually (6) 17:19;45:16;80:9; 97:5;131:20;242:22 uterine (1) 159:8 UTI (2) 8:1;38:7 utility (1) 46:7 utilized (1) 233:9	variety (6) 26:8;28:9;102:4; 110:15;158:21;198:6 various (7) 27:21;39:16;45:17; 79:13;137:13;164:12; 227:3 vary (4) 78:13;131:9;148:5; 206:22 varying (1) 177:17 vast (1) 121:19 Veasley (8) 48:11,11;151:16,16; 152:18,22;178:9,9 Venn (1) 26:19 venue (1) 52:17 verbal (3) 66:6;69:2,4 verbiage (1) 120:11 verify (1) 114:1 versa (2) 90:8;132:20 version (3) 69:12;80:22;81:14 versions (1) 66:3 versus (25) 43:11;67:17;69:2,10; 79:7;82:10;84:22;86:3; 87:3,3;88:17;91:17; 119:17;125:2,11,11; 126:17;129:10,11; 143:8;152:14;159:15; 193:22;231:5;242:15 vestibulodysnia (3) 164:18;178:10;185:16 vice (2) 90:8;132:20 view (8) 15:20;107:5,6;118:21; 146:8;158:4,11;194:1 views (1) 165:8 Vincent (15) 100:21,21;102:20; 153:5,22;155:5;156:2, 21;157:18;158:4,11; 182:17;183:14;199:18; 201:16 Virtually (1) 133:2 visceral (2) 159:3;213:7 visit (3) 77:19;78:10;239:3 visits (1)	178:15 visual (1) 47:15 voice (1) 117:1 voids (1) 140:6 volatility (1) 39:9 vomiting (1) 230:5 VPAQ (2) 184:2;186:9 VQOLs (1) 187:21 VRS (2) 171:9,10 VRSs (1) 184:3 vulvar (1) 198:19 vulvodysnia (25) 6:5;143:1,4;148:18; 151:4,8,10,18,20;152:2, 6,11;153:7;155:16,17; 157:9;163:4;164:7; 165:12,19;179:4;185:2; 186:4,18;187:5 vulvovaginal (4) 176:7;185:4;186:10, 10
V				
<p>vagina (2) 180:15,16 valid (2) 127:17;183:16 validate (2) 114:3;211:10 validated (10) 164:14;165:5;166:8, 15;168:1;171:13; 172:10,12;180:19; 181:21 validation (6) 139:18;172:5,12,15; 180:11;182:20 validity (4) 45:9,16;47:18;52:3 Valorie (5) 174:2,15;175:4;181:4; 243:20 Value (3) 57:18;105:14;131:21 variability (15) 14:5;39:6,10,17; 86:19,20;87:10,11;91:8, 13;96:10;98:2;196:21; 207:20;208:6 variable (6) 35:9;91:18;95:10,19; 98:22;193:13 variables (4) 34:5,16;210:13;237:2 variation (1) 88:16 varies (2) 98:13;132:21</p>				
W				
<p>wait (4) 29:15;76:9;162:14; 191:14 waiting (5) 73:6;106:10;107:1; 181:6;182:10 wants (4) 89:17;122:2;151:15; 243:1 Warren (1) 50:8 wash (2) 108:12;233:21 washes (1) 36:8 washing (1) 115:10 Washington (3) 1:18;22:15;87:2 watery (1) 59:13 way (65) 7:16;21:2;23:17; 26:22;31:17;34:19,21; 38:5;43:7,10,21;47:5; 48:14;49:12;54:5;58:16; 68:2,14;73:9;90:21; 95:10;96:2;100:14,17; 101:12;103:9;107:18;</p>				

113:10,11;114:11; 123:18;128:7;130:22; 131:16;146:18;147:14, 18;148:8;155:9,9;163:6; 168:7;169:5;176:12; 179:16;180:14;183:8; 189:11;192:18;196:9; 203:6;207:4;208:5; 214:19;217:4;220:21; 226:11;228:22;230:16; 232:10,22;233:20;236:2, 18;237:13 ways (13) 43:17;58:21;67:11; 68:5;73:13;119:3; 140:20;152:20;187:5; 199:18;207:8;227:18; 236:16 weaknesses (1) 19:21 website (1) 42:18 weeds (2) 87:16,17 week (44) 11:12;77:20;78:1,13, 15;80:15;85:3,13,14,17, 19;91:9;98:13;100:7; 101:11;104:19,19; 106:3;120:14;125:20; 126:2;144:2;192:13,16; 193:3,17,21,21;194:8; 195:6,12;196:15;197:9, 19;199:12;200:10; 201:1;205:13;207:2,13, 21,22;211:6,6 week-long (2) 97:6;98:22 weekly (5) 78:4;85:7,8;201:22; 204:9 weeks (44) 10:22;37:1,19;38:22; 39:7,13;77:18,20;78:16; 91:4,10;94:17;97:21; 103:12;104:22;105:2; 106:11;107:1,18;113:18, 20;115:4,5;116:9,11,20; 176:1;192:20;193:22; 195:5;197:19;198:4; 201:14;202:1,6,8,14,17; 204:3,3,9;206:1;207:17; 240:5 Weinfurt (1) 136:12 welcome (1) 50:14 well-conceived (1) 92:18 well-quantified (1) 206:21 weren't (5) 9:10;14:21;51:22;	113:7;188:2 WESSELMANN (15) 50:6;160:22;166:13; 170:5;173:8;174:6,14; 176:9;177:11,12; 180:13;187:4,4;225:6,14 Western (1) 178:6 Westin (1) 1:17 whatnot (1) 198:22 what's (18) 9:6;64:11;80:21; 99:20,21;105:18; 108:11;125:3,9;148:3; 194:3;198:8;200:12; 201:4;206:18;219:11; 237:1;242:8 wheel (1) 113:11 whereas (7) 65:4;68:6;87:7; 124:15;176:14;183:4; 195:12 Whereupon (4) 72:17;141:15;211:22; 244:10 wherever (1) 178:5 whole (23) 14:14;21:6;35:14; 49:10;69:1;72:1;85:17; 109:16;126:2;136:14; 137:14;138:1;158:21; 166:18;196:9;204:7; 205:6,15,16;218:7,12; 224:8;239:4 who's (5) 32:2;105:16;155:8; 180:9;202:2 widely (3) 24:4;55:13;181:20 widespread (11) 30:3;35:19;37:14; 41:13,14;42:13;44:6; 50:13;94:14,16;95:16 widespreadness (3) 29:11;46:18;47:4 Wiederhorn (6) 89:20,20;135:20; 137:11;202:5,20 willing (2) 29:7;139:5 win (2) 140:16;217:20 wind-up (1) 46:19 Wisconsin (1) 238:6 wisdom (1) 75:14 wise (1)	75:10 withdraw (1) 169:18 withdrawal (1) 240:14 within (24) 14:6,13;38:2;52:20; 54:3,13;55:5,17;56:18; 60:20,22;75:2;76:15; 84:18;90:2;92:2,99:11; 122:20;130:20;135:9; 137:13;207:14;238:8; 239:21 without (14) 7:12;12:19;77:10; 103:12;115:5;133:15; 134:13;162:5;166:5; 183:15;217:19;218:11; 234:2;243:22 woman (5) 32:7;36:12;154:4; 183:2;207:10 Women (23) 20:21;21:6,11,12; 28:16;31:5;32:20;37:6, 10;102:18;132:22; 151:20;152:2;159:9; 170:12;175:20;196:15, 19,22;197:12;198:17; 201:15;210:11 women's (1) 179:3 wonder (6) 93:12;148:18;149:4; 226:15,22;228:2 wondered (1) 86:20 wonderful (1) 126:21 wondering (5) 85:1;144:13;178:20; 199:11;229:12 word (9) 5:4;67:11;68:8;70:3; 89:17;127:19;139:18; 169:18;222:9 worded (1) 65:18 wording (5) 64:6;70:8,22;118:6; 128:5 words (4) 22:5;45:10;67:10; 105:19 work (24) 22:13;34:8;52:7;76:1, 3,4;85:6;88:14;89:2; 114:21,21;138:7,8; 139:19;149:3;161:22; 164:1,4;171:17;182:20; 202:12,14;208:21; 217:15 worked (3)	22:1;203:3;210:2 working (24) 49:6;54:14;55:22; 56:2,4,6,8,9,18,19,22; 57:1,5,6,10;71:16;72:10; 84:6,15;88:4;118:14; 121:20;181:5;206:13 works (6) 37:6;85:20;127:2,7; 150:6;207:5 world (10) 95:1;111:12;115:6,19; 134:2,10;158:5,6;178:2; 201:8 worms (1) 222:1 worries (1) 87:11 worry (4) 127:11;148:4;172:8; 226:21 worse (26) 30:4,20,20,20,21; 31:15,22;33:7;34:6; 35:7;39:5;45:20;83:21; 84:5;97:19;98:15; 103:20;105:6;108:4; 120:4,5;131:10,11,12; 186:9;225:3 worsened (2) 105:17,21 worsening (2) 33:22;34:22 worst (41) 66:5,18,21;67:1,2,17; 68:8,13,18,20;69:9,10, 20;70:1,3,13,15,18,19; 71:2;79:15;82:10,15; 84:22;85:3,7,14;87:8; 99:21;118:8,12,18; 125:10,11,13;152:14; 153:3;172:6;205:18; 207:15,18 worth (1) 240:16 wrap (1) 241:22 wrapping (1) 229:16 writing (1) 180:9 written (3) 32:17;173:20;176:15 wrong (5) 20:6;90:15;119:11; 127:13;198:1 wrote (1) 159:1	Y year (16) 27:9,13;29:5;41:19; 45:3;47:22;48:17,18; 92:2;94:22;114:12; 129:22;130:21;134:13; 160:17;242:13 years (24) 24:14;28:21;35:13; 36:20;41:19;49:9;50:3; 85:10;87:1,21;90:17; 92:3;93:17;110:4,7; 112:16;113:10;118:3; 136:5;208:22;211:19; 232:13,17;241:9 yes/no (1) 186:6 yesterday (32) 7:15;15:1;19:10; 21:15;24:8;31:10;32:10; 36:21;49:13;55:7;56:21; 62:4;64:16;67:16,20; 73:9;79:6;97:12;101:2; 115:8,20;116:12;117:6; 136:17;141:13;151:18; 154:8;213:5;217:9; 220:20;227:17;240:13 You-all (2) 25:10;243:18 younger (2) 120:21;123:7
			Z zero (3) 12:3;66:18,20	
			X	
			XX (1) 50:22	