

*ACTION - Chemotherapy-Induced Peripheral
Neuropathy (CIPN) Trial Design Considerations*

March 24, 2017

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Page 1

1 ACTTION
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 3 ANALGESIC, ANESTHETIC, AND ADDICTION CLINICAL
 4 TRIAL TRANSLATIONS, INNOVATIONS,
 5 OPPORTUNITIES, AND NETWORKS
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 8 Chemotherapy-Induced Peripheral Neuropathy (CIPN)
 9 Trial Design Considerations
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 12 Friday, March 24, 2017
 13 8:12 a.m. to 3:20 p.m.
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 17 Westin City Center
 18 Washington, D.C.
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Page 3

1 P R O C E E D I N G S
 2 (8:12 a.m.)
 3 DR. FREEMAN: Good morning, everybody.
 4 Welcome to day 2. Before beginning the agenda, the
 5 proceedings, what I thought I would do, very
 6 briefly, is just go over what I envision as being
 7 the goals of the meeting itself.
 8 Could I have the first slide?
 9 Yes. Well, I suppose housekeeping is much
 10 more important than meeting goals, so I want to
 11 read this, same slide that appeared yesterday. I
 12 see check-out time is 12:00. I was told that
 13 people were not speaking closely enough to the
 14 microphone, so when you have questions and
 15 comments, please, we are, as Bob Dworkin mentioned
 16 yesterday, recording the meeting.
 17 Next slide. My slide.
 18 So there were a couple of questions
 19 throughout the day, what is going to come of this,
 20 why we're meeting here. And I want to outline the
 21 point that Bob made earlier on, that there will be
 22 a work product that will be a consequence of this

Page 2

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	NIH Perspective on CIPN	
4	Ann O'Mara, PhD, RN, MPH	7
5	Patient-Reported Symptom Outcome	
6	Measures of CIPN	
7	Guido Cavaletti, MD	34
8	Clinician-Reported Sign Outcome	
9	Measures of CIPN	
10	A. Gordon Smith, MD, FAAN	62
11	Q&A and Panel Discussion	
12	Moderator: Jennifer Gewandter	94
13	Panel Discussion: Identifying Barriers to	
14	Enrollment in CIPN Trials During	
15	Chemotherapy	
16	Moderator: Ellen Lavoie Smith	133
17	Consensus Discussion	
18	Moderator: Jennifer Gewandter	190
19	Adjournment	319
20		
21		
22		

Page 4

1 meeting. It may be one or more work products and
 2 those will be manuscripts.
 3 They will be most likely first authored by
 4 Jennifer Gewandter, and all of you attending will
 5 have the opportunity, if you wish to, one,
 6 contribute and, two, be authors on that manuscript
 7 or those manuscripts.
 8 Just to give the background to this, there
 9 have been a series of very highly cited and
 10 influential manuscripts that have come out of these
 11 ACTTION meetings, that have really changed the
 12 landscape of the territories that they have been
 13 involved in.
 14 So we're hoping that, at the very least,
 15 this will have something that resembles the
 16 influence that those manuscripts have had. And
 17 it's worth looking, for those of you who are new to
 18 those meetings, at the ACTTION website to get some
 19 sense of the contribution to the field that the
 20 ACTTION has made.
 21 So our goals over here are to develop a work
 22 product that outlines a road map for a clinical

Page 5

1 trial to evaluate disease modification of
2 chemotherapy-induced peripheral neuropathy. And
3 this will be primary or secondary prevention, so if
4 you think of the slide that Pamela Horn showed, it
5 is that bar during chemotherapy.
6 By primary intervention, we mean before
7 chemotherapy is started, and secondary
8 intervention, we mean once chemotherapy-induced
9 peripheral neuropathy has manifested in one or
10 other ways. And by disease modification, we mean
11 to prevent or delay the appearance and/or slow the
12 progression of chemotherapy-induced peripheral
13 neuropathy.
14 That is somewhat different -- and I say
15 somewhat because there is a gray zone between
16 disease modification and symptomatic treatment,
17 which at times we attempt to make discrete, but
18 they're not as discrete as often as we attempt to
19 portray, a clinical trial to evaluate symptomatic
20 treatment of CIPN.
21 This is the acute treatment, so not chronic
22 treatment. For example, that was covered in the

Page 6

1 manuscript published a couple of years ago by Ellen
2 Smith. So these are the symptoms that appear, and
3 it's not just pain, during chemotherapy,
4 wonderfully portrayed by Joanna Brell's patient,
5 her case study that she showed yesterday.
6 Then -- and this may or may not be a
7 separate manuscript -- how to assess, how to
8 evaluate, how to measure chemotherapy disruption,
9 so the dose reduction, the discontinuation that
10 occurs during chemotherapy.
11 Then finally, there will be areas that are
12 unknown within 1 to 3, and those will be subject to
13 a research agenda, areas to study. And examples of
14 that may include the suggestions made by Scott and
15 Mike yesterday and reinforced by Sharon about the
16 ways to address in a combined, a composite, a
17 synthesized measure of chemotherapy disruption and
18 symptom modification, the example that Sharon Hertz
19 gave to an approach to chemotherapy-induced nausea
20 and vomiting would be.
21 So that territory is an example of what we
22 might consider to be research agenda.

Page 7

1 So that's the landscape. That's what we
2 would like to accomplish, at least to provide
3 Jennifer with the components of that manuscript,
4 and we will finalize that during the session this
5 afternoon.
6 So let me hand over to my co-chair, Jennifer
7 Gewandter.
8 DR. GEWANDTER: Good morning, everybody.
9 Thank you for coming back the second day to our
10 meeting. It's my pleasure this morning to
11 introduce Dr. Ann O'Mara. She is the program
12 director and head of palliative care research for
13 the Division of Cancer Prevention.
14 Presentation -- Ann O'Mara
15 DR. O'MARA: Thank you, Jennifer, and thanks
16 for the invitation. So my task was to give an
17 overview of the NCI's perspective on CIPN. So
18 three goals that I have, and as you read them, I'm
19 going to give you some background.
20 So I wear two hats. The first hat that I
21 wear is I am involved in the Community Oncology
22 Network, where we do cancer control symptom

Page 8

1 management trials. And I'm going to give you an
2 overview of that, building on what Joanna Brell had
3 talked about yesterday, but going to into a little
4 bit more detail about that clinical trials network.
5 And I'm going to highlight and show you some of the
6 trials that we have done through that network.
7 Then the second hat that I wear is I'm also
8 a program director for the investigator-initiated
9 pool of research projects that come into NIH or
10 into NCI and primarily focused on patients
11 undergoing treatment, and the toxicities, and the
12 psychosocial issues that patients experience,
13 looking at both longitudinal studies in clinical
14 trials.
15 Then I'm going to end with telling you a
16 little bit about what we've learned both from these
17 two portfolios, but more specifically what we've
18 learned from the NCORP portfolio.
19 So the NCORP is comprised of three
20 components. There is what we call the community
21 sites, the minority underserved community sites,
22 and the research bases. We do clinical trials

Page 9

1 across the cancer continuum. We do not do
2 prevention trials. I'm sorry. We do not do
3 disease-treatment trials. Those come from a
4 different funding mechanism. But what we do, do is
5 prevention, symptom toxicity, quality of life,
6 comparative effectiveness, and screening trials, so
7 really across the spectrum.
8 We also have added with this NCORP program
9 more health services, what we call cancer care
10 delivery. We have a high interest in disparities
11 and the underserved population, and then we also
12 work with the NCTNs, also known historically as the
13 cooperative groups, but now known as the National
14 Clinical Trials Network. Those are our old
15 cooperative groups, SWOG, ECOG-ACRIN, et cetera.
16 Along these same lines, there is a very
17 strong community, academic partnership. So what
18 does this look like? So the way I like to explain
19 it is that the research base, as we like to define
20 it, is our scientific engine. This is the group.
21 This is your SWOG, ECOG, Alliance. This is our
22 scientific engine.

Page 10

1 These are the folks that design the trials,
2 and conduct them, and actually manage the data and
3 analyze the data. Then we have our two what I call
4 accrual engines, the community sites which accrue
5 participants to these trials that I highlighted in
6 the previous slide.
7 We also, as I said, have a very keen
8 interest in minority and underserved. And we
9 actually have a number of sites where it is
10 composed of 30 percent minority or underserved
11 populations. So we're very, very interested in
12 that population.
13 So the first bullet is wrong. It's not 12
14 research bases. It's seven research bases. It's
15 five of the cooperative groups and then two cancer
16 centers, Wake Forest and the University of
17 Rochester.
18 Then we have 34 community sites and 12
19 minority and underserved community sites. But
20 across that, we really have 947 components and
21 subcomponents. So it's a really, really big
22 network. And then we also have over 300 of what we

Page 11

1 call cancer care delivery components that try to do
2 or implement health services research.
3 So it's really quite a big network, and this
4 is what it looks like nationally. So it's across
5 the country. I'm going to start backwards. So the
6 research basis, which is in yellow, several of them
7 are located in the Pennsylvania area in
8 Philadelphia, University of Rochester, then Wake
9 Forest, Alliance, and then SWOG out on the west
10 coast. So those are the little yellow ones.
11 The minority and underserved is your purple,
12 again, across most of the south and then up along
13 the east coast, and then the community sites. And
14 as you can see, we have both a distributive
15 network, which means it's a component, and then
16 there are other sites around it, and then a highly
17 integrated system where they're using similar
18 components.
19 The way they manage, the data comes to one
20 site, whereas the distributed is more of a loose
21 federation, as I like to think of it. And then we
22 also have small networks, small practices across

Page 12

1 the country.
2 So it's really quite diverse in terms of how
3 this network looks. And as you can see on the map,
4 it's really across the country.
5 So over the course of a number of
6 years -- it used to be called CCOP, now called
7 NCORP -- we have supported 14 clinical trials and 1
8 natural history study. And all of them were
9 pharmacological interventions.
10 As you look through that list, what you're
11 going to see is that they're all either FDA
12 approved, taking the agent and repurposing it, or
13 some sort of nutritional supplement of some sort.
14 Four of the trials included different
15 chemotherapies. Others targeted specific
16 chemotherapies. Taxane, cisplatin, and oxaliplatin
17 were the three that we had most commonly seen.
18 Seven were prevention and seven were established
19 CIPN, so it was evenly distributed.
20 Then all of the studies were
21 negative -- that's the big take-home message from
22 this trial -- except for duloxetine, Ellen Smith's

Page 13

1 trial. And as she pointed out, and several pointed
2 out, it was a modest change, and it was really a
3 subgroup that showed the best change. Then acetyl
4 L-carnitine actually worsened CIPN in that
5 particular trial.

6 So here is the list of trials. And as you
7 can see, it was really across all of our research
8 bases, starting from the old CCOP before 2014, that
9 supported these trials. And they were all pretty
10 much randomized. They were all RCTs. They were
11 all placebo-controlled. And except for the acetyl
12 carnitine, which I think closed early, they all met
13 their accrual goals.

14 Then here is the continuing list. And what
15 we did is we looked from 2006 through 2011, of all
16 the trials that we have done. So as you can see,
17 there was quite a few of them.

18 Our primary endpoints -- the later trials,
19 the primary endpoint was often measured with the
20 EORTC-CIPN scale as well as David Cella's FACT NTx
21 study. Interestingly, in the early years, when we
22 started to first see some of these CIPN trials, the

Page 14

1 primary endpoint -- and it goes back to one of the
2 discussions yesterday -- the CTCAE was a primary
3 endpoint in some of our very early trials. And we
4 moved away from that and moved into more
5 comprehensive scales.

6 But as Joanna pointed out yesterday, even
7 those measures, which are more specific, more
8 precise, have their problems in terms of precision
9 in exactly what we are measuring.

10 The other issue that I want to point
11 out -- and we talked a little bit about this
12 yesterday -- is the fact that, in most of these
13 trials, the primary endpoint was pain. It was not
14 numbness or tingling. As secondary endpoints in
15 some of the trials, we did look at functional
16 outcomes, but the primary outcome was primarily
17 pain. And the other scale that we also used was
18 the BPI.

19 So now I want to move and talk a little bit
20 about our portfolio, the investigator-initiated,
21 again during the same time period, 2011 to 2016.
22 And when we did this, one of our program analysts

Page 15

1 within our division helped with this. And he
2 really did a great job and, at the end, we asked
3 him to summarize what he thought about this
4 portfolio and about what our trials were all about,
5 and he had some interesting perspectives.

6 So first, I want to talk about some of our
7 funding opportunities. NIH in general is very
8 interested in CIPN, but we're also interested in
9 the larger issue of mechanisms of these symptoms.

10 It is not only CIPN that is problematic for our
11 patients, but fatigue is another one for which we
12 have a very poor understanding of the mechanisms.
13 Cognitive impairment is another one.

14 So as you can see, we have four that are
15 active. None of them really focused on CIPN, but
16 more along the lines of the underpinnings of
17 mechanisms of these different symptoms.

18 Since this slide was made, that one under
19 expired, PQ-9, can be moved up to active. It's now
20 PQ-12. NCI has a series of RFAs out called
21 provocative questions that was started under our
22 former director. It is an RFA, and we were lucky

Page 16

1 enough to have embedded in the last series of
2 provocative questions, PQ-9, which is the molecular
3 and cellular mechanisms underlying the development
4 of cancer therapy toxicities.

5 So it was very broad, but interestingly,
6 many of our applications were in the field of CIPN.
7 And we were successfully able to argue to the NCI
8 leadership that in renewing this RFA, that they
9 include this question again.

10 So it is active. It's now PQ I think 12 or
11 11. But it's basically the same wording, so our
12 interest continues to be in understanding the
13 mechanisms of these toxicities. And then the other
14 expired one that Joanna had talked about was the
15 biomechanisms of peripheral nerve damage and anti-
16 cancer therapy.

17 In this title, what I really want to point
18 out is that it's not just NCI that is interested in
19 CIPN. It is also arthritis, the Complementary and
20 Alternative Medicine Institute, us. Drug abuse is
21 very interested, dental is interested, general
22 medicine, child health and development, the

Page 17

1 nursing, and the neurosciences.
2 Across all of this are program analysts,
3 found applications or found grants that were funded
4 by all of these, different. The bulk of CIPN,
5 though, is funded by cancer and by neurosciences.
6 So during the period of 2011 to 2016, our
7 program analysts identified 61 grants among 81
8 researchers, totaling about \$23 million in direct
9 and indirect costs. Of those 61, 35 were
10 preclinical. And as you can see from the bullets,
11 there were a number of different biomarkers and
12 pathways that were being explored by our
13 preclinical investigators.
14 Two of those grants involved research in
15 both animal models and translational into cancer
16 patients, and the biomarkers and pathways are
17 identified within those two that they were trying
18 to validate in the human population.
19 I'd like to bring your attention to that
20 second-to-last bullet, where 4 of the 37 grants
21 used tumor-bearing animals. That is a very, very
22 low percentage. So primarily, these are animals

Page 18

1 that they're giving chemotherapy to. And our
2 clinicians and NCI staff have pointed out that
3 that's not the human condition of just giving
4 chemotherapy.
5 Our preclinical investigators have pointed
6 out that it is very difficult for getting these
7 tumor animals. The other issue that was brought
8 out in the meeting that Joanna talked about on
9 March 1st that we had on the clinical trials
10 planning meeting is the giving of multiple
11 chemotherapeutic agents to these animals.
12 So the translation to the human has many,
13 many challenges that we're learning from our
14 preclinical population and that the biomarkers were
15 assessed typically only at one point in time. So
16 those were some of the findings of our program
17 analysts from these grants.
18 So there were 26 clinical grants. There was
19 20 cohort longitudinal and there were 6 clinical
20 trials, and primarily amongst the cohort studies
21 that was looking at the trajectory of CIPN, a fair
22 number were genetic discovery and the development

Page 19

1 or testing of new assays or tests for measuring
2 CIPN.
3 Amongst the six clinical trials, two were in
4 acupuncture, two were in exercise, and then the
5 other two were in photon therapy and then the
6 nicotinamide riboside. I don't have the findings
7 from any of those. They have not published in
8 our -- our program analysts did not look into the
9 publications of these.
10 But I think the point that I want to make is
11 that bringing in a clinical trial through NIH is
12 very difficult. They have a five-year point in
13 time in which they can get it accomplished, and
14 getting access to the different agents' different
15 interventions can be very, very expensive.
16 A couple of myths. One myth that I hear
17 frequently when investigators call me is that NIH
18 is not interested in a collaboration with
19 pharmaceutical to test an agent. That is not true.
20 I have had in the past grants where there
21 has been a collaboration with pharma, and they have
22 actually implemented, not in CIPN, in other

Page 20

1 toxicities.
2 The other thing that I've also heard, the
3 other myth that I've heard, is that NIH is not
4 interested in any drug studies, which again is not
5 true. Again, as you can see, we've used photon
6 therapy and other agents, other interventions that
7 have been tested. NIH is not just interested in
8 behavioral interventions. They are interested
9 across the board. It's really the science.
10 The other question that is often posed to me
11 as a program director and to other program
12 directors is when investigators call, they'll say,
13 "Is NCI interested in this particular project?"
14 And my response back is, "Well, is the population
15 cancer?" "Well, yes." "Well, then, if the
16 population is cancer or it is a population that is
17 at risk for cancer, then yes, NCI is interested."
18 NCI's interest in funding is tightly
19 correlated, probably a perfect correlation to how
20 excited peer review is about the project.
21 So it's all about how it falls within our
22 pay line. And as you've heard, our pay line is not

Page 21

1 exactly robust. But that's NCI's interest. We're
2 interested in everything across the cancer
3 population, everything across patients at risk for
4 cancer, but the actual funding of it is based on
5 enthusiasm of peer review.
6 Now, that being said, I have had some
7 success in bringing forth applications that are
8 just shy of our pay line and bringing it to the
9 leadership for funding by exception. I have had
10 particular success, interestingly, in CIPN.
11 I've also had success in some other areas,
12 but I have had success with applications that are
13 just shy of the pay line. And so our interest and
14 funding really are -- they're parallel. There's
15 some overlap. But the actual funding is really
16 based on the excitement of peer review.
17 So our interest in mechanistic studies, so
18 it goes back to those clinical trials that I showed
19 you that were done through NCORP and the robust
20 negativeness of all of them.
21 So we have this 30-year history of funding
22 and supporting this science, and, as I said, a lot

Page 22

1 of negative. But what we also learned as we looked
2 at those studies was that many of these studies
3 were based on empiric data, a sample size of 10 or
4 15. We gave just 10 or 15 patients. We found a
5 good response. It's FDA approved for something
6 else. Let's give it a try. That's come back to a
7 lot of money we've spent to find out that they're
8 negative.
9 Now, was that a bad thing to do? No. I
10 don't think it was a bad thing to do. All of those
11 agents, we can take off the list because we found
12 that they were negative. So I try to put a
13 positive light on this, that we've learned a lot
14 from these negative studies, but by the same token,
15 they weren't mechanistically based.
16 So we have a really very high interest in
17 trying to understand the mechanisms of these
18 symptoms, and so within the context of this
19 meeting, in terms of CIPN. As was pointed out
20 yesterday, I think by Jennifer's presentation, the
21 natural history of symptoms and the natural history
22 of CIPN, we do not have a good handle on. And in

Page 23

1 order to get I think a better handle, that's where
2 our interest has to be.
3 I think you saw it in the NIH-funded studies
4 of the very few clinical trials that we have, that
5 the interest is primarily in longitudinal studies.
6 And I can't talk too much about projects that were
7 not funded, but in listening to peer review, when
8 investigators come in with a clinical trial into
9 peer review looking for NIH funding, if they don't
10 have strong mechanistic underpinnings to that
11 clinical trial, they will not receive a good score.
12 So I think that speaks to the 6 clinical
13 trials that have been funded over the last 5 years,
14 between 2011 and 2016.
15 This is Robert Korycinski. He was our
16 program analyst that did this review for us. And
17 as he read through it, one of the things he came to
18 see was that he felt like they were
19 operating -- our preclinical and our clinical CIPN
20 researchers were operating in two different
21 research paradigms, that the preclinical
22 researchers were investigating a variety of

Page 24

1 biomarkers and pathways, and that our clinical
2 researchers were examining many potential treatment
3 methods, and there wasn't this overlap. And you
4 saw that as I talked about our history of trials
5 that we did through the NCORP.
6 They don't seem to collaborate. One of the
7 things that we had Robert do is look not through
8 all of them, but through a lot of the preclinical
9 grants, and look to see if there was a clinical
10 collaborator or a clinical consultant. And a lot
11 of times, there wasn't. It was a group of
12 preclinical doing this work.
13 So that translation gets lost. I think
14 that's why we see so many of our models, of our
15 animal models that were used in these studies being
16 non-tumor-bearing.
17 Then the collaboration or at least frequent
18 communication should expedite. And when we had our
19 meeting on March 1st, we actually did bring
20 together clinical and preclinical investigators
21 who, from our readings and our understanding of
22 their work, they were very close to identifying

Page 25

1 some interesting mechanistic underpinnings and had
2 tested some agents within the preclinical model,
3 and maybe these were ready for moving into the
4 clinical arena. And then establishing CIPN
5 research teams with both of those. And that was
6 our goal on March 1st with that meeting.
7 Now, that being said, one of the interesting
8 things that I've learned over the
9 years -- particularly not so much in managing the
10 NIH portfolio or NCI portfolio, investigator
11 initiated, but more within NCORP -- as you saw, a
12 lot of these agents are FDA approved. And I would
13 argue, and not only for CIPN, but for many of our
14 toxicities, that interest of pharma is much less
15 than that interest that pharma has in our
16 disease-treatment trials.
17 So engaging pharma and trying to get pharma
18 to support these studies is very, very challenging
19 for our investigators. It's extremely challenging.
20 And I think that's one of the major barriers or
21 challenges that our investigators have, is drug
22 development.

Page 26

1 We have a very, very robust drug development
2 program at NCI for disease treatment. I confess
3 that we do not have that same drug development
4 program. And this is not a secret or anything. We
5 don't have it. We do not have a robust drug
6 development.
7 I think it has to do with a lot of pharma's
8 interest, or mild interest, in developing these
9 drugs for our symptoms and toxicities. It is what
10 it is. And so our investigators are very
11 challenged when they bring forth protocols to us
12 through the NCORP network of how are they going to
13 pay for this drug, how are they going to pay for
14 the placebo, because we don't support that through
15 that network. That's not how our funding stream
16 is. And drug distribution; you saw our network.
17 You saw it across the country.
18 So to provide that kind of funding is a very
19 expensive endeavor. So I would argue to you that
20 when we get to those phase 3 trials, those are the
21 challenges. Phase 1 may be a little bit easier.
22 It's single institution. Maybe you can get support

Page 27

1 for that. But once we start moving this out to a
2 phase 3, I would argue that's one of the biggest
3 challenges that we have.
4 So questions or should we wait for the
5 panel?
6 DR. GEWANDTER: Yes. I think we can have a
7 couple.
8 DR. O'MARA: Joanna?
9 DR. BRELL: Ann, do you remember -- well,
10 you said that there were studies to the NCORP that
11 had functional assessments at secondary endpoints.
12 DR. O'MARA: Yes.
13 DR. BRELL: Do you remember what any of
14 those were?
15 DR. O'MARA: They were primarily the
16 functional domain and the quality-of-life measures.
17 It wasn't anything like observing. It was more of
18 a PRO. I think it was mostly the functional domain
19 on either the EORTC or one of Cella's, David
20 Cella's.
21 Most of them are PROs because, again,
22 through that network, it's got to be quick and

Page 28

1 easy, so to do anything beyond that, it would be
2 difficult.
3 DR. DWORKIN: Ann, thank you for an
4 incredibly informing talk. I really appreciate it.
5 But I have to take issue with one thing, and I
6 think some people in this room are not going to be
7 surprised. To me, a single negative trial, like
8 for example gabapentin or amitriptyline doesn't
9 prove that those drugs aren't efficacious in
10 CIPN --
11 DR. O'MARA: I agree.
12 DR. DWORKIN: -- because, of course, that
13 could be a falsely negative result.
14 DR. O'MARA: Based on the measure, probably.
15 DR. DWORKIN: Well, I don't know. And Jen
16 just published an article examining all of those
17 trials in detail and comes to various conclusions
18 about that.
19 So I think it's essential to me, when I look
20 at that list of trials, to kind of think about are
21 these truly negative results or are they
22 potentially falsely negative results? And when I

Page 29

1 think about that question, I think about the fact
2 that there are about a half a dozen clinical trials
3 now of pregabalin in painful diabetic peripheral
4 neuropathy that are negative, but that's a drug
5 that's FDA approved for painful DPN and that,
6 around the world, is considered first-line.
7 So given half a dozen negative trials of
8 pregabalin and DPN, my issue with your conclusion
9 about those negative trials is could some of those
10 be falsely negative trials?
11 DR. O'MARA: Oh, yeah. Let's take a look at
12 some of them.
13 DR. DWORKIN: We could vote.
14 (Laughter.)
15 DR. O'MARA: I mean, yes. I agree. I
16 agree. I think part of it, too, some of these were
17 earlier, so we're talking 2006. And I don't have
18 all the details, but I think in our earlier trials,
19 it was a more mixed population.
20 So Charles, I'm going to pick on you. On
21 the gabapentin one that you put in, it was more
22 mixed, wasn't it? Wasn't it a mixed population, or

Page 30

1 was it all one agent?
2 DR. LOPRINZI: So I think it was a mixed
3 trial, and I could double-check on that. And
4 whether that's pro or con on it, yes. And there is
5 an interesting story about gabapentin, going back
6 to where it was first discovered.
7 It was first reported at an ASCO abstract
8 that 7 patients who were getting FOLFOX therapy
9 reported in 2000 at ASCO, saying they got
10 neuropathy and they started gabapentin,
11 100 milligrams twice a day. And if it didn't help
12 them, they went up to 300 milligrams a day, a
13 whopping dose.
14 Everybody knows I'm really being facetious
15 because that's a 10th of what you really can give.
16 And all of the patients were able to get up to 14
17 cycles of the FOLFOX therapy.
18 It was never published. But that was the
19 basis for it. And if you really go back -- and
20 I've done this recently. If you look at the
21 literature on this in patients with cancer, it's
22 just -- I'd love for it to be positive. And a lot

Page 31

1 of people say there are some patients it helps.
2 My newest thought process is maybe there are
3 some patients it helps, and maybe our trial is
4 actually true because there are other patients it
5 hurts, and on average, it doesn't do anything. So
6 I'm actually planning to look back at our data to
7 see, did we see disparity. A lot of people got
8 better on the gabapentin, a bunch of people got
9 worse, and the other group, the placebo group, was
10 just right on the line.
11 That might help fulfill that potential
12 thing, that it does help in some patients. And
13 then you stop it in the patients in whom it doesn't
14 help, and you get net benefit, and that might
15 explain clinical.
16 But it would be wonderful to be able to do
17 another trial in that area to try to solve that
18 problem once and for all because it's utilized a
19 lot.
20 DR. DWORKIN: Let me just follow up. I have
21 a car that's 10 years old that I love. And I would
22 bet my beloved car that if NCI gave Ellen Smith

Page 32

1 enough money to do a double-blind, randomized,
2 controlled trial of, say, 300 to 450 milligrams a
3 day of pregabalin in painful CIPN, that she'd have
4 a positive result.
5 The reason I'm saying that is because you
6 said that that kind of study can't be supported by
7 NCI, but of course it can be because pregabalin is
8 on the market and there are investigational
9 pharmacies all over the country that can
10 encapsulate pregabalin and placebo that would allow
11 Ellen to do a definitive phase 3 trial of
12 pregabalin and painful CIPN.
13 So NCI could, assuming Ellen wants to do
14 such a study, I don't know. But Ellen could do
15 that study, and someone could get my car if it's
16 negative, but I think I would end up keeping my
17 car.
18 DR. O'MARA: I think there's probably
19 prejudice within NCI on doing that kind of a trial
20 because of the negative. I think you'd have to
21 come up with a very strong scientific argument in a
22 very specific population of who you think would

Page 33

1 benefit from it, given the findings from Charles's
 2 earlier studies and the other studies --
 3 DR. DWORKIN: We'll do that over the coffee
 4 break.
 5 DR. EVANS: I would make one comment. I
 6 have a car that's 18 years old, so I need a new
 7 one.
 8 (Laughter.)
 9 DR. EVANS: I thought I'd make a comment
 10 about the sort of interpretation of negative
 11 studies, which actually we're pretty poor at, and
 12 you'll hear statisticians barking about confidence
 13 intervals all the time.
 14 But of course, high p-values don't
 15 necessarily mean -- they mean that you couldn't
 16 rule out an effect of zero, but it may also mean
 17 that you can't rule out effects of very important
 18 magnitudes.
 19 So that's why, looking at interval estimates
 20 and trying to figure out, can you rule out
 21 meaningful, or what you consider to be meaningful,
 22 effects with reasonable confidence rather than

Page 34

1 saying I've got a p-value of 0.4; therefore,
 2 there's zero effect, which is incorrect. You
 3 really have to look at interval estimates.
 4 DR. O'MARA: Sure.
 5 DR. GEWANDTER: Next, I would like to
 6 introduce Dr. Cavaletti. I'm not going to butcher
 7 the name of his school because I think you all know
 8 him, so here he is.
 9 Presentation – Guido Cavaletti
 10 DR. CAVALETTI: Thank you. Thank you very
 11 much for this invitation, although I'm not sure I
 12 can thank you for the title of my talk because PRO
 13 seems to be one of the hot topics. And what we say
 14 in Italy, a hot potato for me, because it's not so
 15 easy to have a look at this method to assess CIPN
 16 and my talk with a clear idea. So I'm sorry. I
 17 feel that we will finish my talk with more doubt
 18 than answers.
 19 Why is the issue so complex? We need to
 20 decide which is the best way to assess our patient,
 21 and we have discussed a lot yesterday, because
 22 assessment has a clear implication not directly on

Page 35

1 trials, but on the way we can conduct trials to
 2 identify what is the best approach to prevent, or
 3 to limit, or to rescue our patients when they are
 4 suffering from CIPN.
 5 So the discussion about the assessments and
 6 the assessments tool is one of the most complex in
 7 our setting, and it's one of the reasons why we
 8 don't have good data on the natural history of
 9 CIPN. And there is a clear need for such studies.
 10 So I heard a few minutes ago that this is
 11 one of the goals of the funding bodies here in the
 12 U.S. Unfortunately, that is not the case in
 13 Europe, where wellness on CIPN probably is lower
 14 than in the U.S.
 15 The issue of CIPN is completely different
 16 from the issue we find every day in the field of
 17 peripheral neuropathy, and one of the main reasons
 18 is that we have different actors playing a role in
 19 CIPN. Of course, the oncologist is treating the
 20 cancer, but he is inducing our problem. We as
 21 neurologists are faced with a side effect that we
 22 now know, but we have some difficulty in properly

Page 36

1 scoring and to find a common language with an
 2 oncologist.
 3 Finally, but not really finally, patients,
 4 and that's why we are talking about patient-
 5 reported outcome measure because at the end of the
 6 story, we need to understand which is our best
 7 approach to their problem, and we need that
 8 feedback to understand whether our attempts are
 9 successful or not.
 10 At the moment, the situation is like this.
 11 We as neurologists talk one language, oncologists
 12 another one, and patients even another. And unless
 13 we would be able to find a common language, we
 14 would go on like during the past years when
 15 oncology drug studies gave results, neurology-based
 16 studies another, and we learned later that patients
 17 have even another feeling.
 18 Look at this graph. This is a comparison
 19 just to show you which is the problem in talking
 20 between neurologists and oncologists. This is a
 21 comparison between TNS, and it is a composite scale
 22 used by neurologists and that oncologists do not

<p style="text-align: right;">Page 37</p> <p>1 like. The other is the grading based on the 2 NCI-CTC. 3 What you see in the graph is a nearly 4 perfect correlation between the oncology score and 5 the TNS. But this is the truth. This is what 6 happened in the real population when we tried to 7 make a comparison between our assessment as with a 8 neurological tool and oncologists' assessment with 9 the NCI-CTC. 10 There is a very wide distribution of the 11 results, so it is completely meaningless using 12 these tools and trying to make a comparison. They 13 are talking a different language. 14 So which are the best ways to approach a 15 patient? Which are the best outcome measures? We 16 have a wide option of possible measures: clinical 17 neurophysiological, QSD, composite scores, and PRO. 18 Which is the best? 19 Probably the answer is, there is not the 20 best or the gold standard at the moment, but we 21 need to know exactly what we can get from each of 22 these outcome measures. And once we have</p>	<p style="text-align: right;">Page 39</p> <p>1 using a PRO, I am looking for something that is 2 much more complex because there's a whole of the 3 difficulties expressed by that patient translated 4 into the impact in his or her quality of life. 5 What is extremely important in terms of 6 planning clinical trials is how long we need to 7 follow up on our patients to really see whether 8 there is an effect or not because this is just an 9 example. The literature is becoming quite full of 10 papers looking at long-term or system impairment in 11 patients with neurotoxic chemotherapy. And it's 12 very clear that a substantial number of these 13 patients years after chemotherapy still have 14 symptoms or signs. 15 So this is an important point in clinical 16 trial design. We need to look for these patients. 17 How long we need to look after these patients? Six 18 months after the end of chemo, one year, two years? 19 Of course, this is a huge implication in the design 20 of the trial, but it might be important even 21 looking not immediately after the end of the 22 chemotherapy, which is the outcome of the patient,</p>
<p style="text-align: right;">Page 38</p> <p>1 completely cleared what we are measuring, which is 2 the goal of our study, we can really perform a 3 selection and decide, among the different outcome 4 measure types, which is the best one. 5 In other words, we need to consider which is 6 the feeling of the patient, because we have learned 7 that using instruments, neurophysiology, for 8 instance, is completely useless. 9 I remember when I was much younger, that 10 there were studies where the primary endpoint was a 11 change in some meters per second in the conduction, 12 velocity. It goes much easier having positive 13 results in their studies, but unfortunately, there 14 was no clinical relationship from that study into 15 the clinical practice. 16 So the point is the quality of life of these 17 patients, this is important to be very clear. 18 Every time we are using a patient-reported outcome 19 measure, we are not looking for impairment. We are 20 looking for a change in the quality of life. 21 So we need to understand that if I'm 22 visiting a patient, I can grade impairment. If I'm</p>	<p style="text-align: right;">Page 40</p> <p>1 but maybe looking at the percentage of patients who 2 will remain persistently affected by chemotherapy. 3 So this might be a different endpoint from the 4 standard endpoint of clinical trials. 5 This of course means that we have to follow 6 up with these patients for a long period of time. 7 These patients have cancer, so we have to expect 8 dropouts due to recurrence of the disease or other 9 treatments and so on. So it is something that is 10 very peculiar of patients with CIPN. 11 But what happens if we try to do another 12 kind of comparison? Earlier, we tested 13 neurologists against oncologists. Now we are 14 testing neurologists against patients. It's a 15 complex graph. 16 But to make it very simple, if you look at 17 the bottom graphs, the ideal situation is having 18 this kind of graph, very separate curves, 19 indicating that there is a clear separation between 20 grades when we compare the neurological assessment 21 versus the CIPN 20 score, of course a patient- 22 reported outcome measure, reported by the patient.</p>

Page 41

1 On the left, you see this is the correlation
2 between the NCI-CTC and the CIPN 20. That is
3 fairly good. Lines are clearly separated, so there
4 is a very efficient discrimination between grades
5 across the two systems. But if we look at the
6 other two in the center on the right, the situation
7 is much more confused. And unfortunately, this is
8 what happened when we made the comparison between
9 pin perception and vibration, so two items,
10 including the TNS. That means that our
11 neurological examination did not correlate in terms
12 of grading with the CIPN 20 score.
13 Again, one is better than the other? No.
14 We are simply looking at two different ways to
15 assess the same thing, but we need to be completely
16 aware that if we include in the same trial, for
17 instance in this case, CIPN 20, and NCI-CTC, we
18 simply double the same result. We are looking with
19 two different instruments, and we'll have the same
20 result.
21 If we want to have two different kind of
22 evaluations, so make the comparison between the

Page 42

1 patient and the real neurological assessment, we
2 need to include something that these are a more
3 formal neurological examination.
4 So why collect PRO? They are not being
5 developed to perform clinical trials. They are
6 being developed to assess the quality of life of
7 the patient and to complement traditional scales.
8 Most of the PROs that are in use now, the
9 most widely used, have not been developed per se.
10 They have been developed as a complement of
11 already-existing quality-of-life scales. We
12 sometimes forget this aspect, but they have not
13 been designed to be used alone, which is our
14 advantage for the patient in our use of PRO.
15 Of course, they can provide us the input, so
16 we can have feedback from the patient how these
17 patients feel after our intervention or after
18 chemotherapy, and we can have the independent
19 opinion of this patient.
20 This is another tricky aspect of the
21 problem. It seems from several studies that asking
22 a patient a question or allowing the patient to

Page 43

1 fill in a question could produce different results,
2 even if the domain is the same. And one of the
3 suggestions that came up from these studies is that
4 the patient is care to reporting side effects to
5 the oncologist because they fear to be removed from
6 the treatment or having reduction of the dose.
7 So in a sense, they try to hide the severity
8 of the side effects. This is another interesting
9 aspect to be considered when we are analyzing
10 results.
11 We have generic PRO measurement, condition
12 specific. That's our case. But we have also the
13 possibility of using drug-specific patient-reported
14 outcome measures. This should be decided because
15 it's not so easy to design, implement, and
16 interpret a genetic condition-specific PRO, but the
17 limitations of drug-specific PRO are probably much
18 higher. So the decision should be taken.
19 It's not so easy. We know, for instance,
20 that there are very few oxaliplatin-specific
21 scales, but which is the use of these scales? So
22 we look very quickly at which might be the problem.

Page 44

1 We're using drug-specific PRO measurement outcomes.
2 The release of this kind of guidance was
3 extremely important for the success of PRO. This
4 is very clear. Regulatory agencies in the U.S. and
5 also in Europe sent a message, "We want to hear the
6 patient voice." And this was the basis of the
7 embedding of this measurement as a primary endpoint
8 in several studies and, probably, these PROs were
9 not really ready for this task.
10 This might be one of the arguments we are
11 taking into careful consideration when we decided
12 to develop new tools to be used as a PRO
13 measurement.
14 I took these slides from yesterday's
15 presentation because I tried to highlight some of
16 the points that I was impressed by yesterday. This
17 is a position of the FDA. We need one design,
18 placebo-controlled trials with appropriate
19 endpoints. And we want, for symptom assessments
20 and severity, and objective measures of functional
21 loss. Then we want symptoms selected for studies
22 that are validated using chemotherapy regimen in

Page 45

1 the disease studied.
2 So we need to start again from the patient.
3 And this is crucial because, if you go back to the
4 study population who are the basis of the currently
5 available PRO, probably not all these issues are
6 being properly addressed.
7 Not all the rules for the creation of this
8 PRO are being published, so we still don't know
9 exactly how these PROs have been developed. We
10 just have the result, but we don't know exactly
11 which was the mechanism of the basis of that
12 result, so we cannot exclude that there was some
13 selection bias, for instance, in the high attempts
14 included in the pre-selection and the creation of
15 PRO.
16 The big challenge is to have something that
17 can be used in different trials across different
18 kinds of cancer and to be the real measure of CIPN,
19 not specific, but condition related to CIPN.
20 The last slide was probably a question. If
21 we need to separate acute symptoms from chronic
22 symptoms -- I think this is not a question; this is

Page 46

1 a point. We need to separate acute symptoms from
2 chronic symptoms. There is no evidence at the
3 moment that there is a good reason for keeping them
4 together, although child studies on pain related to
5 [indiscernible], our study on acute symptoms in
6 oxaliplatin-treated patients, probably that's the
7 indication that those patients with the most
8 severe, acute toxicity at the end of the story tend
9 to develop a more severe chronic neurotoxicity.
10 But this does not necessarily imply that the
11 two events are pathogenetically related. This is
12 just a clinical observation, so before using acute
13 symptoms as an interesting endpoint, we need to be
14 really sure that they are two events that are not
15 by chance related, but there is a causal
16 relationship between the two.
17 So that comes to the problem of how to
18 create this PRO. This is, I think, a basic
19 statement. We need to keep everything simple, but
20 not too much. Otherwise, it seems to have solved
21 the problem, but we actually have created a big
22 problem because we are measuring something that is

Page 47

1 completely unpredictable.
2 Developing a PRO is a long process. It
3 takes years. There is no way to produce a reliable
4 PRO in a short period of time because the process
5 is like a circle. We need to start from
6 identifying which is the problem, and then talk
7 with the patient, talk with other healthcare
8 providers, check for the consistency of the items,
9 go back to the patient and test whether it works,
10 and then confirm that our new questionnaire is
11 consistent, is reliable, is valid, in a sense. And
12 validity of these tests is one of the most critical
13 issues to be clearly demonstrated.
14 You need to use something that is able to
15 detect changes. We need to have a movement of the
16 score consistent with the development of the
17 neuropathy, and this change must be as linear as
18 possible. That means that we should be aware that
19 once we believe we have a good questionnaire, you
20 have to go back to test again, and to see whether
21 it is really good in different contexts, in
22 different settings, and probably with different

Page 48

1 populations. That's why it takes so long.
2 Now, this is what we want, of course. I'm
3 coming from Italy, so this is perfection for me.
4 We are not so close at the moment, I guess. And
5 just to show that we are not perfect, I'd like to
6 go back to this old paper, 1998, from the Dutch
7 group, T. Postma and Aaronson, and they made this
8 comparison. This is very, very well known.
9 It was the first evidence that the scales
10 that were currently available at that time were not
11 suitable for performing clinical trials. And what
12 is surprising to me is that the agreement on an
13 important score was this.
14 NCI-CTC, for instance, grade 3, you know
15 much better than me, is a crucial step in the
16 assessment of toxicity. The agreement, the exact
17 agreement between different researchers was very,
18 very low, definitely very low. So the authors
19 concluded that if one would be interested in
20 incorporating patient opinion into the assessment,
21 something you should be implementing, 1998, and
22 they decided that it was start on the new

Page 49

1 questionnaire, that eventually became the CIPN 20,
2 to be used as a complementary tool to the
3 EORTC-QLQ-C30 questionnaire of quality of life.
4 Keep in mind 1998 when they started the process.
5 This is the QLQ-C30. That is a very, very
6 well accepted quality-of-life scale, validated in
7 different languages, different contexts, formally
8 released as a validated scale by the EORTC several
9 years ago.
10 This is what happened in the Dutch group.
11 They started with a very long process, and you see
12 that they moved across all the steps, which are
13 formally considered the gold standard for the
14 development of PRO. They started with selection of
15 the items. They tested, they pre-tested, and the
16 phase 4 that is actually the unfilled validation of
17 this scale is still ongoing, because there is still
18 something to be fixed in the CIPN 20 questionnaire.
19 They use a wide selection of cancers. The
20 number is low because this was the very first phase
21 of creating the questionnaire. This was the result
22 of the job, the scale based on the mix of sensory,

Page 50

1 motor, and autonomic items.
2 Patients have 4 lines to be filled in, so
3 they can grade from not at all up to very much from
4 0 to 3 or 1 to 4, 4-grade scale. The questionnaire
5 has been tested for consistency and validity and
6 overall is working quite efficiently.
7 As it worked quite efficiently, another kind
8 of PRO is the FACT GOG. Again, this is the basic
9 scale, the quality of life that is divided into
10 physical, social, emotional, and functional well-
11 being, so the typical domains you can find in a
12 quality-of-life assessment, and this is the part
13 dedicated to the neurotoxicities that have been
14 added to the basic quality-of-life assessment.
15 The structure looks quite similar. I will
16 go back in details and make a comparison between
17 the two later on. But what is different is that
18 here the patients have five grades to be used and
19 not four. It is not trivial. This means having
20 25 percent more possibilities to grade something
21 that might be good or might be trouble, and we show
22 why it might go to be trouble. Also, the FACT

Page 51

1 GOG-NTx has been tested in different contexts on a
2 wide selection of patients and, again, it works
3 quite efficiently.
4 Then we have other kinds of PROs that are
5 maybe not so efficient when they've been tested.
6 For instance, this is the Peripheral Neuropathy
7 Scale. That is a modification of a pre-existing
8 scale. It's a mixture of functional scale and
9 something that looks like the FACT GOG, actually.
10 And this is another of these questionnaires.
11 They decided to keep things very simple, a
12 completely different approach. What is the
13 threshold for severe toxicity here is highlighted
14 there. That means the patient reports to have some
15 impairment in their daily-life activities, in D and
16 E. And this might be confusing, but they added a
17 list of activities that should be considered when
18 you are reporting impairment. And this is very
19 important because it's not so common in these kind
20 of scales having a checklist of what you consider
21 as important in terms of daily life's activities.
22 Just to make clear the point, if I am a

Page 52

1 piano player, probably my concern is different from
2 my concern if I've been working on the road, for
3 instance. So what does it mean, daily life
4 activities? You need to have a list of which is
5 the reference when you are saying it's impacting on
6 my daily life activity.
7 Then we are moving to the oxaliplatin as an
8 example of what I believe is the worst approach to
9 a questionnaire.
10 (Laughter.)
11 DR. CAVALETTI: This is a mixture of
12 functional neurological impairment, self-reported
13 symptoms with a high risk of doubling results
14 because, in this case, every time you have a
15 positive answer in the upper limbs, it is very,
16 very, very likely you will have a positive answer
17 also in the lower limbs because oxaliplatin behaves
18 like this. If I have symptoms in my hands, 99
19 percent of the patients will also have symptoms in
20 the lower limbs.
21 What is surprising to me is that they
22 propose this kind of questionnaire to patients, and

Page 53

1 you have 10 lines to be filled in by the patient.
2 I think that, at the third line, the patient is
3 already bored and starts making crosses here and
4 there just to get rid of this questionnaire.
5 There is even a different approach. These
6 are a very classical questionnaires, but there is
7 something different that can be done. It's what we
8 tried to do within our academic European, American,
9 Australian network, that it's trying to see whether
10 it would be possible to create a different kind of
11 questionnaire, and we started from these
12 assumptions.
13 Most of the CIPN assessments available when
14 we started our project were based on a mix of
15 disability and quality-of-life items. Some of them
16 were not very, very clear, and they've not been
17 formally tested from the clinometrics standpoint we
18 were in 2010.
19 The big disadvantage of all these
20 questionnaires is that they are based on the
21 classic test theory. That means that moving from 1
22 to 2, from 2 to 3, or from 3 to 4 is exactly the

Page 54

1 same weight. Why, this is probably not the case,
2 actually, because when you stay on a very low
3 score, moving one grade from 0 to 1, probably has
4 no impact. Moving from 3 to 4, for instance,
5 probably the impact is much, much higher. So the
6 mistake that sometimes can be done is using these
7 kind of scales that are ordinal and analyze them as
8 they are linear.
9 There is a theory that I'm not able to
10 explain to you, and probably you are lucky because
11 I tried several times to understand the details,
12 but it's out of my capacity. This Rasch theory is
13 a statistical theory not accepted by all the
14 statisticians, but quite a few, that has the
15 capacity to transform ordinal to interval scales.
16 And based on the fact that the patient response to
17 each item depends on the difficulty of the items,
18 but also on the capacity of the patient to do that.
19 So with a rule that this is only a part of
20 the rule, there is a way. It seems there is a way.
21 I believe there is a way to translate these two
22 concepts into a linear scale that can be assessed

Page 55

1 in a linear way. I will show you what does it
2 mean. But again, the kick-off meeting, when we
3 decided to start this kind of project, was in 2011,
4 and we are not to the end of the story.
5 Ingemar Merkies was the leading person in
6 this project. So we started again with a search of
7 the items from the WHO/ICF list of items. We
8 selected 146 items from the pre-screening
9 selection. We tested with the patient. We go back
10 and we prepare a pre-questionnaire. Then we tested
11 the questionnaire in a population of cancer
12 patients with a stable neuropathy, 281 patients
13 with different kinds of cancer. We tried to mix up
14 the population as much as possible in different
15 countries, and this is the result of the analysis.
16 To make this very, very simple, these are 28
17 items with different complexity. So what you see
18 on the blue bar is the order. That means I am able
19 to do it without any problem. The green is, I am
20 unable to do that. And the red is, I am able, but
21 it's difficult for me.
22 You see that to get out of the bed, if you

Page 56

1 are not able to get out of the bed, it's very easy
2 that the weight of your impairment is relevant in
3 the scale, while if you are not able to run -- that
4 is the last line at the bottom -- it's acceptable
5 that you are not able to run, and the weight of
6 this impairment is much lower in the context of the
7 overall scale of some of the results that will be
8 analyzed.
9 So this is a different approach to the use
10 of PRO. In our validation phase, it was reliable.
11 It was varied across different conditions. In this
12 case, there is a comparison with the NCI-CTC. But
13 what we are doing now is to test for
14 responsiveness, because this is very important, to
15 see whether this questionnaire is moving and to
16 which extent it's able to replicate the changes we
17 are observing from a neurological standpoint in our
18 population.
19 We have just completed recruitment, and we
20 are waiting for the follow-up because we planned to
21 have a six-month follow-up after chemotherapy, and
22 we do hope to have the results reasonably soon.

Page 57

1 So we have discussed all the problems of the
2 PRO. Now, I'd like to move to conclusion to
3 identify which are the strengths and weaknesses of
4 some of them. And again, I go back to the FDA
5 slides because we need to look for efficacy. And
6 my first idea was to follow this advice, seek
7 advice from FDA clinical assessment group. It
8 would be much easier to ask them which is their
9 preferred PRO, but unfortunately, I'm probably not
10 allowed to skip my duties like this.

11 So we decided to use the CIPN 20 in our
12 study instead of the FACT GOG neurotoxicity. Of
13 course, we don't know if it was the right choice,
14 but I would like to show you why we decided to do
15 that.

16 These are the two questionnaires. Some of
17 the questions are pretty much the same in the two
18 questionnaires. For instance, you have tingling in
19 your hands and feet or numbness in your hands and
20 feet. These are the same in the two
21 questionnaires, so probably one is equal to the
22 other.

Page 58

1 Then you have discomfort in the FACT GOG.
2 Discomfort is a little bit generic for me.
3 Discomfort may also include numbness and tingling.
4 Using the CIPN 20, the question is a little bit
5 more precise because they are asking about pain
6 that is not clearly established in the FACT GOG.
7 Then cramps. You have cramps in both
8 questionnaires, but what is very surprising to me,
9 in the FACT GOG, you have joint pain. I'm not
10 really sure that joint pain can be considered a
11 sign of CIPN. In my mind, joint pain is something
12 different.

13 If one of my patients enters my office
14 saying joint pain, I will say, "You are not in the
15 right place probably. You need to go to my
16 colleague." So I don't understand why they
17 included this one.

18 Then trouble with hearing, of course, this
19 depends on the use of cisplatin. And in the
20 FACT GOG, you have another question that, if you
21 are buzzing in here, or ringing, probably if you
22 are buzzing or ringing, you have difficulty in

Page 59

1 hearing. So this is a question that simply doubles
2 the results on the question on hearing.

3 Have trouble with buttoning, yes, this might
4 be quite the same. But probably if you have
5 difficulty in feeling the shape of small objects,
6 you will also have difficulty in buttoning. So
7 again, probably there is a double result from these
8 two questions.

9 "I have trouble working." Why? This is not
10 very clear. You can have trouble working because
11 you are ataxic, you are weak, you are anemic,
12 maybe. There is a lot of reasons why you can have
13 trouble working.

14 The question is, on the CIPN, do you have
15 trouble working because you have foot drop? That
16 is a sign of CIPN, of the motor CIPN. This is very
17 clear. It's not ambiguous.

18 "I feel weak all over." You feel weak or
19 you have reduced strength? They are two different
20 things. So we prefer having a more clear
21 description, which is the symptom.

22 Then there are two things that are

Page 60

1 completely ignored by the FACT GOG. One is ataxia.
2 If a patient is unable to stand because he's unable
3 to feel ground below his feet, it's very, very
4 important. Oxaliplatin, cisplatin, the patient has
5 exactly this kind of symptom, and I think it's
6 quite interesting also having some information
7 about their capacity discriminate between hot and
8 warm.

9 So I think that the CIPN 20 and the FACT GOG
10 are probably both valid from the statistical
11 standpoint, but I would prefer using the CIPN 20
12 because the description of the clinical situation
13 is much more precise, at least in my mind.

14 This does not mean that the questionnaire is
15 perfect. Probably, I think that Ellen and Charles
16 agree with me that the CIPN 20 still needs to be
17 refined. Probably all the autonomic symptoms
18 section is not necessary. It just inflates the
19 score without having useful information. And the
20 reason is that our patients in general do not have
21 relevant autonomic symptoms, at least at the
22 clinical level, so probably this part of the

Page 61

1 questionnaire is not useful.
2 Another big issue, I will leave for
3 discussion, once we have found the perfect
4 questionnaire and we have a number, which is the
5 meaning of these numbers, how big should be the
6 difference between the two arms of our trial to
7 say, yes, we have done a good job? We have
8 something that is really important for our
9 patients.
10 This is of course not a trivial aspect and
11 deserves time to be discussed. So with this
12 dilemma, I leave you, and thank you for your
13 attention.
14 (Applause.)
15 DR. GEWANDTER: In the interest of time,
16 unless anyone has a burning question, [inaudible –
17 off mic].
18 DR. FIELDS: Can't hear you, Jen.
19 DR. GEWANDTER: I just said, in the
20 interests of time, I think we'll move on to
21 Dr. Smith's talk, and then have the questions and
22 the panel, because Dr. Smith's talk is kind of the

Page 62

1 counterpart.
2 So it's my pleasure to introduce Dr. Gordon
3 Smith. He is a professor of neurology at the
4 University of Utah.
5 Presentation – Gordon Smith
6 DR. G. SMITH: Thanks, Jen.
7 It's a pleasure being here. These meetings
8 are always fantastically informative, and I leave
9 feeling energized. And I'm confident we're going
10 to achieve something important here.
11 I was going to thank Roy for inviting me.
12 Here's Roy. And then I saw the topic I had, and my
13 first reaction was that should be easy. And then
14 my immediate second reaction is, wow, that's really
15 hard. And my third reaction is, there's not a lot
16 to say, so I can whatever I want, so I was feeling
17 pretty good. Then I realized that he put me after
18 Guido, at which point I was back to being annoyed
19 at Roy.
20 (Laughter.)
21 DR. G. SMITH: But all kidding aside, I'm
22 going to talk about clinician-reported or

Page 63

1 sign-based outcome measures.
2 This is sort of a road map through what I'd
3 like to talk about. And there will be some overlap
4 with Guido's talk, and that'll help with
5 efficiency. But I'm going to start off with what's
6 been done already, and I'll review some of the
7 lovely data that Jen has summarized yesterday and
8 really focused on the sign measures that had been
9 used in CIPN trials.
10 I'll talk about what's going on now in
11 ongoing trials, at least our ability in an
12 aggregate way to look at this. And then I wanted
13 to give two different perspectives, one a patient
14 perspective and the other sort of a perspective of
15 a clinician investigator.
16 This will touch a little bit I think on the
17 intersection between the last talk on PROs and
18 symptom-based assessments and sign-based
19 assessments in clinical trial design.
20 Then talk about the existing scales, and
21 I'll actually go over a little bit of what's been
22 done in the world of diabetes because we have a lot

Page 64

1 more scales in diabetes than we do for CIPN, and
2 then talk a little bit about aspirationally where
3 we ought to be going, what are the attributes of a
4 good sign-based scale, and why we might want to use
5 them, what the downsides are, and so forth.
6 So I'll start off by reviewing Jen's really
7 fantastic data, and this paper has been submitted
8 and I think is going to be one of the really highly
9 cited papers that come out of ACTTION activities.
10 As Jen told you yesterday, this is a review
11 of 38 articles. And these are the various outcome
12 measures and some aggregate data about them. Just
13 to emphasize how messy this literature is, while
14 about a little over half of papers pre-defined to
15 primary outcome measure and slightly fewer in
16 endpoint, only about a third did this and had a
17 prespecified analytic plan, which is causing some
18 chest pain in the back right of the room right now,
19 probably.
20 These are the different primary outcome
21 measures, and you'll see that they're all over the
22 board, including the NCI-CTC as the most common

Page 65

1 one. And you'll notice that relatively few of
2 these are actually sign based and the most common
3 split between the TNS and its various iterations
4 and then vibration testing. And that's not
5 necessarily good or bad, but it's just a statement
6 of fact.

7 These are the data across all the outcomes,
8 so most of these studies reported at least one
9 secondary outcome measure. And among all outcome
10 measures, you can see the frequency with which they
11 were used based on the type of outcome measure.

12 So for instance, 40 percent, so the
13 plurality reported only symptom measures, whereas
14 only two trials reported only sign measures. And
15 what you'll see here -- and this is surprising to
16 someone who spends a lot of time in the diabetes
17 world and another neuropathy, is that about a
18 quarter of these trials reported a sign measure at
19 all, and 5 percent reported functional measures.

20 And pegboard, as I showed to Pat, was the one that
21 was specifically mentioned in the articles, so I
22 thought both of these seemed relatively low.

Page 66

1 Keep in mind, these trials were not
2 necessarily pain trials, but there's a bit of a
3 pain flavor to them as a meaningful outcome. And
4 perhaps, I worry sometimes that in the CIPN, where
5 we conflate pain with neuropathy severity, this I
6 think is a tangible reflection of that.

7 So as I was thinking about this talk, I
8 reflected on my active experience of this in trials
9 that I've been involved in. One, I'm very involved
10 in and the other, I was involved in for about the
11 length of time it took to send an email.

12 So the first is one we were talking about
13 last night, that Joanna and I are involved in,
14 which is a gene-based therapy to CIPN. And this
15 was a fascinating experience to work with people
16 who are really more neurology and neuropathy
17 focused than cancer focused, other than Dr. Brell,
18 and thinking about how to design this trial.

19 It's not surprising to the oncologist,
20 probably, that the neurologist picked the primary
21 outcome measure of sural sensory amplitude, and
22 there was a lot of discussion about this. And

Page 67

1 among secondary outcome measures, the TNS was one,
2 and then basically risk of incident neuropathy,
3 either clinically defined or defined by clinical
4 features, and electrophysiologic features were the
5 secondary outcome measures.

6 My only other experience was I was at the
7 NeuroNEXT executive committee meeting a few weeks
8 ago, and one of my colleagues from another
9 institution came up and said, "Hey, can I have the
10 UENS? We're planning on using this as our sign
11 measure for a chemotherapy-induced neuropathy
12 trial." I said yes and sent the email.

13 I was a little surprised because it was our
14 scale, so I was flattered by this. But it's not
15 something that I think of as being used commonly in
16 the CIPN space, which to me was a sign of
17 desperation rather than of quality in our scale.

18 (Laughter.)

19 DR. G. SMITH: And so then I thought, well,
20 what are other people doing? Because I really
21 wasn't sure of what scales were really commonly
22 used other than the TNS. So I took a page out of

Page 68

1 Jen -- I channeled my inner Jen -- and I went to
2 clinicaltrials.gov and just looked through all the
3 different trials that are there.

4 So there are 34 studies for CIPN currently
5 on clinicaltrials.gov that are either enrolling or
6 not yet to enroll. And we see similar sorts of
7 phenomenon, unfortunately, going forward that we've
8 seen in the past. You can see that about half of
9 these are using any kind of sign measure.

10 Then the most illegible slide, I think, at
11 the entire meeting, these are the various sign or
12 functional measures used by these trials. And I
13 think the first point is, there is an enormous
14 array, given that only 17 studies actually were
15 using a sign measure.

16 For those that can read -- and I'm told
17 there will be a detailed transcript and I've had
18 slides on the website, the ACTTION website -- but
19 you can see that I've grouped these into
20 examination findings, balance and gait, QST, true
21 examination scales, and other stuff. And for
22 instance, grooved pegboard didn't really fit into

Page 69

1 the others.

2 I think the first point is that most of

3 these studies that are using a sign-based scale

4 aren't really using a scale at all. There are only

5 five instances of using examination scale, and I'm

6 being very permissive because just classifying

7 whether or not people have neuropathy based on the

8 Toronto criteria really isn't a scale, but I

9 included it there out of generosity.

10 It's much more common that either individual

11 modalities are used, and these are often poorly

12 defined. So we're just going to test vibration or

13 monofilament. Sometimes, they're more precisely

14 defined, but not always.

15 I was also impressed that balance and gait

16 functional measures are now being included more

17 frequently, which I think is a positive

18 development, and these are obviously not sign

19 measures, but they are at least often

20 provider-assessed measures. And QST seems to be

21 quite popular as well.

22 So I think the main point, as you can see

Page 70

1 from the back of the room, there's a huge

2 bewildering array of different sign measures, and

3 this has a number of implications for how we might

4 interpret clinical trials.

5 So I wanted to switch to patient

6 perspective. Joanna did a fantastic job starting

7 with this. I wanted to bring it a little closer to

8 home and just repeat some of the wisdom that Ted

9 Burns gave us at the Foundation for Peripheral

10 Neuropathy meeting. And a number of you were

11 there, and many of you know Ted.

12 Ted is at the University of Virginia. He's

13 a neurologist. He had a frontal sinus squamous

14 cell carcinoma and actually developed chemotherapy-

15 induced peripheral neuropathy. And we invited him

16 to the foundation meeting to give us his

17 perspective.

18 He not only has an interest in neuropathy

19 generally, but he has an interest in PRO

20 development and has developed his own scale called

21 the CAP-PRI scale, which we're validating across

22 multiple different centers, and we're actually

Page 71

1 using this in our CIPN cohort as well. He during

2 the midst of his chemotherapy would email us his

3 current CAP-PRI scores, which I thought was very

4 interesting.

5 The take-home point I took for him is that

6 this is a journey. It's not a point in time, and

7 Joanna did this beautifully yesterday. In this

8 slide, which I'll let you peruse, he thought about

9 his goals as a patient based on the time of

10 therapy.

11 Guido mentioned this, and Ted confirmed it,

12 and this was alluded to yesterday, that he actually

13 didn't want to tell his oncologist about his

14 neuropathy symptoms, and actually did not do so.

15 Even knowing all he knows about CIPN and the

16 ultimate risk this might pose him, he did not tell

17 them. He wanted to live, and if he lived with

18 neuropathic pain, that beat the alternative.

19 It goes to the ranking discussion that we

20 heard yesterday from our statistical colleagues.

21 But as he survived and got further away from the

22 turmoil and fear of his cancer and cancer therapy,

Page 72

1 this became more important to him.

2 So why do I bring this up? Well, for a

3 couple of reasons. One, his main focus was not

4 whether he had CIPN, but the functional deficits

5 this caused. So do I have trouble walking, do I

6 have pain, am I falling, and so forth, and what

7 bearing does sign measures have on this?

8 This is a quote from a neurologist. And

9 neurologists love neuropathy sign measures. Right?

10 This is a quote from his paper about CAP-PRI in

11 neurology. And just to emphasize, you don't have

12 to read the whole thing, but, "At no point did I

13 find any meaningful value in the status of my ankle

14 reflex, toe flexion, or extension, or sural sensory

15 amplitude," which really struck me.

16 This doesn't mean that these are useless

17 measures, but from a patient perspective and a

18 neurologist's perspective, it's somewhat surprising

19 to me. This just graphically shows his journey,

20 and he really didn't care about his CIPN status

21 here.

22 So I think this is something we need to

<p style="text-align: right;">Page 73</p> <p>1 think really carefully about, because our clinical 2 trials generally are here, not out here. And it 3 really goes to what Guido was talking about because 4 I suspect the performance of PROs and symptom-based 5 scales evolve over time. We know they do because, 6 here, Ted was denying his neuropathy. 7 Here, he was emailing his friends and 8 colleagues his CAP-PRI score, and here, he cares 9 about his CAP-PRI score. So this suggests this 10 kind of temporal bias is really important in 11 thinking about how we go about our measurements. 12 So conceptually, this is more of an 13 investigator perspective. What are the benefits of 14 using sign scales, and then what are the downsides 15 of using sign scales? 16 This is, to some extent, veering into Roy's 17 strawman territory because, of course, they're 18 useful. Why are they useful? Well, they provide 19 multi-modal information. They provide information 20 about different fiber types, and classes, and 21 functions, and this is important. They provide 22 impairment-specific data and topographical data.</p>	<p style="text-align: right;">Page 75</p> <p>1 looking through Ted's journey through CIPN. 2 Clearly, his report of symptoms was significantly 3 affected by where he was in his therapeutic 4 journey. Sign scales probably have some 5 susceptibility to this, but probably less. 6 But I think, most importantly, sign measures 7 tell us something fundamentally different, and here 8 I will fully embrace Roy's strawman, and I'll throw 9 up a couple of other ones, and we alluded to this 10 yesterday. 11 In a neuropathic pain trial, it is possible 12 that a positive result of an agent is because it 13 causes neuropathy, not solves neuropathy. I don't 14 know of any examples of this, but it's possible. 15 This is one of the reasons that biomarkers such as 16 nerve conduction studies are used not only as a 17 potential efficacy measure, but also as a safety 18 measure. So one could certainly fill up a strawman 19 where an agent reduced symptoms, but worsened 20 actual neuropathy by objective measures. 21 Perhaps a somewhat more plausible strawman 22 is that during the period of axonal regeneration,</p>
<p style="text-align: right;">Page 74</p> <p>1 And this is sort of a classic picture of distal 2 symmetric polyneuropathy. 3 As I start talked about individual sign 4 measures, one thing that's really important is to 5 think about just a very basic neurobiology of 6 neuropathy. That means that you can't just look at 7 the severity of sensory abnormalities in the toe 8 and then use that as a comprehensive metric of that 9 modality across a neuropathy patient or group of 10 patients. 11 We see this all the time with our starting 12 residents, who will come in and say, "In my 13 neuropathy clinic, I saw this guy. He can't feel 14 anything in his toe. He has no vibration, no pin, 15 no touch, and his toe is weak." Then you go, 16 "What's the rest of his body look like? I mean, 17 the toe isn't the problem. Or maybe it's a 18 problem, but it's only part of the problem." 19 Presumably, our sign scales are less 20 susceptible to this stage bias. And again, I 21 apologize to the statisticians. I don't know that 22 there is such a thing, but I made up the term in</p>	<p style="text-align: right;">Page 76</p> <p>1 it's possible that patients will have increased 2 sensory systems. We certainly see this clinically 3 in peripheral nerve injury patients. We see it 4 every morning when we wake up and have to shake up 5 our carpal tunnel syndrome. 6 So one can imagine, particularly in a brief 7 trial that doesn't follow long-term outcomes, that 8 there might be a phase of increased neuropathic 9 symptoms with nerve regeneration. And Pat talked 10 beautifully yesterday about spontaneously firing 11 subepidermal, dermal growth cones. 12 Imagine a scenario where the tight junctions 13 aren't the issue, and these growth cones are able 14 to successfully reinnervate the epidermis. Well, 15 during that phase of reinnervation, one might 16 experience increased symptoms, but improved signs. 17 And so I think this adds a dimensionality and is 18 something that we really need to include. 19 But what are the cons? And I can think of 20 three cons, and two are on this slide. One is, are 21 they meaningful to patients? We need to be mindful 22 of that. Our sign measures do have to have some</p>

Page 77

1 sort of clinical meaning, but we need to think
2 about it throughout the patient's journey, not at
3 one specific point necessarily, and particularly in
4 terms of long-term outcomes and functional
5 outcomes.
6 Then this is a quote from one of Guido's
7 papers. "These are frequently perceived by our
8 oncologists as being too complicated and time
9 consuming." And this kind of goes to the issue
10 that's come up several times about culture and
11 language between different specialties. I think
12 this is not so much about oncologists' perceptions
13 as it is about value in medicine.
14 There's a lot of talk about value. I think,
15 if we have sign scales that are valuable, that were
16 able to demonstrate value, clinical meaning, and
17 performance in clinical trials, I don't think this
18 is an issue. There's a little bit of
19 communication, perhaps, but if our oncology
20 colleagues are telling us that these scales are
21 difficult to use, that probably means they're
22 difficult to use, and we need to communicate about

Page 78

1 why that is and engage in a dialogue, because some
2 of them are difficult to use, some of them perhaps
3 less so.
4 The other thing I wanted to bring up is
5 reproducibility in sign measures. This is a slide
6 that I know Roy and others who live a little bit in
7 the diabetes world had seen. This is the most
8 surreal study I have ever participated in.
9 Peter Dyck, who most of you are familiar
10 with, is at the Mayo Clinic -- and I saw Charles
11 leaning over, making a comment -- did a study that
12 I don't think anyone else would have the chutzpah
13 to do or the courage. He wanted to look at
14 reproducibility and diagnosis of neuropathy. And I
15 was one of the people foolish enough to say, yeah,
16 I'll do that.
17 So what he did is took a group of patients
18 from the Rochester diabetic neuropathy cohort over
19 here. This isn't the way they normally dress, but
20 they were disguised for the first day of the visit.
21 And they were brought in along with a group of
22 supposed experts in diabetic neuropathy from Europe

Page 79

1 and North America.
2 It was as simple as we went through these
3 little cubicles in the Kahler Hotel wearing voice
4 distortion stuff. And they had sunglasses. We'd
5 plug in, and all we had to do was talk to them. We
6 could do anything we wanted aside from nerve
7 conductions, QSTs. We could bring stuff with us.
8 And we had to decide, did they have symptoms, did
9 they have signs.
10 This was great. I mean, these were all my
11 friends like Jim Albers, and James Russell, and Roy
12 was smart enough to see that this was a trap and
13 didn't come.
14 (Laughter.)
15 DR. G. SMITH: We went to Michael's, which
16 is now closed, I'm told, and had a really nice
17 steak dinner, and it was great. It was fun. And
18 it turned out that we were terrible. In fact,
19 there were about a quarter of us that had no
20 statistically significant relationship between what
21 we thought on one day versus the next day, when we
22 did the repeat evaluation.

Page 80

1 We were then brought back by Peter for
2 remediation a year later during a snow storm. And
3 the take-home point is if you agree ahead of time
4 on minimal criteria that one has to meet and make
5 this somewhat structured, you do much better.
6 This goes back to these trials that use just
7 10-gram monofilament or vibration. You can't do
8 that, even if you are an expert in the field. And
9 I suspect the reproducibility of this as we move
10 out maybe gets better. Maybe the non-neuropathy
11 experts do better. I don't know.
12 But clearly, this has implications not only
13 for just diagnostic reproducibility, but also how
14 we employ signs scales and simple issues of is the
15 vibration reduced or not. And if we don't have a
16 discussion about what this precisely means, it's a
17 problem.
18 So I wanted to show you just some scales,
19 and then because there are not very many to talk
20 about in CIPN, I'm going to go through each one of
21 these in a great deal of detail, courtesy of Chris
22 Gibbons, just so you can understand them. And I'm

Page 81

1 really not going to do that. I was hoping that
2 someone would chuckle, but you guys clearly think
3 I'm serious, and we'll just keep going forever.
4 (Laughter.)
5 DR. G. SMITH: Some of these will look
6 familiar to you, so the Total Neuropathy Scale and
7 so forth. I just wanted to show you three of these
8 from the diabetes world.
9 But first, this is a slide. These two
10 slides, Chris put together for the last ACTTION
11 meeting that I was at in which he had to give this
12 same talk, but was able to do so across all of
13 neuropathy, so he had a lot more stuff to work
14 with. So it was less rambling and conjectural, if
15 that's a word in mind.
16 So this shows the contributions -- I'm going
17 to point over here to this side of the room -- of
18 different modalities, a motor sensory reflex, his
19 cranial nerves, and general function of each scale,
20 and the scoring. You can just get a sense of the
21 variability in these scales of the different
22 modalities, and score, and weighting.

Page 82

1 Just to give examples, this is the most
2 commonly used scale in the diabetes world
3 historically, which is the Neuropathy Impairment
4 Score, Lower Leg. This hasn't really been used in
5 CIPN trials, or at least not much to my experience.
6 It has been used in the amyloid polyneuropathy and
7 is being used. And I would never have predicted
8 this would be a useful scale in familial amyloid
9 polyneuropathy, but it turns out to be.
10 This just shows the scoring of it, so these
11 are the muscle power grading, sensory grading,
12 various modalities, and the muscle groups tested.
13 And the points here are, no pun intended, that
14 there are an enormous number of points that go
15 toward muscle grading.
16 The way muscle strength is graded is with an
17 expanded MRC, which I'm going to talk about as
18 another strawman in a moment. This is the face
19 validity of this scale for problems like diabetic
20 neuropathy, CIPN, or frankly maybe to a less extent
21 FAP, is relatively low because they don't cause a
22 lot of weakness. These are kind of wasted points,

Page 83

1 and there are a number of other problems.
2 This is the Utah Early Neuropathy Scale,
3 which I show mainly to point out that there are
4 relatively few scales, TNS being the other one,
5 that actually map out the distribution and severity
6 of sensory loss, which can be useful.
7 But I will say that I love Guido's
8 discussion about the complexity of putting together
9 PROs, and I'm going to turn around and talk about
10 Rasch analysis in a moment. But I think sign
11 scales are put together in an even more random and
12 haphazard way. I put this together, and I did it.
13 It was like I had a cocktail. I was drinking a
14 bourbon one night, and I thought, you know, "I'm
15 going to make a scale and what's important," and we
16 came up with this. And it turns out to be useful.
17 I think what's alarming is it's just as
18 useful as the NIS-LL and other scales, which means
19 that they're probably all really flawed. So we
20 need to think more carefully about the clinometric
21 of our sign scales in the same way that Guido
22 talked about in terms of symptom scales.

Page 84

1 I'm just going to skip over that. So this
2 is the Total Neuropathy Score, which everyone's
3 familiar with. The original TNS included QST and
4 electrophysiology. And you can see how this is
5 scored. So their percentile scores on vibration,
6 and distribution, and in qualitative severity
7 descriptors across these various kind of ordinal
8 categories.
9 The TNS-C, which is here, which is being
10 more commonly used now, eliminates the
11 electrophysiology and quantitative sensory testing,
12 but leaves these seven domains in place.
13 Keep in mind my points about the potential
14 for signs and symptoms to be divergent and the need
15 to be mindful of this. This still is a composite
16 scale of symptoms and signs, which has its
17 strengths, but also has its weaknesses.
18 I wanted to give an example of the problem
19 of composite scales. I couldn't think of one for
20 symptoms and signs, so here, I'm going to show you
21 the data from the NATHAN study.
22 This was actually quite an impressive trial,

Page 85

1 400 diabetic neuropathy patients treated with
2 alpha-lipoic acid over four years. We talked a
3 little bit yesterday about the expense of doing
4 clinical trials, and this is a long one and really
5 an impressive achievement by Dan Ziegler.
6 It was negative. The pre-defined primary
7 outcome measure was a composite of the NIS-LL,
8 which I showed you a moment ago, and an
9 electrophysiologic parameter, so there is some
10 normal deviance, so again, something familiar with
11 the Mayo people.
12 But the reason this was negative -- and the
13 statisticians now are cringing even more and want
14 to take me off the stage -- is that the NIS was
15 positive, but the electrophysiologic measures
16 didn't change. So I'm not saying this is a
17 positive trial. I'm not convinced alpha-lipoic
18 acid is all that useful, but it shows you how the
19 amalgam of nerve conduction studies with this
20 clinical measure dragged down the clinical measure.
21 So one needs to at least be mindful of this
22 risk and composite scales, and I expect there will

Page 86

1 be a robust discussion of that. So I can go a
2 little more quickly through this because Guido
3 already brought up this idea of clinometrics and
4 types of data. But I'm not as smart, so I'm
5 assuming that there are very few people in here
6 who's confused about this as I am, but I'm going to
7 go through it anyway.
8 These are the ranking of different types of
9 data based on the level of information, going from
10 nominal, which is ethnicity, religion, gender, and
11 so forth, to ordinal, to interval, and to ratio.
12 And as Guido pointed out, I'm going to use the MRC
13 as a very real strawman about this.
14 Ordinal scales do not necessarily imply
15 linearity. And then ratio scales, which we don't
16 talk about a lot, are basically interval scales
17 where there's an absolute zero, so that you can say
18 the doubling of the scale has intrinsic meaning.
19 So if I say the doubling of my weight, I
20 went from 150 to 300, that's a times-2 weight, that
21 has some meaning to it because you know what zero
22 weight means.

Page 87

1 So let's talk about the MRC scale just to
2 give an example of why this is so important. The
3 MRC scale, which has been around forever, and every
4 neurologist and really every physician uses -- and
5 someone mentioned to me in casual conversation
6 about their MRC scale after an orthopedic
7 problem -- is displayed here. Everyone's familiar
8 with it.
9 Of course, this is the bane of existence to
10 neurologists, particularly neuromuscular
11 neurologists, because of the number of times we get
12 called by the emergency department, saying, "I've
13 got a patient who's got 4 out of 5 strength
14 everywhere." It's amazing that we're still using
15 it. The basic distribution of weakness in a
16 neuromuscular clinic is here. It's around 4.
17 So therefore, you'll see in the NIS-LL, the
18 strength grading is basically an MRC that's been
19 jury-rigged to have 4 pluses, 4 minuses, 3.75s,
20 these sorts of things to deal with the fact that
21 this ordinal scale obviously lacks linearity. And
22 we use this still, and I hate this scale.

Page 88

1 I still use this to track whether or not
2 patients are responding to therapy, getting worse
3 in a clinical setting. And strength scales often
4 include characteristics, if not the MRC or an
5 expanded MRC.
6 So this is a picture of Rasch, and I don't
7 need to go through this. There are a couple of
8 things. One, I'm appreciative of Guido for
9 willingness to explain this, because I don't
10 understand it at all. And Ted Burns and I were
11 actually asked to write an editorial on this, and
12 it scared the crap out of both of us. And we
13 managed to muddle through without anyone laughing
14 too hard.
15 So the first thing I want to say is, if you
16 have any questions about this, Dr. Cavaletti is the
17 person that you should be speaking with about
18 questions of this. And then I also appreciated
19 your recognition and admission that you didn't
20 understand it particularly well, either. So that
21 made me feel really good and somewhat less foolish
22 than I normally feel.

Page 89

1 So to go back to the MRC, there was an
2 effort to Rasch-transform the MRC. And I just
3 wanted to go over this figure because I think it
4 explains the problem in a visual way that, for me,
5 even though I don't fully understand even this
6 figure, is impactful.
7 So the top shows what an ideal kind of
8 5-point Rasch scale would look like. Right? And
9 so these are basically probability of a score given
10 a particular clinical scenario. So for a score of
11 5, you would see, as you transition from a true 5
12 to a 4, that when you're halfway there, there's a
13 50/50 chance that the patient is going to be scored
14 as a 4 or 5.
15 You can see these probability scores. And
16 you guys can't ask me any questions about this.
17 It's very ordered, and then there are ordered
18 thresholds with this.
19 So in this paper that I suspect Guido may
20 have been on, they did really a herculean effort to
21 Rasch-transform the MRC, including a very large
22 number of patients across different neuromuscular

Page 90

1 disorders, and then a validation cohort, I think,
2 in Guillain-Barre syndrome. And they did this by
3 muscle and even down to, like, the latissimus
4 dorsi. It's a beautiful paper, although somewhat
5 incomprehensible to me.
6 But this is an example of a muscle group
7 that had a normal kind of Rasch characteristic as
8 it were, and it looks a lot like this. But most
9 muscles weren't like this. So this shows the kind
10 of ordering and thresholds of a more typical
11 muscle.
12 You can tell that this is a mess and really
13 not likely to be a very useful scale in determining
14 when patients transition from one to the other. So
15 they actually came up with a Rasch-transform scale
16 that's shown here, which is a lot easier.
17 I talk the talk, but I don't walk the walk.
18 I often tell my residents and fellows about this,
19 and then they go ahead and give me the MRC score
20 over 5 points, so maybe I'll get there. But this
21 is now being applied, and we've already talked
22 about CIPN RODS. And there are now a variety of

Page 91

1 Rasch-transform scales across neuromuscular disease
2 and particularly inflammatory neuropathy, which is
3 where RODS came from and MMN. And I think there's
4 a Rasch-transformed CMT scale.
5 We have a Rasch-transformed TNS, which I
6 won't go into in detail except to say that it
7 eliminated a couple of the categories, eliminated
8 reflexes in autonomic from the 7 domains of the
9 TNS.
10 I think the last point I want to make goes
11 back to this slide I showed of where we are in
12 ongoing trials, which is everywhere and probably
13 nowhere at one time in terms of sign-based outcome
14 measures, and talk a little bit about common data
15 elements, which is not just an NINDS effort. I
16 think it's NIH wide.
17 But for some time now, there's been an
18 effort to bring some sense of order to the various
19 tools that we use in clinical trials. The problems
20 are listed here, that there are no widely-used data
21 standards, that researchers create their own data
22 instruments. This causes problems in comparisons

Page 92

1 between trials or even transforming data for meta-
2 analyses, and makes life particularly difficult for
3 people like Jen, although it's good career
4 stability for you. You're going to be able to do
5 this forever. This is really a problem for data,
6 data sharing.
7 One of the challenges in common data
8 elements is these are made in a reactive way.
9 Several of us have been to NINDS and asked to
10 develop common data elements for neuropathy trials.
11 And what I think was a really ironic,
12 Escher-like [ph] response was we'll get a trial
13 funded, and then we'll do your common data
14 elements.
15 We now have a trial funded, actually, and
16 are having that discussion. So I think working
17 with organizations like NINDS on common data
18 elements or NIH NCI and bringing order to this will
19 be very useful. I think that's one of the reasons
20 these sorts of meetings are particularly valuable,
21 because we've got people from regulatory funding,
22 industry, and academia here to think about this.

Page 93

1 So these are the conclusions. I do think
 2 sign scores provide unique value. We need to use
 3 them. They're underutilized in CIPN trials. I
 4 don't have it on this slide, but I think that part
 5 of the issue is the frequency with which we
 6 conflate pain and neuropathy.
 7 They're not always the same, and not all
 8 CIPN patients have pain. Inclusion of sign
 9 measures in any study is probably warranted, often
 10 even in pain-focused studies. They're all over the
 11 map. We don't have well-validated, or very many
 12 well-validated sign measures for chemotherapy-
 13 induced neuropathy, and we need consensus about
 14 this.
 15 There is I think a fairly urgent need to
 16 think of these in a clinometrically valid way.
 17 Again, Dr. Cavaletti will explain the statistical
 18 methodologies that underlie this and what we should
 19 do, but I too am sold on this idea.
 20 I think the last thing I wanted to do was
 21 just show a slide of Ted. I don't think Ted would
 22 mind me telling this. Now, we've learned, the

Page 94

1 community has learned earlier this week that he's
 2 likely recurred, which is very unfortunate. He's
 3 been kind of a guiding figure for me in a number of
 4 the things that we're working on collaboratively,
 5 including in this.
 6 So I just wanted to share that with you.
 7 Many of you know him, I know, and my thoughts and
 8 prayers are with Ted in this difficult time. And
 9 I'm hopeful that he'll marshal through and will
 10 continue to lead us in this effort. So hopefully
 11 I'm not too far over.
 12 (Applause.)
 13 Q&A and Panel Discussion
 14 DR. GEWANDTER: Thank you for all of your
 15 really good talks. Does anyone have any questions
 16 they'd like to open with?
 17 (No response.)
 18 DR. GEWANDTER: No? Okay. I'll start then.
 19 So I guess the question for me is, you both
 20 presented for measurement that we have a lot of
 21 options and nothing is great. So what can we as a
 22 group do? What can we propose to do?

Page 95

1 I think Guido with the current arms study,
 2 like, where are you guys, what would be helpful
 3 that we could propose that people should be doing?
 4 DR. CAVALETTI: We've heard this morning
 5 that there is a huge network already available for
 6 doing what we need now to test these kind of tools
 7 in a wide setting, in a community-based setting
 8 probably that will be much closer to the real-life
 9 population, and see if they work, and not stopping
 10 trying to do something better.
 11 This is not a satisfactory position now. We
 12 are working on our questionnaire. Probably other
 13 people can work on theirs. But if we will be able
 14 to test quickly this kind of questionnaire,
 15 profiting from these kind of networks, our network,
 16 the network is much larger here, we can reduce the
 17 amount of time that is required for the validation
 18 of these tests, and we can really know if they're
 19 working or not.
 20 So I think that this might be important as a
 21 message. We still need to get information. We
 22 have the platform where we can test these kind of

Page 96

1 tools. And it's not so expensive like performing
 2 an interventional trial, but can provide us all the
 3 information we are still missing.
 4 DR. G. SMITH: I would echo that. This is
 5 easy to do if you bring community together. And
 6 the best example I can think of is Ted's CAP-PRI
 7 score. There are, I don't know, 20 sites that are
 8 validating CAP-PRI. And we're gathering data in
 9 clinic and it's exceptionally easy. In fact, I
 10 don't even need a study coordinator to do it.
 11 We give the patient a form that the IRB says
 12 we have to give them. They look at it, throw it in
 13 the garbage. They fill out the CAP-PRI, which
 14 takes them two minutes. We fill out a RODS, which
 15 takes us a very brief period of time, and then we
 16 just send it off.
 17 So I think building on existing communities,
 18 research communities, or clinical networks to
 19 validate particularly brief PROs is useful. And I
 20 think this goes towards the usability of our
 21 scales, and one can probably do the same thing in
 22 terms of examination scales. Most of us live in

Page 97

1 EMR-driven worlds, and many of these are now built
2 into EPIC. And then that offers another
3 opportunity to gather these during routine clinical
4 care and leverage it for a better understanding and
5 longitudinal cohorts.
6 DR. RICHARDSON: Just one comment on EPIC.
7 You have to be very careful about that tool. We've
8 found it problematic from the point of view of CTC
9 grading, for example, when we tried to incorporate
10 it. They actually put in an old version,
11 version 3, I believe, and that was a disaster for
12 our CLCs, as you can imagine.
13 DR. G. SMITH: We've built all these
14 internally. That's a really good point, yes.
15 DR. RICHARDSON: Yes. That's a good point.
16 Yes, exactly.
17 DR. GEWANDTER: Ellen?
18 DR. LAVOIE SMITH: So I'm thinking about one
19 of the issues that came up yesterday when we were
20 talking about should we include patients with
21 diabetes, and if we do that, how do we evaluate
22 baseline neuropathy in these patients, in that many

Page 98

1 of our trials, we've said, "Well, if they don't
2 have any symptoms of neuropathy, then we let them
3 in the trial." But yet a pure symptom assessment
4 of these patients may not be enough.
5 But I think what I'm taking away from what
6 you said, Dr. Smith, I'm thinking about the fact
7 that these studies are done in oncology settings
8 and that these patients are recruited by
9 oncologists or an oncology team. And if getting an
10 accurate valid sign measure is impossible for a
11 neurologist, then it is really impossible for an
12 oncologist.
13 So I'm extrapolating and thinking that, are
14 we sort of saying that a PRO is good enough?
15 DR. G. SMITH: I'm not saying that. I'm
16 actually saying something different than that. But
17 I'll cut to the chase and say I agree with what he
18 said yesterday in just about everything and the
19 approach to this.
20 What I'm saying is, use of a sign, of a sign
21 measure in this particular setting, would be
22 problematic. So a diabetic patient, where you're

Page 99

1 trying to figure out, well, if they have
2 sub-clinical or sign-based-only neuropathy and
3 that's a patient we don't want to include in a
4 trial, that would be an issue unless you
5 pre-establish the criteria.
6 By and large, I don't think that's a
7 particularly useful thing to do because subtle
8 signs are very common. The way we became
9 reproducible was by agreeing that we were only
10 going to call people neuropathic from a sign
11 perspective if they had just overt signs, really
12 obvious stuff with age adjustment.
13 So I think if one wanted to do that, one can
14 come up with criteria that are easily applied by
15 oncologists and neurologists. I'm not convinced
16 it's necessary. I agree with the metaphor of
17 keeping this simple, and I actually think including
18 diabetic patients without clinically evident
19 neuropathy in CIPN trials is prudent, and one might
20 even argue advantageous from an enrichment
21 perspective.
22 I don't think we necessarily need to

Page 100

1 overcomplicate this issue. Most of us, when we see
2 a patient who's got overt diabetic neuropathy, we
3 know it. And I think, generally speaking, we can
4 rely on that.
5 DR. GEWANDTER: Dr. Dougherty?
6 DR. DOUGHERTY: So I have two questions.
7 The first question is really simple. Can someone
8 boil down to me -- I heard that there are problems
9 with all the tools, but what do we use today? It
10 sounds like the CIPN 20 is where the consensus is.
11 Then the second part of that question, as
12 Ann pointed out, there was a number of compounds
13 that have been tested. Some I think without any
14 scientific merit is pretty clear.
15 But with all that said of negative findings,
16 is that a function of the lack of quality in the
17 assessment tool, and how do we go about trying to
18 remedy that gap, which would then still exist?
19 DR. CAVALETTI: My personal opinion is that,
20 at the moment, the CIPN 20 is the best tool to be
21 used in these kind of health studies, provided that
22 we know that it will probably change over the next

Page 101

1 few years, what is most likely that would be
2 reduced to a possibly 16-item scale.
3 But at the moment, for the reasons I tried
4 to show you before, I think it is the best way to
5 address the issue at the moment.
6 DR. DOUGHERTY: So let me just break in
7 right there because that is a really important
8 point. If there's a consensus that, today, the
9 CIPN 20 is the best tool, shouldn't there be some
10 sort of a consensus statement from a CIPN working
11 group of some type to endorse that product so that
12 that becomes propagated across studies?
13 As I understand and I look at the landscape,
14 this to me is the biggest hurdle to overcome, that
15 there's no uniformity across the landscape as to
16 how things are being appraised.
17 DR. CAVALETTI: I think that oncologists
18 should be the right persons to answer this question
19 because, actually, the problem of using the PRO is
20 raised mainly by the fact that they believe that
21 they cannot assess properly the patient without an
22 instrument. So the use of PRO in a sense is an

Page 102

1 answer to their request to have something they can
2 rely on.
3 So I would like to have the opinion of a
4 couple of people in the room whether they like
5 CIPN 20 or not. And if they don't like it, what
6 they would propose instead of the CIPN 20.
7 DR. LOPRINZI: I can't hold back anymore.
8 (Laughter.)
9 DR. LOPRINZI: So what you guys said, I
10 thought, was beautiful. I thought it was music to
11 my ears, that sort of thing. Well, no instrument
12 is going to be perfect. It never is going to be
13 perfect, and there's always going to be room for
14 improvement in things like that and that sort of
15 thing.
16 The CIPN, using a PRO makes a ton of sense
17 instead of having it interpreted by the nurse or
18 the doctor. Okay? So that makes sense for all
19 sorts of different things. And people have been
20 talking about PROs for 10 years now or so. I've
21 been doing them for 30 years in all of our trials
22 on hot flashes, on mucositis, on anorexia-cachexia,

Page 103

1 and that sort of thing.
2 You can always validate all these. All
3 these validation sort of things generally show that
4 they work out or you change them moderately or
5 mildly. So doing a PRO is necessary. And I think,
6 Guido, I want your slide. I think you did a
7 fabulous job of putting together why the CIPN 20
8 makes the most sense.
9 Deb Barton, a colleague of mine, first
10 illustrated that to me on our baclofen
11 amitriptyline ketamine trial some time ago, and
12 we've been using it ever since that time. It's a
13 nice thing for doing it with either oxaliplatin and
14 with paclitaxel. It's using this exact same
15 instrument. You can compare and contrast what
16 you're seeing from there.
17 If I were in charge -- and I'm never in
18 charge at home -- I would not change the CIPN 20
19 instrument. Rather, I think that not analyzing
20 some of the data in there is plenty fine and all
21 that, but I'd rather keep it the same so you could
22 continue to cross-reference what you've gotten for

Page 104

1 other studies that have looked at it before.
2 There's an improvement in how you look at
3 it, and Ellen has looked at that a lot and all
4 those sort of things. I think you can use the
5 individual questions that are on it, the tingliness
6 versus numbness versus pain in hands and feet
7 versus hands versus feet. So it makes a ton of
8 sense from all of that sort of stuff.
9 I also think that using the CTCAE continues
10 to make sense because that's an even longer
11 historical perspective, and there are comparisons
12 between CTCAE and CIPN 20, and we just had another
13 paper accepted looking at that process of things.
14 So that makes a lot of sense. And I think
15 what was said about the examinations, and said it's
16 too -- we don't get much sense out of it. And I
17 think Peter Dyck's experiment, which I was not
18 aware of -- I know Peter Dyck well. He's the
19 oldest staff member at Mayo, and he's still
20 plugging along at 80-some-odd years old.
21 But we don't know what the references, what
22 the reflexes are on that sort of stuff. And if it

Page 105

1 was being done by neurologists who were doing these
2 trials, which maybe they would do for diabetic
3 neuropathies trials -- I don't know -- but they're
4 not in the mode. They're in the middle of clinic
5 for our patients that we see with chemotherapy
6 neuropathy that we're trying to prevent that, and
7 it's just impossible to bring them on in because
8 they're so expensive and hard to -- everybody's
9 busy with lots of other things. So those are the
10 thoughts that I had on it.

11 DR. GEWANDTER: Thank you. So Roy had one?
12 Sorry. Anna?

13 DR. O'MARA: So from a funder's perspective,
14 just to mix this up a bit, neither as a funder nor
15 our reviewers can really dictate to people seeking
16 funding what measure of the endpoint they're going
17 to use. That's a challenge. That's a huge
18 challenge.

19 DR. LOPRINZI: I don't think the funders
20 should necessarily do that, but I think it could be
21 a statement by a group of people. That doesn't
22 mean other people can't have other standards.

Page 106

1 DR. O'MARA: Yes, I agree.

2 DR. LOPRINZI: But it makes the most sense
3 to me, it's nice for people to use the same thing
4 so you could cross it. Years before, nobody would
5 do it, but I think Guido nicely put out -- that's
6 why we end up choosing that to look at. It just
7 makes the most sense.

8 There are a couple of questions in there
9 that don't make much sense and one that only
10 applies to men about erections, but you ignore
11 that. But it makes sense.

12 DR. DOUGHERTY: That was really the context
13 to the question. As Roy pointed out, he wants
14 product coming out of this.

15 DR. LOPRINZI: Yes.

16 DR. DOUGHERTY: One useful product is to
17 endorse a means of assessment.

18 DR. LOPRINZI: That this group thinks. That
19 doesn't mean everybody else has to use it.

20 DR. DOUGHERTY: It doesn't matter.

21 DR. LOPRINZI: Yes.

22 DR. DOUGHERTY: It's an expert group, and

Page 107

1 this was the consensus from the meeting.

2 DR. RICHARDSON: Pat, I totally agree with
3 both you and Charles. I would say, from my myeloma
4 experience in the FDA, we generated the myeloma
5 community response criteria, for example, that were
6 accepted and uniform. FDA endorsed that by saying
7 that this is accepted and validated clinically. It
8 goes forward.

9 I mean, this is about response criteria to
10 disease, obviously, but my point was that there
11 were response criteria all over the place as,
12 Charles, you may recall from your own exposure to
13 myeloma at Mayo. But the fact of the matter is,
14 that's how we got there. We got there through
15 consensus and documents that were validated going
16 forward.

17 So I agree with you, Charles. It makes
18 sense to use what's been there before and then
19 going forward, look to how that talk could be
20 refined, because certainly from what I've heard
21 today, CIPN 20 makes great sense, as does the CTC.
22 CTC for us will have to remain key because that's

Page 108

1 what we've used, and that's from a regulatory point
2 of view, the standard.

3 DR. LOPRINZI: People will argue the CIPN 20
4 hasn't been validated.

5 DR. RICHARDSON: Yes.

6 DR. LOPRINZI: There's always room for more
7 validation of validation of validation sort of
8 thing. It drives me crazy on there. But it has
9 been validated I think as well as anything else
10 was.

11 DR. RICHARDSON: Yes.

12 DR. LOPRINZI: There's still arguments about
13 how it's best to do it, and that's nature. That's
14 science.

15 DR. GEWANDTER: Gordon? And then Roy has a
16 question.

17 DR. G. SMITH: Don't let the perfect be the
18 enemy of the good. So I just wanted to reflect on
19 a couple of things about signs. One, I want to
20 thank you for thinking that neurologists are
21 expensive, because we usually feel undervalued, but
22 don't tell our dean because we're trying to get

Page 109

1 more. I think that point goes to what I think will
2 be some of the discussion in a moment about
3 recruitment, and culture, and how partnerships
4 between oncology and neurology look like. And we
5 can talk about that then, but I think that's
6 critically important to our shared success.
7 But this also goes towards both a
8 qualitative sensitivity on the part of those who
9 are designing these sign-based scales to those who
10 are using them. I think this goes towards Guido's
11 quote about the scales being too complicated. And
12 then the reflexes come up time and time again.
13 It's not surprising to me that in the Rasch
14 transformation of the TNS, the two things that
15 disappeared were autonomic and reflexes. I don't
16 think you have to be a rocket scientist or a
17 neurosurgeon to understand why that is.
18 So I think the application of clinometric
19 tools to evaluating these measures, as well as a
20 qualitative sensitivity to those who are actually
21 implementing them, will be very helpful. And I
22 totally agree with Pat that the deliverable from

Page 110

1 this ought to be a set of collaborative
2 recommendations about what ought to be done here
3 and now.
4 DR. DOUGHERTY: And then as well, just to
5 follow up on my original question that we then
6 dumped on or got away from, you then turned the
7 perspective back on history. And of the clinical
8 trials done so far in this indication, which used
9 what we would recommend as the current best tools,
10 didn't use those. So that would mean, then, that
11 the endpoints of those studies would still be
12 unknown.
13 DR. GEWANDTER: Thank you. So Daniela
14 actually had a question a while ago.
15 DR. DASTROS-PIEI: Just a quick follow-up
16 on the slides. It would be nice to have a
17 consensus if the signs scales are needed in this
18 clinical trial, especially for new active drugs,
19 perhaps. And if so, what would be the minimum
20 scale, minimum necessary?
21 DR. GEWANDTER: I think maybe you guys can
22 think about that, and we can talk about that in the

Page 111

1 consensus part, like if you could think of one sign
2 scale or a few would be the good ones.
3 DR. DASTROS-PIEI: A few or set of them? I
4 mean, I think there was something on a slide.
5 DR. DOUGHERTY: Thank you for bailing me
6 out.
7 (Laughter.)
8 DR. GEWANDTER: Jen?
9 DR. BRELL: So I agree that we should have a
10 consensus to use the CIPN 20, but that doesn't mean
11 it has to be the primary outcome or primary
12 endpoint. So within each trial, we still can have
13 different endpoints. Maybe we would use a PRO
14 that's more specific for whichever drug we happen
15 to be studying. But I think, yes, for consistency,
16 we should have it somewhere. It should be
17 collected somewhere in all of our trials.
18 I know this is a little bit off. We want to
19 keep this simple. We want to use, and expand on,
20 and improve on things that we're already doing.
21 But one thing I don't think we've talked about much
22 yet is a functional tests, and whether or not there

Page 112

1 are some good functional tests that we could use
2 that have some validity that could be quickly done
3 in the clinic, and maybe even a better way to
4 screen our diabetics that are entering trials and
5 people with other types of neuropathy entering the
6 trial.
7 So I would like to think some more about
8 this and maybe entertain this.
9 DR. GEWANDTER: I think that's a really good
10 point. Do any of you want to say anything about
11 functional scales or should we think about that for
12 later, too?
13 DR. G. SMITH: I could just make one point.
14 We have a couple of trials going on and soon to be
15 a third in diabetic or pre-diabetic neuropathy, and
16 we're really trying to look at the relationship
17 between biomarkers and functional scales. So we're
18 doing detailed kind of balance and mobility with
19 many best tests timed up and go, 6-minute walks,
20 and so forth.
21 I've been struck, even in just screening
22 diabetic patients, that the limits on mobility and

Page 113

1 function are often driven by other things that
2 dwarf neuropathy. And I think it's incredibly
3 important, but it's also really challenging. I
4 think Roy was going to say something.
5 DR. GEWANDTER: Roy?
6 DR. FREEMAN: A couple of things. With
7 regard to patient-reported outcomes, I'd like to
8 hear the case for actually using the CTCAE other
9 than for AE, because just looking at it in terms of
10 a scale, the granularity, the likelihood of
11 responsivity, it seems to me that it just is very
12 unlikely to be a valuable scale.
13 I've heard I think two speakers already this
14 morning making the case for retaining it. I want
15 to be more convinced. I like the fact that we're
16 moving towards some kind of a consensus, but I'd
17 like to flush that out a little bit more.
18 So that's one point. The second is -- and
19 this is a much more general statement -- to me, one
20 of the unfortunate aspects of developing scales is
21 only right at the very end do we assess
22 responsivity.

Page 114

1 It really strikes me as -- perhaps because
2 Guido is sitting behind me and watching how the
3 scale is being developed, it reminded me of a high-
4 performance Italian car, which looks perfect, has
5 all of the criteria that you would want in a car,
6 and then you attempt to drive it on a cold, snowy
7 morning in Boston, and it just doesn't do the job.
8 So to me, I think there are two aspects of
9 scales. The one is to characterize, and there, I
10 think that's relatively easy. We can characterize
11 function. We can characterize features of an
12 examination. But for a group like this, the most
13 important aspect is responsivity. How does it
14 respond to an intervention?
15 My concern is we only find that out after 10
16 years. And you're beginning to get there with your
17 Rasch-modified scale, but I'd like us to -- and
18 it's not necessarily part of this meeting. And
19 I've said this many times, for example, to Ingemar
20 when he has transformed his scale so that it has
21 perfect psychometric or clinometric
22 characteristics, does it actually work in the real

Page 115

1 world.
2 So that was the second point. The third
3 point relates to the clinical exam, the signs. And
4 Gordon was quite right. I felt that it was a
5 set-up. And it was a set-up. And I think it's
6 important to understand this, too. And I want us
7 to draw the right conclusions about the
8 neurological examination.
9 That scale, the NIS-LL, or the NIS, was a
10 scale that really emanated in the ALS and chronic
11 inflammatory demyelinating polyneuropathy world,
12 which this is a motor world, and it was
13 superimposed on diabetic peripheral neuropathy,
14 which rarely works certainly initially when we are
15 implementing clinical trials in the sensory and
16 autonomic world.
17 It failed in a number of clinical trials,
18 countless clinical trials. And one of the thoughts
19 was that it failed, or at least the hypothesis that
20 was behind that surreal meeting was that it failed
21 because the clinicians could not adequately
22 implement the trial, which may be true but

Page 116

1 unrelated.
2 It was not just neurologists. It was
3 actually diabetologists as well who attended the
4 meeting. And they were left, as Gordon said, to
5 their own devices, which is never a good idea. And
6 there was no reproducibility.
7 The second gathering, they were not left to
8 their own devices, and they were trained, which is
9 critical in any clinical trial when a PRO or a CRO
10 is implemented and told what's normal and abnormal.
11 And it was said, no microneurology. If it's
12 abnormal, then it's really abnormal, and then
13 reproducibility was actually very good.
14 So I actually think the message of that
15 experiment and of clinical signs are hard to
16 conduct a clinical trial with training for these
17 aspects to be really reinforced.
18 That aside, though, I think the question of
19 signs and utility of signs is a really very
20 important question, how it relates to function,
21 whether it is or is not an adequate surrogate. I
22 think it probably is a question that is worthy of

Page 117

1 another meeting, but that to me is the question
2 because signs may respond very early to an
3 intervention long before functional measures
4 actually change.
5 The implication has always been the tacit
6 understanding is that that's why we are interested
7 in signs. That's why we do neurophysiology,
8 because these respond early, and the
9 assumption -- and there are some data, but not
10 great data to suggest that this is accurate -- is
11 that this is a surrogate for a long-term benefit.
12 DR. GEWANDTER: So I think that brings up a
13 couple really god points. The first relates to
14 something that Gordon said, that maybe signs might
15 be more useful potentially for early prevention,
16 detecting early prevention or disease modifying,
17 and then the PROs might be more useful when we're
18 doing treatment. So I think the relative
19 usefulness of these, we might want to consider
20 differently for the different stages of the trials
21 that we're doing.
22 One other thing that I wanted to bring up is

Page 118

1 this idea of responsiveness. I think when you guys
2 talk about these and that surreal meeting, whether
3 you could diagnose healthy patients versus patients
4 who have diabetic neuropathy, that's a pretty big
5 difference, though. And our trials are trying to
6 potentially detect smaller differences and the
7 effects of the drugs.
8 So is there any merit to designing your
9 endpoint not only -- or choosing your measures not
10 only based on CIPN and the amalgam of symptoms of
11 CIPN and signs, but what you think your drug might
12 actually do.
13 I'm not a neurologist, so this might
14 actually be really naïve, but in treatment, at
15 least, I think about, I'm doing an intervention
16 that seems to help mostly for cramping, but really
17 not for pain. So if I'm going to do the CIPN 20,
18 there's a whole bunch of stuff in there. And am I
19 going to cover up a response to cramping that might
20 be really big, depending on who I include in my
21 trial. And obviously, I think we're glossing over
22 this idea that measurement's the only challenge in

Page 119

1 terms of whether a trial is inconclusive or
2 negative.
3 But is a composite that includes all of
4 these symptoms always the right choice? And I
5 don't know if that's the right answer. Anybody?
6 DR. LOPRINZI: I can comment, and maybe I'm
7 talking too much. But one, with the CTCAE, there
8 are pros and cons. It drives my wife crazy. What
9 are the pros and what are the cons for using it?
10 And the cons for using it is that it's not perfect.
11 The pros of using it are that it's got
12 history. We've been using it for a long time, and
13 it'd be nice to know, as we do in the future, how
14 we're comparing to that. It correlates very well
15 with data from other measures such as
16 patient-reported outcomes, such as the CIPN 20
17 instrument.
18 It's easy to do. The docs are going to do
19 it and whatnot. It's not perfect in any way,
20 shape, or form, but it's easy enough to do. We're
21 used to it. We've been doing it on lots of
22 different trials for lots of different times, even

Page 120

1 though it's really unproven.
2 Pros are going to be the primary endpoint.
3 They're much better. They always have been better
4 to ask it directly from the patient and have them
5 write it down instead of have it translated by the
6 nurse and the doctor. So that's going to be I
7 think where your more primary is, so that it's not
8 going to be as primary and it's not going to tap
9 the patient-reported outcomes.
10 So those, as I see it, make the reason for
11 continued use of the CTCAE. It's kind of like why
12 you put down the pulse and the blood pressure.
13 It's easy to do and all that sort of thing. We've
14 been doing it for forever and a day.
15 But as far as the other, you said there are
16 big differences between diabetic neuropathy and
17 normal people, and yet you're trying to find very
18 small ones. It makes all the more sense, more the
19 reason why the signs are going to be very, very
20 difficult to do. If you guys could find one that
21 you guys could do, neurologists, to make a
22 difference, and that us non-neurologists could do,

Page 121

1 and it's easy, that would be easy.
2 But also, I don't see a difference in the
3 treatment versus the prevention trials. It's still
4 patient-reported outcomes that should be the most
5 important things, I think, in there, unless you had
6 a fabulous sign that's going to --
7 DR. DOUGHERTY: One other thing, though, is
8 that we heard yesterday, that the FDA is interested
9 in a functional outcome as well.
10 DR. LOPRINZI: Yes. And if you could do a
11 functional outcome, that would be wonderful and
12 great, but what is it and let's --
13 DR. DOUGHERTY: I'm not disagreeing with the
14 patient-reported outcome, but I think if we can get
15 to the point where we're making a recommendation on
16 a PRO tool, then as well, in order to check the
17 box, as the FDA was guiding yesterday, we probably
18 need to at least come up with some type of
19 recommended sign or functional measure as well.
20 DR. GEWANDTER: I just want to clarify, and
21 maybe Sharon can help me with this. I don't think
22 when the FDA said "function," they mean signs.

Page 122

1 They mean like balance or -- right? Is that true?
2 DR. HERTZ: It does not have to be a sign.
3 DR. GEWANDTER: Did you have something else
4 you wanted to say?
5 DR. HERTZ: I'm interested in the question
6 of responsiveness because this comes up in a lot of
7 different therapeutic areas when trying to pick
8 scales. And it's a little bit of a chicken-and-an-
9 egg thing because if we don't have therapies that
10 we know work, because we have no way of detecting
11 them, how do we tell if the scale works?
12 So I'm wondering whether the use of scales
13 in longitudinal studies, where we know there's
14 going to be potentially progression, is one way to
15 do that. And if so, if that should be captured in
16 the discussion today. Because when you think about
17 different therapeutic areas that don't really have
18 known effective, consistently effective treatments,
19 the scale development issue comes up, and the
20 responsiveness issue is really challenging.
21 DR. G. SMITH: Can I comment on this?
22 Because I've got perhaps a different perspective

Page 123

1 than certainly the oncologists have. I mean, my
2 entry into CIPN was actually in the lab, but my
3 clinical entry was tackling, trying, struggling
4 with this issue in diabetic and cryptogenic
5 neuropathy, where the disease changes incredibly
6 slowly, and we don't have anything that works. So
7 how do you know your measures are responsive? It
8 could take forever.
9 So 20 years ago, when I first started my
10 job, I thought, "I want to figure this out. How am
11 I going to figure it out?" I need a disease that
12 its natural history is predictable, it develops, it
13 gets worse, and then it gets better on its own.
14 I thought, "Well, gee, that sounds like
15 CIPN." A lot of patients develop CIPN. They get
16 better. You know that they're going to get it.
17 This is a great population in which to validate
18 neuropathy tools.
19 My career has been spent repetitively trying
20 to do this, and we've made four different, I think,
21 attempts to collaborate to do this, and it finally
22 is succeeding. And we're now using both the tools

Page 124

1 that we've discussed here as well as others, and
2 skin biopsy and so forth, in an effort to look at
3 responsiveness.
4 And I guess my question for everyone and
5 somewhat of a challenge is, it's not perfect, but
6 it's certainly an appealing opportunity to do
7 natural history, longitudinal studies with these
8 metrics. And we'll know if they're able to detect
9 CIPN, and some people will get better. And we can
10 actually check their responsiveness during the
11 denouement [?] of the condition.
12 DR. LOPRINZI: We've actually done that. We
13 have natural history study trials with paclitaxel
14 and with oxaliplatin. Our calcium magnesium study
15 was a natural history straw, since the calcium
16 magnesium didn't work.
17 It shows that, over time, if you look at
18 scores, up here is good. They go down. You finish
19 therapy. For oxaliplatin, they get worse for three
20 more months, and then they go up to better. And
21 with paclitaxel, right when you finish it, they
22 start going up right away on average.

Page 125

1 So we know that, and we also have that with
2 CTCAE, that we have that sort of thing. So they've
3 shown that they're responsive over time in the play
4 field that we know get neuropathy. How do we know
5 it gets neuropathy? Because everybody tells us,
6 and we all know that chemotherapy causes
7 neuropathy.
8 But the scales do work. The CIPN 20 has
9 been shown like that, and across a number of
10 different drugs. So it works, not perfect.
11 DR. GEWANDTER: So Bob and then Ellen?
12 DR. DWORKIN: This conversation makes me
13 want to ask Mike McDermott a question, which is,
14 within Parkinson's disease trials, are
15 patient-reported, quality-of-life outcomes more or
16 less responsive to efficacious treatments than sign
17 movement disorder, objective measures, across
18 30 years of Parkinson's disease trials?
19 DR. MCDERMOTT: Less.
20 DR. DWORKIN: So the quality-of-life
21 patient-reported outcomes are less responsive to
22 L-DOPA, et al. than the objective measures?

Page 126

1 DR. G. SMITH: Yes. I mean, one caveat for
2 that, as a neurologist, we measure what we can, not
3 necessarily what we ought to. And so if you look
4 at -- and Mike probably knows this better than I.
5 I'm not a Parkinson's doctor. But the disability
6 and function in Parkinson's is driven, to a great
7 extent, by non-motor phenotypes. Right? And what
8 does L-DOPA fix? It fixes the motor phenotypes.
9 So the UPDRS is sensitive to motor changes
10 and responsive to a drug that changes motor
11 function, but what this also may mean is that the
12 drugs that we have that are effective and do elicit
13 a response aren't really meaningful for patients.
14 I don't know if I stated that.
15 DR. MCDERMOTT: But here, exactly the point,
16 I mean, things like quality of life make up so many
17 different things. That's why I think they tend to
18 be less responsive to treatments that are targeted
19 at specific things, exactly right.
20 DR. GEWANDTER: Is it about this?
21 DR. FREEMAN: It's exactly about this.
22 DR. G. SMITH: This is going to be on that

Page 127

1 Mike McDermott, a statistician, told me that I was
2 right about something, so that's good.
3 (Laughter.)
4 DR. FREEMAN: This really reinforces the
5 notion that we need to think of signs as potential
6 surrogates that may be reasonably likely to predict
7 a functional improvement. And I think the
8 Parkinson's studies really emphasize that, that the
9 signs may be more responsive to the intervention,
10 but there is.
11 We know, after years of study, that there is
12 a relationship between that improvement and
13 functional outcomes even though the one is more
14 responsive than the other. So I think this perhaps
15 reinforces the notion. I think there's always a
16 danger of going from one disease to another. But
17 to some extent, this provides at least some
18 intellectual support for the notion that signs may
19 be a surrogate.
20 DR. GEWANDTER: Gordon, in your data, you'll
21 be able to look at that. Right? Because you're
22 going to have signs and functional data, you can

Page 128

1 look to see?
2 DR. G. SMITH: We have signs and functional
3 data. In our CIPN cohort, I don't know. We're not
4 getting as much functional data.
5 I just wanted to emphasize Roy's point in
6 response to this concern that oncologists can't do
7 these fancy neurology tests and the take-home from
8 Peter Dyck's study.
9 It's actually I think quite simple. These
10 are not hard to do. The ones that are hardest, we
11 can get rid of and reflexes perhaps are that. But
12 our ability to grade sensation or strength actually
13 is good as long as you agree ahead of time what
14 you're grading. I don't think it's that hard.
15 I think that's the take-home point, that
16 there needs to be training and there needs to be
17 just criteria set. And these are simple. And a
18 year later with -- it wasn't detailed training. It
19 was 20 minutes sitting around talking, and our
20 reproducibility skyrocketed. And this included
21 endocrinologists who I think everyone recognizes
22 are not as capable as oncologists in doing these

Page 129

1 sorts of things.
2 DR. GEWANDTER: I think Ellen maybe will
3 have the last question before break.
4 DR. LAVOIE SMITH: I just want to go back to
5 the concern about the CIPN 20 and whether or not
6 it's potentially responsive. So I just want to say
7 that we have an ongoing RO3 that's a psychometric
8 study where we're specifically evaluating the
9 CIPN 20. And we've just collected data via
10 prospective longitudinal study where patients
11 completed the CIPN 20 at baseline and 12 weeks
12 later after getting chemotherapy.
13 So we should have some good data pretty soon
14 about that issue.
15 DR. CAVALETTI: A few things. We are also
16 doing in the States where we can make a comparison
17 between our two populations because in our response
18 to the study for the RODS -- for the Rasch-built
19 questionnaire, we were also testing other kinds of
20 measurements so we can test again the
21 responsiveness of the tool.
22 But I'm quite sure, as Charles said before,

Page 130

1 the problem is not the responsiveness of the scale.
2 The problem is which is the meaningful difference
3 between an active drug and a placebo arm. That's
4 the big point, and we don't have the answer. But
5 I'm not concerned about responsiveness of the
6 scale. We are sure that they will move.
7 There's no problem. We are using CIPN 20,
8 and we score them using the sum of the results.
9 And then we can extrapolate some of the items to
10 see how it works or not, as Charles was suggesting.
11 Actually, it is not exactly the scoring
12 system the RTC will release. And at the moment, we
13 are using this kind of scoring simply because the
14 official way of weighting the different items has
15 not yet been released by the RTC. But this is what
16 happened with QLQ-C30. It's not just the sum of
17 the scores. There's a manual that allows us to
18 score the system.
19 So that's why we need to be aware. We can
20 go on working on the CIPN 20, but we are working
21 with an instrument that is not validated. That is
22 a big point. I know that Charles is not happy

Page 131

1 about that. But I am not saying we don't use that.
2 What I'm saying is that, probably in the future, we
3 will have to rescore our previous data with an
4 official way of scoring and grading the results
5 that has not yet been released.
6 Scales. We are definitely overestimating
7 our importance. The TNS nurse is done by nurses.
8 It is very simple, just requires training. And I'm
9 not unconvinced that once we are planning a big
10 trial with 100 patients embedded into a trial, we
11 should be also able to train 20 people to perform a
12 TNS-C.
13 If you don't want to use a resolution of a
14 TNS as a grading system for responsiveness of our
15 treatment, we can use them for screening the
16 patients at baseline, and we can pre-define that if
17 a patient has a score more than, what you want, 2,
18 in that case, he has something that is peripheral
19 neuropathy. And if we don't want having a patient
20 with peripheral neuropathy into the trial, we can
21 use that threshold to screen the patient.
22 We are discussing yesterday how to say that

Page 132

1 this patient has a neuropathy that should be
2 included in the trial or not. This might be a
3 possible way.
4 Finally, my comment on NCI-CTC. In my mind,
5 there is only one reason for keeping the NCI-CTC
6 into the trial, and it is for historical reasons.
7 There is no other reasonable scientific based
8 reason for keeping the NCI-CTC into a trial,
9 because it doesn't work, and it duplicates the
10 result of CIPN 20. I have shown you that you have
11 the same results.
12 So the only real reason for keeping the
13 NCI-CTC into the trial is that we have the same
14 scale that we use over the last 20 years. But from
15 a scientific standpoint, it's complete nonsense.
16 There is scientific evidence that it's not useful,
17 so we should keep the tool because we have to work
18 with people that use the NCI-CTC for years, but
19 it's not working. So we need to be aware that it's
20 not working. We have to accept that point.
21 So keeping into the trial, but please be
22 aware that that it is not working.

Page 133

1 DR. GEWANDTER: I think that's a good note
2 to break on.
3 (Laughter.)
4 DR. FREEMAN: This was not preplanned, by
5 the way.
6 (Laughter.)
7 DR. GEWANDTER: If you can be back by 11:00,
8 so we can promptly start at 11:00, because we only
9 have an hour for the discussion on recruitment. So
10 that would be really good. Thanks.
11 (Whereupon, at 10:40 a.m., a recess was
12 taken.)
13 DR. GEWANDTER: We're going to get started,
14 so if everyone could sit down, please, that would
15 be good. I'd like to introduce Ellen Smith. She
16 is going to be chairing our next session. She's
17 from Michigan.
18 Panel Discussion
19 DR. LAVOIE SMITH: I think it probably would
20 be best if we start with introductions, since we've
21 heard more from someone here but maybe less from
22 others.

Page 134

1 DR. CLEARY: I'm James Cleary. I'm a
2 medical oncologist at Dana-Farber. I specialize in
3 GI malignancies and do early-phase clinical trials.
4 DR. WEN: I'm Patrick Wen. I'm a
5 neurologist at Dana-Farber.
6 DR. LAVOIE SMITH: So I've been asked to
7 moderate this session probably mainly because of
8 the duloxetine trial that we know was a positive
9 trial, but it certainly wasn't an easy trial to
10 conduct.
11 So I think what I'll do is I'll begin with a
12 brief story about some of the trials and
13 tribulations that were an issue with that study,
14 and then summarize, perhaps, several different
15 categories of areas that either have been raised
16 multiple times here at this meeting and/or that are
17 relevant to that experience with that trial, that
18 do, I think, influence recruitment feasibility.
19 And I'll just throw these ideas out, and then we
20 can discuss.
21 The duloxetine trial was conducted through a
22 large cancer cooperative group network, and at the

Page 135

1 time, that was the CALGB, which is now merged with
2 the alliance. So it was a randomized
3 placebo-controlled trial. We recruited 231
4 participants from probably somewhere around a
5 hundred sites. So the study was open at all of the
6 participating CALGB institutions and community
7 sites.
8 We had difficulty recruiting, and it took
9 probably a good 6 to 8 months before recruitment
10 picked up. So we were only recruiting perhaps 1 or
11 2 patients per month. And if you think about this
12 was open potentially at 100 sites, that was really
13 problematic. And so the CALGB DSMB was threatening
14 that we were going to close the study on several
15 occasions.
16 So ultimately, we were able to be
17 successful. So let me from there, perhaps, outline
18 some of the factors that I think either influenced
19 our inability or the challenges to recruit, but in
20 addition, factors that helped us to ultimately be
21 successful.
22 The first factors that I'll outline have

Page 136

1 really already been raised in one degree or another
2 throughout our conversations over the last several
3 days. So first, that feasibility is so obviously
4 linked to methods. So we've already talked about
5 how the eligibility criteria really impacts your
6 ability to recruit patients.
7 So for the duloxetine trial, because the
8 drug was an anti-depressant, because it had a
9 black-box warning label, the eligibility criteria
10 for that particular study was very stringent. We
11 did not allow patients to participate if they were
12 taking anti-depressants of any type.
13 Well, so what cancer patient isn't taking an
14 anti-depressant? So that was very challenging.
15 And there were other factors related to eligibility
16 criteria that, again, made it tough.
17 Next, related to the prior discussion about
18 measurement, we did not include any sign measures.
19 We used patient-reported outcome measures. Chronic
20 pain was the primary outcome variable. We used the
21 BPI.
22 So one factor that made it easier to recruit

Page 137

1 is that we had a simple way of evaluating the
2 outcome that could be implemented across multiple
3 sites without excessive training of staff, so that
4 was important.
5 Then there's the issue of the intervention.
6 So how interested are people in this intervention?
7 How difficult is that intervention to implement?
8 So related to how interested people were,
9 feasibility of recruitment is also very much linked
10 to getting people's buy-in about whether or not
11 this is an important trial.
12 So as we were developing this trial, again
13 within the cooperative group system, we were going
14 to be potentially recruiting patients that had
15 painful paclitaxel or oxaliplatin-induced
16 neuropathy, so we're really targeting mainly the
17 breast and the GI populations.
18 So as we were developing the study, it was
19 important that we worked with the physicians, and
20 the nurses, and the CRAs that manage those
21 populations. So within the cooperative group,
22 there is a very good mechanism for vetting when

Page 138

1 you're developing a study.
2 So you go to the breast cancer committee and
3 you talk to the breast oncologists. You go to the
4 GI committee and you talk to those folks. And
5 together, it's an opportunity to employ maybe
6 community participatory research techniques and
7 that you're getting input from a lot of folks.
8 So then the next issue that is very
9 important has to do with, again, what is your
10 primary outcome measure, what's your target
11 population, and as a result of those concerns, do
12 you need to do a multi-site study or can you do a
13 single-site study?
14 So this was a chronic pain study, and we've
15 already heard that chronic pain is not as
16 prevalent. So if only 20 to 40 percent of patients
17 develop pain, then you have to find those patients,
18 which means you need a multi-site approach to be
19 able to identify them. So at some of these 100
20 sites, we recruited 1 patient. So they opened the
21 trial for 1 patient.
22 Next, data collection methods. Again, we've

Page 139

1 already talked about how they have to be simple if
2 you're going to do a multi-site study. The timing
3 of the outcome measure needs to be aligned with
4 when patients are coming into the clinic anyway for
5 routine follow-up, so making certain that you're
6 being sensible and practical in how you align your
7 measurement.
8 Then there's the infrastructure. So again,
9 we had the CALGB infrastructure to help us with
10 this. We were able to identify dedicated
11 recruiters, dedicated nurses that were really
12 excited about the study, so they worked really hard
13 at their site. So some sites recruited 50-60
14 people because they had a person that really spent
15 a lot of time with it.
16 We ultimately had to open it up to the CTSU
17 mechanism, which is an NCI-based mechanism that
18 opens up the trial to not just the CALGB
19 cooperative group, but to all the other cooperative
20 groups, so ECOG and RTOG. So when we did that, the
21 recruitment numbers escalated dramatically.
22 The last thing I'll say, and then we can

Page 140

1 open it up to what folks think, there's an issue
2 that's important that has to do with training and
3 education.
4 We all know that when usually you open up a
5 study, it takes a while to get it ramped up. So
6 people don't remember it. There are many competing
7 trials. So here, you have a symptom intervention
8 study that sometimes is competing with the time
9 that an oncologist or hematologist has to give to
10 maybe a study that's all about treating the
11 disease. So there are those issues.
12 So we've found that we needed to continually
13 educate and remind. We used the Cooperative Group
14 Network, where everyone comes together a couple
15 times a year to, again, go to the breast cancer
16 group, go to the GI group, go to the nurses, go to
17 the CRAs, say, "Remember our study? Well, here's
18 what recruitment looks like. We're not recruiting
19 very well. We're at risk of having to close this
20 study. Can you do something to ramp it up, or what
21 advice would you give me as a PI? Is there a way
22 that I might amend this study so that we would be

Page 141

1 more likely to recruit?"
2 We had posters, so we had a big giant poster
3 in the lobby of the cooperative group meeting that
4 described the study, showed recruitment. So it's
5 sort of like it's advertising. It's getting the
6 word out, and then, again, keeping people updated.
7 We're recruiting well, we're not recruiting well,
8 we really need you, that kind of thing.
9 So let me stop there, and maybe -- I mean,
10 I'm not quite certain how we want to move forward,
11 maybe just open it up for comments or questions,
12 and we can go from there.
13 DR. KATZ: Hi. Thanks. I have a question.
14 I wonder if you could describe -- you gave a very
15 nice description of the heroics that you had to go
16 through once the protocol was initiated. I wonder
17 if you could talk about what came before that, from
18 the time of conceptualization of the protocol to
19 that first patient, what you had to go through, how
20 long that took before you could even get to that
21 point.
22 DR. LAVOIE SMITH: So the time that it took

Page 142

1 us from the time I wrote the initial concept, to
2 the time that we published our results was five
3 years. We had drug company support, so Lilly
4 provided drug and placebo. That meant that we had
5 to go through the scientific review processes at
6 Lilly. And they had two different divisions. They
7 had an oncology division and a neurology division,
8 so both divisions had to review the protocol, vet
9 it, provide feedback back, please change this,
10 please do that.
11 So that was one level of scientific review.
12 Then there was the scientific review at the
13 cooperative group level. So at that time, it was a
14 little bit more difficult, but you'd develop a
15 concept.
16 Again, you go to all these various groups,
17 you get their buy-in. Then at that point, there
18 was an executive committee within the cooperative
19 group. They had to approve it. From there, it
20 went to the NCI.
21 So all of that probably took -- I mean, I
22 don't know for sure, but I recall that it took a

Page 143

1 good year. So what I typically say is that these
2 kinds of studies can't be the only study in your
3 portfolio because they take a lot of time to move
4 them forward.
5 DR. DWORKIN: So to the best of my
6 knowledge, there's never been a completed industry-
7 sponsored trial of CIPN. So I guess my question to
8 Ellen, if you were a drug company, I don't know,
9 Merck, Novartis, Lilly, Pfizer, and you wanted to
10 do a study like yours with the deep pockets of a
11 large drug company, would it have been easier
12 because of those financial resources, or would it
13 have been more difficult because you wouldn't have
14 been able to access these NCI clinical trial sites?
15 DR. LAVOIE SMITH: So I think it would have
16 been more difficult. I mean, certainly drug
17 companies have access to multi-site studies because
18 they have a lot of money. So I suppose it could
19 have gone either way. Right?
20 So for this particular study, there was no
21 way that we could have done it at a single
22 institution or even at two or three. So we would

Page 144

1 have had to either use the cooperative group
2 mechanism or a drug company mechanism to open the
3 study at multiple sites.
4 To conduct a study like this within the
5 cooperative group -- and Charles can maybe comment
6 on this -- at the time, there was no access. There
7 were not enough funds to pay for drug and placebo,
8 so we had to use the drug company to get the drug.
9 Now, I think maybe there's a different mechanism to
10 support similar studies through the cooperative
11 group. Yes? No?
12 DR. LOPRINZI: Yes, kind of. Let me say a
13 bit more there. So I agree with what you said in
14 there, and it does take a year to get a concept
15 approved. And the chance you're going to get the
16 concept approved is 30 percent or something like
17 that over, and it will take that year to get that
18 sort of thing out of there. So it is a long
19 process and all those sort of things, 30 to
20 40 percent is probably reasonable.
21 But the cooperative group things are nice
22 because NCI pays for statistics, et cetera, but you

Page 145

1 have to go through that process of review. There
2 are non-NCI-related cooperative groups. There's
3 the AFT and Alliance Foundation Trials Group.
4 There's the ACCRU, A-C-C-R-U, which was developed
5 from Mayo when we had the NCCTG, which is basically
6 a cooperative oncology group without a government.
7 In the ACCRU, which I happen to chair, I'm
8 the vice chair of that and run the symptom control
9 part of it, so you can consider that a conflict of
10 interest if you want. But there, we are able to do
11 that, and we have a hundred members of ACCRU, and
12 not everybody participates in every study, but that
13 sort of thing.
14 So there are those sort of mechanisms that
15 can be utilized. Otherwise, a pharmaceutical
16 company could get a CRO and then get their own
17 group there. There are advantages and
18 disadvantages to those sort of things. The nice
19 thing with having the group process is that they
20 can develop protocols, or they can be drug company
21 protocols, and they just help facilitate accrual to
22 them. But those are different processes where that

Page 146

1 can work.
2 DR. GEWANDTER: Can you elaborate on what
3 you mean by just help recruit to them? You said
4 they could either run them or just help recruit to
5 them.
6 DR. LOPRINZI: So there are different ways.
7 Sometimes, a company will come to us and ask us.
8 They have an idea. Or we've actually gone to a
9 company and said, "Hey, we'd like to do this study
10 of looking at apixaban versus low-molecular heparin
11 for preventing blood clots."
12 Then we went to the company, and then they
13 said, "Yes, we'll support you in terms of drug and
14 funds for doing this thing." And then we develop
15 the protocol, and have the whole protocol
16 development office, and all that sort of thing,
17 take it through IRBs, and send it out to the group
18 members, and all that sort of thing. So we have
19 kind of a full-service process there.
20 We also have a process whereby if a drug
21 company has a trial that they're doing, that they
22 develop, they wrote it, and they just want somebody

Page 147

1 to put patients on it, they can send it to us.
2 We will go through a review process and say
3 do we think this is scientifically sound, do we
4 think this is safe, et cetera, et cetera. If we
5 buy into it, then we say, yes, we'll do that. And
6 it's their protocol, but we'll then send it out to
7 our members, ask them who wants to participate, and
8 then facilitate the administrator process of making
9 that happen. And they do it completely through
10 ACCRU.
11 Then we have a situation where a drug
12 company will have their own CRO at a bunch of
13 institutions, and then they might also have ACCRU
14 that used that for getting more institutions. And
15 the nice way about that is that they don't have to
16 contract with each of the institutions of ACCRU.
17 They contract with ACCRU, and then we take care of
18 the contract with the institutions.
19 So does that help answer your question?
20 DR. WEN: Some of the challenges that you
21 have for your trials are similar to the ones we
22 have in neurooncology. We have relatively small

Page 148

1 patient populations, limited resources, limited
2 interest from industry.
3 There are several ways to approach this.
4 One is to improve the efficiency of your accrual.
5 The other is to make your trials more efficient.
6 And one great inefficiency is that you have a
7 control arm in each trial that's separate. So if
8 you had a mechanism where you had a single control
9 arm and multiple agents being tested, that would
10 immediately cut your patient number.
11 So in neurooncology, we set up several
12 platform trials where we build a mechanism. We've
13 been working with Don Berry at MD Anderson using
14 these Bayesian adaptive designs with the hope that
15 we can get an answer with fewer patients.
16 Then because we have this mechanism, we hope
17 that companies will have a lower threshold to come
18 to us, to bring their agents. So that would be a
19 slightly different way of looking at how to
20 approach this problem.
21 DR. LAVOIE SMITH: Another factor has to do
22 perhaps with concern around conflict of interest.

Page 149

1 So if the drug company is sponsoring a trial as
2 opposed to a large cooperative group or similar
3 type of network, perhaps there may be some
4 difference in the way the results are viewed. I
5 don't know.

6 DR. FREEMAN: It was really interesting
7 hearing you speak about the duloxetine trial,
8 interesting because I would have thought about it
9 before I heard the challenges that you faced, that
10 that was the low-hanging fruit. And it turns out
11 it's not that low hanging.

12 But the issues that are confronting us
13 during this meeting, the prevention, primary and
14 secondary, during the chemotherapy or before the
15 chemotherapy process, or the acute symptomatic
16 treatment, I think are even more challenging.

17 I'd be really interested to hear from the
18 panel how to implement this, how to get oncologists
19 engaged in this process. And I understand that the
20 three or four of you are speaking to the choir. I
21 think community oncologists, which may be where
22 this will need to be done, will be even more

Page 150

1 challenging. So I'd like to be able to understand
2 mentally how this could be implemented.

3 DR. CLEARY: It's interesting. When I think
4 about trials, I think the two trials, the trial you
5 ran and the trial Charles ran using calcium
6 magnesium, were somewhat different. The trial you
7 ran, where people already had neuropathy, in that
8 setting, I wonder, the setting where that could
9 have been evaluated could have been by an
10 oncologist. That's certainly more convenient, or
11 you could even send those patients to a neurologist
12 because, when we have patients after therapy with
13 terrible neuropathy, we don't know what to do with
14 them. And the patients are more than happy to go
15 over to a neurologist and do it.

16 With Charles's trial, it was really
17 interesting to me that he basically packaged the
18 consent form of FOLFOX. So basically, the
19 oncologist would go and talk to the person about
20 FOLFOX. But while talking to them about FOLFOX,
21 he'd say, "But you might only not get calcium
22 magnesium to see if that helps neuropathy."

Page 151

1 I think your trial wouldn't have accrued as
2 well if he had just done a calcium magnesium
3 intervention. I think, really, by linking it with
4 the FOLFOX, that initial treatment conversation
5 that we're going to put you on FOLFOX and then, by
6 the way, this is a trial testing whether calcium
7 magnesium helps, I think that helps the accrual.

8 DR. LOPRINZI: I think in that trial there,
9 when we specifically set it up, I did not set up
10 the rules and regulations for how they gave their
11 FOLFOX. It had to be FOLFOX there, but I didn't
12 actually set up in our protocol what they had to do
13 for dose modifications. I said, "That's all what
14 the oncologist does normally. They'll do the dose
15 modifications. They'll do that sort of thing."

16 So I stayed out of that sort of thing, and
17 we gave calcium magnesium versus not, and then we
18 collected what dose they got, and then had to fill
19 out the questionnaires, and the CIPN 20, and the
20 CTCAE there, but it was used to doing, so we have
21 it that way.

22 The treatment trial, Ellen, you might say

Page 152

1 you could send it to a neurologist, but that's
2 actually another hard thing to do because the
3 patient is in the medical oncology office, and
4 that's when you can talk to them and help put them
5 on the study as opposed to, we'll send you to a
6 neurologist and maybe they'll put you on the study,
7 but that's a week or so later you get the neurology
8 consult. And then they had to do that and they're
9 not normally seeing the neurologist, so it adds a
10 complicating aspect of that thing.

11 So there is no big problem with getting
12 patients to accrue, patients to these studies. If
13 you set it up, it's got to be scientifically sound
14 but clinically doable. And those two things, you
15 simply say they aren't yet, but you have to be
16 careful you don't try to put too many bells and
17 whistles on. So I say it's like putting your hand
18 in the cookie jar. You won't get anything out if
19 you make it too complex.

20 But you have to have it scientifically sound
21 but clinically doable. And the community sites,
22 they have put hundreds of patients -- they've put

Page 153

1 over a thousand patients on our clinical trials
2 with neuropathy. I think that's probably right,
3 but close to that sort of thing over time. They
4 had pretty good rates, too.
5 DR. GEWANDTER: So I'm actually surprised to
6 hear you say that you think it's easier to recruit
7 patients for a primary prevention study than
8 potentially secondary because colleagues of mine
9 have said, well, you know, at the beginning,
10 there's so much to think about. They're deciding
11 about what treatment they want, so it's kind of
12 overwhelming to then add on do you want to consider
13 this study? And it might actually be easier while
14 they're getting their first infusion, they're just
15 sitting there, asking them at that time.
16 Do any of you have any comments on that?
17 DR. CLEARY: Again, I think the reason his
18 trial was successful was, if it would have been a
19 trial of just sign a consent form that you will or
20 will not get calcium magnesium infusion, I don't
21 think it would have accrued at all, because that
22 really would have been an extra step for the

Page 154

1 oncologists. But the brilliance of his approach
2 was he linked it in with the FOLFOX.
3 DR. GEWANDTER: So you're thinking it's more
4 about the oncologists' time than the patient's
5 willingness or --
6 DR. CLEARY: It's also where the
7 oncologist's focus is, yes.
8 DR. LOPRINZI: But let me follow up on your
9 other thing, too. So I think, actually, some of
10 our trials have been treatment of established
11 chemotherapy neuropathy. And nowadays, if I'm
12 doing a treatment of established chemotherapy
13 neuropathy, I generally don't do that in a time
14 while they're still getting the chemotherapy. I
15 think it's better to separate those things.
16 You can do it while they're getting
17 chemotherapy. In our baclofen amitriptyline
18 ketamine study, two people who had established
19 chemotherapy neuropathy. They could still be
20 getting neurotoxic chemotherapy, and a third of
21 them still were. I think it's easier not to have
22 that group in there, but there are plenty of people

Page 155

1 out there with established chemotherapy neuropathy
2 for that.
3 For prevention of neuropathy, there's two
4 ways to do it. One is to do it before they get
5 that first dose. And that's what we did on the
6 calcium magnesium study, and it worked pretty well.
7 Other times, we've actually allowed before
8 the second dose because it's so much going on with
9 their getting their first dose of chemotherapy, and
10 this and that, and with that, and I'm worried about
11 this and all that sort of stuff, to think about the
12 neuropathy things, and sometimes before the second
13 dose, with the rationale being that neuropathy is a
14 cumulative sort of thing, and one dose isn't
15 probably going to hurt you too much, but if you get
16 10 or 12 doses, you're going to get that and,
17 therefore, why'd you prevent it.
18 But the other aspect of it is, if you want
19 to prevent any neuropathy, maybe you should start a
20 week prior, which is really, really hard because it
21 doesn't fit very well. But you can put patients
22 with established neuropathy -- they're not hard to

Page 156

1 accrue to studies because there are so many of them
2 out there and about. And you send out an
3 advertisement, anybody got chemotherapy neuropathy,
4 and they just come flooding to your office.
5 DR. LAVOIE SMITH: I think, Dr. Katz, you
6 were next, and then Dr. Brell after you.
7 DR. BRELL: I'm staying on this topic. I
8 just think, in general, especially with my
9 experience with the prevention trials at NCI, that
10 prevention trials are harder in general to get
11 patients on because they have to imagine having
12 this thing you're trying to prevent, and it's hard.
13 And neuropathy is really hard. Unless they know
14 someone who has it, it's a concept they don't
15 understand as well.
16 So of course, everything's going on when
17 you're first trying to put them on chemotherapy.
18 But I just think, in general, historically, it's
19 been more difficult to accrue to those trials.
20 DR. RICHARDSON: I just want to add a little
21 bit to that by saying that in the context of
22 myeloma, obviously there is a perception amongst

Page 157

1 patients that it's part of the underlying disease.
2 And the other thing is that we have very active
3 engagement from IMF and MMRF, who are our major
4 patient advocacy groups, and they alert patients to
5 the fact that neuropathy is a big problem not only
6 from the disease itself, but from therapy coming.
7 So when we did our sort of landmark
8 bortezomib monotherapy study, we didn't offer an
9 active intervention. What we offered was actually
10 a descriptive trial. We offered a proactive
11 approach to dose reduction and schedule change. We
12 also integrated our complementary strategies of
13 emollients and supplements in an organized fashion.
14 So patients started on their supplements before
15 they began therapy, and we introduced the
16 emollients as well.
17 Our nursing team are committed to educating
18 them, and guiding them, and monitoring them through
19 it. We also had a commitment to IV hydration as
20 well. We used intravenous bortezomib in that
21 study.
22 That's actually one thing that I was just

Page 158

1 going to say that folks hadn't touched on I think
2 in the meeting so far. And, Charles, you and I
3 talked about it last night, this whole concept for
4 patients as well as for us as clinicians studying
5 neuropathy, this whole issue of route of
6 administration, PK, and pharmacodynamic effects of
7 the drugs we're giving, because that's an
8 incredibly important variable to build into any
9 trial that you do with a preventative or
10 therapeutic agent targeting neuropathy. You have
11 to really understand that aspect of it, just as a
12 sidebar.
13 But going back to the point, when we did
14 this study, we offered all of these things. And
15 really, the essence of the trial was descriptive.
16 And yet, patients were very happy to participate.
17 We didn't have anybody unwilling to do so because
18 of the skin biopsies, the extra nerve testing.
19 Everyone was willing to do it.
20 But I think if it's just carefully
21 explained, carefully framed, and it's understood
22 that neuropathy is part of the territory with your

Page 159

1 illness and very much a part of the territory with
2 your therapy, our accrual was not a problem at all.
3 DR. GEWANDTER: You had people do skin
4 biopsies and they --
5 DR. RICHARDSON: We did. We did skin
6 biopsies on the lower extremities to what we
7 discussed with Pat yesterday.
8 DR. LOPRINZI: In a subset of patients.
9 DR. RICHARDSON: Yes, and subsequently as
10 well. And we were able to show neurite fallout.
11 We were able to show axonal loss across treatment,
12 small fiber loss across treatment.
13 DR. GEWANDTER: Do you pay them a lot? Did
14 you pay them a lot to do the skin biopsy?
15 DR. RICHARDSON: We didn't pay them at all.
16 Why? No. I mean, IRB would absolutely put the
17 kibosh on anything like that. We are not even
18 allowed to offer, without IRB approval,
19 reimbursement for travel. We're not allowed to.
20 No, because it's considered discriminatory, because
21 there are some people who would need it, some
22 people who wouldn't. So it'd be viewed as an

Page 160

1 inducement. So we're not allowed to do that.
2 I mean I think that's actually slightly
3 ridiculous because, at the end of the day, it's an
4 expense for the patient, but they will not allow us
5 to do that because it's an inducement. So how we
6 get around that is we put access patients to the
7 LLS, the Leukemia Lymphoma Society, to the chronic
8 disease funds, and sponsors and other partners
9 voluntarily donate to those funds. And those
10 organizations in turn support patients. But our
11 IRBs will not allow us to reimburse patients for
12 anything.
13 DR. WEN: I think it's hard to underestimate
14 the importance of having the oncologist be an
15 advocate. Those trials were a success because of
16 Paul. I mean, he went after everything. And
17 similarly for breast cancer trials, having Charles
18 be there probably made a huge difference.
19 I think, if you had someone else coming in
20 with a trial without the contact and influence, it
21 doesn't go nearly as well. And then having the
22 patient advocacy groups be an important part of

Page 161

1 this is also critical I think.
2 DR. LOPRINZI: Then not necessarily the
3 physicians, the nurses, too, can be the advocate
4 for this thing many times, clinicians or the team.
5 DR. RICHARDSON: The nursing piece is vital.
6 DR. KATZ: We're sort of all dancing around
7 an issue, but I want to see if I can maybe put my
8 heart right there in the middle of it. There's a
9 reason why there are no industry-funded studies of
10 treatments for chemotherapy-induced peripheral
11 neuropathy. That's not an accident.
12 I myself have been working with companies
13 who are interested in studying various kinds of
14 pharmacological treatments for neuropathic pain for
15 20 years now, and multiple times a year, I've sat
16 around the table with those companies to try to
17 help them figure out which type of neuropathic pain
18 syndrome they should study.
19 Chemotherapy-induced peripheral neuropathy
20 always comes up at those meetings, and this is for
21 a couple of decades now. I've gone with a number
22 of those companies straight through, very detailed

Page 162

1 feasibility assessments, so it's not a casual
2 thing. And I've never been with a single company
3 yet who's decided to actually study chemotherapy-
4 induced peripheral neuropathy. And the reason for
5 that is because the feasibility assessments that we
6 all do show that it's not feasible.
7 The reasons are the ones that we've heard
8 here already, where no drug company has two and a
9 half years to start to sort through the bewildering
10 array of acronyms, where my own head is spinning
11 just after the last day or so, and to start the
12 lengthy political discourse that's required to
13 eventually maybe have a 30 percent chance a year
14 later, or whatever it is, of getting your study
15 approved.
16 And recruitment is very difficult. So I
17 agree with the comments that people have made, that
18 if you're trying to recruit for a symptom study, it
19 has to come through the oncologist. It can't come
20 through anywhere else. You know, having worked for
21 10 years at the Dana-Farber Cancer Institute
22 myself, trying to beat the bushes and recruit those

Page 163

1 patients, it just doesn't work.
2 So I think that it's great to discuss all
3 these methodological issues that we've been
4 discussing over the last day or so. That's
5 critically important. But unless we get real about
6 what it's going to take to set up an infrastructure
7 that's going to facilitate pharmaceutical companies
8 actually making this process feasible for the
9 average pharmaceutical company, we are going to
10 continue to see what we have seen, which is no
11 industry-sponsored studies in this area.
12 DR. LOPRINZI: I think the 30 percent thing
13 is getting it NCI approved, and that sort of stuff,
14 and getting it developed, and all that. It does
15 take time for a company to work and get through
16 things. It's probably not much shorter. It takes
17 a year or more than that sort of thing for it.
18 But they can be done. When the ASCO
19 guidelines came out and I helped to co-chair that
20 process with Dawn Hershman, there were 48 studies
21 that had been done in terms of trying to prevent
22 neuropathy. None of them are positive.

Page 164

1 So it demonstrates, though, that they can be
2 done, and through the cooperative groups, we've
3 done them, not just the calcium magnesium, but
4 other ones like that.
5 Then there's fewer ones that have actually
6 been done for treatment of established, although
7 that might even be easier. There are like eight
8 trials that came up there, and Ellen's was the one
9 that was significantly positive.
10 DR. KATZ: I'm hearing you, and this is
11 exactly the disconnect that I think we should
12 explore. I think unless we can get to the bottom
13 of why industry perceives that these studies are
14 not feasible -- I think at this meeting, that would
15 be a worthwhile thing to try to sort out, because
16 there is a disconnect. And unless we figure that
17 out, maybe investigator-initiated studies or small
18 NCI-funded studies may end up being done, but not
19 industry-sponsored studies.
20 DR. GEWANDTER: So Joanna, maybe you can
21 answer this. How are the antiemetic studies done?
22 They had to recruit oncology patients, and they

Page 165

1 were done by drug companies for a side effect
 2 treatment.
 3 DR. RICHARDSON: I think that's a very good
 4 point. I mean, I totally hear where Nat's coming
 5 from. I think, however, I would argue it slightly
 6 differently. I would suggest that it needs just
 7 revisiting with our pharma partners how we do this,
 8 rather than necessarily say it's an us-and-them
 9 type of situation and the division grows; rather,
 10 do it the other way.
 11 I was reminded -- and Pat reminded me of
 12 this -- that by accident, we ran into our
 13 experience with tanespimycin, an HSP 90 inhibitor
 14 combined with bortezomib, a striking reduction in
 15 neuropathy, even by CTC criteria, which was so
 16 interesting, because, as you pointed out earlier,
 17 CTC criteria are so insensitive. But even with
 18 that tool, we saw it.
 19 So we combined two active drugs and saw
 20 actually a reduction in neurotoxicity because the
 21 HSP 70 effect was probably important in reducing
 22 inflammation.

Page 166

1 I think that both drug partners there got
 2 very excited, Millennium on the one hand, and at
 3 that time, it was under Kosan before it was bought
 4 by BMS. And BMS was very excited. But
 5 unfortunately, we then ran into a drug substance
 6 problem where we couldn't get the product to where
 7 it needed to be, and batch-to-batch inconsistency
 8 killed the drug. It was a disaster, but that's a
 9 different story.
 10 The point is that both pharma partners were
 11 very interested when the signal emerged. So pharma
 12 is interested. It's a question of how it's
 13 contextualized and how it's structured.
 14 So Pat, maybe you can --
 15 DR. DOUGHERTY: Along those lines, we've
 16 recruited into two longitudinal studies, and we did
 17 one small nerve protection study. We didn't have a
 18 big problem. I mean, maybe it's something about
 19 patient flow because we got gobs of patients.
 20 The only thing that we found
 21 difficult -- and this was now four or five years
 22 ago -- was finding treatment-naïve myeloma

Page 167

1 patients. Now, that was a bear. But to get
 2 treatment-naïve CRC patients, we enrolled 100 and
 3 something in a little over two years' time.
 4 I would think that in this particular case,
 5 for CIPN, if you explain to the patients that,
 6 look, this is the complication that's likely going
 7 to drive you out of therapy and this intervention
 8 may keep you on therapy if you're in the active
 9 arm. I would think that would be a huge incentive
 10 for patients to sign up, particularly if you make
 11 it easy for them.
 12 If you make the assessments too onerous,
 13 then they're not going to be interested after a
 14 while, as we saw with the presentation earlier,
 15 because when they're in therapy, they want to
 16 survive.
 17 But if you keep it easy, and they have a
 18 friendly face that they're used to seeing each time
 19 they come to the center -- and that they're going
 20 to have to wait to get into the clinics anyway, so
 21 to take a little extra time to meet their buddy
 22 who's going to walk them around the center and go

Page 168

1 about that, we didn't find it difficult. But it
 2 really is that face that meets them at the door.
 3 That I think is crucial to any of these.
 4 DR. RICHARDSON: I think that echoes what
 5 you heard from Pat about nursing, and myself about
 6 nursing, and the team approach. But I do think
 7 also that this is a plug that really echoes with
 8 Charles and where we partner in the alliance.
 9 The large group studies or group mechanisms
 10 can address the issue, Pat, you've touched on,
 11 which is the patient availability, newly diagnosed
 12 patients, for example, with myeloma. We have study
 13 groups that could address that, but having said
 14 that, in the broader sense, the alliance, for
 15 example, might be a great platform.
 16 Wouldn't you agree, Charles?
 17 DR. LOPRINZI: Yes. The patients can be
 18 accrued on either treatment or prevention trials,
 19 and through a cooperative group or a group that's
 20 not part of NCI. So they're available. Alliance
 21 is the name of a cooperative group, or now there's
 22 an alliance. Yes, so you have to be careful. Yes.

Page 169

1 DR. DOUGHERTY: They partner between
2 centers.
3 DR. LOPRINZI: Yes. That can be done. That
4 can be done.
5 DR. WEN: The issue with the NCI groups,
6 though, as we all know is that it's incredibly
7 slow, and painful, and inefficient. And I'm sorry
8 to be naïve and not know what the scope of action
9 is. But for instance, if it was possible to set up
10 a clinical trials group to screen treatments
11 outside of a lot of regulatory issues, that would
12 be attractive for companies.
13 I mean, that's what we're doing in
14 neurooncology, because it's been so frustrating to
15 go through the NCI mechanism. And we're hoping
16 that this will accelerate the development of drugs
17 for our tumors, but it could also be used for other
18 things, including CIPN.
19 If you have a system that is relatively
20 efficient and you can eliminate -- most of your
21 drugs are like drugs for brain tumors. They're not
22 going to work. So you don't want to spend doing

Page 170

1 these big phase 3 trials to show that they all
2 don't work. You want to get rid of the ones that
3 don't work quickly. And you need a better
4 mechanism than what you have now.
5 DR. RICHARDSON: To echo that, then, where
6 is the solution with the groups? Well, Charles
7 knows this mechanism because I think the breast
8 group in particular have been highly successful in
9 it.
10 In the alliance, we recognized that there's
11 this divergence between the CTEP and NCI platform,
12 which does take a long time and typically is driven
13 by phase 3 large comparator trials, which are an
14 enormous investment of time, and energy, and
15 resources.
16 In the alliance, we built this separate
17 mechanism called the AFT, and it's the Alliance
18 Foundation for Trials, and it's basically designed
19 to be much more industry friendly, much quicker,
20 and it's not vulnerable to the same sort of
21 roadblocks that you run into at the NCI when you
22 get to the third committee, and for whatever

Page 171

1 reason, they just say, "No way, Jose."
2 So basically, you've got a much faster
3 mechanism of early drug development. So in the
4 myeloma committee, for example, we have a number of
5 initiatives going through the AFT of early-phase
6 efforts, which are much randomized phase 2s, for
7 example, that are going through that pathway, and
8 they're moving much faster than comparable efforts
9 on a much larger scale that go through the NCI
10 mechanism.
11 That's in no way to diminish the NCI
12 mechanism because it's incredibly important, but
13 it's built for a different sort of question, and
14 these smaller trials are built for AFT.
15 DR. DWORKIN: So I wonder if the answer to
16 Nat's question is that the pharmaceutical companies
17 interested in developing drugs for either painful
18 CIPN or CIPN in general haven't known about this
19 AFT possibility.
20 I mean, I certainly have consulted with some
21 of the companies that Nat discusses, and I haven't
22 known about this. And so it may simply be that,

Page 172

1 with all due respect, you guys haven't informed us
2 guys about the resources that exist because
3 personally I think that --
4 DR. RICHARDSON: AFT is brand new. The AFT
5 is new, so don't feel that you've been left out of
6 the fold. But AFT is brand new. But the breast
7 group in the alliance has been highly successful.
8 DR. LOPRINZI: Yes. AFT and ACCRU, the
9 group I mentioned, are similar situations. ACCRU
10 has been around longer. It's been around for 15
11 years or something like that. And AFT to date has
12 not done any symptom control trials, I don't think.
13 DR. RICHARDSON: No. But the therapeutic
14 trials have been very successful.
15 DR. LOPRINZI: Yes. They have been, yes.
16 DR. RICHARDSON: Most importantly, they've
17 been small scale. So in other words, to your
18 point, Nat, that you don't want to be launching
19 into these massive phase 3s that are potential
20 doldrums or worse for new drugs. You want proof of
21 principle, hypothesis-generating earlier-phase
22 trials. We have a mechanism that then addresses

Page 173

1 Pat's incredibly important point, which is your
2 patient population. You want to make sure you
3 access who you need to you treat.
4 DR. LOPRINZI: Basically, you want to go to
5 investigators who have done chemotherapy neuropathy
6 trials, and then they can help you through the
7 mechanism. And that might be conflict of interest
8 because I've done more than most other people, but
9 that's the way.
10 Whether you put it through -- when I talk to
11 groups, put one through the cooperative oncology
12 group, the nice thing about that is, it's cheaper
13 because NCI pays for the statistics, and data
14 management, et cetera, et cetera, or you can go
15 through the ACCRU mechanism, which costs more
16 money, but is quicker. But they're actually
17 available out there.
18 DR. DWORKIN: Charles, just to be fanciful
19 for a moment, could ACCRU do a 400-patient
20 trial -- and I'm not proposing this trial -- of
21 whether pregabalin has a preventive effect in
22 patients initiating taxane chemotherapy?

Page 174

1 Is that something that, if one had the
2 resources, the financial resources, ACCRU could
3 actually get completed? Because that's Nat's
4 question really, a phase 3 trial.
5 DR. LOPRINZI: Yes, that could be done. We
6 just completed a randomized, placebo-controlled
7 trial of pregabalin for trying to prevent
8 chemotherapy -- paclitaxel-induced neuropathy.
9 Breast Cancer Research Foundation provided
10 funds for me, and I ran it and I ran it through
11 ACCRU. It was a small study because NCI wouldn't
12 approve it before, although I tried to get that
13 approved before. I even said Bob Dworkin said it
14 was a great idea, and he'd bet his car on it, but
15 they still didn't approve it back then.
16 So I ran this 46-patient study, 23 per arm,
17 which has little, little power, but to see if there
18 were pilot data to help support that we could go
19 forward with a larger placebo-controlled trial.
20 What we ended up showing in that particular
21 trial was that it looked like it actually helped to
22 prevent the acute neurotoxicity from paclitaxel,

Page 175

1 the aches and pains that people get that used to
2 call them arthralgia, myalgia, which in my mind are
3 really neuralgia. But it didn't have any suggested
4 benefit in terms of numbness, tingling, shooting,
5 burning pain during the time of chemotherapy and
6 for six months there afterwards.
7 So that wasn't enough for me to say, hey, I
8 got enough pilot data to suggest that didn't need a
9 p equals 0.5, but it would have been nice to have a
10 split in the curves enough to do that sort of
11 thing. So, yes. But those can be done.
12 DR. DASTROS-PITEI: Just a comment from an
13 international perspective, so outside the U.S.
14 Clinical studies, we have seen done, were done in
15 an alliance, were done in the population, which was
16 an adjuvant population, a CIC adjuvant. Obviously,
17 it was easier to recruit.
18 But what was interesting is, in Europe, the
19 patients need to consent to the treatment, to the
20 chemotherapy. I don't know if it's the same in the
21 U.S. So they come to me, so adjusting your
22 assessments to the times needed for oncology

Page 176

1 assessments is very important.
2 We have the benefit in Europe and back in
3 the U.K. that they need to consent two weeks before
4 the chemo starts. So that's a good opportunity to
5 actually consent them for the study if they're
6 happy to start into a prevention study.
7 So going to the point is try to match as
8 much as possible the oncology assessments, bearing
9 in mind that, however, there will be some
10 assessments which perhaps need to be done in
11 between.
12 So there's some for that. We need to find a
13 way to attract the patients and keep them engaged.
14 And I think the nursing staff time is probably the
15 best investment.
16 DR. LOPRINZI: But if you want to do a bunch
17 of neurologic tests, and biopsies, and all that
18 sort of stuff, you need a two-week -- yeah, you
19 need something like that because that's just too
20 unfriendly to do.
21 If you listen to the group earlier this
22 morning that says that those tests, you probably

Page 177

1 don't need to get biopsies and tests like that, and
2 we don't need to get -- we don't have the signs yet
3 to get. We've got to work on the neurologists to
4 figure out those signs that are easy, doable, and
5 whatnot.
6 We don't have now, but we have been able to
7 take patients who have received chemotherapy, and,
8 oftentimes, in a day or two, and say, hey, we got
9 this sort of thing and here's a consent form. You
10 fill out this patient-reported outcome, or the
11 doctor assesses neuropathy in the clinic the way
12 they normally do. And then you go ahead and
13 randomize to calcium magnesium versus not and do
14 that.
15 So it can be done, it has been done, but if
16 you need a bunch of tests ahead of time, that's
17 where I say you need to make it clinically feasible
18 and scientifically sound.
19 DR. LAVOIE SMITH: If you need measures in
20 between the routine follow-up visits, it depends on
21 what it is that you need. And patient-reported
22 outcome measures can easily be collected via paper

Page 178

1 and mailed in, electronically. So that's something
2 else to consider again so that it's a feasible
3 approach.
4 DR. DASTROS-PITEI: Maybe subgroups for very
5 intensive assessments, which would be maybe
6 [indiscernible] assessments or others. Then maybe
7 this subgroup analysis and the subgroup of patients
8 are more useful, so not in the whole study, but
9 maybe focusing on subgroup of signs.
10 DR. LAVOIE SMITH: Over here?
11 DR. G. SMITH: I was just wondering how much
12 thought has been given to perhaps aspects of
13 pragmatic trials that might help in some ways.
14 There are registrational trials -- or pragmatic
15 trials that are now submitted for registration
16 purposes, and the idea behind can you use
17 registries to recruit patients.
18 You generally simplify the data you collect
19 to try to collect the important things. And the
20 idea is, generally, you can hopefully improve
21 recruitment and reduce some costs.
22 You are a lot more lenient on entry criteria

Page 179

1 in general, but I'm wondering if there might be not
2 every aspect of that, but whether there are pockets
3 that might be utilized to help in that regard.
4 DR. LAVOIE SMITH: The first thing that
5 comes to mind for me is that it depends upon,
6 again, what your intervention is.
7 So if I take us back to the duloxetine study
8 with a norepinephrine serotonin reuptake inhibitor
9 that can't be used with a variety of other drugs,
10 and has black-box warning labels, and you need to
11 make certain that people are X, Y, Z, then
12 sometimes the intervention really precludes the
13 ability to do that. But there probably are other
14 circumstances where that might work.
15 DR. LOPRINZI: I think the English have been
16 particularly good at this over the years. But
17 still, it's a randomization process to A versus B,
18 or C, or D, whatever you have in there. But on the
19 eligibility criteria, you can have a long, long,
20 long lists of these sort of things, and a long list
21 of things, and all these things which really has a
22 very, very tight group you have there, or you can

Page 180

1 open it up. You want safety, but you also want it
2 to be generalizable to patients there.
3 So there are ways. And I think our success
4 has been to try to be pragmatic with them. That's
5 user friendly enough to do them and yet
6 scientifically sound.
7 DR. DOUGHERTY: Charles, look at a finer
8 grain. One of the things that struck me as we did
9 our longitudinal studies is that the patients were
10 so rude as to go home after receiving chemotherapy.
11 And the critical days that I've always wanted to
12 measure is that 3 to 5 days after each round.
13 When you did your assessments, didn't you
14 get them prior? You got them the day that they
15 were coming back for their next round prior to
16 chemo, or did you get them in those intervals,
17 those critical intervals, when they're generally at
18 home?
19 DR. LOPRINZI: The answer is yes.
20 DR. DOUGHERTY: Well, I shouldn't have asked
21 you more questions. Did you get them --
22 DR. LOPRINZI: I'm going to go forward a bit

Page 181

1 there.

2 So for both of the agents, we've looked at

3 paclitaxel and for oxaliplatin. They both have

4 chronic neuropathy that we've been talking about,

5 and they both have acute neuropathy problems, the

6 cold, numbness, and crampiness with oxaliplatin,

7 the aches and pains central, that sort of thing for

8 that.

9 So on each of those trials, we had patients

10 fill out a questionnaire on day 1 before they got

11 any chemotherapy, asking them about chronic

12 neuropathy and acute symptoms. And then we had

13 them fill out questionnaires daily for 7 days, a

14 piece of paper --

15 DR. DOUGHERTY: At home?

16 DR. LOPRINZI: -- write it down, please do

17 that, mailing it, something to mail back, that sort

18 of thing. So we did it for 7 days, right before

19 their next chemotherapy and afterwards.

20 Now, on the every-two-week oxaliplatin

21 doses, because those are done every two weeks, then

22 they had a week off where they didn't have to do

Page 182

1 anything and then they did that week after week.

2 On our 12-week weekly paclitaxel, they

3 filled out questionnaires. 12 times 7 is 84 days.

4 Is that right? Okay. They filled out

5 questionnaires for 84 days. The ones afterwards

6 were the acute sort of thing, and then on the day

7 of treatment, right before treatment, we asked the

8 chronic questions.

9 Then we had them fill them out once a month

10 for six months afterwards. And our data completion

11 is 90 percent-ish, that we get the questionnaires

12 back. Some people have done this by iPads, and

13 phones, and that sort of stuff, which is another

14 way.

15 So it's easily doable. We've done it,

16 reported it, so you can get that.

17 DR. LAVOIE SMITH: Anna?

18 DR. BRELL: I want to make two comment

19 questions. One is regarding the willingness of

20 pharmaceutical companies to be involved in these

21 types of trials, and it's my understanding that a

22 pharmaceutical company would probably do what it

Page 183

1 takes to get an FDA indication. They would

2 probably suffer through whatever processes they

3 have to suffer through.

4 But my understanding is that we still don't

5 have good enough measures, outcome measures, for

6 the pharmaceutical company to use to be able to go

7 to the FDA and say, "We saw a difference. We saw a

8 meaningful difference between arm A and arm B."

9 DR. DWORKIN: That's true for pain. That

10 might have been an obstacle for peripheral

11 neuropathy as an indication, but for pain

12 associated with CIPN, we know how to measure it.

13 DR. BRELL: Then it is a process.

14 DR. GEWANDTER: The patients that have

15 chronic neuropathic pain, like the people that you

16 might be thinking about when you're talking to drug

17 companies about a treatment for neuropathic pain,

18 there are a lot fewer of those patients available

19 than if you're trying to do a prevention trial.

20 So it would be a lot harder to get enough

21 sites without going to the cooperative groups for

22 that kind of study than it might be for, you want

Page 184

1 to enroll 400. Like Dr. Dougherty said he can 200

2 patients and approach the study just at his site.

3 So I think that it depends on the population,

4 potentially, like how hard it will be to recruit

5 them.

6 DR. KATZ: Yes. The amount of suffering the

7 company has to go through certainly depends upon

8 the population and that depends upon the protocol,

9 as was discussed. But the pharmaceutical companies

10 will not go through an infinite amount of suffering

11 to get an indication.

12 Let's say we're talking about neuropathic

13 pain. There are options. I can do a painful

14 diabetic neuropathy study. I can do a post-

15 herpetic neuralgia study, or at least I used to be

16 able to. And chemotherapy neuropathy, they're not

17 going to go through an infinite amount of planning

18 and suffering.

19 They've got timelines, they've got budgets,

20 and for the pharmaceutical companies, time is the

21 most important factor, much more important than the

22 actual study budget in most cases. And uncertainty

Page 185

1 is the second most important variable. If you
2 combine very long periods of time with a lot of
3 uncertainty about the outcome, that's very rarely
4 going to go in anybody's clinical development plan.
5 DR. BRELL: I guess I'm thinking of the
6 times when someone's developed a drug that doesn't
7 work in all the other indications you said, and
8 then, oh, by the way, is there one last indication.
9 Can we get a CIPN indication? And we see that.
10 But I can make another quick point about
11 what Jennifer said about trying to learn lessons
12 from other trials and other symptom and toxicity
13 management trials.
14 It's different scales. So if you're doing a
15 trial for dermatitis, you can measure very clearly
16 how much of the skin was involved in a trial for
17 this or a trial for that.
18 So I don't know if we can learn as many
19 lessons going to other toxicity management trials
20 as we can learn lessons from what our esteemed
21 neurologist colleagues are telling us with their
22 work in diabetes and other illnesses.

Page 186

1 DR. GEWANDTER: So I wasn't thinking about
2 measuring. I was thinking about what sites do
3 industry work with to get cancer patients who are
4 undergoing treatment. That's what I was thinking.
5 Where have they been able to get those patients
6 exactly?
7 DR. BRELL: If it's an industry-sponsored
8 trial, a lot of times, they do have their own
9 networks. And so they use their own large networks
10 to get accrual.
11 DR. LAVOIE SMITH: We're going to have to
12 wrap it up here.
13 DR. GEWANDTER: Thank you.
14 DR. FREEMAN: So very quickly, some
15 housekeeping.
16 Lunch is at the usual place. The session
17 begins at 1:00. The afternoon session is the
18 critical piece. It's the time when we try and
19 build a consensus, agree upon what we can agree
20 upon, disagree upon what we can't agree upon, and
21 give Jennifer the material for her manuscript, so
22 please be on time.

Page 187

1 I know people do have flights and are
2 leaving perhaps before the scheduled end, so 1:00.
3 (Whereupon, at 12:05 p.m., a lunch recess
4 was taken.)
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Page 188

1 AFTERNOON SESSION
2 (1:08 p.m.)
3 DR. FREEMAN: So the final round, typically,
4 two things happen during this round. It's the most
5 interesting, and it's the round when people start
6 to trickle out. So we want to try and accomplish
7 as much as we can as early as possible.
8 Just to focus the discussion, what I want to
9 do is to say that this session will be done with
10 two approaches in mind, because I now want to go
11 from what I said were the goals initially to the
12 focus.
13 The discussion will be, as we go through
14 point by point, were a clinical trial to be done
15 tomorrow and we have members of the audience who
16 are contemplating doing clinical trials tomorrow,
17 what would you recommend for eligibility,
18 endpoints, trial design, measurements throughout
19 the trial.
20 So were it to be done tomorrow, the best
21 we've got with the understanding that these all
22 have flaws, all have warts, but the best we've got

Page 189

1 for tomorrow. And then, were this trial to be done
 2 in five years' time, what's the research agenda so
 3 that a more perfect trial can be done in five
 4 years' time? So that is the approach.
 5 One or two other things just very quickly,
 6 and that is, I think somebody asked about receipts
 7 and reimbursements. I want to make sure that
 8 everybody knows that you will get a stipend for
 9 participating in the meeting and that no receipts
 10 are necessary, at least as far as sending to the
 11 organizers.
 12 Then because there won't be time when
 13 everybody is in the audience, I think I want to, on
 14 behalf of all of us, thank Valerie and Andrea, who
 15 aren't hearing me say this, but at least they'll
 16 hear us clap --
 17 (Applause.)
 18 DR. FREEMAN: -- for putting together a
 19 remarkable meeting, for organizing it so smoothly,
 20 and for getting us safely here at least and
 21 hopefully safely home.
 22 So now, I'm going to hand over to Jen, who

Page 190

1 will chair this part of the meeting.
 2 Consensus Discussion
 3 DR. GEWANDTER: Perfect. So we are going
 4 to, in two and a half hours, try to make some
 5 decisions about, as Roy said, measures, endpoints,
 6 and eligibility criteria. So we're going to start
 7 with measures. So what do we all think?
 8 It seemed like, during the last discussion,
 9 the EORTC CIPN 20 is what we would recommend as the
 10 best PRO for right now. Is that true? Does anyone
 11 want to maybe say something else?
 12 (No response.)
 13 DR. GEWANDTER: Nothing? And would you say
 14 the others are bad, are there others that you might
 15 consider -- I don't know that we want to
 16 necessarily say this is the one you should
 17 definitely use. We could say you recommend it.
 18 Is there another one that is also
 19 potentially useful or really none?
 20 DR. G. SMITH: So we're using the NTSS-6.
 21 Again, as a diabetes person, we're familiar with
 22 it. And it seems to work pretty well for kind of a

Page 191

1 quantitative symptom identification measure. I
 2 don't know if it's a good outcome measure. And
 3 it's brief, six.
 4 DR. GEWANDTER: Cool.
 5 DR. FREEMAN: Maybe to give some background
 6 on that, one of the challenges with many of the
 7 diseases that we are interested in is that symptoms
 8 are focused on pain. And the beauty on that
 9 questionnaire, which is not widely used or even
 10 known outside of diabetes -- and I've been a
 11 personal advocate for this instrument -- is that it
 12 deals with non-painful sensory systems, things like
 13 numbness, things like paresthesias.
 14 It has been used and is in clinical trials
 15 trialed by Lilly, and it is a well-validated
 16 instrument. Now, I have proposed its use to a
 17 number of pharma companies, but it has not been
 18 part of chemotherapy-induced peripheral neuropathy.
 19 And I would agree, it's a short, simple, and well-
 20 validated instrument.
 21 Now, I don't want to jump too quickly away
 22 from this discussion of CIPN 20 is the one and

Page 192

1 only. I think there are issues. And I think
 2 Charles made some points, and I know others are
 3 considering using some of these PROs as part of
 4 their at least secondaries or even co-primary
 5 outcomes.
 6 So I think we should at least hear what
 7 people have to say about the other patient-reported
 8 outcome measures.
 9 DR. GEWANDTER: So Simon?
 10 DR. HAROUTOUNIAN: I just wanted to comment
 11 that we are using currently the Neuropathic Pain
 12 Symptom Inventory, the NPSI, in the setting of
 13 oxaliplatin- and paclitaxel-induced neuropathy.
 14 And again, it has painful descriptors and non-
 15 painful descriptors.
 16 My experience is that we have been capturing
 17 pretty reasonably the most annoying, bothersome
 18 symptom in most of the patients. And I think it
 19 just allows you enough variability to capture the
 20 diverse type of symptoms that the patients report.
 21 I don't know that anyone has used it in CIPN
 22 previously. In other neuropathic pain conditions,

Page 193

1 it is pretty common. But I think it's pretty
2 useful, but we don't have the study results yet.
3 DR. GEWANDTER: It's pretty focused on pain.
4 Right? There's only two non-pain symptoms. So the
5 outcome would be pretty dominated by pain.
6 DR. HAROUTOUNIAN: Agreed.
7 DR. GEWANDTER: Bob?
8 DR. DWORKIN: So we all know that, when you
9 make recommendations, the immediate next question
10 is, did you do a systematic review, what is the
11 evidence base, et cetera for the recommendations
12 you're making.
13 So my question is for you, Jen, because I
14 can't remember. It seems, whatever we suggest
15 about the PROs will need to be consistent with
16 what's in your muscle and nerve article, which is
17 the systematic review. And if it's not consistent
18 with your muscle and nerve article, then we're not
19 going to have any way of justifying the
20 recommendations.
21 DR. GEWANDTER: So we didn't make any
22 recommendations in that review. We only looked at

Page 194

1 the content validity. And actually, the EORTC has
2 one of the better content validities.
3 DR. DWORKIN: So that's exactly what I meant
4 by consistency.
5 DR. GEWANDTER: Yes. So if we were to say
6 that, right now, the EORTC is the best, they did
7 some of the best work, at least published work, for
8 content validity, that would be consistent.
9 DR. LOPRINZI: If I could add, I think the
10 easy way to take care of this is that
11 patient-reported outcomes are recommended, number
12 one. Second sentence, the EORTC CIPN 20 was
13 preferred. Next sentence, there are other ones
14 that might be okay in other situations such as X,
15 Y, Z, and Q. And then you cover the bases.
16 DR. GEWANDTER: Okay.
17 DR. FREEMAN: Be more specific. Jen is much
18 too agreeable, and I'm far more argumentative. In
19 other situations like what?
20 DR. LOPRINZI: Like what people talk about?
21 I don't think there's a ton of differences between
22 them, and if I saw a study that was done with FACT-

Page 195

1 GOG-NTX, I wouldn't disbelieve it because it wasn't
2 done with a CIPN 20 instrument. I love Guido's
3 slide. I asked him for it where he compared them.
4 And I know there's some stuff in there about joints
5 that don't have anything to do with the price of
6 tea in China.
7 So you could spend a long time going through
8 all those things. We actually do in our protocols
9 go through why did we pick CIPN 20; we could have
10 picked this, could have picked this, could have
11 picked this; but it's just got the right questions,
12 and it's not perfect. I wish the pain question
13 wouldn't say shooting, burning, because some people
14 say it's not, and you can supplement it with other
15 things.
16 DR. GEWANDTER: Joanna, and then Pat?
17 DR. BRELL: I think the way I look at it is
18 the CIPN 20 is sort of the anchor, something that
19 we want to have somewhere in the objectives for our
20 study for comparison's sake. But each study will
21 have additional PROs that are related to the agent
22 in question.

Page 196

1 So if it's pain, if it's other neuropathies,
2 it'll be more specific, but I would recommend
3 having the CIPN in all of them as a secondary
4 endpoint at least.
5 DR. GEWANDTER: So what you're saying is,
6 this would be a good general neuropathy CIPN
7 measure, but that when necessary, adding other PRO
8 symptom measures that are related to either your
9 disease or your intervention would be the best.
10 DR. BRELL: Might be more specific to what
11 you're studying.
12 DR. GEWANDTER: Sounds great.
13 DR. FREEMAN: So Daniela and Matt, you guys
14 have thought about this a little. What would you
15 say?
16 DR. DASTROS-PITEI: We focus on CIPN 20 just
17 because the evidence in the literature is around
18 it. I'm not sure about the FACT GOG, so I think
19 we'll probably have to think about this as a
20 special secondary.
21 My question is going back to pain. Are we
22 not measuring pain at all apart from what's in the

Page 197

1 CIPN 20? Is this something that can be a
2 consensus?
3 DR. FREEMAN: My stance would be, we are
4 measuring pain, but we just are not only measuring
5 pain. I think traditionally that the studies have
6 focused on pain, and I think there is a sense that
7 pain is, at the very least, not the only feature of
8 chemotherapy-induced peripheral neuropathy and may
9 be a less relevant feature for some patients,
10 particularly later on. That would be my take.
11 DR. GEWANDTER: My bias, I guess because
12 what I do, is I would always include a 0 to 10 pain
13 scale. Why not? And then definitely not as the
14 primary in a CIPN study, but I think Sharon has a
15 comment.
16 DR. HERTZ: I actually have a question, and
17 I've been waiting to see if anyone was going to
18 bring this up for the whole meeting. So we use the
19 term numbness and tingling quite a bit. I'm not
20 sure I understand how those two are the same thing.
21 And I notice that the terms are often used together
22 in a lot of the instruments.

Page 198

1 So I'm trying to figure out what's the
2 difference between tingling and pain, and then are
3 there other neuropathic symptoms that we're
4 missing, and if there are, are they even relevant
5 in this particular realm.
6 So to me, paresthesias, which I will rename
7 tingling, are painful. They may not be
8 dysesthesias, meaning turning something not painful
9 into painful. But when I have paresthesias just
10 from my foot falling asleep, I consider that pretty
11 painful.
12 So I guess I would like to hear what people
13 think about those distinctions and are they just
14 because I'm a neurologist, and I naturally think
15 that way, and they're not meaningful distinctions?
16 DR. GEWANDTER: Bob and then Pat?
17 DR. DWORKIN: Sharon, I'll try to keep this
18 simple. The IASP defines -- and for those of you
19 who are IASP members know this, if I'm incorrect
20 about this, correct me. My recollection is the
21 IASP defines paresthesias as abnormal sensations
22 that are neither painful nor unpleasant. They

Page 199

1 define dysesthesias as abnormal sensations that are
2 unpleasant, but not painful, and pain is pain.
3 So in our diagnostic criteria, we've tried
4 to adhere to that distinction of painful sensations
5 versus non-painful paresthesias and dysesthesias.
6 But I don't know that that's the way those terms
7 are used in neurology. But that is I think how the
8 IASP defines those terms.
9 DR. HERTZ: Can I just ask, in follow-up,
10 can someone help me understand what's a non-
11 painful -- what is a paresthesia if it wouldn't be
12 considered painful? When does that happen and what
13 do patients report? Because it seems that if they
14 weren't painful, they wouldn't raise as much
15 concern. But am I just again not getting it? I
16 mean, I have not spent a lot of time in this arena,
17 in this context.
18 DR. DOUGHERTY: So the numbness and the
19 tingling, the reason they're both put together, is
20 that when patients were given just open word
21 descriptor lists, and there's a whole bunch of
22 words there to describe different types of pain,

Page 200

1 almost always, they pick numbness and tingling.
2 And I mentioned yesterday that the patients
3 will say that they have, for example, numbness and
4 tingling in some area between pain and normal. And
5 they say that it's not painful, but it's annoying.
6 It's irritating.
7 I think pain simply is an intensification of
8 that tingling, so that it gets to the point now,
9 now it's gone from just tingling so that your
10 foot's barely asleep to, now, it's downright pin
11 pricks and it starts to morph into burning. So
12 folks are very specific about how they describe it.
13 Now, once you get into the painful areas, I
14 do agree I've never heard or rarely heard them use
15 the word "shooting," but burning is very common.
16 I've also heard folks have picked things like
17 gnawing. One lady said it felt like rats were
18 biting her on her fingers. Now, I didn't ask her
19 what experience she had in that, but in any case,
20 that's how she described it.
21 So I think that it's a gradation between no
22 sensation bothering them, and then it's gone -- it

Page 201

1 feels like a fat lip, which clearly is not painful,
2 but it's annoying right after the dentist. So that
3 would be a paresthesia.
4 Now, the tingling gets into the realm
5 bordering on dysesthesia.
6 DR. LOPRINZI: Just to clarify a moment, the
7 CIPN 20 asks for numbness specifically from
8 tingling. So it asks for numbness, another
9 question for tingling, another one for pain in the
10 hands and toes, hands and fingers, and separate
11 questions. So there are six questions, separate
12 for the toes and feet.
13 I've gotten to the point, when I see a lot
14 of patients who are actually having this that were
15 treated with Scrambler therapy and that sort of
16 thing, the numbness and the tingling are
17 discomforts is the word I'd put to it, not
18 necessarily pain.
19 When we look at the CIPN 20 instrument, the
20 integral patients who have numbness and tingling,
21 it's almost on top of each other. If you look at
22 numbness versus tingling grade, 80 percent are on

Page 202

1 the diagonal, where it's the same score. But pain
2 versus tingling is 80 percent. It's above in the
3 tingling area and not the discovery, so that they
4 are there.
5 And the patients say, "It's hard for me to
6 describe what these things are," and I always tell
7 them, "I know it's hard for you to describe, but
8 it's harder for me to describe it for you." And
9 then they understand that and come up with those
10 things.
11 DR. GEWANDTER: Gordon had a comment?
12 DR. G. SMITH: Yes. I think it's an
13 interesting question, so a couple of points. At
14 the risk of talking about pain in front of Bob
15 Dworkin, I'm going to do it anyway, and it's a good
16 thing I'm all the way across the room so I have an
17 escape.
18 I think there's an affect of component to
19 pain. Pain is whatever a patient says pain is, and
20 I don't think it's just a matter of
21 intensification. I think that's part of it.
22 All the time, we see people who say, "I've

Page 203

1 got terrible pins and needles." "Is it painful?"
2 "No. It's not painful." And then I scratch my
3 head and go, "I don't understand," but I have to
4 respect their judgment. So I think there's that
5 issue of personal perspective on what's pain and
6 not.
7 I think another aspect of that is, I've had
8 the same personal experience. I've never had
9 paresthesias that I didn't find painful, but I've
10 also never had neurotoxic chemotherapy, I don't
11 have diabetes, and I don't know what pathologic
12 paresthesias feel like. So I think it's important
13 for us not to lay on our personal experience. I
14 guess maybe one of us has a neuropathy and can
15 speak to that.
16 I think the last point I'd make is, numbness
17 is the second-least favorite word as a practicing
18 neurologist. The first is dizziness. And because
19 I'm a neuromuscular person, I don't have to deal
20 with that. As soon as someone says dizzy, I go,
21 "Go see the dizzy people."
22 But I'd say 10 percent of my ALS patients

Page 204

1 will say their first symptom was numbness. "What
2 do you mean by numbness?" "Well, it was heavy. I
3 couldn't move it." "You mean weak?" "No, just was
4 numb."
5 So I think it's one of those terms that is
6 even more content devoid than paresthesias. I
7 mean, we use it to mean loss of sensation, and I
8 think it works well in these sorts of scales.
9 DR. FREEMAN: I think the way neurologists
10 think about this -- and I am including Sharon in
11 the group -- is that we divide symptoms into
12 positive and negative symptoms.
13 Positive symptoms are things like tingling,
14 paresthesias, and negative symptoms are loss of
15 sensation. And I agree with Gordon that I've
16 always thought of numbness as a negative sensation,
17 loss, a negative symptom, loss of sensation. But
18 at least in the United States, it is a positive
19 symptom, and patients will speak about painful
20 numbness.
21 I learned to think of these as a continuum.
22 You have a positive symptom, let's say

Page 205

1 paresthesias, or any positive symptom, or any
2 positive sensation, which can be on a continuum
3 from pleasant, and we know positive sensations that
4 are pleasant, to unpleasant.
5 I think, if we look at the IASP
6 classification of paresthesias, there are people
7 who I'm sure would say, "If it didn't go on for a
8 long time, I would say it was quite pleasant." And
9 there would be people who would say that, "This is
10 really unpleasant." And that's what IASP would
11 classify as dysesthesias.
12 But I think the realm of sensory of
13 sensation, sensory symptoms, is along that
14 continuum, and there are some that are painful and
15 some that are not. And I think that, to me, is a
16 useful way of thinking about it.
17 DR. GEWANDTER: Matt, did you want to add
18 something?
19 DR. JARPE: Yes. I just wanted to make sure
20 that we're capturing interference items in the PRO,
21 so Gordon's comment about mood made me think of
22 this. I am not familiar with all the details of

Page 206

1 the CIPN 20. Are we capturing effect on sleep,
2 effect on mood, effect on daily function, that kind
3 of thing?
4 DR. GEWANDTER: So they're not in the
5 CIPN 20, but I think that you could easily include
6 in your trial a measure of sleep. And I think I
7 would argue, actually, that it would be better to
8 have that as a separate measure, but still very
9 important to include.
10 DR. JARPE: I mean, I think the BPI captures
11 those pretty well.
12 DR. GEWANDTER: The BPI captures
13 specifically pain interference with sleep.
14 DR. JARPE: Right, right.
15 DR. GEWANDTER: Yes.
16 DR. JARPE: But I don't know if there's a
17 way to do that.
18 DR. GEWANDTER: Right. So I think that
19 that's actually really interesting. It's one of
20 the things I think about a lot. And I'm not
21 familiar with any measure that specifically says,
22 "Tell me how your CIPN symptoms have interfered

Page 207

1 with your X, Y, and Z," but I think that that's
2 something that we should work on making.
3 Yes?
4 DR. LAVOIE SMITH: I think that's why the
5 EORTC advocates that the CIPN 20 is used along with
6 the QLQ-30, which does evaluate the other
7 co-occurring symptoms.
8 DR. GEWANDTER: But it doesn't actually say
9 how do your symptoms affect, like do the symptoms
10 we're interested in affect your quality of life,
11 which I think is really important for understanding
12 how important these things are to patients.
13 DR. LOPRINZI: But you could put those in a
14 scale from 0 to 10 that's a validated instrument
15 thing, any question you want, as long as you put
16 the endpoints on it. You could add those into it.
17 DR. GEWANDTER: Yes. I think that's a good
18 idea.
19 Yes, Joanna?
20 DR. BRELL: I'd like to hear everyone's
21 opinion as far as other symptoms we might be
22 missing. I hear a lot of patients talk about their

Page 208

1 hand and arm feeling cold. And I don't know if
2 that's related to concomitant vascular disease or
3 if that's something that other people hear
4 frequently.
5 DR. HAROUTOUNIAN: We hear it quite a lot
6 with oxaliplatin. At least in the study, patients
7 are just telling their hands feel cold.
8 DR. DASTROS-PITEI: The cold hypersensitive
9 is a hallmark of oxaliplatin. And I think, in
10 fact, NTx-12, there is a question about
11 cold-induced symptoms. And I'm not sure about
12 CIPN 20, if there's a specific question about cold.
13 But for NTx-12, they've added one question about
14 the oxaliplatin.
15 DR. GEWANDTER: But Joanna, you're not
16 saying cold-induced symptoms, cold-induced pain.
17 You're just saying, just in general, when I'm
18 standing here, my hands feel cold?
19 DR. BRELL: Exactly, yes, when I'm going
20 about my daily
21 DR. GEWANDTER: Yes, which I don't think is
22 in the measures very frequently, no. I don't

Page 209

1 remember of any. But I have actually reviewed the
 2 measures and I have checkboxes. I can look and
 3 see.
 4 DR. FREEMAN: I can never let this go. So
 5 Guido was fairly ruthless in his dissection of
 6 FACT-GOG-NTX. Is everybody in agreement with that?
 7 It seemed to me that there was either overlap or
 8 the questions were not of value. Is there anybody
 9 who wants to advocate for this instrument?
 10 DR. LAVOIE SMITH: The CIPN 20?
 11 DR. GEWANDTER: The FACT.
 12 DR. FREEMAN: The FACT.
 13 DR. LOPRINZI: I wouldn't do both. You
 14 could just get question after question. So I
 15 wouldn't do both. I would go with the CIPN as
 16 preferred, but there are other options in there.
 17 And if a FACT group had their own study and they
 18 wanted to do it, I wouldn't want this committee to
 19 say, "That's a terrible, terrible study."
 20 DR. DASTROS-PITEI: You would or you would
 21 not?
 22 DR. LOPRINZI: I would not do both. I would

Page 210

1 not recommend both because you're getting the
 2 patient to answer too many questions. But if David
 3 Cella's group was doing a chemotherapy neuropathy
 4 trial, I wouldn't put it in a way and say, "You're
 5 crazy if you don't use the CIPN 20." I wouldn't.
 6 DR. FREEMAN: So it sounds like we have
 7 consensus there. Then one last point that I would
 8 make, and I think probably, just in the interest of
 9 time, we should begin to include the research
 10 agenda. It seemed to me, looking at the CIPN 20,
 11 that the autonomic questions at face value were
 12 useless. I think this should be part of the
 13 research agenda.
 14 Visual blurring is so non-specific, it's not
 15 even worth regarding this as a symptom, but the way
 16 they asked about symptoms which were meant to
 17 address all the static hypotension were not
 18 particularly good. And I'm not sure how the
 19 question that deals with erectile function in
 20 males, but that's always a challenge.
 21 DR. DOUGHERTY: So I just want to point out
 22 before we leave the PROs that I think it was last

Page 211

1 year that Charlie Cleeland's group came up with
 2 another instrument that they tried to set up as
 3 specifically directed at cancer-treatment-related
 4 neuropathies. So you might want to include that
 5 potentially on a list of other PRO devices.
 6 I think, again, just to try to draw a
 7 consensus, I think to say that CIPN 20 is a
 8 recommended PRO tool as Charles laid out in a few
 9 sentences, and here are some other options.
 10 DR. RICHARDSON: Jennifer, do we agree on
 11 the signs or are we coming to that?
 12 DR. GEWANDTER: We are coming. That's next.
 13 DR. RICHARDSON: Good.
 14 DR. GEWANDTER: Do you have an opinion?
 15 DR. RICHARDSON: No, no. It's just, in
 16 terms of the other aspect, as we discussed earlier,
 17 not only because it's so relevant in regulatory
 18 drug trials, obviously, CTC-NCI version 4 and
 19 beyond are part of that, not necessarily for an
 20 outcome measure for this, but they would be
 21 incorporated as part of it, period, anyway.
 22 I'm only saying that because there's a real

Page 212

1 disconnect between regulatory science and clinical
 2 science. You're going to have to have that until
 3 NCI-CTC change, but the FDA will absolutely require
 4 that.
 5 So any statement we make, we recognize that
 6 that has to be also part of it, not as a primary
 7 outcome measure, but as something that's measured
 8 because, again, in oncology trials, we absolutely
 9 have to have that. If you don't have that built in
 10 IRBs, everyone will throw out their eyes with their
 11 hands.
 12 So I think we just have to recognize that's
 13 a reality.
 14 DR. GEWANDTER: So you mean as a safety,
 15 like an adverse event measure?
 16 DR. RICHARDSON: Exactly. That's part of
 17 safety. The point is --
 18 DR. FREEMAN: On the AE side.
 19 DR. GEWANDTER: Yes, right.
 20 DR. RICHARDSON: The point is that
 21 everything we do historically has been based upon
 22 CTC version 4 and beyond. And the reality is, we

Page 213

1 look at grade 2 painful neuropathy, for example, as
2 being a cutoff, which is well established in all
3 the therapeutic trials we've done.
4 To reverse that without addressing it would
5 be a major move, which I think would require
6 validation at least, but in any event would also be
7 a major regulatory hurdle.
8 DR. GEWANDTER: Okay. Thank you.
9 So let's move on to signs. Let's cover all
10 the measures, and then we'll talk about what we
11 think we need to do for research agenda. So for
12 sign measures, I think the TNS probably has the
13 best or the most research done on it in CIPN.
14 Do you guys agree? So is that one that
15 people think is probably, if you had to say, use
16 one tomorrow, or are there any others that people
17 would like to advocate for?
18 DR. DASTROS-PITEI: The clinical TNS.
19 DR. GEWANDTER: Yes, so the one that Ellen
20 and Guido have done, like you're validated it with
21 training people and stuff. Right? Is that the C,
22 TNS-C?

Page 214

1 DR. CAVALETTI: On the clinical version.
2 DR. GEWANDTER: So is that the one that you
3 would recommend using if we're going to use any
4 sign measure? Is that a yes?
5 DR. LOPRINZI: Is it a sign or is it a
6 combination of a sign and a PRO? So it's not
7 really a sign, it's a composite.
8 DR. GEWANDTER: Right. That's true. It's a
9 composite as well. Gordon, please, say something.
10 DR. G. SMITH: That's what I was going to
11 say. I mean, I would say use it, but it is a
12 composite measure.
13 DR. GEWANDTER: So what would you say -- so
14 should we have a sign only that we recommend?
15 DR. G. SMITH: Well, I thought you were
16 going to -- yes. I mean, I think there would be
17 utility in having a sign-only scale. And
18 certainly, in the diabetes world, we separate the
19 two, and I'm not sure that there's a problem with
20 the TNS, but I can certainly think of scenarios
21 where one would want a pure sign measure.
22 So I don't know whether you take a look at

Page 215

1 the performance of the TNS and existing data sets
2 by separating out the symptoms and signs. I mean,
3 that would seem to be fairly low-hanging fruit.
4 DR. GEWANDTER: So what exactly you mean by
5 that is just taking the symptoms part of the TNS,
6 the sign part of the TNS, and just comparing what
7 happens to them, like how well they correlate. Is
8 that what you're saying?
9 DR. G. SMITH: No. I mean just in looking
10 at the performance of the scale. I'm not sure that
11 there's a great deal of utility of having a symptom
12 subset. But the signs and the TNS are very similar
13 to, like, the Toronto scale or what we've done in
14 the UENS.
15 So I think having a pure sign-based measure
16 is useful, and given that there's been a great deal
17 of experience with the TNS-C and CIPN research and
18 trials, we have the data. So if one wanted to look
19 at its performance, it ought to be doable, one
20 would think.
21 DR. GEWANDTER: Okay. Sounds good.
22 DR. FREEMAN: Since you brought it up, one

Page 216

1 of the weaknesses of the TNS and one of the
2 strengths of your scale is that it gives the small
3 fibers, your scale, examines the small fibers in a
4 little more detail. That's the one.
5 The other is -- and I don't know if this
6 part is a strength or a weakness, but the fact is
7 that it looks at distribution. And I'm not sure
8 how you scale it and how you measure it, but there
9 is a proximal to distal gradient measure, which
10 your scale has, which the TNS does not have, to my
11 knowledge anyway. Now, there are advantages and
12 disadvantages.
13 DR. G. SMITH: The TNS actually has that.
14 DR. FREEMAN: Does have that.
15 DR. G. SMITH: I think Toronto has it, the
16 UENS has it, and TNS has it.
17 DR. FREEMAN: What about the small fiber
18 question?
19 DR. G. SMITH: I think the TNS has it, yes.
20 So it has pin sensibility. It's done in a
21 different way. And so it includes -- I can look to
22 see. I actually pulled it up. It's the pin and

Page 217

1 fingers, toes, wrist, ankle, elbow, knee. Ours is
2 only lower extremity, but it does have that kind of
3 anatomic topographical distribution.
4 DR. FREEMAN: So just hearing Gordon
5 describe this, is this something the oncologists
6 are going to be able to do, would be willing to do?
7 I don't think we want to rush to a recommendation
8 or consensus.
9 DR. RICHARDSON: Roy, I just want to say,
10 the science testing is all about physical
11 examination of findings with a tuning fork, and the
12 vibration sense, et cetera. Correct? It's
13 physical exam reflex elicitation and so forth?
14 DR. FREEMAN: Yes.
15 DR. RICHARDSON: I think with the bortezomib
16 trials, we did this. I've got to be honest with
17 you. My neurological examination skills are pretty
18 rudimentary. I'm British trained, so they're not
19 entirely hopeless, I think. But having said that,
20 Patrick finds things that I don't, but having said
21 that also, I'm not quite sure -- again, involving
22 neurologists, we typically involved neurologists

Page 218

1 when we found issues that we were concerned about.
2 For the upfront trial that we did with bortezomib,
3 we did a formal neurological assessment with our
4 partners in neurology. That did add substantial
5 expense to the trial, no question about it, but I
6 do think it was worth it.
7 So I think you could require physical
8 examination and TNS testing as a grid by the
9 practicing clinician, but in clinical trials, it
10 might be reasonable to emphasize, notwithstanding
11 that rather eccentric experience with those people
12 in all the blue suits, recommending expert
13 neurological involvement or neurology
14 participation.
15 I mean, I don't know if that just puts all
16 the trials out of range for cost, but it certainly
17 seems to me reasonable. I don't know. Jim, if you
18 want to.
19 DR. GEWANDTER: Jim?
20 DR. CLEARY: I agree with Paul. I just
21 think, especially in terms of feasibility of
22 trials, to ask the oncologists to do these

Page 219

1 exams -- they know they're not very good at it, and
2 I'm speaking for myself, I'm not very good at
3 them -- they're not going to be very excited about
4 it, and I'm also worried about the reproducibility.
5 But also, it might make the trial less attractive.
6 I think if you're going to do signs, make it
7 something so simple that a research nurse could do
8 it, because a research nurse will have a very
9 different attitude than an oncologist with a busy
10 waiting room who's trying to get to his patients,
11 or as Paul suggested, just partner with a
12 neurologist to have the exams. But having the
13 oncologist do the signs, I don't think will be very
14 good.
15 DR. GEWANDTER: I don't think it's
16 really -- at least from my experience with the
17 cooperative groups, if you're going to run a trial
18 through there, it's not realistic that the
19 oncologists are going to do it. But I think,
20 Ellen -- I mean, I won't speak for you, but I think
21 you and also Guido have validated the TNS in a way
22 that you have a training video, and someone like a

Page 220

1 research assistant can do it with reliability.
2 Is that true?
3 DR. LAVOIE SMITH: Yes. So we've tested
4 even a bit more abbreviated version of the TNS,
5 where it includes the distal to proximal extension
6 items of numbness, tingling, pain, reflexes, and
7 vibration, and have tested that in kids and in
8 adults.
9 Then specifically in a pediatric multisite,
10 R01, we created a training video that was posted on
11 a website, and then did a train-the-trainer
12 approach with neurologists at individual sites,
13 validating skill once someone learned how to do it.
14 We've used this training mechanism at
15 multiple sites around the county and have been able
16 to validate that the assessor can be trained in a
17 way that is appropriate, and that neurologist
18 assessment of that person confirms that.
19 DR. GEWANDTER: Have you done anything to
20 see if there's any inter-grader reliability?
21 DR. SMITH: Yes. So we tested inter-rater
22 reliability with the person that we trained. And

Page 221

1 the people that we trained were nurses, fellows,
2 physical therapists, med students, and then had
3 their exams repeated by a neurologist to evaluate
4 the correlation, and it was good. I mean, reflexes
5 are tricky.
6 DR. GEWANDTER: So it's interesting because
7 I'm doing a small study right now, and I have a
8 research assistant who's actually using the UENS
9 and a neurologist. And the sample size is really
10 small, so I can't do any statistics on it, but she
11 gets pretty close to the neurologist, except for
12 reflexes.
13 DR. SMITH: We eliminated the strength item
14 just because we don't see that very often.
15 DR. GEWANDTER: Well, maybe it's possible.
16 DR. LOPRINZI: So listening to Gordon -- I
17 think that Ellen's been able to show that, yes, you
18 can do that and it correlates very well. But when
19 I listen to Gordon, it turned out that it didn't
20 seem to make much difference in diabetes and the
21 other.
22 DR. GEWANDTER: I don't think that's what he

Page 222

1 said. He said that when they were trained, it did
2 make a big difference.
3 DR. G. SMITH: I completely agree, and I
4 wasn't articulate enough. If you take a bunch of
5 neurologists, put them in a room, and say, "Figure
6 out if this person has signs of neuropathy," we
7 aren't particularly reproducible.
8 If you sit down with us ahead of time and
9 say, "Here are what we consider signs," we do
10 incredibly well. And it's not because we're
11 neurologists. We see this I think in
12 endocrinology. And really, this has always baffled
13 me, because our endocrinology colleagues do this
14 just fine, and they don't have any more neurology
15 training or no neurology mojo, and certainly less
16 neurology mojo than any British-trained physician
17 has.
18 We also have our study coordinators actually
19 trained to do the UENS, but the only thing that's
20 really difficult is reflexes. And I'll go to the
21 Rasch-transformed TNS, which got rid of the
22 autonomic questions and got rid of the reflex

Page 223

1 assessment.
2 I think reflexes are hard, but they're not
3 only hard for oncologists. The beautiful thing
4 about being an attending is you always disagree
5 with the residents about the reflexes, and you're
6 right. And when you're a resident, you're wrong.
7 So I think this is actually a lot easier
8 than we're making it. And I think this is one of
9 these communication and cultural issues that I have
10 full confidence that every oncologist in this room
11 could be trained to do the TNS perfectly well in a
12 way that wouldn't be terribly obtrusive, and that
13 we just haven't done a good job of doing that.
14 That's just my perspective
15 DR. LOPRINZI: We haven't shown yet that it
16 provides value added to the patient-reported
17 outcomes.
18 DR. G. SMITH: I think there's face validity
19 that it tells us something different. I suppose
20 you're right that we haven't. But we haven't
21 really used it very extensively, and I think the
22 literature right now is dominated by symptom-based

Page 224

1 trials. As we're thinking about prevention trials
2 and looking at actual disease prevention as opposed
3 to symptom prevention, then it makes sense that it
4 would be useful.
5 DR. FREEMAN: So maybe just to frame this
6 discussion a little, I think the utility of the
7 examination is twofold. The first is diagnostic,
8 to make sure that there is a greater likelihood
9 that the patient in front of you has the neuropathy
10 and doesn't have arthritis or something of that
11 nature. That's one.
12 In disease modifying, it has a different
13 dimension, and one of the ways that at least this
14 has -- and we'll talk about the special
15 investigation -- been used in the past, not
16 successfully as of yet, although perhaps at least
17 in Europe, successfully as far as amyloid
18 peripheral neuropathy goes, the way it has been
19 used is as a surrogate measure for the important
20 feels, functions, and survives type questions.
21 I think it's important to consider, as we
22 think about this, is the examination -- and here,

Page 225

1 it's obviously very important to here, both today
2 and even more so in the future when companies go to
3 the FDA, would the exam -- and it has been in
4 diabetic peripheral neuropathy, either standing
5 alone or as part of a composite, is it considered a
6 potential surrogate perhaps for approval under
7 subpart H for what really matters, the way the
8 patient feels, functions, and survives.
9 So I really want to say that the exam
10 actually is potentially important.
11 DR. LOPRINZI: So it's a research question.
12 DR. FREEMAN: No.
13 DR. LOPRINZI: If it's potentially
14 important, then I think that --
15 DR. FREEMAN: I don't want to say
16 potentially. I mean if the FDA accepts for
17 chemotherapy-induced peripheral neuropathy that
18 this is a surrogate measure for approval, then it
19 is important. The potential lies in the hands of
20 whether the pharmaceutical industry can make a case
21 to the FDA as to the importance of this as a
22 potential surrogate measure for approval under

Page 226

1 subpart H, which is to say that an additional trial
2 needs to be done in the future.
3 DR. RICHARDSON: Right. And Roy, if I may,
4 in that same context, to echo the point that Jim
5 made and Charles as well as the oncologists, I
6 totally agree with Dr. Smith's comment earlier.
7 Having said that, I think that if you do an
8 oncology assessment, say, with each cycle, if
9 you're in an approval setting with regulatory
10 approval, it makes sense that a neurologist
11 validates the finding because at the end of the
12 day, that will add strength to it. It's what we
13 found with our own experience hands on.
14 In reality, however well trained we are, our
15 neurologists differed. They found things
16 differently than we did, and that's okay. I mean,
17 I just think that if you're designing a study, why
18 wouldn't you have the oncologists assess every one
19 to two weeks, or every visit, or clinician every
20 visit -- because we do that with bortezomib, for
21 example, routinely anyway -- but then have a
22 neurologist validate the finding at a different

Page 227

1 period, say, every two or three cycles, because
2 again, that adds an internal control that I think
3 would make us feel more comfortable.
4 I mean, what do you think, Jim? Because it
5 was very nice of Dr. Smith to say what he did, but
6 I think at the same time, the reality is, in a busy
7 clinic, we take shortcuts, don't we?
8 DR. CLEARY: Yes. And I just worry because
9 they're going to be so busy that the data won't be
10 that good. I do think if you could show that
11 nurses could do it, they have a very different
12 attitude than the oncologists will have. They'll
13 view that as their job. They'll take it very
14 seriously, whereas the oncologist will just try to
15 go very, very quickly.
16 DR. GEWANDTER: I think that Ellen and
17 Guido's work has shown that that is possible, and
18 also Gordon's, too.
19 DR. DOUGHERTY: In this same context,
20 really, the QST could be brought in underneath the
21 signs category instead of over there someplace out
22 on a peninsula. But if you have a well-trained

Page 228

1 post doc, they can do a lot of these assays quite
2 effectively.
3 The important thing about some sort of
4 quantitative sign or other measure is as long as
5 you include one for A beta fibers, A delta fibers,
6 and C fibers, an important outcome of any potential
7 clinical study, you may end up only impacting a
8 subgroup of fibers, you can maintain pain with
9 either A or C fibers.
10 So to understand the results of your
11 clinical trial as potentially impacting one group
12 of fibers but not another, you could still have
13 pain, and that metric won't move. But you could
14 still get a positive result out of your trial,
15 nevertheless.
16 DR. GEWANDTER: So it's already 1:48, so I
17 wonder if we should try to decide on a sign measure
18 that we would all agree on. I don't know that
19 we're going to be able to agree today that you
20 should or shouldn't include a sign measure in your
21 CIPN trials, but maybe what we could agree on is,
22 if so, which one would be the best.

Page 229

1 Does anyone have anything to say about that?
2 DR. LOPRINZI: I don't think you do that,
3 because I think we could just move on from this
4 thing. But if in fact your EORTC CIPN 20 curves
5 vary greatly, i.e., the patients, if they have
6 treatment, they all get better, and the patients
7 who got placebo, they don't; or the ones who start
8 off with prevention, they never get worse and the
9 other ones get better, then the heck whatever sort
10 of thing that doesn't matter there. And if it's
11 the other way, if the curves don't change at all,
12 then it doesn't really matter what the reflex was
13 that we don't know how to measure anyway.
14 So I think that if the FDA requires it, then
15 a company is stuck by that sort of thing. I don't
16 think we should recommend to the FDA to require it
17 because I don't think it's been shown that it
18 provides value added. It's a research-type
19 question.
20 DR. FREEMAN: Maybe I'll frame the question.
21 And I just wanted to prepare Sharon because I'm
22 going to put her on the spot just a little.

Page 230

1 We spoke this morning about Parkinson's
2 disease and how the drugs actually change the
3 clinical examination before they change the CIPN 20
4 equivalent. And one of the issues is, of course,
5 that when you have an intervention that is disease
6 modifying, the subtle aspects, the components that
7 build up disability and the functional measures
8 that we assess will change first if they are going
9 to work.
10 I have some experience with the familial
11 amyloid polyneuropathy trials, where the measures
12 that were the most sensitive to intervention were
13 things like strength of the big toe and strength of
14 the dorsiflexes. And the case that was made was
15 these should be considered a surrogate measure for
16 function, able to climb up stairs, not tripping
17 when you walk over a curve.
18 To me, that was a strong argument for
19 consideration of approval under subpart H, which is
20 to say that a real trial needs to be done,
21 satisfying the FDA criteria that it improves the
22 way a patient feels, functions, and survives.

Page 231

1 So the question that I'm about to ask is the
2 obvious one. And I know there are things you could
3 say or things you can't say, but is there a stance
4 that you can give us some insight as to how the FDA
5 might consider the neurological examination as a
6 surrogate measure?
7 DR. HERTZ: So there are a lot of different
8 pieces there. Within this particular context, I
9 will turn around and ask you certain questions
10 back, and that's how one might consider a variety
11 of different endpoints, and what to focus on, and
12 the like.
13 So we have prevention, we have symptom
14 management, and we have potentially corrective
15 disease-modifying agents that we might want to be
16 studying. And depending on what you want to study
17 or what you think your drug can do is what you
18 should be measuring.
19 So in the context of really wanting a
20 functional outcome in an objective manner, so true
21 signs, then I think that a properly captured
22 neurologic examination can be helpful. But how are

Page 232

1 you going to quantify it, and how are you going to
2 maintain consistency from one site to another, or
3 from one subject to another depending on who your
4 study staff will be on any given day?
5 So I don't have an answer that it is or
6 isn't acceptable, but those are the kinds of
7 questions that would be asked if it was going to be
8 something that was going to be relied on as a
9 surrogate.
10 Alternatively, a different type of objective
11 measure of function might be considered, and we run
12 into this trouble all the time of, other than nerve
13 conduction studies, which can be fairly protocol
14 driven, are there any others.
15 Years ago, we looked at QST and found it was
16 highly operator dependent, so we've been reluctant
17 to look at that, and that's for neuropathy, painful
18 neuropathy, in general. But I wouldn't say it can
19 never be back on the table.
20 So what we mostly want to see, if we're
21 looking for something that's going to evaluate
22 signs, in particular, nerve function, is something

Page 233

1 that is reliable and reproducible, because if it's
2 going to be a surrogate, it's one step removed.
3 So that's not answering your question, and
4 I'm sorry. But I will say that in the context of
5 therapy that we think might actually improve
6 function, we would be willing to consider a
7 functional outcome, especially if it is expected to
8 greatly pre-date the PRO-measured outcome. So
9 considering a surrogate for the primary in a
10 subpart H-type thing is certainly a possibility.
11 For any of you who have been involved in
12 disease-modifying neuropathy studies that have come
13 through the agency, we ask for nerve conduction
14 studies. And then someone says, "But nobody walks
15 into the office complaining that my nerve
16 conduction velocity has declined by 2 meters per
17 second," and that's true. But at least it's an
18 objective measure.
19 Whether or not it's relevant, for instance,
20 in a diabetic, for instance, is that going to
21 ultimately result in fewer or longer delay until
22 there are foot ulcers and amputation, well, that's

Page 234

1 a long-term commitment to follow-up. That would be
2 part of a subpart H approval, but it would at least
3 provide time to get on the market, and then fund
4 additional studies that way for a commercial
5 development program.
6 DR. GEWANDTER: Thank you.
7 So it's 2:00, so do we care about getting a
8 sign consensus on the sign measure? So can we try
9 to get a consensus on, if you were going to include
10 a sign measure, which one would it be? Any
11 suggestions? Gordon?
12 DR. G. SMITH: Can I ask a different
13 question? Sorry. I think the problem with that is
14 most of us probably don't know anything about most
15 of those sign measures. And I wonder if there
16 might be consensus that in a trial that is intended
17 to prevent neuropathy or alter the disease course,
18 not primarily to manage symptoms, that a sign
19 measure ought to be included. And I wonder whether
20 our ability to render a judgment about which of
21 these is appropriate might be best served by having
22 everyone look at them and provide feedback after

Page 235

1 the meeting.
2 DR. GEWANDTER: That sounds good. And I
3 agree with you that face valid-wise, it seems more
4 important to have the sign measure in the early
5 prevention studies than potentially after you've
6 already had the symptoms and you're trying to treat
7 those symptoms.
8 DR. FREEMAN: In that context, I want to
9 just say that, at the moment, Chris Gibbons and
10 Jennifer are in the middle of a project looking at
11 these quantified neurological examinations. And if
12 anybody has any views, feels that their particular
13 instrument should be include, that we may have left
14 those out, please, before it's too late, let us
15 know.
16 DR. GEWANDTER: Okay. So the only thing
17 left on the list is skin biopsy, and I know we've
18 talked a lot about how that could potentially be a
19 barrier to recruitment. So I guess the question
20 is, is there anyone who wants to really strongly
21 champion the idea that we should include skin
22 biopsies in our studies and see if the FDA

Page 236

1 potentially would be willing to make them a
2 surrogate endpoint.
3 Sharon, do you have anything to say?
4 DR. HERTZ: The easy part for me is to say,
5 as long as it fits the criteria that I just
6 described.
7 DR. GEWANDTER: So for that criteria, how
8 much evidence do you need that a decrease in
9 intraepidermal nerve fiber density correlates with
10 potentially long-term deficit in neuropathy or
11 something? What kind of evidence do you want for
12 that?
13 DR. HERTZ: So in terms of what it takes to
14 make a surrogate sufficient to stand alone and no
15 longer be part of a subpart H approval is kind of
16 the question there. So initially, changes in blood
17 pressure were really surrogates because nobody
18 again walks in saying, "I think my blood pressure
19 is up 5 millimeters." They'd walk in with a heart
20 attack or a stroke, kidneys stop working, and those
21 are the important downstream correlations.
22 But over time, it was determined that

Page 237

1 certain amounts of improvement in blood pressure
2 can translate reliably into these clinical
3 benefits. So now, any hypertensive trials really
4 don't require these long-term clinical benefits.
5 So here, for nerve fiber density or any
6 other sign that is potentially a surrogate for some
7 type of bigger outcome, it's kind of a two-stage
8 process.
9 If there's enough data to show that there's
10 a very good correlation between changes in the sign
11 and the desired endpoint, you would dump all of
12 that into your application. Not dump. You would
13 assemble all of that in a nice, logical
14 conversation to describe why your measure is
15 capable of serving for your study, and in the
16 absence of that would be an argument for why it's a
17 reasonable surrogate, again with a longer-term
18 follow-up that would be needed to then ultimately
19 support that.
20 Because the next question is, how much
21 difference, right? So I don't know. Is 2 meters
22 per second less slowing in a DPN patient in the

Page 238

1 course of a year ever going to translate into
2 anything? I don't know. But that's why there's
3 these added commitments to those kinds of things.
4 Is that better than nothing? It might be. It
5 might be the equivalent of nothing.
6 So when we do these kinds of surrogate
7 approvals, there are all kinds of language that
8 says this is what was found, and we don't know if
9 it's going to translate yet. But presumably, at
10 the time the decision is made, there will be a good
11 argument to support a positive decision to accept
12 it.
13 DR. GEWANDTER: Okay.
14 DR. FREEMAN: So Gordon, as part of your
15 studies on skin biopsy, have you looked in the same
16 way that others have looked at the relationships
17 among sural nerve biopsy, nerve fiber density,
18 motor conduction velocity meters per second, and
19 changing the clinical examination over time?
20 Because one of the issues with this is that
21 we are dealing in the small-fiber realm in many of
22 the neuropathies that we are interested in, and

Page 239

1 nerve conduction studies are not particularly
2 helpful.
3 DR. G. SMITH: So we have a lot of data in
4 diabetes. And one of the challenges, as you know,
5 is it doesn't change very much. And so looking at
6 the relationship between change and measures hasn't
7 been particularly productive because they don't
8 change much, except skin biopsy and every study
9 we've done seems to change.
10 All the natural history data is of decline,
11 and our studies have thus far really been focused
12 on lifestyle-based intervention, one sees an
13 effect. And I don't know whether that's clinically
14 meaningful or not yet. I think in the IGTN study,
15 there was a weak correlation in a very small sample
16 size between change in INFD and change in pain.
17 Cross-sectionally, it correlates beautifully
18 in our hands with actually pain with examination
19 scores and with nerve conduction studies. These
20 all, in a cross-sectional fashion, seem to relate
21 to one another.
22 We're trying to answer this in a cohort of

Page 240

1 patients who are getting paclitaxel. And what's
2 interesting is that we are having a hard time
3 convincing people to have skin biopsies, I think
4 mainly because this is an oncology setting. I
5 don't think we've fully sold our oncology
6 colleagues on it. But we get nerve conduction
7 studies on everyone, and we're finding that nerve
8 conduction studies are often normal in patients who
9 have clinically obvious neuropathy, which is
10 interesting.
11 Of the people who have had skin biopsy,
12 which is probably about -- and we're only doing
13 this in people who have neuropathy -- maybe 10
14 percent are abnormal or something. It's really
15 remarkable how often they're normal.
16 So we don't have those data, but our hope is
17 we've got a proposal in the process to try to
18 answer this question with CIPN, where I think we
19 have a better hope of understanding at least the
20 relationship in change in both nerve conduction
21 studies and INFD.
22 Again, this is non-glabrous distal leg INFD

Page 241

1 and PROs. And we're not really looking at function
2 in this population, but one could. We are doing
3 that in diabetes, and we're doing that in our
4 lifestyle base and are soon to start an
5 intervention study to try and get at this.
6 DR. FREEMAN: So clearly, this is research
7 agenda material and quite critical research agenda
8 material.
9 DR. GEWANDTER: So if nobody has any other
10 things to say about that, I think we should move on
11 to our next challenge.
12 DR. EVANS: Can I just make one comment? I
13 just thought I'd throw this out there. But
14 surrogacy is a very high bar, and it's much higher
15 than most people realize. It's certainly further
16 beyond correlation. Correlation is fairly weak as
17 a bar.
18 Some of the cancer folks may relate to this
19 because even the most famous surrogate in cancer
20 being progression of some type is frequently
21 questioned about how good of a surrogate it is.
22 It's supposed to be a surrogate for improving

Page 242

1 survival, and half the time, it doesn't play out.
2 And there's a lot in the literature even
3 questioning things like that, that they really have
4 to be predictive, which is a much higher bar than
5 most people think it is.
6 DR. MCDERMOTT: Just to add to that, it's
7 also treatment specific. You can imagine
8 treatments that have an effect on the surrogate but
9 don't ultimately have an effect on the clinical
10 endpoint and vice versa, which makes it even more
11 of a minefield.
12 I would suggest couching this in terms of
13 these measures might be useful for proof-of-
14 concepts sorts of studies or early leads types of
15 things rather than thinking about it in terms of
16 surrogate approval.
17 DR. GEWANDTER: Yes, Joanna?
18 DR. BRELL: Before we move on, I just want
19 to make sure, if we're listing research agenda
20 topics, to further assess more functional testing.
21 DR. GEWANDTER: Yes. Thank you for
22 reminding me. And maybe Drs. Dougherty and Gordon

Page 243

1 can help me with a list of functional endpoints to
2 propose since we didn't really talk about it too
3 much here, like the things that you're doing with
4 diabetes and stuff. That would be great.
5 So moving on, I'm not really sure -- I don't
6 know if we account really make a choice right now
7 or come up with a research agenda of how to -- so
8 we have to decide how to measure CIPN, but once we
9 measure the severity, what do we want to do with
10 that?
11 So after hearing my presentation and Mike
12 and Scott's presentations, do we have a consensus
13 of what might be the best endpoints to use. Any
14 thoughts?
15 DR. LOPRINZI: So you're asking for
16 prevention trials?
17 DR. GEWANDTER: Yes.
18 DR. LOPRINZI: If you're doing a prevention
19 of chemotherapy neuropathy, which is different than
20 a treatment established, so you're talking about
21 chemo.
22 DR. GEWANDTER: We're not covering treatment

Page 244

1 of established chemo after --
2 DR. LOPRINZI: So this is prevention. Okay.
3 So it's prevention --
4 DR. GEWANDTER: Yes, yes.
5 DR. LOPRINZI: Then I like what we've heard
6 from statisticians of area under the curve seems to
7 make a lot of sense to me as opposed at 1 month, or
8 3 months, or 6 months, or 12 months, area under the
9 curve during the time of treatment.
10 I think it's important if you're doing a
11 prevention trial and you're using your prevention
12 drug, that you follow them for six months
13 afterwards and make sure that the neuropathy
14 doesn't get really bad once you stop the drug and
15 the drug actually was not preventing the
16 neuropathy, but rather was masking it.
17 So it'd be very important to know that after
18 you stop the drug, you didn't get all bad
19 neuropathy and even worse than you would have
20 before, because you were continuing chemotherapy
21 through that whole time and just treating it with
22 an opioid-type medication for there. But I think

Page 245

1 area under the curve.
2 DR. RICHARDSON: I would just also echo that
3 and, at the same time, Jennifer, my only other
4 thought would be, I touched on earlier this morning
5 or before lunch rather, the idea of the neurotoxic
6 drugs that you've given, having a clear
7 understanding of -- you mentioned percentage of
8 full course, but I think it needs to be a little
9 bit more in depth than that, dose interruptions,
10 dose delays, and just to bear in mind some of the
11 PK issues because at the end of the day, there's
12 also tremendous patient-to-patient variability in
13 those.
14 It just warrants attention and also, parts
15 of supportive care because, for example, with
16 bortezomib, we've learned that subQ may have a
17 lower Cmax -- it does have a lower Cmax than IV.
18 And there has then been this passion for reducing
19 neurotoxicity in that context, and it does appear
20 to be real.
21 Having said that, the tools that they used
22 were just CTC. They weren't more sophisticated

Page 246

1 than that. And very, very importantly, the reality
2 is that we're seeing high-grade neuropathy still
3 despite subQ because the volume of distribution
4 changes with hydration, which we used to do all the
5 time and we now have revisited because,
6 essentially, volume of distribution matters, we
7 think. And it makes sense from everything I've
8 heard over the last two days.
9 So just to bear that in mind as you design
10 these. In other words, what you're giving as your
11 neurotoxin matters. And if all the focus is on the
12 preventative agent, you might lose the wood from
13 the trees if you've got variability with the
14 neurotoxic drugs you're using that may confound
15 your outcome, especially in a randomized setting.
16 DR. GEWANDTER: I mean, I don't want to skip
17 ahead too quickly, but then is what you're saying
18 that you advocate potentially for some kind of
19 composite measure that includes both severity of
20 neuropathy and how much chemotherapy you've
21 received? Is that what you're saying? Or you're
22 just saying you have to think about how much

Page 247

1 chemotherapy --
2 DR. RICHARDSON: I'm saying in the context
3 of trial design, it's very important to understand
4 it. So it builds on Charlie's point. It builds on
5 the concept of what you've given to each patient of
6 a neurotoxic drug.
7 I mean, just speaking for ourselves, for
8 example, bortezomib dosing in a randomized setting
9 with a chemo preventative will be very complex
10 because you'll have dose adjustments, different
11 strategies. And the thing is not to underestimate
12 the impact of that on what happened to your
13 neurotoxic drug, because, again, you can have a
14 tremendous confounding effect if that variance is
15 too high.
16 DR. GEWANDTER: Yes, yes. So I think that
17 is the main challenge of what we're doing, and to
18 choose an endpoint where we can -- because I think
19 if we listen to what Mike talked about yesterday,
20 you can't really just throw those people out who
21 don't get the full dose, and you can't adjust for
22 that.

Page 248

1 DR. RICHARDSON: No, no. That's not what
2 I'm saying. As a clinical trialist, on the
3 oncologic side, what I'm saying is, you put here
4 full course, percentage of full course. My only
5 point about that analysis is that's too simplistic
6 potentially for the neurotoxin delivered.
7 So you may want to look more carefully at
8 how you -- that chemotherapy-received category is,
9 from our point of view as oncologists, rather
10 simple. You may want to be much more --
11 DR. GEWANDTER: So do you have any specific
12 suggestions for what -- like if you had to
13 operationalize an endpoint that --
14 DR. RICHARDSON: Yes. I mean, the
15 operationalization is you'll have to catalog how
16 was drug given, obviously were there root
17 variances, for example. Not that that happens with
18 oxaliplatin, of course, but it certainly happens
19 with bortezomib. And at the same time, what other
20 confounding events were occurring?
21 I mean, my point is, in your trial design,
22 to underestimate the importance of that could lead

Page 249

1 to a very large phase 3 effort that is
2 then -- especially as we've heard, the sensitivity
3 of our tools can be so variable, please don't
4 forget that piece of it is my only point.
5 DR. GEWANDTER: Okay.
6 DR. DASTROS-PITEI: With the cumulative dose
7 of the drug, sometimes it's related to the
8 individual patient. And I think what's also
9 important to understand is the interruptions or
10 discontinuations, what are these due to? So are
11 they due to neuropathy or hematology adverse
12 events, or other adverse events?
13 This is I think important to be captured to
14 put it in the context, so you know what much damage
15 is due to neuropathy per se on the chemotherapy
16 that the patient was supposed to receive.
17 So if there's a percentage of the
18 theoretical dose, the patient should receive it.
19 There are different ways to calculate, but the most
20 common is the total cumulative dose.
21 DR. LOPRINZI: I think both are important.
22 The simplest way to do it and what we utilized

Page 250

1 before is looking at the area under the curve and
2 looking at that, we use that as our primary
3 endpoint.
4 Then separate from that, looking at the dose
5 of chemotherapy, the average dose, or when people
6 quit taking full dose, or whatever on those things.
7 And if they both go along with each other, that's
8 fine.
9 If there is some sort of interaction, again,
10 that somebody continued a full dose like this and
11 people got more neuropathy, but they added a bigger
12 dose, as Patrick said, it's per dose that they got,
13 then you sort through that. So you can put up some
14 statistical rules to that sort of thing. So think
15 of them separate, and then combine them together if
16 need be.
17 DR. GEWANDTER: Can we let Mike comment?
18 DR. MCDERMOTT: Yes. I think that the
19 biggest message from Scott's talk yesterday was
20 just the opposite, that you need to take these
21 things together and analyze them together in the
22 same patient, somehow.

Page 251

1 Now, the operationalization of this is the
2 part that's tricky. The one way that was suggested
3 yesterday was, well, if they have to modify their
4 dose, call them the worst endpoint. You can do
5 finer gradations than that if you want to based on
6 how much dose you receive or something like that.
7 That needs more thought. But I think that looking
8 at these things separately, I don't think that that
9 is -- I don't think that's a good idea.
10 DR. LOPRINZI: I think you have to think
11 about them separately, but figure out how to marry
12 them together. It's just easier to think about
13 them separately, and then with some statistical
14 rule, you can marry them together by going by dose
15 instead of time.
16 DR. DASTROS-PITEI: But are you thinking of
17 a composite of this?
18 DR. MCDERMOTT: I think you have to.
19 DR. DASTROS-PITEI: -- or an analysis, which
20 takes into account the --
21 DR. GEWANDTER: He's saying a composite for
22 each patient, so each patient, they received at

Page 252

1 least 75 percent of their planned chemo and they
2 didn't get worse than X neuropathy. That's a very
3 simple dichotomous way to combine them, but then
4 Mike also proposed this ranking system where you
5 can maybe have a little bit more than just two
6 options.
7 So I think this is a very complicated
8 discussion that might be hard for us to talk about
9 here, and it might be easier if we put together
10 some proposals. Like I could do this with the help
11 of Mike and Scott, and obviously Bob and Roy, and
12 then maybe we could send that around.
13 Maybe a better use of our time right now
14 would be to go back to the inclusion/exclusion
15 criteria for right now if you think that's
16 reasonable, and then we can come back to this if we
17 have time.
18 DR. FREEMAN: Yes. I'd like to hear a
19 little more discussion about this before we leave
20 it to us to do this in small session, because the
21 challenge with this territory is that there are
22 several moving parts. There's the chemotherapeutic

Page 253

1 regimen, there's the neuropathy, and there's also
2 the drug, which different drugs will have different
3 mechanisms of action, different times when they
4 worked. So I think we should maybe just air the
5 issues related to each one of these territories.
6 So with respect to the neuropathy, there are
7 different ways in which we can assess it. We can
8 assess the time to an event, whichever we decide,
9 what we decide the appearance of a neuropathy is.
10 We can look at the severity of the
11 neuropathy, and we can look at that at a fixed time
12 point or we can look at the area under the curve.
13 And before we jump to the beauty of area under the
14 curve, which obviously has its appeal, to some
15 extent, whether this is going to be a sensitive
16 measure will depend on the nature of the
17 intervention.
18 The problem with area under the curve is
19 that if there is useless data in the beginning, if
20 there's noise, if there is acute toxicity from
21 specific drugs, which is unrelated to what we're
22 going to see six months later, the effect of a drug

Page 254

1 may be washed out.
2 So I think it's really important to dissect
3 out separately the individual components, to
4 dissect out also the nature of what I call the
5 disruption of the chemotherapeutic regimen, because
6 this takes several points as well and also how
7 frequently that occurs, because in certain
8 regimens, it occurs more frequently than others.
9 And then finally, and this is the challenge, to
10 come up with some novel way, if we need to, that
11 combines these.
12 So what I would like to hear is just if
13 anybody can elaborate on what I've said, if anybody
14 has a different view of this, I'd like to hear it
15 to help us think about this in a more quiet
16 session.
17 DR. LOPRINZI: At the risk of talking too
18 much, I think you look at all of these issues. I
19 sent you a protocol on our calcium magnesium study
20 and look at that. We have a chart of the 8 or 10
21 things we look at. And you look at the time, the
22 area under the curve. You look at the time to

Page 255

1 grade 1 neuropathy, to grade 2, to grade 3
2 neuropathy. You look at the dose, all those
3 different things, and you can set up your
4 statistical rules, how you put those things
5 together.
6 But you have to look at them I think
7 individually, like you're putting out there during
8 the time of chemotherapy and there afterwards, and
9 then work with a statistician to say how do we
10 marry these things together?
11 DR. HAROUTOUNIAN: I'd just add one comment.
12 I think while thinking about the mechanisms of
13 neurotoxicity with most of the agents, I think we
14 don't really even know whether the neurotoxicity is
15 related to peak plasma concentrations, trough
16 plasma concentrations over time, total AUC, and
17 even same patients getting the 85-milligrams per
18 meters squared oxaliplatin, their individual PK
19 profile might be quite different, which might
20 affect their development of neuropathy or not.
21 The question is, do we add individual
22 pharmacokinetics as a research agenda, at least

Page 256

1 something to think about? I'm not saying we need
2 to take full PK profile of each of the chemotherapy
3 drugs and to compare, but maybe there are certain
4 key parameters such as peak plasma concentration or
5 some kind of trial for something to try to relate
6 to the individual differences.
7 DR. LOPRINZI: All that stuff gets I think
8 sorted out initially when you figure out how to
9 give the drug, and the toxicities, and all those
10 sorts of things. So we're talking about people who
11 are getting the drug all the same way, over 20
12 minutes, over an hour. That's something that's
13 determined ahead of time.
14 DR. HAROUTOUNIAN: That's correct.
15 DR. LOPRINZI: That's something that someone
16 might want to do to help figure out if that affects
17 neuropathy. And they've done that at times where
18 they used to give paclitaxel over one hour versus
19 24 hours and all that sort of stuff.
20 But assume all that is done, and it's all
21 given in the same way. So that takes care of a lot
22 of that PK thing. That's another thing to figure

Page 257

1 out, which one's worse, the peak effect or the area
2 under the curve of the drug for that?
3 Let me just get in here one more part of it,
4 if I can. So then the individual variability --
5 and there is individual variability. We've looked
6 at that, and we can look at the area under the
7 curve for the neuropathy thing and show that that's
8 related to Charcot-Marie-Tooth type gene, and then
9 people look at other things. A lot of things, we
10 don't understand.
11 That takes good care of the randomization
12 process in the balance of patients for that. So
13 that's why you have groups of patients. You can't
14 do a study with two patients, one who got and one
15 who didn't, because of all these variations for
16 that aspect.
17 DR. HAROUTOUNIAN: I'm just wondering if
18 there is a drug that is targeting peak plasma
19 concentration-related toxicity, which might be
20 above a certain point in a certain subset of the
21 population with drug -- again, I'm not saying this
22 is something that we should do to every patient in

Page 258

1 a study, but this is something to keep in mind if
2 we want to look more specifically into the
3 mechanism.
4 DR. GEWANDTER: So that's what I was going
5 to say. It could help explain potentially why it
6 didn't work in some patients and worked in others
7 potentially.
8 So I think one thing that might be useful is
9 if the oncologists could help us. If we did want
10 to make -- I think that Dr. Richardson clearly
11 enunciated that it's complicated operationalizing
12 how to quantify discontinuations and disruptions.
13 So can you guys give us some tips on what we
14 would need to consider if we wanted to turn
15 discontinuation or disruption of chemotherapy into
16 an endpoint? Like what things do we need to
17 consider? How could we start to try to think about
18 that?
19 DR. LOPRINZI: So you asked for oncologists.
20 So what you do is you ask how much drug did each
21 person get at each day. So that will help
22 establish whether they got the drug and whether it

Page 259

1 was 100 percent, so all that sort of thing. And
2 the other thing you could add in, if they didn't
3 get 100 percent drug, why not? Was it because
4 blood count was low or was it because of
5 neuropathy?
6 Then having that information, then you know
7 how much drug everybody got over time, or was it
8 just a change because it was somebody's birthday
9 and they decided to wait a week, whatever, how much
10 they got over time and why they didn't get 100
11 percent of dose?
12 DR. GEWANDTER: Dr. Cleary, do you have a
13 thought on that?
14 DR. CLEARY: I agree with what he said.
15 These things are done very standardly on oncology
16 clinical trials, so I don't think it will be very
17 hard for the oncology sites to do that, because
18 we're used to having this sort of data entry. And
19 I think that it can give you data about why people
20 miss doses, as he said, and also give you a
21 cumulative dose.
22 DR. GEWANDTER: So you're saying maybe

Page 260

1 having the information on cumulative dose would be
2 useful.
3 DR. CLEARY: Yes, but also if a dose
4 reduction happened, why did it happen, because
5 another reason someone might dose-reduce
6 oxaliplatin has nothing to do with neuropathy.
7 Maybe the person's cell counts were low that day.
8 So you have to know if they did dose-reduce, why
9 did they do it?
10 DR. GEWANDTER: Joanna, do you have a
11 thought?
12 DR. BRELL: I think that would be relatively
13 easy to capture. But I also think PKs on some of
14 these drugs and their association with the
15 neuropathy might help inform this as well.
16 DR. RICHARDSON: Yes. And the way you
17 tackle that, Jen, just to give you practical
18 aspects of it, is you do subsets. So you do it at
19 centers that can do it. You don't have to do it
20 across the trial, but you want to maybe do it at
21 centers that can do it. And the reason why is
22 because then you can provide to the regulatory

Page 261

1 authorities that's got a nice correlative
2 population, base data, or whatever you want to do.
3 Also, you might want to do that in the context of
4 more exploratory, early-phase data as well.
5 DR. GEWANDTER: So part of the research
6 agenda.
7 DR. FREEMAN: So I just want to be clear on
8 this, that if the statistician is going to work out
9 this novel endpoint, that in some way normalizes
10 the neuropathy for dose of chemotherapy received,
11 you're recommending that they take into account the
12 cumulative dose.
13 DR. LOPRINZI: Yes, but not just the
14 cumulative dose, the cumulative dose over time. If
15 they get a dose now and a dose a year later, that's
16 two doses versus two doses a week later. So I'm
17 being facetious, I know, but cumulative dose over
18 time.
19 DR. FREEMAN: Over time. So what you're
20 saying is, then, the dose and dose -- let's call it
21 dose intensity, so --
22 DR. LOPRINZI: No. We'll just -- yes.

Page 262

1 DR. FREEMAN: -- so this is -- then Paul has
2 made and Joanna also introduced the notion that the
3 dose may be less relevant than actually the
4 pharmacokinetic profile of the dose. How strongly
5 do people feel about that?
6 DR. LOPRINZI: The pharmacokinetic profile I
7 think is figuring out if that affects how the drug
8 causes neuropathy over time. It has nothing to do
9 with what drug you're giving to try to prevent. I
10 think that stuff gets figured out in the phase 1
11 study and the phase 2 study, early on there.
12 But in the clinical trial, where you're
13 looking at X versus Y, X versus placebo, the
14 pharmacokinetics, yes, might help determine whether
15 it's a peak or area under the curve. And I think
16 it fits with -- first of all, to what Pat said
17 before, too. It's not necessarily the effect over
18 time, but the effect per dose. It's actually both.
19 DR. RICHARDSON: Yes. So I agree with you,
20 Charles, it's a mix of exploratory versus
21 confirmatory. I mean, the only reason I say it is
22 because that I guess would be addressed

Page 263

1 appropriately in the phase 2 as we get proof of
2 principle trial sets.
3 My only point is that the population-based
4 PK studies as part of phase 3, we do. We do, do
5 those, and we do do those for the noxious agents.
6 So the point is, it's not impossible, and that
7 probably would be a very nice discussion with the
8 agency as to how much they would need and what they
9 would want, to just understand variance between
10 patient populations so that you don't lose the
11 ability to at least evaluate the impact of the
12 neurotoxic drug and how that interacts with your
13 intervention.
14 I'm kind of thinking out loud a bit here,
15 but the reason I'm doing it is because I'm struck
16 by everything that was said by Nat earlier that,
17 literally, to date, intervention trials and CIPN
18 have failed. And the question is why.
19 The point is, I think one of the huge
20 variables that have occurred to me, listening over
21 the last two days, is the variance that we see in
22 what we give in terms of our agents that drive the

Page 264

1 neurotoxicity, and then the beautiful presentation
2 by Pat yesterday of the complexity of the biology.
3 So all I'm trying to do is help give you
4 ideas to think about how you can correct for all
5 these confounders.
6 DR. FREEMAN: Can I ask Sharon just a
7 question? So if we somehow come up with this novel
8 endpoint that drug X diminishes neuropathic burden
9 per unit chemotherapeutic agent received, however
10 we define neuropathic burden and however we define
11 chemotherapeutic agent received, does that look
12 like a label that --
13 DR. HERTZ: I don't even know how to answer
14 that.
15 DR. FREEMAN: Yes. That's what bothers me
16 about it.
17 DR. HERTZ: I would say -- this one's a
18 little harder than some of the other areas because
19 of the nexus with receiving enough of your chemo.
20 So I wouldn't say anything's off the table.
21 DR. DOUGHERTY: So following to that and
22 listening to this entire conversation, I think

Page 265

1 we've complicated things a bit by conflating two
2 endpoints, and that's why we're struggling.
3 The first endpoint is, does this agent X
4 given with chemotherapy Y, help them get through
5 chemotherapy without such a heavy symptom burden
6 that they have to drop out?
7 Number two -- and this could be a separate
8 drug -- a year after your chemotherapy, deemed
9 successful, whatever that criteria is, do you have
10 less neuropathy at that point?
11 So there's during the treatment and then
12 there's how does it impact your ultimate outcome.
13 I think those are potentially two separate
14 endpoints.
15 DR. LOPRINZI: This is very, very confusing
16 as we're trying to look at each individual part
17 together. And I understand why Sharon's saying
18 what she's saying. It's just how do you put this
19 little piece into the overall picture?
20 So I hadn't thought about this before, but
21 one thing that I think would be interesting to do,
22 and I might threaten to do it on myself anyway if

Page 266

1 Sharon would allow me, is to say, "Why am I sending
2 to you, the FDA, my calcium magnesium clinical
3 trial that was done, and all that sort of stuff,
4 and have you look at it and say, 'Yeah, this was a
5 good trial,' or, 'No, we'd need X, Y, Z, and Q,'"
6 or anything like that?
7 But that way, that's sort of a process. I'm
8 not asking for FDA approval on it or anything; in
9 fact, it was a negative study. But is that sort of
10 a protocol that would make sense?
11 The other sort of thing could be done as
12 your duloxetine trial, treatment trial, to say does
13 this make sense or how would people recommend you
14 ought to have changed these two things?
15 Those are two different types of trials
16 we're talking about, and then you could say how do
17 we make these trials better? There were some
18 terrible trials. But that would make more sense I
19 think than trying to pick off each of these
20 individual things alone.
21 DR. HERTZ: I can't imagine how we could
22 give you that kind of feedback, because it's always

Page 267

1 so situationally dependent. And it could be the
2 absolutely perfect trial for that drug and not
3 serve another one quite well. So I really would be
4 reluctant to commit to doing something like that.
5 I think it makes more sense to have this
6 body decide if this makes sense, or for any given
7 drug and any given intent of that drug's action,
8 why does that particular study make sense is really
9 the question.
10 The reality is, there's not going to be one
11 answer for every -- there are so many variables.
12 There's so many unknowns. I could imagine this
13 being a situation in which we get two similar-type
14 programs with different researchers involved and
15 very different approaches, and both being
16 acceptable. That's why it's very hard for us to
17 commit to giving that kind of feedback.
18 DR. LOPRINZI: And something like that
19 doesn't mean that you would have to say everything
20 has to be done like this. But the other way of
21 potentially doing it is the group take one of these
22 protocols, or take two of these protocols and say

Page 268

1 everybody shoot at this and see how do we build
2 upon this as opposed to looking at each individual
3 thing to say, look -- because there are a lot of
4 people in here who have never developed a protocol
5 and don't see these particular patients. So
6 anyway --
7 DR. FREEMAN: Let's move on to the next
8 phase of this.
9 DR. GEWANDTER: I just want to say one thing
10 relating to what Pat said. I totally agree with
11 you that I think that they're two separate
12 objectives. And I think that the objective of
13 trying to prevent neuropathy, like six months after
14 you've finished chemo, doesn't necessarily have to
15 deal with some of these other issues as much as if
16 you want to look at the neuropathy at the end of
17 chemo or throughout chemo, and how do we deal with
18 how discontinuations affect that severity.
19 I think in the paper, we will say that there
20 are these different kinds of study objectives. And
21 for this study objective in particular, meaning the
22 one where do we want to consider, make a composite,

Page 269

1 that one I think is probably the most complicated.
2 So I think that we will just point out that they're
3 separate objectives, and there will be separate
4 endpoints depending on the objective.
5 So I want to recognize like we didn't really
6 address what you said and that I totally agree. I
7 think that's a really important differentiation to
8 make, and we'll make it in the paper.
9 DR. FREEMAN: So before we move on to the
10 next phase, I think listening to this discussion,
11 it's clear that there are a number of issues that
12 are going to be challenging to resolve in a very
13 clear-cut way. And I do want to say that, as we've
14 said all throughout the meeting, there will be a
15 publication from this. It will require everybody's
16 participation.
17 I don't think it's going to be one of those
18 that everybody will sign off on immediately. I
19 want to be sure that everybody recognizes that this
20 will be a participatory process, and that, please,
21 in your areas of expertise, commit to being very
22 involved in the writing process.

Page 270

1 DR. GEWANDTER: We talked a lot about this
2 yesterday, which is why I put it last. But I think
3 we want to kind of go back to some of these and
4 just see if my read of the consensus was correct
5 and if anyone has anything else to say.
6 So for the first one, for localized and
7 metastatic cancers, I think what I was hearing
8 yesterday was, if we need more data on safety, so
9 obviously anything that has a new mechanism, we
10 need to start in metastatic cancers from the FDA's
11 perspective for a safety reason. But then in terms
12 of ideally for efficacy trials and actually proving
13 efficacy, actually sticking to earlier-stage
14 cancers would actually be better.
15 Was I right in hearing that or does anyone
16 have anything to say about that?
17 DR. DASTROS-PITEI: My understanding from
18 yesterday was that metastatic cancers, yes, perhaps
19 for proof-of-concept study, just to give a sense of
20 the safety. But I think it was recognized that
21 measuring safety -- I mean, impact on the
22 chemotherapy effect of the drug, of the active

Page 271

1 drug, it's actually quite difficult because,
2 obviously, it implies long-term follow-up looking
3 at DFS, or PFS, or overall survival, which will not
4 happen in a proof-of-concept study.
5 So I think we need to understand a little
6 bit better. Although it makes sense that the
7 metastatic cancer population is the one which is
8 probably more vulnerable and more fragile, is this
9 the one really which is going to give that safety
10 measure quickly?
11 DR. GEWANDTER: So are you saying that
12 because it's going to take a long time, that we
13 should be doing efficacy at the same time in that
14 population? Is that what you're saying?
15 DR. DASTROS-PITEI: Safety, so I guess the
16 early studies, for immediate -- I guess for
17 biomarkers of safety like hematology platelets, I
18 don't know, neutrophils and so on, probably this
19 does makes sense. But I don't know if it's
20 correlated necessarily with the metastatic
21 population.
22 I'm just concerned, how long would these

Page 272

1 studies need to be in order to show that there's an
2 effect on safety, if you know?
3 DR. GEWANDTER: Sharon, do you want to
4 comment? No? Okay.
5 Joanne?
6 DR. BRELL: I hate to put off making
7 decisions and seeming wishy-washy, but I think it
8 depends on whether or not we use localized or
9 metastatic cancers depends on the cancer and
10 depends on the chemo they received.
11 So first-line, even second-line metastatic
12 breast and metastatic colon, these patients are
13 usually very fit, and they can live for years with
14 metastatic disease and live really good lives. So
15 they would be good subjects to follow while still
16 being in a metastatic situation.
17 DR. GEWANDTER: So Sharon, would those
18 people be -- I don't know. Maybe you can't answer
19 from this, but the people that have the metastatic
20 cancer as she was just describing that live for
21 like three years, would they be in the group of
22 people for the higher-risk interventions?

Page 273

1 DR. HERTZ: From the consults that we get
2 from our oncology group about selecting the patient
3 population, the concern is -- I remember one
4 particular IND that came in where the treatment for
5 the neuropathy specifically targeted the mechanism
6 of action of the chemo, so we were all very nervous
7 about that because it seemed, yes, it would work.
8 So would dose reduction. You know what I mean? It
9 seemed very nerve-racking to give that to somebody
10 who would potentially have a cure without it.
11 So the thinking is are you going to -- the
12 concern is will there be a negative impact on the
13 survival of an individual because of the
14 intervention for the neuropathy?
15 So if somebody doesn't have a chance for a
16 cure, that's sort of the first cutoff. And then,
17 in terms of whether somebody who's got a fairly
18 good longer prognosis, but not a cure, then it's
19 going to depend on are you giving the drug during
20 chemo or after chemo, are you giving it before? So
21 there's all these different considerations.
22 I'm trying to think of what we've seen, and

Page 274

1 I don't have that kind of clear grasp for the
2 details like some of the others in my group. So I
3 wouldn't say that's not a population that could be
4 studied, but why the risk to that population is
5 acceptable should come in with the protocol, any
6 considerable risk, whatever the risk might be.
7 DR. BRELL: I would think, before we would
8 come forward with anything, we would have studied
9 whether or not there was an effect. I mean, of
10 course, long-term data is the best, but I think we
11 would have looked at that before we even bring it
12 forward.
13 DR. GEWANDTER: When you say we would have
14 looked at that, do you mean preclinically or what
15 do you mean by that?
16 DR. BRELL: Yes, preclinically, and maybe
17 graphically, and then a longer-term follow-up
18 depending on the cancer and the natural history of
19 the cancer. But we have to decide -- we have to
20 make sure we've eliminated to the best of our
21 ability any loss of efficacy with the treatment
22 that we would give, a loss of efficacy of

Page 275

1 chemotherapy with any treatment we would give. But
2 we would look at that way before.
3 DR. HERTZ: Well, you know, that sounds very
4 obvious to you and perhaps everyone else in this
5 group, but I can tell you it is not obvious to
6 everyone submitting an IND. So that's why those
7 consultations have really focused a lot on those,
8 because we often don't get a well-considered
9 evaluation of that risk.
10 DR. GEWANDTER: So as far as the paper goes,
11 I think we could say that, at first, if there is no
12 good understanding of the risk of the new agent in
13 terms of the effects on chemotherapy, that starting
14 in a more advanced cancer with less curative
15 potential is recommended, or you should consider
16 that. I think that's maybe where we would end our
17 recommendation on that.
18 Do you have anything to say about that?
19 Okay.
20 Moving on, I think everyone agreed it seemed
21 like the one thing was that we should do one type
22 of chemotherapy at a time, so oxaliplatin

Page 276

1 separately from taxane separately from bortezomib.
2 But there was still a little bit of question about
3 one cancer type, so I think we had a discussion of,
4 can GI go with pancreatic if they're getting the
5 same type of chemo? So I just wanted to open that
6 back up for discussion a little bit. Yes?
7 DR. CLEARY: When you said one or multiple
8 chemotherapies, I think for preventative, it should
9 be one chemo, but for one where people already have
10 neuropathy, I think it could be preventative.
11 DR. GEWANDTER: So we're not talking about
12 people who already have neuropathy after chemo like
13 Ellen's study, but do you think that is true even
14 for acute symptoms? If you're trying to treat
15 established acute symptoms during chemotherapy, do
16 you also think it could be more than one type of
17 chemotherapy, or at that point still?
18 DR. CLEARY: I think it should say one type,
19 but I would say --
20 DR. GEWANDTER: During chemotherapy, one
21 type.
22 DR. CLEARY: -- it can be multiple cancer

Page 277

1 types getting the same chemo.
2 DR. GEWANDTER: So you think multiple cancer
3 types with the same type of chemo is okay, yes, for
4 prevention and --
5 DR. BRELL: With the same regimen.
6 DR. GEWANDTER: Same regimen. So when you
7 say regimen, do you mean the same type, like
8 oxaliplatin, or do you mean oxaliplatin, twice
9 every 2 weeks for 6 months?
10 DR. BRELL: FOLFOX, FOLFIRONOX. Pick one.
11 DR. GEWANDTER: But what if some people get
12 FOLFOX, like, for 6 cycles, some get for -- I'm
13 making these numbers up because I don't really know
14 it by heart, but what do you think about it? Does
15 it have to be the same exact one regimen?
16 DR. BRELL: Well, it depends on what we know
17 about dosing and exposure.
18 DR. GEWANDTER: Okay.
19 DR. FREEMAN: I guess we ought to be clear
20 on this. So FOLFOX, 6, irrespective of underlying
21 cancer, you would say, is okay?
22 DR. GEWANDTER: Yes. I think so, too.

Page 278

1 DR. FREEMAN: Yes. Good. It makes sense.
2 DR. CLEARY: But I think the point you were
3 just making, I think the number of cycles are going
4 to get important. So a FOLFOX, 6, 12 cycles, no
5 matter what type of cancer, I think that's okay, or
6 8 cycles. You've just got to make regiment, number
7 of cycles, and then whatever cancer is fine.
8 DR. BRELL: Number of cycles or total dose?
9 DR. CLEARY: Like planned number of cycles.
10 DR. FREEMAN: Over time.
11 DR. CLEARY: Yes.
12 DR. BRELL: Yes.
13 DR. GEWANDTER: [Inaudible – off mic] -- is
14 what you're saying. So let's say -- I don't know
15 if this would ever happen, but 6 cycles, but then
16 some people are getting a little bit higher dose at
17 each cycle than someone else.
18 Does that ever happen?
19 DR. BRELL: There are different types of
20 FOLFOX with different levels of oxaliplatin. So
21 you'd have to pick the dose of oxaliplatin you
22 wanted to give.

Page 279

1 DR. GEWANDTER: Right.
2 DR. CLEARY: You can standardize that,
3 though. She's absolutely right. But you can say
4 everyone should get oxaliplatin, 85 milligrams,
5 straight from the start.
6 DR. GEWANDTER: So at the risk of opening up
7 a can of worms, if we did that, if we said, okay,
8 you have to have the same regiment of FOLFOX. It
9 could be whatever cancer type, is that going to
10 restrict the number of patients to where it's
11 prohibitive?
12 DR. CLEARY: I don't think so. I think,
13 generally speaking, most people use the same FOLFOX
14 across the country.
15 DR. GEWANDTER: Sure. Great.
16 DR. DOUGHERTY: Respectfully, I disagree.
17 Even within a given FOLFOX regimen, people are
18 going to miss doses, et cetera. So in fact, no one
19 is going to get the exact same therapy. It's going
20 to get customized to each patient.
21 I say, as long as it's the same agent, your
22 variables are going to be cumulative dose over time

Page 280

1 irrespective of which cohort you're treating. So
2 take them all. It'll all come out in the analysis.
3 DR. LAVOIE SMITH: You can control for cum
4 dose.
5 DR. CLEARY: His point is a really good one.
6 DR. DOUGHERTY: You can control for that.
7 DR. LAVOIE SMITH: Cumulative dose is a
8 covariate.
9 DR. GEWANDTER: Planned dose is a covariate,
10 not actual dose as a covariate.
11 DR. SMITH: Oh, yeah, yeah, yeah.
12 MALE VOICE: Cum dose.
13 DR. GEWANDTER: But you can't make
14 cumulative dose that someone actually gets a
15 covariate. It has to be potentially their planned
16 dose because your treatment can affect -- well, you
17 can't make things that you change after
18 randomization a covariate.
19 Mike, please? Yes. Okay. Thank you.
20 DR. CLEARY: I was just going to agree with
21 what you said. I think his point is a good one.
22 There are lots of dose reductions that go on, but

Page 281

1 in the beginning, everyone has the same plan.
2 DR. GEWANDTER: But you can't control that.
3 Yes. Exactly. Yes. Sorry. Let me be more clear.
4 Exactly.
5 So we want the same plan. We can't control
6 what happens after, and that's the reason we're all
7 here, actually, honestly. But the same plan is a
8 good thing.
9 Do you agree with that, or do you think that
10 we should include more than one plan?
11 DR. DOUGHERTY: I think as long as it's the
12 same agent and you have some patients who are
13 getting more chemo quicker or for a longer period
14 of time, I don't understand how that really impacts
15 the overall outcomes.
16 You're going to have an understanding of how
17 effective this drug is against this neurotoxic
18 agent at some dosing schedule. And again, I think,
19 even within FOLFOX, people are going to get more or
20 less as they go along. So I don't understand how
21 that is really that important.
22 DR. DASTROS-PITEI: It's for the protocol.

Page 282

1 So we say we get this population, which will be
2 treated with FOLFOX, 12 cycles.
3 DR. DOUGHERTY: So it's for the ideal world.
4 It's for the packaging.
5 DR. GEWANDTER: Gordon, please?
6 DR. G. SMITH: I have the world's most naïve
7 oncology question, and so please laugh quietly, not
8 loudly. And that is, is the likelihood of a dose
9 reduction different with the same chemotherapeutic
10 regimen between cancers?
11 So if someone with rectal cancer is getting
12 FOLFOX, are they more or less likely, or no more or
13 less likely, to have to have a dose modification
14 compared to the same regimen in a different
15 malignancy? That was my only concern with this
16 conversation.
17 DR. RICHARDSON: Yes. I think that's very
18 disease specific. I think, frankly, doses we use
19 of certain drugs -- and for example, bortezomib,
20 mantle cell lymphoma versus doses used in myeloma,
21 I would not study those two diseases together just
22 because they're getting bortezomib-based therapy,

Page 283

1 not least of which because in mantle cell lymphoma,
2 the neurotoxic signal may be different because of
3 the disease. They differ as well. So just be very
4 careful about that variance.
5 I can't speak to GI, and Jim can comment
6 more there, but we're very cautious in heme
7 malignancies because of -- for example, creatinine
8 clearances between myeloma patients and mantle cell
9 lymphoma patients, even though they're getting the
10 same neurotoxic drug, are radically different.
11 DR. CLEARY: That's really interesting to
12 hear what Paul said, especially with multiple
13 myeloma causing neuropathy. I actually consider,
14 within GI malignancies, we see the same number of
15 dose reductions, whether it's rectal, pancreatic,
16 or colon.
17 DR. GEWANDTER: Thank you. That's good to
18 know.
19 DR. DOUGHERTY: Paul's bringing up, though,
20 a really special case because it seems that CIPN
21 engages in a neuroimmune type of response. And
22 once you have different immunological cells going

Page 284

1 up, down, and sideways, then basically you're
2 getting at the fundamental pathophysiology of CIPN.
3 So there, I think you've got great variability.
4 But I think, in an adjuvant setting for a
5 solid tumor, you have less of a confound based on
6 that substrate. So I think that you could take
7 pancreatic, colorectal cancers, each getting
8 FOLFOX, if it's FOLFOX 6 or 9 as long -- as long as
9 oxaliplatin is the neurotoxic agent, I think your
10 dropouts, your dose reductions are all going to be
11 pretty much generic across those different classes
12 DR. DASTROS-PITEI: You did say "adjuvant."
13 You did say the word "adjuvant" setting.
14 DR. DOUGHERTY: Well, I did say "adjuvant."
15 I'm still stuck on adjuvant because it's --
16 DR. DASTROS-PITEI: Which I think is
17 essential to what we've spoken, because I think we
18 can impact a little bit in this setting.
19 DR. DOUGHERTY: The reason I said that is
20 because metastatic, to me, is going to be recurrent
21 metastatic.
22 DR. DASTROS-PITEI: Exactly. And they will

Page 285

1 have already had perhaps --
2 DR. DOUGHERTY: Exactly.
3 DR. DASTROS-PITEI: -- oxaliplatin
4 neurotoxicity injury before.
5 DR. DOUGHERTY: So I buy the argument about
6 doing a trial in metastatic for safety, but for
7 your indication, I don't think so, because, likely,
8 those folks will have had agent ahead of time. If
9 they don't have neuropathy, then they're neuropathy
10 resistant.
11 DR. DASTROS-PITEI: Yes. We had that
12 discussion yesterday.
13 DR. RICHARDSON: My counter -- this is not
14 really a counter; it's a complementary statement to
15 Pat's -- is that you could envisage trials and GI
16 malignancy that could be done specific to
17 oxaliplatin. And then you could have supportive
18 studies that could expand your label, Daniela. And
19 the advantage you would offer in myeloma is a
20 highly-defined at-risk population.
21 DR. DASTROS-PITEI: That's the point, yes.
22 DR. RICHARDSON: And that's the point. And

Page 286

1 I think the FDA ladies left for just a moment, but
2 I believe the point is that -- I mean, certainly
3 speaking to the group we deal with, which is led by
4 Ann Farrell, and they're just top notch, they
5 absolutely get myeloma. And the advantage is
6 they've got such a database. Bortezomib to them
7 was a lead approval for myeloma. It was first one
8 in 30 years when it was approved in 2003.
9 So the point is that they really know the
10 base. So from our pharma partners' point of view,
11 that is a very friendly group because they
12 understand the issues.
13 So do you see my point, Jen? You can go
14 big, as Pat is suggesting correctly, with things as
15 important as oxaliplatin CIPN, but then you can
16 also drill down to expand your label into specific
17 diseases.
18 This is the kind of stuff I was alluding to
19 earlier, Jen, about this mix of clinical science
20 and regulatory science, and, again, having the FDA
21 person here is so helpful because they can
22 obviously guide you in that.

Page 287

1 The other take-away -- I'm so sorry. I have
2 to leave now because I've got to get back to
3 Boston. But the other piece is I've always found,
4 certainly with the division we've worked in at the
5 FDA, they love to talk early and often. And the
6 more time you spend with them sitting around the
7 table, hashing out early-phase design as well as
8 late-phase design, they're fantastic.
9 What we've learned very much the hard way is
10 if you come in with a sponsor and show them the big
11 massive phase 3, be prepared that that's a
12 high-risk strategy. You really need to start very
13 early and talk with them little and often and then
14 big and often as the project moves forward.
15 DR. GEWANDTER: Thank you.
16 So Gordon, did you have something to say
17 here?
18 DR. G. SMITH: Yes. I just had a follow-up,
19 and I'm just thinking of the idea of including
20 patients with different malignancies. And the
21 follow-up to my first question, which you reassured
22 me about, is differences in prognosis.

Page 288

1 So let's say you're using the same FOLFOX
2 regimen for rectal cancer versus pancreatic cancer.
3 One of those sounds a lot scarier to me. And if
4 there's a worse prognosis in one or a different set
5 of complications that can occur, that conceivably
6 could contaminate PROs or other outcome measures.
7 Is that a potential worry in lumping
8 different malignancies together?
9 DR. CLEARY: You're right. They do have
10 very, very different prognoses. I think the one
11 disadvantage of lumping them together is, if you
12 have someone on adjuvant FOLFOX for a rectal cancer
13 and colon cancer, the chance that they're going to
14 get recurrent disease while they're on the FOLFOX
15 is low, very low, whereas with pancreatic cancer,
16 it's higher.
17 So the chance that that pancreatic cancer,
18 you thought they were going to get 8 cycles, and
19 all of a sudden, 3 or 4 cycles in, you realize they
20 have liver metastasizes, you need to get off FOLFOX
21 and do something else, yes, that's a real risk.
22 DR. GEWANDTER: Discontinuing their

Page 289

1 chemotherapy? So you'd want to leave them out.
2 DR. DASTROS-PITEI: And they would be
3 dropped off the treatment completely. They dropped
4 completely.
5 DR. GEWANDTER: So then you don't want those
6 people in the trial because anyone who's going to
7 discontinue chemo -- so actually, this is a very
8 good point.
9 One of the things that we made in the
10 systematic review, if there are predictors of
11 discontinuing chemotherapy that we can identify for
12 reasons other than neuropathy, to make them
13 exclusion criteria. So if there's anything that
14 you guys know of that is a predictor like that,
15 adding that to the paper would be a good thing. So
16 maybe we could say that you want to stay away from
17 pancreatic cancer for that reason.
18 DR. CLEARY: I could go either way. I
19 think, because of enrollment issues, having
20 pancreatic patients on there is helpful because you
21 could say if it's a randomized study, there will be
22 the same number of pancreatic dropouts in both

Page 290

1 arms.
2 But it is true that, if you're not as
3 worried about enrollment as accrual, yes, that
4 there's going to be a lot more pancreatic patients
5 who stop FOLFOX earlier because of disease
6 progression.
7 DR. GEWANDTER: Thanks. That's really
8 helpful.
9 Did you want to comment?
10 DR. FREEMAN: I just want to ask the
11 statisticians a question. This, I wanted to ask
12 yesterday, so it's a little delayed, but before we
13 move away from endpoints.
14 The rationale that you guys would have for
15 not doing a standard analysis of covariance using
16 as your endpoint neuropathy burden and your
17 covariate some kind of measure of chemotherapy
18 intensity, say cumulative dose, why are you not
19 happy with that as an analytic approach?
20 DR. MCDERMOTT: Because treatment itself can
21 have an impact on the cumulative dose of
22 chemotherapy.

Page 291

1 DR. FREEMAN: So yes, okay. That makes
2 sense to me. I do understand that. So wouldn't
3 co-varying full treatment then actually help you?
4 DR. MCDERMOTT: Say again.
5 DR. FREEMAN: Wouldn't you use that as your
6 covariate because treatment will have an effect,
7 that would potentially have an effect on the
8 cumulative dose? Wouldn't that analysis then take
9 that into account?
10 Or maybe let me reword it, then. Is there a
11 way of taking that into account?
12 DR. MCDERMOTT: There's a way of doing it.
13 There are methods that are relatively recently
14 developed, that are fairly complex and assumption
15 laden, that are based on what is called causal
16 inference that can try to tease that out. But I
17 think that a strategy of building that into the
18 outcome rather than trying to covariate would be
19 probably wiser.
20 DR. EVANS: As a general rule, you can
21 create more problems than you solve by trying to
22 correct for things that happen after randomization.

Page 292

1 You can get yourself into trouble.
2 At randomization, you have the expectation
3 of balance with respect to everything except
4 treatment assignment, and you don't need to know
5 about it, and you don't need to measure it. And it
6 protects you from your own ignorance because you
7 don't even have to know what it is.
8 So if you start trying to correct
9 afterwards, the problem is that people self-select
10 themselves essentially in the treatment groups if
11 you're going to end up comparing or try to evaluate
12 whether dosing is going on. You're reacting to a
13 complex evaluation of multiple endpoints.
14 So some of the examples I showed yesterday
15 were you could evaluate effects on peripheral
16 neuropathy. And you may say, well, the disease
17 burden of peripheral neuropathy is very low.
18 Right? Well, that may be very low because the
19 patient switched out of treatment, of chemotherapy
20 treatment. Maybe they didn't tolerate it and had
21 to switch therapy. So now, you're getting all
22 twisted in a knot because you're trying to

Page 293

1 understand these complex processes.
2 The other way you can really evaluate it,
3 that we talked about yesterday, is instead of
4 trying to break it into pieces, you evaluate a
5 patient. And if a patient has good or poor
6 peripheral neuropathy outcomes and what about their
7 uses in chemotherapy, whether they're good or bad,
8 the amount of chemotherapy in the context of the
9 trial, you're right, the trial you're conducting is
10 an outcome.
11 If you want to compare whether low doses, or
12 high doses, or certain dosing strategies are
13 different, then you can randomize to those outcomes
14 and make sure you've got a fair comparison. But
15 the actual doses and so forth that are observed are
16 outcomes. And in many ways, you want to refrain
17 from trying to figure out whether, in an imaginary
18 world, had everybody adhered to the way you thought
19 they would adhere, what you would have gotten.
20 That's a different question. And frankly, you
21 can't analyze it with the integrity of
22 randomization because you didn't randomize it that

Page 294

1 way.
2 DR. GEWANDTER: So what were we talking
3 about? So the multiple cancer types. I think we
4 have enough to put something down on paper that you
5 guys can comment on.
6 If I read the discussion correctly
7 yesterday, we kind of all agreed that pre-existing
8 conditions associated with neuropathy were okay as
9 long as the patient didn't already have neuropathy.
10 Does anyone disagree with that?
11 (No response.)
12 DR. GEWANDTER: So then the question is how
13 do we define people not already having neuropathy?
14 And so based on our discussion yesterday, I just
15 propose this possibility as can we come up with a
16 cutoff where we say, if they have below this -- so
17 there's a couple options.
18 One is, they don't have any of the symptoms
19 that are in your symptom PRO at all. So that's one
20 option. Another option is, we have a max cutoff on
21 something like the TNS or the UENS and no symptoms.
22 So does anyone have any comments on this

Page 295

1 proposal?
2 DR. G. SMITH: So we have guidance from the
3 diabetes literature, and I'm thinking of the
4 symptom component of the MNSI, the Michigan
5 Neuropathy Screening Instrument, where I forget the
6 percentage, but a very large percentage of patients
7 who have diabetes without neuropathy will flag a
8 couple of the items on that positive.
9 It's a matter of, I suppose, sensitivity,
10 and specificity, and cutoff, but I think the cutoff
11 score on the MNSI that has the best diagnostic
12 reliability is like 6 or 7, whereas, I don't know,
13 30 percent of people will answer 2.
14 So I think it depends on how important it is
15 to exclude patients who have neuropathy, and I
16 think Guido's idea of using a pre-defined cutoff on
17 a scale that you're using in the trial makes a lot
18 of sense.
19 DR. GEWANDTER: Okay. Sorry. Let me make
20 sure I heard you right. Your recommendation would
21 be to use a pre-defined cutoff for an outcome
22 measure you're using.

Page 296

1 Is that what you said?
2 DR. G. SMITH: I think one would want to do
3 that when it makes sense to do it.
4 DR. GEWANDTER: You sound like Sharon.
5 DR. G. SMITH: That's a compliment. I was
6 just telling Sharon. She's cringing now.
7 DR. GEWANDTER: I think we can work with
8 that. Okay?
9 DR. FREEMAN: Look, I think this is an area
10 where I think there was an array of opinions. My
11 interpretation is that this is something that I
12 think we will use your ability to be wishy-washy,
13 Gordon, because I don't think we came to a
14 definitive conclusion.
15 DR. G. SMITH: That's called nuance, Roy.
16 DR. DOUGHERTY: I think we were all in
17 agreement yesterday that as far on your PRO
18 instrument, it should be zero.
19 DR. GEWANDTER: Yes. I think we all agree
20 with that, yes.
21 DR. DOUGHERTY: As far as the signs go, we
22 didn't get to a consensus on what sign, if any

Page 297

1 signs. So why don't you lay out some sign options,
2 and then we can come up -- if we all agree on a set
3 of signs, we can then come up, well, what level
4 should that sign be at baseline in order to be
5 acceptable. But right now, it's such a void as to
6 what we're talking about when we get into the sign
7 category, that --
8 DR. GEWANDTER: Can't make that choice here.
9 DR. FREEMAN: Yes. I think that's very
10 reasonable.
11 DR. GEWANDTER: I think also, what Bob
12 mentioned before, I think, Gordon, taking from the
13 diabetes literature, if there are some cutoffs that
14 have some sensitivity and specificity worked out,
15 that we could potentially propose them. But
16 proposing a cutoff just because it's what we think
17 is good and we don't have any data for might be a
18 little tenuous.
19 DR. DOUGHERTY: That's what I'm saying. Go
20 ahead, lead with your chin, and then we'll find out
21 once you lay something out.
22 DR. GEWANDTER: Or it could be also a

Page 298

1 research agenda to find what could that be.
2 DR. G. SMITH: I would say that requiring
3 your PRO to be zero may be unrealistic. It depends
4 on the PRO. I mean, on any given day, I probably
5 fulfill at least one criteria of most PROs
6 depending on how much sleep and coffee I've had in
7 the morning.
8 I would be cautious about making a blanket
9 statement that the PRO has to be zero. I think it
10 probably depends on the PRO and the specific items
11 and characteristics of the instrument, which is
12 wishy-washy.
13 DR. GEWANDTER: Well, we'll think about
14 that, I think.
15 DR. LAVOIE SMITH: And I would just caution
16 that -- I mean, I don't disagree that a TNS cutoff
17 or some kind of sign cutoff might be a good idea.
18 But when we think about having to administer a PRO
19 or to do a TNS exam prior to determining if
20 someone's eligible in a busy onc clinic, is just a
21 bit challenging, for feasibility.
22 DR. GEWANDTER: That's good feedback. Thank

Page 299

1 you.
2 DR. FREEMAN: Yes. So maybe just before we
3 jump from this thing, Daniela, what are you doing,
4 what are you considering doing? Matt, what are you
5 considering doing?
6 DR. DASTROS-PITEI: At the moment, we're
7 looking at the CTNS, but maybe I've heard so much
8 about reflexes that we may need to reconsider it to
9 make sure that it's reliably done. If we do it by
10 training, or not doing them, then --
11 DR. FREEMAN: This is as an inclusion
12 criteria. You are excluding patients with
13 neuropathy and you are using some kind of cutoff
14 for doing that.
15 Matt, have you thought it through thus far?
16 DR. JARPE: We haven't really set up a
17 prevention trial, so it's not really relevant.
18 DR. GEWANDTER: Do you know what the cutoff
19 is going to be? I mean, you don't have to tell me,
20 but how did you choose it?
21 DR. DASTROS-PITEI: Yes. We looked at the
22 age related, so we were careful about those which

Page 300

1 may be affected by age.
2 DR. FREEMAN: That's fine. Yes. I think
3 that's fine.
4 DR. GEWANDTER: But I think what Ellen said
5 is important. We'll have to think about that.
6 DR. DASTROS-PITEI: The question is, do we
7 use the money for eligibility and then we don't use
8 them anymore, or we use them at the beginning,
9 screening and baseline, and then at the very end.
10 DR. GEWANDTER: Maybe in Europe, it might
11 not be as -- because you said you have that consent
12 two weeks before, like maybe it won't be as hard as
13 it would be in America to do that.
14 DR. DASTROS-PITEI: So you see, if you get
15 them at the beginning, at least two weeks before,
16 yes, because you automatically do all the tests you
17 need to do for chemotherapy as well at that point,
18 all the labs and everything else. So it's a good
19 time to move, as the time.
20 DR. GEWANDTER: So I think there are
21 previous neurotoxic treatments. I was convinced at
22 our talk yesterday that we want to exclude these

Page 301

1 people because they could be the people who are
2 just lucky enough to never get neuropathy, and so
3 putting them in a prevention trial is a bad idea.
4 Does anyone disagree with that statement?
5 DR. SIMON: Do you refer to neurotoxic
6 chemotherapy or any neurotoxic potential drugs?
7 DR. GEWANDTER: I was thinking chemotherapy.
8 DR. LAVOIE SMITH: Any neurotoxic.
9 DR. SIMON: Because these drugs are popping
10 up. I think there are recent studies on
11 fluoroquinolones causing peripheral neuropathy
12 potentially, and 90 percent of people would have
13 gotten fluoroquinolones at a certain point in time.
14 Where do we make a cutoff of drugs that are
15 causing neurotoxicity at a higher prevalence or
16 higher severity versus metronidazole or something
17 like that?
18 DR. DASTROS-PITEI: Within the previous
19 exclusion criteria, which is the neuropathy,
20 pre-existing neuropathy, wouldn't that get rid of
21 some of this if there's been neurotoxic injury and
22 it's still persistent?

Page 302

1 DR. FREEMAN: No. But this is the exposure.
2 DR. GEWANDTER: Yes.
3 DR. DASTROS-PITEI: So on the exposure if it
4 really was clinically relevant or not?
5 DR. GEWANDTER: So I think that's what
6 you're saying. Right? Like, which drugs are we
7 talking about, and how severe, and how often do
8 they cause neuropathy, and how good is the evidence
9 kind of thing.
10 DR. SIMON: To me, it makes sense to exclude
11 neurotoxic chemotherapy.
12 DR. BRELL: Or if they're adjuvant therapy,
13 they should be chemo naïve, and we couldn't do this
14 trial unless they're chemo naïve.
15 DR. DASTROS-PITEI: Not metastatic.
16 DR. BRELL: I mean, they might have had
17 chemo for other cancers, so did we exclude anyone
18 who's had a prior cancer, which is really common in
19 treatment studies.
20 DR. DASTROS-PITEI: Chemo naïve, it's a
21 really good definition, though.
22 DR. BRELL: So you can make a list of all

Page 303

1 the known CIPN-causing chemotherapy agents, but you
2 can't make a list of all the probably thousands of
3 other agents that could be related to neuropathy as
4 well.
5 DR. SIMON: Vitamin B6 could cause
6 neuropathy.
7 DR. BRELL: Yes. I mean, the list could be
8 endless.
9 DR. GEWANDTER: I think we want things that
10 are very well agreed upon to cause neuropathy as
11 exclusions. I mean, we can't get crazy and start
12 excluding everything, because, like you said, if
13 you exclude something where 90 percent of the
14 population has had it, you don't have a study. But
15 I think that's a good point that we'll have to
16 think about when we're writing.
17 So there's no one who feels strongly that we
18 should include people who have had previous
19 neurotoxic chemotherapies and things that are very
20 well known to be neurotoxic? No. Good.
21 So allowing concomitant treatments that are
22 thought to help neuropathy, what do people think?

Page 304

1 I think for prevention and treatment, it may be
2 different, so let's talk about prevention first.
3 So we should not allow? Should?
4 DR. BRELL: Well, if we don't want someone
5 coming in with an existing, active, difficult-to-
6 treat neuropathy, they're already excluded.
7 DR. GEWANDTER: So what would that list of
8 drugs be? Yes. So what would that list of drugs
9 be, you think?
10 DR. DASTROS-PITEI: Above empty noise as a
11 summary?
12 DR. BRELL: For the list of drugs that we
13 treat neuropathy with.
14 DR. DOUGHERTY: Yesterday, we had this
15 discussion, and it was quite clear. If we're
16 excluding people that had neuropathy, then they're
17 probably not getting a drug for neuropathy. But if
18 they're on something like -- and we talked about
19 depression. There are a number of patients who
20 have cancer that are depressed and are on an
21 anti-depressant.
22 So if it's an SSRI, then they're probably

Page 305

1 okay. If they're on desipramine or something like
2 that, then maybe that's not good.
3 DR. GEWANDTER: So I guess the question is,
4 what are you basing that distinction on, like what
5 data?
6 DR. DOUGHERTY: Well, because other
7 neuropathic pains are treated with the tricyclics,
8 but they're not treated with the SSRIs.
9 DR. GEWANDTER: So you're basing it on
10 neuropathic pain.
11 DR. DOUGHERTY: Right.
12 DR. DASTROS-PITEI: So any drugs for
13 neuropathic pain, I guess.
14 DR. FREEMAN: No. I think the point Bob
15 made was that if there's any component of your
16 assessment that involves neuropathic pain, then you
17 do not want the patients to be on a drug that
18 treats neuropathic pain.
19 DR. G. SMITH: I can present a real
20 strawman. This is a real, live strawman. So I
21 don't know what you call that, but it exists. And
22 that's the trial that Joanna and I are working on,

Page 306

1 which is a disease prevention trial.
2 It's a phase 2, using electrophysiology as a
3 primary outcome measure and the secondary, the TNS,
4 but there's no pain measure as certainly one of the
5 main outcomes. And perhaps it's buried in the long
6 list and would therefore make no sense to preclude
7 a patient taking, I don't know, gabapentin, for
8 something else during the course of the trial.
9 It's not going to contaminate any of the measures.
10 Right?
11 So that's a great strawman. Right? So
12 there, you wouldn't really need to worry about
13 this.
14 If that patient was going to start
15 taking -- I can't think of a potentially effective
16 disease-altering neuropathy-preventing drug, but if
17 there were one, then that would pose a problem.
18 But that's a true strawman because I don't know
19 that that exists.
20 DR. HAROUTOUNIAN: And I think if we exclude
21 anyone who is on opioids, or NSAIDs, or tramadol,
22 we are going to exclude quite a lot of people,

Page 307

1 considering that just 30 percent of the adult
2 population have some kind of chronic pain.
3 DR. GEWANDTER: So what I'm hearing is if
4 pain is a major part of your outcome measure, we
5 exclude drugs for neuropathic pain. If your
6 outcome measure doesn't have pain -- so if it's one
7 of the sign measures, then you wouldn't necessarily
8 want to exclude those patients.
9 Is that what I'm hearing?
10 DR. LAVOIE SMITH: It all depends on if we
11 believe all the negative trials. That's the
12 challenge.
13 DR. GEWANDTER: So are you saying that we
14 don't know if these pain drugs could work for these
15 other neurological symptoms and signs?
16 DR. DASTROS-PITEI: I think we're saying
17 that studies which were done before may not have
18 been big enough to show an effect of this type.
19 DR. GEWANDTER: For CIPN, you mean.
20 DR. DASTROS-PITEI: Yes.
21 DR. GEWANDTER: But I think a lot of those
22 drugs would be covered under they work for other

Page 308

1 pain conditions.
2 DR. HERTZ: Jen?
3 DR. GEWANDTER: Yes?
4 DR. HERTZ: I think that even the ones that
5 might work that, I mean, have had negative studies,
6 do we really think that anything is so good, we
7 just haven't realized it yet, that it would
8 completely mask neuropathy?
9 So I think it could add to the background
10 noise, but unless you really think there is
11 something very, very symptom minimizing, it'll be
12 some background noise. But hopefully they will
13 overall randomize out, and it won't really
14 necessarily have a huge effect on detecting a
15 signal.
16 So I think it sort of depends. I mean, if
17 somebody comes up with something and it looks like
18 it has a pretty substantial symptomatic effect,
19 you're going to target that much more than
20 duloxetine, even though we knew it works a bit.
21 How much do you have to cut it out is depending on
22 how much of a signal you think you can detect, and

Page 309

1 is it enough to create too much noise?
2 DR. G. SMITH: What about the duration of
3 the trial, too? If this is a short-term trial for
4 oxaliplatin, cold allodynia, or whatever, then
5 you're going to do something different from an
6 ethical perspective than if it's a, let's say,
7 one-year or two-year trial looking at chronic
8 neuropathic pain.
9 So it's probably not ethical or at least you
10 need to think through the desirability of excluding
11 patients from taking any neuropathic pain agent in
12 a long study.
13 DR. GEWANDTER: That's a good idea. That's
14 a good point.
15 DR. LAVOIE SMITH: All we did in the
16 duloxetine trial is we excluded neuroleptics and
17 anti-depressants, but we allowed patients who were
18 on stable doses of opioids, and we defined what
19 stable mean, that they were allowed to participate
20 because you can't ethically say they can't take
21 anything.
22 DR. DASTROS-PITEI: Is there a difference

Page 310

1 between the groups who took opioids and those who
2 did not? No?
3 DR. LAVOIE SMITH: No. And we found that
4 people who were on opioids, more of them came off
5 of them that were in the duloxetine group as
6 opposed to the placebo group.
7 DR. GEWANDTER: So you didn't require that
8 they were at stable doses the whole time?
9 DR. LAVOIE SMITH: We didn't require that
10 they come off. We required that they were stable
11 for a two-week period prior to beginning the trial
12 and that their doses didn't increase by more than
13 10 percent up or down --
14 DR. GEWANDTER: They were allowed to
15 decrease them.
16 DR. SMITH: -- but they were allowed to
17 continue.
18 DR. GEWANDTER: Interesting. Actually,
19 that's a good point. Go ahead.
20 DR. LAVOIE SMITH: Say it again.
21 DR. DASTROS-PITEI: You were allowed to stop
22 documenting --

Page 311

1 DR. SMITH: Yes.
2 DR. GEWANDTER: Actually, that brings up
3 something interesting that I didn't even put on the
4 slide before. We're talking about right now, like
5 concomitant medications, are you allowed to keep
6 taking -- let's say you're taking duloxetine for
7 depression.
8 But in a prevention study, where you have
9 these potentially bad acute neurotoxicities, what
10 are we going to do about rescue? And that's
11 something that we didn't even put up there, which I
12 think is probably an issue, I mean, to think about.
13 I don't know.
14 Do you want to say something?
15 DR. FREEMAN: I'm interested to hear, again,
16 Daniela, Daniela and Matt. Have you thought about
17 rescue in your trials?
18 DR. DASTROS-PITEI: We have. This is a
19 difficult one because this population, particularly
20 when they're very -- but it's difficult and it's
21 not difficult in a way, because they don't have so
22 much pain. So the rescue is the standard rescue

Page 312

1 many use.
2 DR. FREEMAN: Right. And to some extent, it
3 depends on our endpoint as well. If we are using
4 an area under the curve assessment, where I think
5 the acute neurotoxicity is a contaminant more than
6 anything else, then it becomes less relevant, and
7 we will do anything to keep patients in the trial.
8 So that's using a fixed endpoint one month, two
9 months afterwards.
10 If we're thinking of area under the curve,
11 then it becomes a real issue, and particularly,
12 again, getting back to the real challenge of
13 designing a trial, which are the moving parts of
14 the chemotherapy regimen and the neuropathy burden.
15 DR. HAROUTOUNIAN: I think it would be
16 important for the paper to address the issue of a
17 rescue analgesic medication, whether we're
18 limiting, or just recording carefully, or whatever
19 we're doing.
20 DR. DASTROS-PITEI: Yes. But what is the
21 other issue I think with this population is that
22 they may have actually cancer pain, not CIPN

Page 313

1 necessarily, but the pain related with cancer. And
2 I think that requires its own -- obviously, opioids
3 is what some of these patients get.
4 DR. LAVOIE SMITH: I'm having a hard time
5 hearing you.
6 DR. DASTROS-PITEI: I'm saying this
7 population will get cancer pain, some of them, not
8 CIPN pain, but cancer pain. And that obviously
9 needs addressing and measuring very carefully. And
10 it's not rescue release, the treatment for the
11 baseline disease, in a way, but it needs to be
12 taken into account.
13 DR. GEWANDTER: Right.
14 DR. DASTROS-PITEI: But the randomization
15 should take care of it, I think.
16 DR. GEWANDTER: Yes. It just adds noise.
17 That's all.
18 DR. BRELL: If we're studying the adjuvant
19 patients, they should have minimal cancer pain,
20 maybe a little bit of post-op pain. That shouldn't
21 be as much of an issue at all. And then I don't
22 know what lessons we can take from other pain

Page 314

1 trials and how they managed rescue pain, a rescue
2 analgesic for pain.
3 DR. SIMON: I think if it's mastectomies
4 with breast cancer, we need to consider a
5 persistent post-mastectomy pain because 20,
6 30 percent of patients might develop pain that
7 might require treatment with anti-neuropathic
8 medications or analgesics. Just again, some noise
9 that could be added to that cohort.
10 DR. BRELL: Again, it depends on the
11 outcome. The outcome is pain.
12 DR. DASTROS-PITEI: That's a neuropathic-
13 type pain.
14 DR. SIMON: Sorry?
15 DR. DASTROS-PITEI: The chronic post-
16 surgical persistent pain, it's a neuropathic-type
17 pain.
18 DR. SIMON: Yes, that's what I'm --
19 DR. DASTROS-PITEI: And I think that is a
20 confounder for the CIPN, then, because the
21 CIPN -- yes. I think this probably is worth
22 thinking about in moving.

Page 315

1 DR. FREEMAN: We hope to have excluded those
2 patients.
3 DR. DASTROS-PITEI: Yes.
4 DR. GEWANDTER: Actually, that's a good
5 point because specifically excluding those patients
6 might be a new exclusion criteria than what we've
7 talked about already, because if you ask people to
8 think about their hands and their feet when they're
9 filling out their PROs for peripheral neuropathy,
10 you might not capture that in the exclusion that
11 we've talked about so far.
12 So if we wanted to exclude people because
13 they have post-op mastectomy pain, we have to say
14 that specifically. And what will that do to
15 recruitment?
16 DR. BRELL: Depends on what we're studying.
17 A lot of patients, there's less post-mastectomy
18 pain if you've only had a lumpectomy. So maybe
19 we'll be okay even though we exclude the
20 mastectomies.
21 DR. G. SMITH: So Roy, can I ask a question?
22 I guess this would also be a statistical question.

Page 316

1 You've mentioned several times the worry about
2 acute pain syndromes creating an issue in an area-
3 under-the-curve analysis. But couldn't you just
4 say we're going to start the area under the curve
5 one month after initiation of chemotherapy, or at
6 some time point where you expect to be beyond this
7 common and fairly predictable side effect?
8 DR. GEWANDTER: The acute is associated with
9 each cycle. Right?
10 DR. G. SMITH: Right. So yes, that's a fair
11 point.
12 (Crosstalk.)
13 DR. GEWANDTER: So it would have to be after
14 you finish chemo completely --
15 DR. G. SMITH: Yes.
16 DR. GEWANDTER: -- which that is a really
17 probably --
18 DR. SMITH: Fair point.
19 DR. GEWANDTER: -- clinically meaningful
20 endpoint. It's just you have to have a lot of
21 people in your trial because not that many people
22 are going to end up with chronic, so it's a huge

Page 317

1 undertaking.
2 DR. FREEMAN: Yes. But it's a legitimate
3 point, and I'm really beginning to think that
4 that's one way of dealing with this, is to say,
5 okay, during the chemotherapeutic cycle, there is
6 an enormous amount of noise that maybe we don't
7 care about. We obviously care about it as far as
8 the patient suffering is concerned, but we really
9 aren't interested in 1 month, 2 month, 3 month, 4,
10 where some of the noise at least has attenuated.
11 And maybe that's an approach to all of this.
12 So I'm trying to -- behind my question to
13 the statisticians is trying not to -- they're
14 moving parts. There are a lot of issues with this
15 trial. If we can reduce it to the kinds of trial
16 that we are familiar to in some way, it may be
17 easier to implement. And that's why I am
18 sympathetic with the point you're making.
19 DR. GEWANDTER: I think one thing we can do
20 is maybe do some sample size calculations,
21 depending on different assumptions for incidents
22 three months after chemo and see how big the trials

Page 318

1 would have to be. And we think about putting that
2 in the paper, because that does simplify things if
3 you do it that way and see if they're ridiculously
4 large or not.
5 DR. DASTROS-PITEI: Incidence of CIPN
6 3 months --
7 DR. GEWANDTER: Yes, incidence of, like,
8 30 percent at 3 months and see how big would your
9 study have to be to recruit people at the
10 beginning, do a primary prevention study. If your
11 incidence is only 30 percent at 3 months,
12 that's --
13 DR. DASTROS-PITEI: I see what you mean,
14 yes.
15 DR. GEWANDTER: We can make some different
16 assumptions of what the incidence is from,
17 like -- 30 is what was in the systematic review,
18 but there was a huge variability, so we can take
19 the bottom of the confidence interval and the top
20 of the confidence interval and see how many people
21 would we need, if we wanted to just make it simple
22 and do that.

Page 319

1 DR. FREEMAN: I think we're good.
2 DR. GEWANDTER: All right. I think we're
3 good. We ended a little early, 10 minutes.
4 DR. FREEMAN: Let me finish and say just a
5 couple points. Obviously, this is one of the more
6 challenging of these kinds of meetings, that at
7 least I have been to. The major challenge is that
8 there really are so many issues and inter-related
9 issues.
10 The manuscript, I think it places an
11 enormous burden on Jennifer's shoulders, and I
12 think we all need to help enormously with her. And
13 I think the oncologists, the clinical trialists,
14 the statisticians, the neurologists, and industry
15 will each have their part to play.
16 So thank you to everybody for participating.
17 DR. GEWANDTER: Thanks, everybody, for
18 coming.
19 Adjournment
20 DR. FREEMAN: It's been really interesting.
21 I've learned a lot. And I hope we can move this
22 along and have another meeting about this kind of

Page 320

1 thing soon. So thank you very, very much.
2 DR. LAVOIE SMITH: Thank you for pulling it
3 together.
4 (Applause.)
5 (Whereupon, at 3:20 p.m., the meeting was
6 adjourned.)
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17
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19
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21
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	244:8;278:4;282:2	53:18		1:13;3:2
\$	12:00 (1) 3:12	2011 (5) 13:15;14:21;17:6; 23:14;55:3	4	80 (2) 201:22;202:2
\$23 (1) 17:8	12:05 (1) 187:3	2014 (1) 13:8	4 (16) 17:20;49:16;50:2,4; 53:22;54:4;87:13,16,19, 19;89:12,14;211:18; 212:22;288:19;317:9	80-some-odd (1) 104:20
[12-week (1) 182:2	2016 (3) 14:21;17:6;23:14	40 (3) 65:12;138:16;144:20	81 (1) 17:7
[(1) 124:11	14 (2) 12:7;30:16	2017 (1) 1:12	400 (2) 85:1;184:1	84 (2) 182:3,5
[inaudible (2) 61:16;278:13	146 (1) 55:8	23 (1) 174:16	400-patient (1) 173:19	85 (1) 279:4
[indiscernible (2) 46:5;178:6	15 (3) 22:4,4;172:10	231 (1) 135:3	450 (1) 32:2	85-milligrams (1) 255:17
[ph (1) 92:12	150 (1) 86:20	24 (2) 1:12;256:19	46-patient (1) 174:16	9
0	16-item (1) 101:2	25 (1) 50:20	48 (1) 163:20	9 (1) 284:8
0 (4) 50:4;54:3;197:12; 207:14	17 (1) 68:14	26 (1) 18:18	4-grade (1) 50:4	90 (4) 165:13;182:11; 301:12;303:13
0.4 (1) 34:1	18 (1) 33:6	28 (1) 55:16	5	947 (1) 10:20
0.5 (1) 175:9	1998 (3) 48:6,21;49:4	281 (1) 55:12	5 (9) 23:13;65:19;87:13; 89:11,11,14;90:20; 180:12;236:19	99 (1) 52:18
1	1st (3) 18:9;24:19;25:6	2s (1) 171:6	50/50 (1) 89:13	A
1 (14) 6:12;12:7;26:21;50:4; 53:21;54:3;135:10; 138:20,21;181:10; 244:7;255:1;262:10; 317:9	2	3	50-60 (1) 139:13	Aaronson (1) 48:7
1:00 (2) 186:17;187:2	2 (15) 3:4;53:22,22;131:17; 135:11;213:1;233:16; 237:21;255:1;262:11; 263:1;277:9;295:13; 306:2;317:9	3 (24) 6:12;26:20;27:2; 32:11;48:14;50:4;53:22, 22;54:4;97:11;170:1,13; 174:4;180:12;244:8; 249:1;255:1;263:4; 287:11;288:19;317:9; 318:6,8,11	5-point (1) 89:8	abbreviated (1) 220:4
1:08 (1) 188:2	2:00 (1) 234:7	3.75s (1) 87:19	6	ability (8) 63:11;128:12;136:6; 179:13;234:20;263:11; 274:21;296:12
1:48 (1) 228:16	20 (62) 18:19;40:21;41:2,12, 17;49:1,18;57:11;58:4; 60:9,11,16;96:7;100:10, 20;101:9;102:5,6;103:7, 18;104:12;107:21; 108:3;111:10;118:17; 119:16;123:9;125:8; 128:19;129:5,9,11; 130:7,20;131:11;132:10, 14;138:16;151:19; 161:15;190:9;191:22; 194:12;195:2,9,18; 196:16;197:1;201:7,19; 206:1,5;207:5;208:12; 209:10;210:5,10;211:7; 229:4;230:3;256:11; 314:5	3:20 (2) 1:13;320:5	6 (11) 18:19;23:12;135:9; 244:8;277:9,12,20; 278:4,15;284:8;295:12	able (37) 16:7;30:16;31:16; 36:13;47:14;54:9;55:18, 20;56:1,3,5,16;76:13; 77:16;81:12;92:4;95:13; 124:8;127:21;131:11; 135:16;138:19;139:10; 143:14;145:10;150:1; 159:10,11;177:6;183:6; 184:16;186:5;217:6; 220:15;221:17;228:19; 230:16
10 (15) 22:3,4;31:21;53:1; 102:20;114:15;155:16; 162:21;197:12;203:22; 207:14;240:13;254:20; 310:13;319:3	200 (1) 184:1	30 (14) 10:10;102:21;125:18; 144:16,19;162:13; 163:12;286:8;295:13; 307:1;314:6;318:8,11,17	6 (1) 112:19	abnormal (6) 116:10,12,12;198:21; 199:1;240:14
10:40 (1) 133:11	2000 (1) 30:9	300 (4) 10:22;30:12;32:2; 86:20	7	abnormalities (1) 74:7
10:40 (1) 133:11	2003 (1) 286:8	30-year (1) 21:21	7 (6) 30:8;91:8;181:13,18; 182:3;295:12	above (3) 202:2;257:20;304:10
100 (8) 30:11;131:10;135:12; 138:19;167:2;259:1,3,10	2006 (2) 13:15;29:17	34 (2) 10:18;68:4	70 (1) 165:21	absence (1) 237:16
10-gram (1) 80:7	2010 (1)	35 (1) 17:9	75 (1) 252:1	absolute (1) 86:17
10th (1) 30:15		37 (1) 17:20	8	absolutely (6) 159:16;212:3,8;267:2; 279:3;286:5
11 (1) 16:11		38 (1) 64:11	8 (4) 135:9;254:20;278:6; 288:18	abstract (1)
11:00 (2) 133:7,8		3s (1) 172:19	8:12 (2)	
12 (9) 10:13,18;16:10; 129:11;155:16;182:3;				

30:7	45:17;49:12;56:11;65:7;	148:14	307:1	age (3)
abuse (1)	70:21;74:9;81:12;84:7;	add (12)	adults (1)	99:12;299:22;300:1
16:20	89:22;91:1;101:12,15;	153:12;156:20;194:9;	220:8	agencies (1)
academia (1)	125:9,17;137:2;159:11,	205:17;207:16;218:4;	advanced (1)	44:4
92:22	12;202:16;260:20;	226:12;242:6;255:11,	275:14	agency (2)
academic (2)	279:14;284:11	21;259:2;308:9	advantage (3)	233:13;263:8
9:17;53:8	action (4)	added (9)	42:14;285:19;286:5	agenda (14)
accelerate (1)	169:8;253:3;267:7;	9:8;50:14;51:16;	advantageous (1)	3:4;6:13,22;189:2;
169:16	273:6	208:13;223:16;229:18;	99:20	210:10,13;213:11;241:7,
accept (2)	active (12)	238:3;250:11;314:9	advantages (2)	7;242:19;243:7;255:22;
132:20;238:11	15:15,19;16:10;66:8;	ADDICTION (1)	145:17;216:11	261:6;298:1
acceptable (5)	110:18;130:3;157:2,9;	1:3	adverse (3)	agent (18)
56:4;232:6;267:16;	165:19;167:8;270:22;	adding (2)	212:15;249:11,12	12:12;19:19;30:1;
274:5;297:5	304:5	196:7;289:15	advertisement (1)	75:12,19;158:10;
accepted (5)	activities (5)	addition (1)	156:3	195:21;246:12;264:9,
49:6;54:13;104:13;	51:15,17,21;52:4;64:9	135:20	advertising (1)	11;265:3;275:12;
107:6,7	activity (1)	additional (3)	141:5	279:21;281:12,18;
accepts (1)	52:6	195:21;226:1;234:4	advice (3)	284:9;285:8;309:11
225:16	actors (1)	address (7)	57:6,7;140:21	agents (14)
access (6)	35:18	6:16;101:5;168:10,13;	advocacy (2)	18:11;20:6;22:11;
19:14;143:14,17;	ACTTION (7)	210:17;269:6;312:16	157:4;160:22	25:2,12;148:9,18;181:2;
144:6;160:6;173:3	1:1;4:11,18,20;64:9;	addressed (2)	advocate (6)	231:15;255:13;263:5,
accident (2)	68:18;81:10	45:6;262:22	160:15;161:3;191:11;	22;303:1,3
161:11;165:12	actual (7)	addresses (1)	209:9;213:17;246:18	agents' (1)
accomplish (2)	21:4,15;75:20;184:22;	172:22	advocates (1)	19:14
7:2;188:6	224:2;280:10;293:15	addressing (2)	207:5	aggregate (2)
accomplished (1)	actually (95)	213:4;313:9	AE (2)	63:12;64:12
19:13	10:2,9;13:4;19:22;	adds (4)	113:9;212:18	ago (10)
account (6)	24:19;31:4,6;33:11;	76:17;152:9;227:2;	affect (6)	6:1;35:10;49:9;67:8;
243:6;251:20;261:11;	46:21;49:16;51:9;54:2;	313:16	202:18;207:9,10;	85:8;103:11;110:14;
291:9,11;313:12	63:21;65:2;68:14;70:14,	adequate (1)	255:20;268:18;280:16	123:9;166:22;232:15
ACCRU (13)	22:71;12,14;83:5;84:22;	116:21	affected (3)	agree (39)
145:4,7,11;147:10,13,	88:11;90:15;92:15;	adequately (1)	40:2;75:3;300:1	28:11;29:15,16;60:16;
16,17;172:8,9;173:15,	97:10;98:16;99:17;	115:21	affects (2)	80:3;98:17;99:16;106:1;
19;174:2,11	101:19;109:20;110:14;	adhere (2)	256:16;262:7	107:2,17;109:22;111:9;
A-C-C-R-U (1)	113:8;114:22;116:3,13,	199:4;293:19	AFT (10)	128:13;144:13;162:17;
145:4	14;117:4;118:12,14;	adhered (1)	145:3;170:17;171:5,	168:16;186:19,19,20;
accrual (8)	123:2;124:10,12;128:9,	293:18	14,19;172:4,4,6,8,11	191:19;200:14;204:15;
10:4;13:13;145:21;	12;130:11;146:8;	adjourned (1)	afternoon (2)	211:10;213:14;218:20;
148:4;151:7;159:2;	151:12;152:2;153:5,13;	320:6	7:5;186:17	222:3;226:6;228:18,19,
186:10;290:3	154:9;155:7;157:9,22;	Adjournment (1)	afterwards (8)	21;235:3;259:14;
accru (4)	160:2;162:3;163:8;	319:19	175:6;181:19;182:5,	262:19;268:10;269:6;
10:4;152:12;156:1,19	164:5;165:20;173:16;	adjust (1)	10;244:13;255:8;292:9;	280:20;281:9;296:19;
accrued (3)	174:3,21;176:5;194:1;	247:21	312:9	297:2
151:1;153:21;168:18	195:8;197:16;201:14;	adjusting (1)	again (52)	agreeable (1)
accurate (2)	206:7,19;207:8;209:1;	175:21	11:12;14:21;16:9;	194:18
98:10;117:10	216:13,22;221:8;	adjustment (1)	20:4,5;27:21;41:13;	Agreed (4)
acetyl (2)	222:18;223:7;225:10;	99:12	45:2;47:20;50:8;51:2;	193:6;275:20;294:7;
13:3,11	230:2;233:5;239:18;	adjustments (1)	55:2,6;57:4;59:7;74:20;	303:10
aches (2)	244:15;262:3,18;270:12,	247:10	85:10;93:17;109:12;	agreeing (1)
175:1;181:7	13,14;271:1;280:14;	adjutant (10)	129:20;136:16;137:12;	99:9
achieve (1)	281:7;283:13;289:7;	175:16,16;284:4,12,	138:9,22;139:8;140:15;	agreement (5)
62:10	291:3;310:18;311:2;	13,14,15;288:12;302:12;	141:6;142:16;153:17;	48:12,16,17;209:6;
achievement (1)	312:22;315:4	313:18	178:2;179:6;190:21;	296:17
85:5	acupuncture (1)	administer (1)	192:14;199:15;211:6;	ahead (11)
acid (2)	19:4	298:18	212:8;217:21;227:2;	80:3;90:19;128:13;
85:2,18	acute (18)	administration (1)	236:18;237:17;240:22;	177:12,16;222:8;
acronyms (1)	5:21;45:21;46:1,5,8,	158:6	247:13;250:9;257:21;	246:17;256:13;285:8;
162:10	12;149:15;174:22;	administrator (1)	281:18;286:20;291:4;	297:20;310:19
across (35)	181:5,12;182:6;253:20;	147:8	310:20;311:15;312:12;	air (1)
9:1,7;10:20;11:4,12,	276:14,15;311:9;312:5;	admission (1)	314:8,10	253:4
22;12:4;13:7;17:2;20:9;	316:2,8	88:19	against (3)	al (1)
21:2,3;26:17;41:5;	adaptive (1)	adult (1)	40:13,14;281:17	125:22

<p>alarming (1) 83:17</p> <p>Albers (1) 79:11</p> <p>alert (1) 157:4</p> <p>align (1) 139:6</p> <p>aligned (1) 139:3</p> <p>Alliance (13) 9:21;11:9;135:2; 145:3;168:8,14,20,22; 170:10,16,17;172:7; 175:15</p> <p>allodynia (1) 309:4</p> <p>allow (6) 32:10;136:11;160:4, 11;266:1;304:3</p> <p>allowed (11) 57:10;155:7;159:18, 19;160:1;309:17,19; 310:14,16,21;311:5</p> <p>allowing (2) 42:22;303:21</p> <p>allows (2) 130:17;192:19</p> <p>alluded (2) 71:12;75:9</p> <p>alluding (1) 286:18</p> <p>almost (2) 200:1;201:21</p> <p>alone (4) 42:13;225:5;236:14; 266:20</p> <p>Along (11) 9:16;11:12;15:16; 78:21;104:20;166:15; 205:13;207:5;250:7; 281:20;319:22</p> <p>alpha-lipoic (2) 85:2,17</p> <p>already-existing (1) 42:11</p> <p>ALS (2) 115:10;203:22</p> <p>alter (1) 234:17</p> <p>Alternative (2) 16:20;71:18</p> <p>Alternatively (1) 232:10</p> <p>although (8) 34:11;46:4;90:4;92:3; 164:6;174:12;224:16; 271:6</p> <p>always (21) 62:8;69:14;93:7; 102:13;103:2;108:6; 117:5;119:4;120:3; 127:15;161:20;180:11;</p>	<p>197:12;200:1;202:6; 204:16;210:20;222:12; 223:4;266:22;287:3</p> <p>amalgam (2) 85:19;118:10</p> <p>amazing (1) 87:14</p> <p>ambiguous (1) 59:17</p> <p>amend (1) 140:22</p> <p>America (2) 79:1;300:13</p> <p>American (1) 53:8</p> <p>amitriptyline (3) 28:8;103:11;154:17</p> <p>among (5) 17:7;38:3;65:9;67:1; 238:17</p> <p>amongst (3) 18:20;19:3;156:22</p> <p>amount (6) 95:17;184:6,10,17; 293:8;317:6</p> <p>amounts (1) 237:1</p> <p>amplitude (2) 66:21;72:15</p> <p>amputation (1) 233:22</p> <p>amyloid (4) 82:6,8;224:17;230:11</p> <p>ANALGESIC (3) 1:3;312:17;314:2</p> <p>analgesics (1) 314:8</p> <p>analyses (1) 92:2</p> <p>analysis (9) 55:15;83:10;178:7; 248:5;251:19;280:2; 290:15;291:8;316:3</p> <p>analyst (1) 23:16</p> <p>analysts (5) 14:22;17:2,7;18:17; 19:8</p> <p>analytic (2) 64:17;290:19</p> <p>analyze (4) 10:3;54:7;250:21; 293:21</p> <p>analyzed (1) 56:8</p> <p>analyzing (2) 43:9;103:19</p> <p>anatomic (1) 217:3</p> <p>anchor (1) 195:18</p> <p>and/or (2) 5:11;134:16</p>	<p>Anderson (1) 148:13</p> <p>Andrea (1) 189:14</p> <p>anemic (1) 59:11</p> <p>ANESTHETIC (1) 1:3</p> <p>animal (2) 17:15;24:15</p> <p>animals (4) 17:21,22;18:7,11</p> <p>ankle (2) 72:13;217:1</p> <p>Ann (6) 7:11,14;27:9;28:3; 100:12;286:4</p> <p>Anna (2) 105:12;182:17</p> <p>annoyed (1) 62:18</p> <p>annoying (3) 192:17;200:5;201:2</p> <p>anorexia-cachexia (1) 102:22</p> <p>anti- (1) 16:15</p> <p>anti-depressant (3) 136:8,14;304:21</p> <p>anti-depressants (2) 136:12;309:17</p> <p>antiemetic (1) 164:21</p> <p>anti-neuropathic (1) 314:7</p> <p>anymore (2) 102:7;300:8</p> <p>anything's (1) 264:20</p> <p>apart (1) 196:22</p> <p>apixaban (1) 146:10</p> <p>apologize (1) 74:21</p> <p>appeal (1) 253:14</p> <p>appealing (1) 124:6</p> <p>appear (2) 6:2;245:19</p> <p>appearance (2) 5:11;253:9</p> <p>appeared (1) 3:11</p> <p>Applause (4) 61:14;94:12;189:17; 320:4</p> <p>application (2) 109:18;237:12</p> <p>applications (4) 16:6;17:3;21:7,12</p> <p>applied (2) 90:21;99:14</p>	<p>applies (1) 106:10</p> <p>appraised (1) 101:16</p> <p>appreciate (1) 28:4</p> <p>appreciated (1) 88:18</p> <p>appreciative (1) 88:8</p> <p>approach (21) 6:19;35:2;36:7;37:14; 51:12;52:8;53:5;56:9; 98:19;138:18;148:3,20; 154:1;157:11;168:6; 178:3;184:2;189:4; 220:12;290:19;317:11</p> <p>approaches (2) 188:10;267:15</p> <p>appropriate (3) 44:18;220:17;234:21</p> <p>appropriately (1) 263:1</p> <p>approval (12) 159:18;225:6,18,22; 226:9,10;230:19;234:2; 236:15;242:16;266:8; 286:7</p> <p>approvals (1) 238:7</p> <p>approve (3) 142:19;174:12,15</p> <p>approved (10) 12:12;22:5;25:12; 29:5;144:15,16;162:15; 163:13;174:13;286:8</p> <p>area (20) 11:7;31:17;163:11; 200:4;202:3;244:6,8; 245:1;250:1;253:12,13, 18;254:22;257:1,6; 262:15;296:9;312:4,10; 316:4</p> <p>area- (1) 316:2</p> <p>areas (9) 6:11,13;21:11;122:7, 17;134:15;200:13; 264:18;269:21</p> <p>arena (2) 25:4;199:16</p> <p>argue (8) 16:7;25:13;26:19; 27:2;99:20;108:3;165:5; 206:7</p> <p>argument (5) 32:21;230:18;237:16; 238:11;285:5</p> <p>argumentative (1) 194:18</p> <p>arguments (2) 44:10;108:12</p>	<p>arm (8) 130:3;148:7,9;167:9; 174:16;183:8,8;208:1</p> <p>arms (3) 61:6;95:1;290:1</p> <p>around (19) 11:16;29:6;83:9;87:3, 16;128:19;135:4; 148:22;160:6;161:6,16; 167:22;172:10,10; 196:17;220:15;231:9; 252:12;287:6</p> <p>array (4) 68:14;70:2;162:10; 296:10</p> <p>arthralgia (1) 175:2</p> <p>arthritis (2) 16:19;224:10</p> <p>article (3) 28:16;193:16,18</p> <p>articles (2) 64:11;65:21</p> <p>articulate (1) 222:4</p> <p>ASCO (3) 30:7,9;163:18</p> <p>aside (3) 62:21;79:6;116:18</p> <p>asleep (2) 198:10;200:10</p> <p>aspect (12) 42:12,20;43:9;61:10; 114:13;152:10;155:18; 158:11;179:2;203:7; 211:16;257:16</p> <p>aspects (6) 113:20;114:8;116:17; 178:12;230:6;260:18</p> <p>aspirationally (1) 64:2</p> <p>assays (2) 19:1;228:1</p> <p>assemble (1) 237:13</p> <p>assess (12) 6:7;34:15,20;41:15; 42:6;101:21;113:21; 226:18;230:8;242:20; 253:7,8</p> <p>assessed (2) 18:15;54:22</p> <p>assesses (1) 177:11</p> <p>assessment (19) 34:22;37:7,8;40:20; 42:1;48:16,20;50:12,14; 57:7;98:3;100:17; 106:17;218:3;220:18; 223:1;226:8;305:16; 312:4</p> <p>assessments (17) 27:11;35:5,6;44:19;</p>
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53:13;63:18,19;162:1,5; 167:12;175:22;176:1,8, 10;178:5,6;180:13 assessor (1) 220:16 assignment (1) 292:4 assistant (2) 220:1;221:8 associated (3) 183:12;294:8;316:8 association (1) 260:14 assume (1) 256:20 assuming (2) 32:13;86:5 assumption (2) 117:9;291:14 assumptions (3) 53:12;317:21;318:16 ataxia (1) 60:1 ataxic (1) 59:11 at-risk (1) 285:20 attack (1) 236:20 attempt (3) 5:17,18;114:6 attempts (3) 36:8;45:13;123:21 attended (1) 116:3 attending (2) 4:4;223:4 attention (3) 17:19;61:13;245:14 attenuated (1) 317:10 attitude (2) 219:9;227:12 attract (1) 176:13 attractive (2) 169:12;219:5 attributes (1) 64:3 AUC (1) 255:16 audience (2) 188:15;189:13 Australian (1) 53:9 authored (1) 4:3 authorities (1) 261:1 authors (2) 4:6;48:18 automatically (1) 300:16	autonomic (8) 50:1;60:17,21;91:8; 109:15;115:16;210:11; 222:22 availability (1) 168:11 available (7) 45:5;48:10;53:13; 95:5;168:20;173:17; 183:18 average (4) 31:5;124:22;163:9; 250:5 aware (6) 41:16;47:18;104:18; 130:19;132:19,22 away (8) 14:4;71:21;98:5; 110:6;124:22;191:21; 289:16;290:13 axonal (2) 75:22;159:11	barely (1) 200:10 barking (1) 33:12 barrier (1) 235:19 barriers (1) 25:20 Barton (1) 103:9 base (5) 9:19;193:11;241:4; 261:2;286:10 based (22) 21:4,16;22:3,15; 28:14;37:1;49:22;53:14, 20;54:16;65:2,11;69:7; 71:9;86:9;118:10;132:7; 212:21;251:5;284:5; 291:15;294:14 baseline (6) 97:22;129:11;131:16; 297:4;300:9;313:11 bases (5) 8:22;10:14,14;13:8; 194:15 basic (5) 46:18;50:8,14;74:5; 87:15 basically (12) 16:11;67:2;86:16; 87:18;89:9;145:5; 150:17,18;170:18; 171:2;173:4;284:1 basing (2) 305:4,9 basis (5) 11:6;30:19;44:6;45:4, 11 batch-to-batch (1) 166:7 Bayesian (1) 148:14 bear (3) 167:1;245:10;246:9 bearing (2) 72:7;176:8 beat (2) 71:18;162:22 beautiful (4) 90:4;102:10;223:3; 264:1 beautifully (3) 71:7;76:10;239:17 beauty (2) 191:8;253:13 became (3) 49:1;72:1;99:8 becomes (3) 101:12;312:6,11 becoming (1) 39:9 bed (2)	55:22;56:1 began (1) 157:15 begin (2) 134:11;210:9 beginning (10) 3:4;114:16;153:9; 253:19;281:1;300:8,15; 310:11;317:3;318:10 begins (1) 186:17 behalf (1) 189:14 behaves (1) 52:17 behavioral (1) 20:8 behind (4) 114:2;115:20;178:16; 317:12 bells (1) 152:16 beloved (1) 31:22 below (2) 60:3;294:16 benefit (5) 31:14;33:1;117:11; 175:4;176:2 benefits (3) 73:13;237:3,4 Berry (1) 148:13 best (32) 13:3;34:20;35:2;36:6; 37:14,15,18,20;38:4; 96:6;100:20;101:4,9; 108:13;110:9;112:19; 133:20;143:5;176:15; 188:20,22;190:10;194:6, 7;196:9;213:13;228:22; 234:21;243:13;274:10, 20;295:11 bet (2) 31:22;174:14 beta (1) 228:5 better (29) 23:1;31:8;41:13; 48:15;80:5,10,11;95:10; 97:4;112:3;120:3,3; 123:13,16;124:9,20; 126:4;154:15;170:3; 194:2;206:7;229:6,9; 238:4;240:19;252:13; 266:17;270:14;271:6 bewildering (2) 70:2;162:9 beyond (5) 28:1;211:19;212:22; 241:16;316:6 bias (4) 45:13;73:10;74:20;	197:11 big (27) 10:21;11:3;12:21; 45:16;46:21;53:19;61:2, 5;118:4,20;120:16; 130:4,22;131:9;141:2; 152:11;157:5;166:18; 170:1;222:2;230:13; 286:14;287:10,14; 307:18;317:22;318:8 bigger (2) 237:7;250:11 biggest (3) 27:2;101:14;250:19 biology (1) 264:2 biomarkers (7) 17:11,16;18:14;24:1; 75:15;112:17;271:17 biomechanisms (1) 16:15 biopsies (7) 158:18;159:4,6; 176:17;177:1;235:22; 240:3 biopsy (7) 124:2;159:14;235:17; 238:15,17;239:8;240:11 birthday (1) 259:8 bit (37) 8:4,16;14:11,19; 26:21;58:2,4,6,3;16,21; 64:2;66:2;77:18;78:6; 85:3;91:14;105:14; 111:18;113:17;122:8; 142:14;144:13;156:21; 180:22;197:19;220:4; 245:9;252:5;263:14; 265:1;271:6;276:2,6; 278:16;284:18;298:21; 308:20;313:20 biting (1) 200:18 black-box (2) 136:9;179:10 blanket (1) 298:8 blood (6) 120:12;146:11; 236:16,18;237:1;259:4 blue (2) 55:18;218:12 blurring (1) 210:14 BMS (2) 166:4,4 board (2) 20:9;64:22 Bob (10) 3:15,21;125:11; 174:13;193:7;198:16; 202:14;252:11;297:11;
	B			
	B6 (1) 303:5 back (43) 7:9;14:1;20:14;21:18; 22:6;30:5,19;31:6;45:3; 47:9,20;48:6;50:16; 55:9;57:4;62:18;64:18; 70:1;80:1,6;89:1;91:11; 102:7;110:7;129:4; 133:7;142:9;158:13; 174:15;176:2;179:7; 180:15;181:17;182:12; 196:21;231:10;232:19; 252:14,16;270:3;276:6; 287:2;312:12 background (5) 4:8;7:19;191:5;308:9, 12 backwards (1) 11:5 baclofen (2) 103:10;154:17 bad (9) 22:9,10;65:5;190:14; 244:14,18;293:7;301:3; 311:9 baffled (1) 222:12 bailing (1) 111:5 balance (6) 68:20;69:15;112:18; 122:1;257:12;292:3 bane (1) 87:9 bar (5) 5:5;55:18;241:14,17; 242:4			

305:14 bodies (1) 35:11 body (2) 74:16;267:6 boil (1) 100:8 bordering (1) 201:5 bored (1) 53:3 bortezomib (12) 157:8,20;165:14; 217:15;218:2;226:20; 245:16;247:8;248:19; 276:1;282:19;286:6 bortezomib-based (1) 282:22 Boston (2) 114:7;287:3 both (32) 8:13,16;11:14;17:15; 25:5;58:7;60:10;65:22; 88:12;94:19;107:3; 109:7;123:22;142:8; 166:1,10;181:2,3,5; 199:19;209:13,15,22; 210:1;225:1;240:20; 246:19;249:21;250:7; 262:18;267:15;289:22 bothering (1) 200:22 bothers (1) 264:15 bothersome (1) 192:17 bottom (4) 40:17;56:4;164:12; 318:19 bought (1) 166:3 bourbon (1) 83:14 box (1) 121:17 BPI (4) 14:18;136:21;206:10, 12 brain (1) 169:21 brand (2) 172:4,6 break (5) 33:4;101:6;129:3; 133:2;293:4 breast (10) 137:17;138:2,3; 140:15;160:17;170:7; 172:6;174:9;272:12; 314:4 Brell (35) 8:2;27:9,13;66:17; 111:9;156:6,7;182:18;	183:13;185:5;186:7; 195:17;196:10;207:20; 208:19;242:18;260:12; 272:6;274:7,16;277:5, 10,16;278:8,12,19; 302:12,16,22;303:7; 304:4,12;313:18; 314:10;315:16 Brell's (1) 6:4 brief (5) 76:6;96:15,19;134:12; 191:3 briefly (1) 3:6 brilliance (1) 154:1 bring (14) 17:19;24:19;26:11; 70:7;72:2;78:4;79:7; 91:18;96:5;105:7; 117:22;148:18;197:18; 274:11 bringing (5) 19:11;21:7,8;92:18; 283:19 brings (2) 117:12;311:2 British (1) 217:18 British-trained (1) 222:16 broad (1) 16:5 broader (1) 168:14 brought (6) 18:7;78:21;80:1;86:3; 215:22;227:20 buddy (1) 167:21 budget (1) 184:22 budgets (1) 184:19 build (5) 148:12;158:8;186:19; 230:7;268:1 building (3) 8:2;96:17;291:17 builds (2) 247:4,4 built (6) 97:1,13;170:16; 171:13,14;212:9 bulk (1) 17:4 bullet (2) 10:13;17:20 bullets (1) 17:10 bunch (7) 31:8;118:18;147:12;	176:16;177:16;199:21; 222:4 burden (7) 264:8,10;265:5; 290:16;292:17;312:14; 319:11 buried (1) 306:5 burning (5) 61:16;175:5;195:13; 200:11,15 Burns (2) 70:9;88:10 bushes (1) 162:22 busy (5) 105:9;219:9;227:6,9; 298:20 butcher (1) 34:6 buttoning (2) 59:3,6 buy (2) 147:5;285:5 buy-in (2) 137:10;142:17 buzzing (2) 58:21,22	38:2,22;42:15,16,18; 45:17;50:3,11;53:7; 54:6,22;58:10;59:10,12; 62:16;65:10;67:9;68:8, 16,19;69:22;76:6,19; 80:22;81:20;83:6;84:4; 86:1,17;89:15;90:12; 94:21,22;95:13,16,18, 22;96:2,6,21;97:12; 99:13;100:3,7;102:1; 103:2,15;104:4;105:15; 109:5;110:21,22; 111:12;114:10,11; 119:6;121:14,21; 122:21;124:9;126:2; 127:22;128:11;129:16, 20;130:9,19;131:15,16, 20;133:7,8;134:20; 138:12;139:22;140:20; 141:12;144:5;145:9,15, 20,20;146:1,2;147:1; 148:15;152:4;154:16; 155:21;161:3,7;163:18; 164:1,12,20;166:14; 168:10,17;169:3,4,20; 173:6,14;175:11;177:15, 22;178:16,20;179:19,22; 182:16;184:1,13,14; 185:9,10,15,18,20; 186:19;188:7;189:3; 195:14;197:1;199:9,10; 203:14;205:2;209:2,4; 214:20;216:21;220:1, 16;221:18;225:20; 228:1,8;231:4,17,22; 232:13,18;234:8,12; 237:2;241:12;242:7; 243:1;247:13,18;249:3; 250:13,17;251:4,14; 252:5,16;253:7,7,10,11, 12;254:13;255:3;257:4, 6;258:13;259:19; 260:19,21,22;264:4,6; 272:13;275:5;276:4,22; 279:2,3,7;280:3,6,16; 283:5;284:18;286:13,15, 21;288:5;289:11; 290:20;291:16,20; 292:1;293:2,13;294:5, 15;296:7;297:2,3; 302:22;305:19;308:22; 313:22;315:21;317:15, 19;318:15,18;319:21 Cancer (64) 7:13,22;9:1,9;10:15; 11:1;16:4,16;17:5,15; 20:15,16,17;21:2,4; 30:21;35:20;40:7,45;18; 55:11,13;66:17;71:22, 22;134:22;136:13; 138:2;140:15;160:17; 162:21;174:9;186:3; 241:18,19;271:7;272:9,	20;274:18,19;275:14; 276:3,22;277:2,21; 278:5,7;279:9;282:11; 288:2,2,12,13,15,17; 289:17;294:3;302:18; 304:20;312:22;313:1,7, 8,19;314:4 cancers (9) 49:19;270:7,10,14,18; 272:9;282:10;284:7; 302:17 cancer-treatment-related (1) 211:3 capable (2) 128:22;237:15 capacity (4) 54:12,15,18;60:7 CAP-PRI (8) 70:21;71:3;72:10; 73:8,9;96:6,8,13 capture (3) 192:19;260:13;315:10 captured (3) 122:15;231:21;249:13 captures (2) 206:10,12 capturing (3) 192:16;205:20;206:1 car (8) 31:21,22;32:15,17; 33:6;114:4,5;174:14 carcinoma (1) 70:14 care (15) 7:12;9:9;11:1;43:4; 72:20;97:4;147:17; 194:10;234:7;245:15; 256:21;257:11;313:15; 317:7,7 career (2) 92:3;123:19 careful (6) 44:11;97:7;152:16; 168:22;283:4;299:22 carefully (7) 73:1;83:20;158:20,21; 248:7;312:18;313:9 cares (1) 73:8 carnitine (1) 13:12 carpal (1) 76:5 case (15) 6:5;35:12;41:17; 43:12;52:14;54:1;56:12; 113:8,14;131:18;167:4; 200:19;225:20;230:14; 283:20 cases (1) 184:22 casual (2) 87:5;162:1
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<p>catalog (1) 248:15</p> <p>categories (3) 84:8;91:7;134:15</p> <p>category (3) 227:21;248:8;297:7</p> <p>causal (2) 46:15;291:15</p> <p>cause (4) 82:21;302:8;303:5,10</p> <p>caused (1) 72:5</p> <p>causes (4) 75:13;91:22;125:6; 262:8</p> <p>causing (4) 64:17;283:13;301:11, 15</p> <p>caution (1) 298:15</p> <p>cautious (2) 283:6;298:8</p> <p>Cavaletti (11) 34:6,9,10;52:11; 88:16;93:17;95:4; 100:19;101:17;129:15; 214:1</p> <p>caveat (1) 126:1</p> <p>CCOP (2) 12:6;13:8</p> <p>cell (5) 70:14;260:7;282:20; 283:1,8</p> <p>Cella's (4) 13:20;27:19,20;210:3</p> <p>cells (1) 283:22</p> <p>cellular (1) 16:3</p> <p>Center (4) 1:17;41:6;167:19,22</p> <p>centers (5) 10:16;70:22;169:2; 260:19,21</p> <p>central (1) 181:7</p> <p>certain (12) 139:5;141:10;179:11; 231:9;237:1;254:7; 256:3;257:20,20; 282:19;293:12;301:13</p> <p>certainly (21) 75:18;76:2;107:20; 115:14;123:1;124:6; 134:9;143:16;150:10; 171:20;184:7;214:18, 20;218:16;222:15; 233:10;241:15;248:18; 286:2;287:4;306:4</p> <p>cetera (9) 9:15;144:22;147:4,4; 173:14,14;193:11;</p>	<p>217:12;279:18</p> <p>chair (3) 145:7,8;190:1</p> <p>chairing (1) 133:16</p> <p>challenge (13) 45:16;105:17,18; 118:22;124:5;210:20; 241:11;247:17;252:21; 254:9;307:12;312:12; 319:7</p> <p>challenged (1) 26:11</p> <p>challenges (10) 18:13;25:21;26:21; 27:3;92:7;135:19; 147:20;149:9;191:6; 239:4</p> <p>challenging (10) 25:18,19;113:3; 122:20;136:14;149:16; 150:1;269:12;298:21; 319:6</p> <p>champion (1) 235:21</p> <p>chance (7) 46:15;89:13;144:15; 162:13;273:15;288:13, 17</p> <p>change (26) 13:2,3;38:11,20; 47:17;85:16;100:22; 103:4,18;117:4;142:9; 157:11;212:3;229:11; 230:2,3,8;239:5,6,8,9,16, 16;240:20;259:8;280:17</p> <p>changed (2) 4:11;266:14</p> <p>changes (8) 47:15;56:16;123:5; 126:9,10;236:16; 237:10;246:4</p> <p>changing (1) 238:19</p> <p>channeled (1) 68:1</p> <p>characteristic (1) 90:7</p> <p>characteristics (3) 88:4;114:22;298:11</p> <p>characterize (3) 114:9,10,11</p> <p>Charcot-Marie-Tooth (1) 257:8</p> <p>charge (2) 103:17,18</p> <p>Charles (22) 29:20;60:15;78:10; 107:3,12,17;129:22; 130:10,22;144:5;150:5; 158:2;160:17;168:8,16; 170:6;173:18;180:7; 192:2;211:8;226:5;</p>	<p>262:20</p> <p>Charles's (2) 33:1;150:16</p> <p>Charlie (1) 211:1</p> <p>Charlie's (1) 247:4</p> <p>chart (1) 254:20</p> <p>chase (1) 98:17</p> <p>cheaper (1) 173:12</p> <p>check (3) 47:8;121:16;124:10</p> <p>checkboxes (1) 209:2</p> <p>checklist (1) 51:20</p> <p>check-out (1) 3:12</p> <p>chemo (28) 39:18;176:4;180:16; 243:21;244:1;247:9; 252:1;264:19;268:14,17, 17;272:10;273:6,20,20; 276:5,9,12;277:1,3; 281:13;289:7;302:13,14, 17,20;316:14;317:22</p> <p>chemotherapeutic (7) 18:11;252:22;254:5; 264:9,11;282:9;317:5</p> <p>chemotherapies (4) 12:15,16;276:8; 303:19</p> <p>chemotherapy (77) 5:5,7,6;3,8,10,17;18:1, 4;39:11,13,22;40:2; 42:18;44:22;56:21;71:2; 105:5;125:6;129:12; 149:14,15;154:11,12,14, 17,19,20;155:1,9;156:3, 17;173:5,22;174:8; 175:5,20;177:7;180:10; 181:11,19;184:16; 203:10;210:3;243:19; 244:20;246:20;247:1; 249:15;250:5;255:8; 256:2;258:15;261:10; 265:4,5,8;270:22;275:1, 13,22;276:15,17,20; 289:1,11;290:17,22; 292:19;293:7,8;300:17; 301:6,7;302:11;303:1; 312:14;316:5</p> <p>chemotherapy- (3) 70:14;93:12;162:3</p> <p>Chemotherapy-Induced (11) 1:8;5:2,8,12;6:19; 67:11;161:10,19; 191:18;197:8;225:17</p> <p>chemotherapy-received (1) 248:8</p>	<p>chest (1) 64:18</p> <p>chicken-and-an- (1) 122:8</p> <p>child (2) 16:22;46:4</p> <p>chin (1) 297:20</p> <p>China (1) 195:6</p> <p>choice (4) 57:13;119:4;243:6; 297:8</p> <p>choir (1) 149:20</p> <p>choose (2) 247:18;299:20</p> <p>choosing (2) 106:6;118:9</p> <p>Chris (3) 80:21;81:10;235:9</p> <p>chronic (17) 5:21;45:21;46:2,9; 115:10;136:19;138:14, 15;160:7;181:4,11; 182:8;183:15;307:2; 309:7;314:15;316:22</p> <p>chuckle (1) 81:2</p> <p>chutzpah (1) 78:12</p> <p>CIC (1) 175:16</p> <p>CIPN (145) 1:8;5:20;7:17;12:19; 13:4,22;15:8,10,15;16:6, 19;17:4;18:21;19:2,22; 21:10;22:19,22;23:19; 25:4,13;28:10;32:3,12; 34:15;35:4,9,13,15,19; 40:10,21;41:2,12,17; 45:18,19;49:1,18;53:13; 57:11;58:4,11;59:14,16, 16;60:9,11,16;63:9; 64:1;66:4,14;67:16; 68:4;71:1,15;72:4,20; 75:1;80:20;82:5,20; 90:22;93:3,8;99:19; 100:10,20;101:9,10; 102:5,6,16;103:7,18; 104:12;107:21;108:3; 111:10;118:10,11,17; 119:16;123:2,15,15; 124:9;125:8;128:3; 129:5,9,11;130:7,20; 132:10;143:7;151:19; 167:5;169:18;171:18, 18;183:12;185:9;190:9; 191:22;192:21;194:12; 195:2,9,18;196:3,6,16; 197:1,14;201:7,19; 206:1,5,22;207:5; 208:12;209:10,15;210:5,</p>	<p>10;211:7;213:13; 215:17;228:21;229:4; 230:3;240:18;243:8; 263:17;283:20;284:2; 286:15;307:19;312:22; 313:8;314:20,21;318:5</p> <p>CIPN-causing (1) 303:1</p> <p>circle (1) 47:5</p> <p>circumstances (1) 179:14</p> <p>cisplatin (3) 12:16;58:19;60:4</p> <p>cited (2) 4:9;64:9</p> <p>City (1) 1:17</p> <p>clap (1) 189:16</p> <p>clarify (2) 121:20;201:6</p> <p>classes (2) 73:20;284:11</p> <p>classic (2) 53:21;74:1</p> <p>classical (1) 53:6</p> <p>classification (1) 205:6</p> <p>classify (1) 205:11</p> <p>classifying (1) 69:6</p> <p>CLCs (1) 97:12</p> <p>clear (20) 34:16,22;35:9;38:17; 39:12;40:19;44:4;51:22; 53:16;59:10,17,20; 100:14;245:6;261:7; 269:11;274:1;277:19; 281:3;304:15</p> <p>clearances (1) 283:8</p> <p>clear-cut (1) 269:13</p> <p>cleared (1) 38:1</p> <p>clearly (10) 41:3;47:13;58:6;75:2; 80:12;81:2;185:15; 201:1;241:6;258:10</p> <p>Cleary (23) 134:1,1;150:3;153:17; 154:6;218:20;227:8; 259:12,14;260:3;276:7, 18,22;278:2,9,11;279:2, 12;280:5,20;283:11; 288:9;289:18</p> <p>Cleeland's (1) 211:1</p> <p>climb (1)</p>
---	---	---	--	--

<p>230:16 clinic (10) 74:13;78:10;87:16; 96:9;105:4;112:3;139:4; 177:11;227:7;298:20 CLINICAL (89) 1:3;4:22;5:19;8:4,13, 22:9;14;12:7;18:9,18, 19;19:3,11;21:18;23:4,8, 11,12,19;24:1,9,10,20; 25:4;29:2;31:15;37:16; 38:14,15;39:6,15;40:4; 42:5;46:12;48:11;57:7; 60:12,22;63:19;67:3; 70:4;73:1;77:1,16,17; 85:4,20,20;88:3;89:10; 91:19;96:18;97:3;110:7, 18;115:3,15,17,18; 116:9,15,16;123:3; 134:3;143:14;153:1; 169:10;175:14;185:4; 188:14,16;191:14; 212:1;213:18;214:1; 218:9;228:7,11;230:3; 237:2,4;238:19;242:9; 248:2;259:16;262:12; 266:2;286:19;319:13 clinically (11) 67:3;76:2;99:18; 107:7;152:14,21; 177:17;239:13;240:9; 302:4;316:19 clinicaltrials.gov (2) 68:2,5 clinician (3) 63:15;218:9;226:19 clinician-reported (1) 62:22 clinicians (4) 18:2;115:21;158:4; 161:4 clinics (1) 167:20 clinometric (3) 83:20;109:18;114:21 clinometrically (1) 93:16 clinometrics (2) 53:17;86:3 close (6) 24:22;48:4;135:14; 140:19;153:3;221:11 closed (2) 13:12;79:16 closely (1) 3:13 closer (2) 70:7;95:8 clots (1) 146:11 Cmax (2) 245:17,17 CMT (1)</p>	<p>91:4 coast (2) 11:10,13 co-chair (2) 7:6;163:19 cocktail (1) 83:13 coffee (2) 33:3;298:6 Cognitive (1) 15:13 cohort (9) 18:19,20;71:1;78:18; 90:1;128:3;239:22; 280:1;314:9 cohorts (1) 97:5 cold (8) 114:6;181:6;208:1,7, 8,12,18;309:4 cold-induced (3) 208:11,16,16 collaborate (2) 24:6;123:21 collaboration (3) 19:18,21;24:17 collaborative (1) 110:1 collaboratively (1) 94:4 collaborator (1) 24:10 colleague (2) 58:16;103:9 colleagues (8) 67:8;71:20;73:8; 77:20;153:8;185:21; 222:13;240:6 collect (3) 42:4;178:18,19 collected (4) 111:17;129:9;151:18; 177:22 collection (1) 138:22 colon (3) 272:12;283:16;288:13 colorectal (1) 284:7 combination (1) 214:6 combine (3) 185:2;250:15;252:3 combined (3) 6:16;165:14,19 combines (1) 254:11 comfortable (1) 227:3 coming (12) 7:9;48:3;106:14; 139:4;157:6;160:19; 165:4;180:15;211:11,</p>	<p>12;304:5;319:18 comment (22) 33:5,9;78:11;97:6; 119:6;122:21;132:4; 144:5;175:12;182:18; 192:10;197:15;202:11; 205:21;226:6;241:12; 250:17;255:11;272:4; 283:5;290:9;294:5 comments (5) 3:15;141:11;153:16; 162:17;294:22 commercial (1) 234:4 commit (3) 267:4,17;269:21 commitment (2) 157:19;234:1 commitments (1) 238:3 committed (1) 157:17 committee (7) 67:7;138:2,4;142:18; 170:22;171:4;209:18 common (17) 36:1,13,51;19;64:22; 65:2;69:10;91:14;92:7, 10,13,17;99:8;193:1; 200:15;249:20;302:18; 316:7 commonly (5) 12:17;67:15,21;82:2; 84:10 communicate (1) 77:22 communication (3) 24:18;77:19;223:9 communities (2) 96:17,18 Community (15) 7:21;8:20,21;9:17; 10:4,18,19;11:13;94:1; 96:5;107:5;135:6;138:6; 149:21;152:21 community-based (1) 95:7 companies (16) 143:17;148:17; 161:12,16,22;163:7; 165:1;169:12;171:16, 21;182:20;183:17; 184:9,20;191:17;225:2 company (21) 142:3;143:8,11;144:2, 8;145:16,20;146:7,9,12, 21;147:12;149:1;162:2, 8;163:9,15;182:22; 183:6;184:7;229:15 comparable (1) 171:8 comparative (1) 9:6</p>	<p>comparator (1) 170:13 compare (4) 40:20;103:15;256:3; 293:11 compared (2) 195:3;282:14 comparing (3) 119:14;215:6;292:11 comparison (12) 36:18,21;37:7,12; 40:12;41:8,22;48:8; 50:16;56:12;129:16; 293:14 comparisons (2) 91:22;104:11 comparison's (1) 195:20 competing (2) 140:6,8 complaining (1) 233:15 complement (2) 42:7,10 Complementary (4) 16:19;49:2;157:12; 285:14 complete (1) 132:15 completed (5) 56:19;129:11;143:6; 174:3,6 completely (14) 35:15;37:11;38:1,8; 41:15;47:1;51:12;60:1; 147:9;222:3;289:3,4; 308:8;316:14 completion (1) 182:10 complex (9) 34:19;35:6;39:2; 40:15;152:19;247:9; 291:14;292:13;293:1 complexity (3) 55:17;83:8;264:2 complicated (6) 77:8;109:11;252:7; 258:11;265:1;269:1 complicating (1) 152:10 complication (1) 167:6 complications (1) 288:5 compliment (1) 296:5 component (4) 11:15;202:18;295:4; 305:15 components (7) 7:3;8:20;10:20;11:1, 18;230:6;254:3 composed (1)</p>	<p>10:10 composite (16) 6:16;36:21;37:17; 84:15,19;85:7,22;119:3; 214:7,9,12;225:5; 246:19;251:17,21; 268:22 compounds (1) 100:12 comprehensive (2) 14:5;74:8 comprised (1) 8:19 con (1) 30:4 conceivably (1) 288:5 concentration (1) 256:4 concentration-related (1) 257:19 concentrations (2) 255:15,16 concept (7) 142:1,15;144:14,16; 156:14;158:3;247:5 concepts (2) 54:22;242:14 conceptualization (1) 141:18 conceptually (1) 73:12 concern (10) 52:1,2;114:15;128:6; 129:5;148:22;199:15; 273:3,12;282:15 concerned (4) 130:5;218:1;271:22; 317:8 concerns (1) 138:11 concluded (1) 48:19 conclusion (3) 29:8;57:2;296:14 conclusions (3) 28:17;93:1;115:7 concomitant (3) 208:2;303:21;311:5 condition (4) 18:3;43:11;45:19; 124:11 conditions (4) 56:11;192:22;294:8; 308:1 condition-specific (1) 43:16 conduct (5) 10:2;35:1;116:16; 134:10;144:4 conducted (1) 134:21 conducting (1)</p>
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293:9 conduction (12) 38:11;75:16;85:19; 232:13;233:13,16; 238:18;239:1,19;240:6, 8,20 conductions (1) 79:7 cones (2) 76:11,13 confess (1) 26:2 confidence (5) 33:12,22;223:10; 318:19,20 confident (1) 62:9 confirm (1) 47:10 confirmatory (1) 262:21 confirmed (1) 71:11 confirms (1) 220:18 conflate (2) 66:5;93:6 conflating (1) 265:1 conflict (3) 145:9;148:22;173:7 confound (2) 246:14;284:5 confounder (1) 314:20 confounders (1) 264:5 confounding (2) 247:14;248:20 confronting (1) 149:12 confused (2) 41:7;86:6 confusing (2) 51:16;265:15 conjectural (1) 81:14 cons (5) 76:19,20;119:8,9,10 consensus (22) 93:13;100:10;101:8, 10;107:1,15;110:17; 111:1,10;113:16; 186:19;190:2;197:2; 210:7;211:7;217:8; 234:8,9,16;243:12; 270:4;296:22 consent (7) 150:18;153:19; 175:19;176:3,5;177:9; 300:11 consequence (1) 3:22	consider (21) 6:22;33:21;38:5; 51:20;117:19;145:9; 153:12;178:2;190:15; 198:10;222:9;224:21; 231:5,10;233:6;258:14, 17;268:22;275:15; 283:13;314:4 considerable (1) 274:6 consideration (2) 44:11;230:19 Considerations (2) 1:9;273:21 considered (10) 29:6;43:9;49:13; 51:17;58:10;159:20; 199:12;225:5;230:15; 232:11 considering (5) 192:3;233:9;299:4,5; 307:1 consistency (5) 47:8;50:5;111:15; 194:4;232:2 consistent (5) 47:11,16;193:15,17; 194:8 consistently (1) 122:18 consult (1) 152:8 consultant (1) 24:10 consultations (1) 275:7 consulted (1) 171:20 consults (1) 273:1 consuming (1) 77:9 contact (1) 160:20 contaminant (1) 312:5 contaminate (2) 288:6;306:9 contemplating (1) 188:16 content (4) 194:1,2,8;204:6 context (16) 22:18;56:6;106:12; 156:21;199:17;226:4; 227:19;231:8,19;233:4; 235:8;245:19;247:2; 249:14;261:3;293:8 contexts (3) 47:21;49:7;51:1 contextualized (1) 166:13 continually (1)	140:12 continue (4) 94:10;103:22;163:10; 310:17 continued (2) 120:11;250:10 continues (2) 16:12;104:9 continuing (2) 13:14;244:20 continuum (4) 9:1;204:21;205:2,14 contract (3) 147:16,17,18 contrast (1) 103:15 contribute (1) 4:6 contribution (1) 4:19 contributions (1) 81:16 control (10) 7:22;145:8;148:7,8; 172:12;227:2;280:3,6; 281:2,5 controlled (1) 32:2 convenient (1) 150:10 conversation (6) 87:5;125:12;151:4; 237:14;264:22;282:16 conversations (1) 136:2 convinced (4) 85:17;99:15;113:15; 300:21 convincing (1) 240:3 co-occurring (1) 207:7 cookie (1) 152:18 Cool (1) 191:4 cooperative (25) 9:13,15;10:15;134:22; 137:13,21;139:19,19; 140:13;141:3;142:13, 18;144:1,5,10,21;145:2, 6;149:2;164:2;168:19, 21;173:11;183:21; 219:17 coordinator (1) 96:10 coordinators (1) 222:18 co-primary (1) 192:4 corrective (1) 231:14 correctly (2)	286:14;294:6 correlate (2) 41:11;215:7 correlated (2) 20:19;271:20 correlates (4) 119:14;221:18;236:9; 239:17 correlation (8) 20:19;37:4;41:1; 221:4;237:10;239:15; 241:16,16 correlations (1) 236:21 correlative (1) 261:1 cost (1) 218:16 costs (3) 17:9;173:15;178:21 couching (1) 242:12 count (1) 259:4 counter (2) 285:13,14 counterpart (1) 62:1 countless (1) 115:18 countries (1) 55:15 country (6) 11:5;12:1,4;26:17; 32:9;279:14 counts (1) 260:7 county (1) 220:15 couple (20) 3:18;6:1,19;16;27:7; 72:3;75:9;88:7;91:7; 102:4;106:8;108:19; 112:14;113:6;117:13; 140:14;161:21;202:13; 294:17;295:8;319:5 courage (1) 78:13 course (25) 12:5;28:12;32:7; 33:14;35:19;39:19;40:5, 21;42:15;48:2;57:13; 58:18;61:10;73:17;87:9; 156:16;230:4;234:17; 238:1;245:8;248:4,4,18; 274:10;306:8 courtesy (1) 80:21 covariance (1) 290:15 covariate (8) 280:8,9,10,15,18; 290:17;291:6,18	co-varying (1) 291:3 cover (3) 118:19;194:15;213:9 covered (2) 5:22;307:22 covering (1) 243:22 crampiness (1) 181:6 cramping (2) 118:16,19 cramps (2) 58:7,7 cranial (1) 81:19 crap (1) 88:12 CRAs (2) 137:20;140:17 crazy (4) 108:8;119:8;210:5; 303:11 CRC (1) 167:2 create (5) 46:18;53:10;91:21; 291:21;309:1 created (2) 46:21;220:10 creating (2) 49:21;316:2 creatinine (1) 283:7 creation (2) 45:7,14 cringing (2) 85:13;296:6 criteria (28) 69:8;80:4;99:5,14; 107:5,9,11;114:5; 128:17;136:5,9,16; 165:15,17;178:22; 179:19;190:6;199:3; 230:21;236:5,7;252:15; 265:9;289:13;298:5; 299:12;301:19;315:6 critical (7) 47:12;116:9;161:1; 180:11,17;186:18;241:7 critically (2) 109:6;163:5 CRO (3) 116:9;145:16;147:12 cross (1) 106:4 crosses (1) 53:3 cross-reference (1) 103:22 cross-sectional (1) 239:20 Cross-sectionally (1)
---	---	---	--	---

<p>239:17 Crosstalk (1) 316:12 crucial (3) 45:3;48:15;168:3 cryptogenic (1) 123:4 CTC (7) 97:8;107:21,22; 165:15,17;212:22; 245:22 CTCAE (8) 14:2;104:9,12;113:8; 119:7;120:11;125:2; 151:20 CTC-NCI (1) 211:18 CTEP (1) 170:11 CTNS (1) 299:7 CTSU (1) 139:16 cubicles (1) 79:3 cultural (1) 223:9 culture (2) 77:10;109:3 cum (2) 280:3,12 cumulative (15) 155:14;249:6,20; 259:21;260:1;261:12,14, 14,17;279:22;280:7,14; 290:18,21;291:8 curative (1) 275:14 cure (3) 273:10,16,18 current (3) 71:3;95:1;110:9 currently (4) 45:4;48:10;68:4; 192:11 curve (15) 230:17;244:6,9;245:1; 250:1;253:12,14,18; 254:22;257:2,7;262:15; 312:4,10;316:4 curves (4) 40:18;175:10;229:4, 11 customized (1) 279:20 cut (3) 98:17;148:10;308:21 cutoff (14) 213:2;273:16;294:16, 20;295:10,10,16,21; 297:16;298:16,17; 299:13,18;301:14 cutoffs (1)</p>	<p>297:13 cycle (4) 226:8;278:17;316:9; 317:5 cycles (13) 30:17;227:1;277:12; 278:3,4,6,7,8,9,15; 282:2;288:18,19</p> <p style="text-align: center;">D</p> <p>daily (6) 51:21;52:3,6;181:13; 206:2;208:20 daily-life (1) 51:15 damage (2) 16:15;249:14 Dan (1) 85:5 Dana-Farber (3) 134:2,5;162:21 dancing (1) 161:6 danger (1) 127:16 Daniela (6) 110:13;196:13; 285:18;299:3;311:16,16 DASTROS-PITEI (45) 110:15;111:3;175:12; 178:4;196:16;208:8; 209:20;213:18;249:6; 251:16,19;270:17; 271:15;281:22;284:12, 16,22;285:3,11,21; 289:2;299:6,21;300:6, 14;301:18;302:3,15,20; 304:10;305:12;307:16, 20;309:22;310:21; 311:18;312:20;313:6, 14;314:12,15,19;315:3; 318:5,13 data (59) 10:2,3;11:19;22:3; 31:6;35:8;63:7;64:7,12; 65:7;73:22,22;84:21; 86:4,9;91:14,20,21;92:1, 5,6,7,10,13,17;96:8; 103:20;117:9,10; 119:15;127:20,22;128:3, 4;129:9,13;131:3; 138:22;173:13;174:18; 175:8;178:18;182:10; 215:1,18;227:9;237:9; 239:3,10;240:16; 253:19;259:18,19;261:2, 4;270:8;274:10;297:17; 305:5 database (1) 286:6 date (2) 172:11;263:17</p>	<p>David (3) 13:20;27:19;210:2 Dawn (1) 163:20 day (24) 3:4,19;7:9;30:11,12; 32:3;35:16;78:20;79:21, 21;120:14;160:3; 162:11;163:4;177:8; 180:14;181:10;182:6; 226:12;232:4;245:11; 258:21;260:7;298:4 days (9) 136:3;180:11,12; 181:13,18;182:3,5; 246:8;263:21 DC (1) 1:18 deal (8) 80:21;87:20;203:19; 215:11,16;268:15,17; 286:3 dealing (2) 238:21;317:4 deals (2) 191:12;210:19 dean (1) 108:22 Deb (1) 103:9 decades (1) 161:21 decide (9) 34:20;38:3;79:8; 228:17;243:8;253:8,9; 267:6;274:19 decided (9) 43:14;44:11;48:22; 51:11;55:3;57:11,14; 162:3;259:9 deciding (1) 153:10 decision (3) 43:18;238:10,11 decisions (2) 190:5;272:7 decline (1) 239:10 declined (1) 233:16 decrease (2) 236:8;310:15 dedicated (3) 50:13;139:10,11 deemed (1) 265:8 deep (1) 143:10 deficit (1) 236:10 deficits (1) 72:4 define (5)</p>	<p>9:19;199:1;264:10,10; 294:13 defined (5) 67:3,3;69:12,14; 309:18 defines (3) 198:18,21;199:8 definitely (4) 48:18;131:6;190:17; 197:13 definition (1) 302:21 definitive (2) 32:11;296:14 degree (1) 136:1 delay (2) 5:11;233:21 delayed (1) 290:12 delays (1) 245:10 deliverable (1) 109:22 delivered (1) 248:6 delivery (2) 9:10;11:1 delta (1) 228:5 decade (1) 77:16 demonstrated (1) 47:13 demonstrates (1) 164:1 demyelinating (1) 115:11 denouement (1) 124:11 density (3) 236:9;237:5;238:17 dental (1) 16:21 dentist (1) 201:2 denying (1) 73:6 department (1) 87:12 depend (2) 253:16;273:19 dependent (2) 232:16;267:1 depending (8) 118:20;231:16;232:3; 269:4;274:18;298:6; 308:21;317:21 depends (19) 54:17;58:19;177:20; 179:5;184:3,7,8;272:8,9, 10;277:16;295:14; 298:3,10;307:10;</p>	<p>308:16;312:3;314:10; 315:16 depressed (1) 304:20 depression (2) 304:19;311:7 depth (1) 245:9 dermal (1) 76:11 dermatitis (1) 185:15 describe (8) 141:14;199:22; 200:12;202:6,7,8;217:5; 237:14 described (3) 141:4;200:20;236:6 describing (1) 272:20 descriptions (3) 59:21;60:12;141:15 descriptive (2) 157:10;158:15 descriptor (1) 199:21 descriptors (3) 84:7;192:14,15 deserves (1) 61:11 Design (14) 1:9;10:1;39:16,19; 43:15;44:17;63:19; 66:18;188:18;246:9; 247:3;248:21;287:7,8 designed (2) 42:13;170:18 designing (4) 109:9;118:8;226:17; 312:13 designs (1) 148:14 desipramine (1) 305:1 desirability (1) 309:10 desired (1) 237:11 desperation (1) 67:17 despite (1) 246:3 detail (5) 8:4;28:17;80:21;91:6; 216:4 detailed (4) 68:17;112:18;128:18; 161:22 details (5) 29:18;50:16;54:11; 205:22;274:2 detect (4) 47:15;118:6;124:8;</p>
---	---	---	--	--

<p>308:22 detecting (3) 117:16;122:10;308:14 determine (1) 262:14 determined (2) 236:22;256:13 determining (2) 90:13;298:19 develop (11) 4:21;44:12;46:9; 92:10;123:15;138:17; 142:14;145:20;146:14, 22;314:6 developed (13) 42:5,6,9,10;45:9; 70:14,20;114:3;145:4; 163:14;185:6;268:4; 291:14 developing (7) 26:8;47:2;113:20; 137:12,18;138:1;171:17 development (18) 16:3,22;18:22;25:22; 26:1,3,6;47:16;49:14; 69:18;70:20;122:19; 146:16;169:16;171:3; 185:4;234:5;255:20 develops (1) 123:12 deviance (1) 85:10 devices (3) 116:5,8;211:5 devoid (1) 204:6 DFS (1) 271:3 diabetes (19) 63:22;64:1;65:16; 78:7;81:8;82:2;97:21; 185:22;190:21;191:10; 203:11;214:18;221:20; 239:4;241:3;243:4; 295:3,7;297:13 diabetic (18) 29:3;78:18,22;82:19; 85:1;98:22;99:18;100:2; 105:2;112:15,22; 115:13;118:4;120:16; 123:4;184:14;225:4; 233:20 diabetics (1) 112:4 diabetologists (1) 116:3 diagnose (1) 118:3 diagnosed (1) 168:11 diagnosis (1) 78:14 diagnostic (4)</p>	<p>80:13;199:3;224:7; 295:11 diagonal (1) 202:1 dialogue (1) 78:1 dichotomous (1) 252:3 dictate (1) 105:15 differ (1) 283:3 differed (1) 226:15 difference (14) 61:6;118:5;120:22; 121:2;130:2;149:4; 160:18;183:7,8;198:2; 221:20;222:2;237:21; 309:22 differences (5) 118:6;120:16;194:21; 256:6;287:22 different (119) 5:14;9:4;12:14;15:17; 17:4,11;19:14,14;23:20; 35:15,18;37:13;38:3; 40:3;41:14,19,21;43:1; 45:17,17;47:21,22,22; 48:17;49:7,7;50:17; 51:1,12;52:1;53:5,7,10; 55:13,14,17;56:9,11; 58:12;59:19;63:13; 64:20;68:3;70:2,22; 73:20;75:7;77:11;81:18, 21;86:8;89:22;98:16; 102:19;111:13;117:20; 119:22,22;122:7,17,22; 123:20;125:10;126:17; 130:14;134:14;142:6; 144:9;145:22;146:6; 148:19;150:6;166:9; 171:13;185:14;199:22; 216:21;219:9;223:19; 224:12;226:22;227:11; 231:7,11;232:10; 234:12;243:19;247:10; 249:19;253:2,2,3,7; 254:14;255:3,19; 266:15;267:14,15; 268:20;273:21;278:19, 20;282:9,14;283:2,10, 22;284:11;287:20; 288:4,8,10;293:13,20; 304:2;309:5;317:21; 318:15 differentiation (1) 269:7 differently (3) 117:20;165:6;226:16 difficult (23) 18:6;19:12;28:2; 55:21;77:21,22;78:2;</p>	<p>92:2;94:8;120:20;137:7; 142:14;143:13,16; 156:19;162:16;166:21; 168:1;222:20;271:1; 311:19,20,21 difficulties (1) 39:3 difficult-to- (1) 304:5 difficultly (6) 35:22;54:17;58:22; 59:5,6;135:8 dilemma (1) 61:12 dimension (1) 224:13 dimensionality (1) 76:17 diminish (1) 171:11 diminishes (1) 264:8 dinner (1) 79:17 direct (1) 17:8 directed (1) 211:3 directly (2) 34:22;120:4 director (4) 7:12;8:8;15:22;20:11 directors (1) 20:12 disability (3) 53:15;126:5;230:7 disadvantage (2) 53:19;288:11 disadvantages (2) 145:18;216:12 disagree (6) 186:20;223:4;279:16; 294:10;298:16;301:4 disagreeing (1) 121:13 disappeared (1) 109:15 disaster (2) 97:11;166:8 disbelieve (1) 195:1 discomfort (3) 58:1,2,3 discomforts (1) 201:17 disconnect (3) 164:11,16;212:1 discontinuation (2) 6:9;258:15 discontinuations (3) 249:10;258:12;268:18 discontinue (1) 289:7</p>	<p>Discontinuing (2) 288:22;289:11 discourse (1) 162:12 discovered (1) 30:6 discovery (2) 18:22;202:3 discrete (2) 5:17,18 discriminate (1) 60:7 discrimination (1) 41:4 discriminatory (1) 159:20 discuss (2) 134:20;163:2 discussed (7) 34:21;57:1;61:11; 124:1;159:7;184:9; 211:16 discusses (1) 171:21 discussing (2) 131:22;163:4 discussion (30) 35:5;61:3;66:22; 71:19;80:16;83:8;86:1; 92:16;94:13;109:2; 122:16;133:9,18; 136:17;188:8,13;190:2, 8;191:22;224:6;252:8, 19;263:7;269:10;276:3, 6;285:12;294:6,14; 304:15 discussions (1) 14:2 disease (33) 5:1,10,16;26:2;40:8; 45:1;91:1;107:10; 117:16;123:5,11;125:14, 18;127:16;140:11; 157:1,6;160:8;196:9; 208:2;224:2,12;230:2,5; 234:17;272:14;282:18; 283:3;288:14;290:5; 292:16;306:1;313:11 disease-altering (1) 306:16 disease-modifying (2) 231:15;233:12 diseases (3) 191:7;282:21;286:17 disease-treatment (2) 9:3;25:16 disguised (1) 78:20 disorder (1) 125:17 disorders (1) 90:1 disparities (1)</p>	<p>9:10 disparity (1) 31:7 displayed (1) 87:7 disruption (4) 6:8,17;254:5;258:15 disruptions (1) 258:12 dissect (2) 254:2,4 dissection (1) 209:5 distal (4) 74:1;216:9;220:5; 240:22 distinction (2) 199:4;305:4 distinctions (2) 198:13,15 distortion (1) 79:4 distributed (2) 11:20;12:19 distribution (9) 26:16;37:10;83:5; 84:6;87:15;216:7;217:3; 246:3,6 distributive (1) 11:14 divergence (1) 170:11 divergent (1) 84:14 diverse (2) 12:2;192:20 divide (1) 204:11 divided (1) 50:9 Division (6) 7:13;15:1;142:7,7; 165:9;287:4 divisions (2) 142:6,8 dizziness (1) 203:18 dizzy (2) 203:20,21 doable (5) 152:14,21;177:4; 182:15;215:19 doc (1) 228:1 docs (1) 119:18 doctor (4) 102:18;120:6;126:5; 177:11 documenting (1) 310:22 documents (1) 107:15</p>
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<p>doldrums (1) 172:20</p> <p>domain (3) 27:16,18;43:2</p> <p>domains (3) 50:11;84:12;91:8</p> <p>dominated (2) 193:5;223:22</p> <p>Don (1) 148:13</p> <p>donate (1) 160:9</p> <p>done (69) 8:6;13:16;21:19; 30:20;53:7;54:6;61:7; 63:6,22;98:7;105:1; 110:2,8;112:2;124:12; 131:7;143:21;149:22; 151:2;163:18,21;164:2, 3,6,18,21;165:1;169:3,4; 172:12;173:5,8;174:5; 175:11,14,14,15;176:10; 177:15,15;181:21; 182:12,15;188:9,14,20; 189:1,3;194:22;195:2; 213:3,13,20;215:13; 216:20;220:19;223:13; 226:2;230:20;239:9; 256:17,20;259:15;266:3, 11;267:20;285:16; 299:9;307:17</p> <p>door (1) 168:2</p> <p>dorsi (1) 90:4</p> <p>dorsiflexes (1) 230:14</p> <p>dose (66) 6:9;30:13;43:6; 151:13,14,18;155:5,8,9, 13,14;157:11;245:9,10; 247:10,21;249:6,18,20; 250:4,5,6,10,12,12; 251:4,6,14;255:2; 259:11,21;260:1,3; 261:10,12,14,14,15,15, 17,20,20,21;262:3,4,18; 273:8;278:8,16,21; 279:22;280:4,7,9,10,12, 14,16,22;282:8,13; 283:15;284:10;290:18, 21;291:8</p> <p>dose-reduce (2) 260:5,8</p> <p>doses (14) 155:16;181:21; 259:20;261:16,16; 279:18;282:18,20; 293:11,12,15;309:18; 310:8,12</p> <p>dosing (5) 247:8;277:17;281:18; 292:12;293:12</p>	<p>double (2) 41:18;59:7</p> <p>double-blind (1) 32:1</p> <p>double-check (1) 30:3</p> <p>doubles (1) 59:1</p> <p>doubling (3) 52:13;86:18,19</p> <p>doubt (1) 34:17</p> <p>Dougherty (37) 100:5,6;101:6;106:12, 16,20,22;110:4;111:5; 121:7,13;166:15;169:1; 180:7,20;181:15;184:1; 199:18;210:21;227:19; 242:22;264:21;279:16; 280:6;281:11;282:3; 283:19;284:14,19;285:2, 5;296:16,21;297:19; 304:14;305:6,11</p> <p>down (13) 85:20;90:3;100:8; 120:5,12;124:18; 133:14;181:16;222:8; 284:1;286:16;294:4; 310:13</p> <p>downright (1) 200:10</p> <p>downsides (2) 64:5;73:14</p> <p>downstream (1) 236:21</p> <p>dozen (2) 29:2,7</p> <p>DPN (3) 29:5,8;237:22</p> <p>DR (632) 3:3;7:8,11,15;27:6,8,9, 12,13,15;28:3,11,12,14, 15;29:11,13,15;30:2; 31:20;32:18;33:3,5,9; 34:4,5,6,10;52:11;61:15, 18,19,21,22;62:2,6,21; 66:17;67:19;79:15;81:5; 88:16;93:17;94:14,18; 95:4;96:4;97:6,13,15,17, 18;98:6,15;100:5,5,6,19; 101:6,17;102:7,9; 105:11,13,19;106:1,2, 12,15,16,18,20,21,22; 107:2;108:3,5,6,11,12, 15,17;110:4,13,15,21; 111:3,5,8,9;112:9,13; 113:5,6;117:12;119:6; 121:7,10,13,20;122:2,3, 5,21;124:12;125:11,12, 19,20;126:1,15,20,21, 22;127:4,20;128:2; 129:2,4,15;133:1,4,7,13, 19;134:1,4,6,14;132,22;</p>	<p>143:5,15;144:12;146:2, 6;147:20;148:21;149:6; 150:3;151:8;153:5,17; 154:3,6,8;156:5,5,6,7, 20;159:3,5,8,9,13,15; 160:13;161:2,5,6; 163:12;164:10,20; 165:3;166:15;168:4,17; 169:1,3,5;170:5;171:15; 172:4,8,13,15,16;173:4, 18;174:5;175:12; 176:16;177:19;178:4,10, 11;179:4,15;180:7,19, 20,22;181:15,16;182:17, 18;183:9,13,14;184:1,6; 185:5;186:1,7,11,13,14; 188:3;189:18;190:3,13, 20;191:4,5;192:9,10; 193:3,6,7,8,21;194:3,5,9, 16,17,20;195:16,17; 196:5,10,12,13,16; 197:3,11,16;198:16,17; 199:9,18;201:6;202:11, 12;204:9;205:17,19; 206:4,10,12,14,15,16,18; 207:4,8,13,17,20;208:5, 8,15,19,21;209:4,10,11, 12,13,20,22;210:6,21; 211:10,12,13,14,15; 212:14,16,18,19,20; 213:8,18,19;214:1,2,5,8, 10,13,15;215:4,9,21,22; 216:13,14,15,17,19; 217:4,9,14,15;218:19, 20;219:15;220:3,19,21; 221:6,13,15,16,22; 222:3;223:15,18;224:5; 225:11,12,13,15;226:3, 6;227:5,8,16,19;228:16; 229:2,20;231:7;234:6, 12;235:2,8,16;236:4,7, 13;238:13,14;239:3; 241:6,9,12;242:6,17,18, 21;243:15,17,18,22; 244:2,4,5;245:2;246:16; 247:2,16;248:1,11,14; 249:5,6,21;250:17,18; 251:10,16,18,19,21; 252:18;254:17;255:11; 256:7,14,15;257:17; 258:4,10,19;259:12,12, 14,22;260:3,10,12,16; 261:5,7,13,19,22;262:1, 6,19;264:6,13,15,17,21; 265:15;266:21;267:18; 268:7,9;269:9;270:1,17; 271:11,15;272:3,6,17; 273:1;274:7,13,16; 275:3,10;276:7,11,18, 20,22;277:2,5,6,10,11, 16,18,19,22;278:1,2,8,9, 10,11,12,13,19;279:1,2, 6,12,15,16;280:3,5,6,7,9,</p>	<p>11,13,20;281:2,11,22; 282:3,5,6,17;283:11,17, 19;284:12,14,16,19,22; 285:2,3,5,11,13,21,22; 287:15,18;288:9,22; 289:2,5,18;290:7,10,20; 291:1,4,5,12,20;294:2, 12;295:2,19;296:2,4,5,7, 9,15,16,19,21;297:8,9, 11,19,22;298:2,13,15, 22;299:2,6,11,16,18,21; 300:2,4,6,10,14,20; 301:5,7,8,9,18;302:1,2,3, 5,10,12,15,16,20,22; 303:5,7,9;304:4,7,10,12, 14;305:3,6,9,11,12,14, 19;306:20;307:3,10,13, 16,19,20,21;308:2,3,4; 309:2,13,15,22;310:3,7, 9,14,16,18,20,21;311:1, 2,15,18;312:2,15,20; 313:4,6,13,14,16,18; 314:3,10,12,14,15,18,19; 315:1,3,4,16,21;316:8, 10,13,15,16,18,19;317:2, 19;318:5,7,13,15;319:1, 2,4,17,20;320:2</p> <p>dragged (1) 85:20</p> <p>dramatically (1) 139:21</p> <p>draw (2) 115:7;211:6</p> <p>dress (1) 78:19</p> <p>drill (1) 286:16</p> <p>drinking (1) 83:13</p> <p>drive (3) 114:6;167:7;263:22</p> <p>driven (4) 113:1;126:6;170:12; 232:14</p> <p>drives (2) 108:8;119:8</p> <p>drop (2) 59:15;265:6</p> <p>dropouts (3) 40:8;284:10;289:22</p> <p>dropped (2) 289:3,3</p> <p>Drs (1) 242:22</p> <p>Drug (73) 16:20;20:4;25:21; 26:1,3,5,13,16;29:4; 36:15;111:14;118:11; 126:10;130:3;136:8; 142:3,4;143:8,11,16; 144:2,7,8,8;145:20; 146:13,20;147:11; 149:1;162:8;165:1;</p>	<p>166:1,5,8;171:3;183:16; 185:6;211:18;231:17; 244:12,14,15,18;247:6, 13;248:16;249:7;253:2, 22;256:9,11;257:2,18, 21;258:20,22;259:3,7; 262:7,9;263:12;264:8; 265:8;267:2,7;270:22; 271:1;273:19;281:17; 283:10;304:17;305:17; 306:16</p> <p>drugs (33) 26:9;28:9;110:18; 118:7;125:10;126:12; 158:7;165:19;169:16,21, 21;171:17;172:20; 179:9;230:2;245:6; 246:14;253:2,21;256:3; 260:14;282:19;301:6,9, 14;302:6;304:8,8,12; 305:12;307:5,14,22</p> <p>drug's (1) 267:7</p> <p>drug-specific (3) 43:13,17;44:1</p> <p>DSMB (1) 135:13</p> <p>due (5) 40:8;172:1;249:10,11, 15</p> <p>duloxetine (11) 12:22;134:8,21;136:7; 149:7;179:7;266:12; 308:20;309:16;310:5; 311:6</p> <p>dump (2) 237:11,12</p> <p>dumped (1) 110:6</p> <p>duplicates (1) 132:9</p> <p>duration (1) 309:2</p> <p>during (26) 5:5;6:3,10;7:4;14:21; 17:6;36:14;71:1;75:22; 76:15;80:2;97:3;124:10; 149:13,14;175:5;188:4; 190:8;244:9;255:7; 265:11;273:19;276:15, 20;306:8;317:5</p> <p>Dutch (2) 48:6;49:10</p> <p>duties (1) 57:10</p> <p>dwarf (1) 113:2</p> <p>Dworkin (18) 3:15;28:3,12,15; 29:13;31:20;33:3; 125:12,20;143:5; 171:15;173:18;174:13; 183:9;193:8;194:3;</p>
--	---	---	--	---

198:17;202:15 Dyck (2) 78:9;104:18 Dyck's (2) 104:17;128:8 dysesthesia (1) 201:5 dysesthesias (4) 198:8;199:1,5;205:11	88:11 educate (1) 140:13 educating (1) 157:17 education (1) 140:3 effect (27) 33:16;34:2;35:21; 39:8;165:1,21;173:21; 206:1,2,2;239:13;242:8, 9;247:14;253:22;257:1; 262:17,18;270:22; 272:2;274:9;291:6,7; 307:18;308:14,18;316:7 effective (5) 122:18,18;126:12; 281:17;306:15 effectively (1) 228:2 effectiveness (1) 9:6 effects (8) 33:17,22;43:4,8; 118:7;158:6;275:13; 292:15 efficacious (2) 28:9;125:16 efficacy (7) 57:5;75:17;270:12,13; 271:13;274:21,22 efficiency (2) 63:5;148:4 efficient (4) 41:4;51:5;148:5; 169:20 efficiently (3) 50:6,7;51:3 effort (7) 89:2,20;91:15,18; 94:10;124:2;249:1 efforts (2) 171:6,8 egg (1) 122:9 eight (1) 164:7 either (19) 12:11;27:19;67:3; 68:5;69:10;88:20; 103:13;134:15;135:18; 143:19;144:1;146:4; 168:18;171:17;196:8; 209:7;225:4;228:9; 289:18 elaborate (2) 146:2;254:13 elbow (1) 217:1 electronically (1) 178:1 electrophysiologic (3) 67:4;85:9,15	electrophysiology (3) 84:4,11;306:2 elements (5) 91:15;92:8,10,14,18 elicit (1) 126:12 elicitation (1) 217:13 eligibility (7) 136:5,9,15;179:19; 188:17;190:6;300:7 eligible (1) 298:20 eliminate (1) 169:20 eliminated (4) 91:7,7;221:13;274:20 eliminates (1) 84:10 Ellen (18) 6:1;12:22;31:22; 32:11,13,14;60:15; 97:17;104:3;125:11; 129:2;133:15;143:8; 151:22;213:19;219:20; 227:16;300:4 Ellen's (3) 164:8;221:17;276:13 else (16) 22:6;78:12;106:19; 108:9;122:3;160:19; 162:20;178:2;190:11; 270:5;275:4;278:17; 288:21;300:18;306:8; 312:6 email (3) 66:11;67:12;71:2 emailing (1) 73:7 emanated (1) 115:10 embedded (2) 16:1;131:10 embedding (1) 44:7 embrace (1) 75:8 emerged (1) 166:11 emergency (1) 87:12 emollients (2) 157:13,16 emotional (1) 50:10 emphasize (5) 64:13;72:11;127:8; 128:5;218:10 empiric (1) 22:3 employ (2) 80:14;138:5 empty (1)	304:10 EMR-driven (1) 97:1 encapsulate (1) 32:10 end (21) 8:15;15:2;32:16;36:5; 39:18,21;46:8;55:4; 106:6;113:21;160:3; 164:18;187:2;226:11; 228:7;245:11;268:16; 275:16;292:11;300:9; 316:22 endeavor (1) 26:19 ended (2) 174:20;319:3 endless (1) 303:8 endocrinologists (1) 128:21 endocrinology (2) 222:12,13 endorse (2) 101:11;106:17 endorsed (1) 107:6 endpoint (30) 13:19;14:1,3,13; 38:10;40:3,4;44:7; 46:13;64:16;105:16; 111:12;118:9;120:2; 196:4;236:2;237:11; 242:10;247:18;248:13; 250:3;251:4;258:16; 261:9;264:8;265:3; 290:16;312:3,8;316:20 endpoints (17) 13:18;14:14;27:11; 44:19;110:11;111:13; 188:18;190:5;207:16; 231:11;243:1,13;265:2, 14;269:4;290:13;292:13 enemy (1) 108:18 energized (1) 62:9 energy (1) 170:14 engage (1) 78:1 engaged (2) 149:19;176:13 engagement (1) 157:3 engages (1) 283:21 engaging (1) 25:17 engine (2) 9:20,22 engines (1) 10:4	English (1) 179:15 enormous (5) 68:13;82:14;170:14; 317:6;319:11 enormously (1) 319:12 enough (23) 3:13;16:1;32:1;78:15; 79:12;98:4,14;119:20; 144:7;175:7,8,10;180:5; 183:5,20;192:19;222:4; 237:9;264:19;294:4; 301:2;307:18;309:1 enrichment (1) 99:20 enroll (2) 68:6;184:1 enrolled (1) 167:2 enrolling (1) 68:5 enrollment (2) 289:19;290:3 entering (2) 112:4,5 enters (1) 58:13 entertain (1) 112:8 enthusiasm (1) 21:5 entire (2) 68:11;264:22 entirely (1) 217:19 entry (4) 123:2,3;178:22; 259:18 enunciated (1) 258:11 envisage (1) 285:15 envision (1) 3:6 EORTC (8) 27:19;49:8;190:9; 194:1,6,12;207:5;229:4 EORTC-CIPN (1) 13:20 EORTC-QLQ-C30 (1) 49:3 EPIC (2) 97:2,6 epidermis (1) 76:14 equal (1) 57:21 equals (1) 175:9 equivalent (2) 230:4;238:5 erectile (1)
--	--	--	--	---

210:19 erections (1) 106:10 escalated (1) 139:21 escape (1) 202:17 Escher-like (1) 92:12 especially (7) 110:18;156:8;218:21; 233:7;246:15;249:2; 283:12 essence (1) 158:15 essential (2) 28:19;284:17 essentially (2) 246:6;292:10 establish (1) 258:22 established (12) 12:18;58:6;154:10,12, 18;155:1,22;164:6; 213:2;243:20;244:1; 276:15 establishing (1) 25:4 esteemed (1) 185:20 estimates (2) 33:19;34:3 et (10) 9:15;125:22;144:22; 147:4,4;173:14,14; 193:11;217:12;279:18 ethical (2) 309:6,9 ethically (1) 309:20 ethnicity (1) 86:10 Europe (7) 35:13;44:5;78:22; 175:18;176:2;224:17; 300:10 European (1) 53:8 evaluate (12) 5:1,19;6:8;97:21; 207:6;221:3;232:21; 263:11;292:11,15;293:2, 4 evaluated (1) 150:9 evaluating (3) 109:19;129:8;137:1 evaluation (3) 79:22;275:9;292:13 evaluations (1) 41:22 EVANS (4) 33:5,9;241:12;291:20	even (58) 14:6;36:12,17;39:20; 43:2;53:5;71:15;80:8; 83:11;85:13;89:5,5; 90:3;92:1;93:10;96:10; 99:20;104:10;112:3,21; 119:22;127:13;141:20; 143:22;149:16,22; 150:11;159:17;164:7; 165:15,17;174:13; 191:9;192:4;198:4; 204:6;210:15;220:4; 225:2;241:19;242:2,10; 244:19;255:14,17; 264:13;272:11;274:11; 276:13;279:17;281:19; 283:9;292:7;308:4,20; 311:3,11;315:19 evenly (1) 12:19 event (3) 212:15;213:6;253:8 events (5) 46:11,14;248:20; 249:12,12 eventually (2) 49:1;162:13 everybody (16) 3:3;7:8;30:14;106:19; 125:5;145:12;189:8,13; 209:6;259:7;268:1; 269:18,19;293:18; 319:16,17 everybody's (2) 105:8;269:15 everyone (13) 124:4;128:21;133:14; 140:14;158:19;212:10; 234:22;240:7;275:4,6, 20;279:4;281:1 everyone's (3) 84:2;87:7;207:20 everything's (1) 156:16 every-two-week (1) 181:20 everywhere (2) 87:14;91:12 evidence (8) 46:2;48:9;132:16; 193:11;196:17;236:8, 11;302:8 evident (1) 99:18 evolve (1) 73:5 exact (4) 48:16;103:14;277:15; 279:19 exactly (22) 14:9;21:1;37:21;45:9, 10;53:22;60:5;97:16; 126:15,19,21;130:11;	164:11;186:6;194:3; 208:19;212:16;215:4; 281:3,4;284:22;285:2 exam (5) 115:3;217:13;225:3,9; 298:19 examination (18) 41:11;42:3;68:20,21; 69:5;96:22;114:12; 115:8;217:11,17;218:8; 224:7,22;230:3;231:5, 22;238:19;239:18 examinations (2) 104:15;235:11 examines (1) 216:3 examining (2) 24:2;28:16 example (25) 5:22;6:18,21;28:8; 39:9;52:8;84:18;87:2; 90:6;96:6;97:9;107:5; 114:19;168:12,15;171:4, 7;200:3;213:1;226:21; 245:15;247:8;248:17; 282:19;283:7 examples (4) 6:13;75:14;82:1; 292:14 exams (3) 219:1,12;221:3 except (6) 12:22;13:11;91:6; 221:11;239:8;292:3 exception (1) 21:9 exceptionally (1) 96:9 excessive (1) 137:3 excited (5) 20:20;139:12;166:2,4; 219:3 excitement (1) 21:16 exclude (12) 45:12;295:15;300:22; 302:10,17;303:13; 306:20,22;307:5,8; 315:12,19 excluded (3) 304:6;309:16;315:1 excluding (5) 299:12;303:12; 304:16;309:10;315:5 exclusion (4) 289:13;301:19;315:6, 10 exclusions (1) 303:11 executive (2) 67:7;142:18 exercise (1)	19:4 exist (2) 100:18;172:2 existence (1) 87:9 existing (4) 63:20;96:17;215:1; 304:5 exists (2) 305:21;306:19 expand (3) 111:19;285:18;286:16 expanded (2) 82:17;88:5 expect (3) 40:7;85:22;316:6 expectation (1) 292:2 expected (1) 233:7 expedite (1) 24:18 expense (3) 85:3;160:4;218:5 expensive (5) 19:15;26:19;96:1; 105:8;108:21 experience (19) 8:12;66:8,15;67:6; 76:16;82:5;107:4; 134:17;156:9;165:13; 192:16;200:19;203:8, 13;215:17;218:11; 219:16;226:13;230:10 experiment (2) 104:17;116:15 expert (3) 80:8;106:22;218:12 expertise (1) 269:21 experts (2) 78:22;80:11 expired (2) 15:19;16:14 explain (7) 9:18;31:15;54:10; 88:9;93:17;167:5;258:5 explained (1) 158:21 explains (1) 89:4 exploratory (2) 261:4;262:20 explore (1) 164:12 explored (1) 17:12 exposure (4) 107:12;277:17;302:1, 3 expressed (1) 39:3 extension (2)	72:14;220:5 extensively (1) 223:21 extent (7) 56:16;73:16;82:20; 126:7;127:17;253:15; 312:2 extra (3) 153:22;158:18;167:21 extrapolate (1) 130:9 extrapolating (1) 98:13 extremely (3) 25:19;39:5;44:3 extremities (1) 159:6 extremity (1) 217:2 eyes (1) 212:10
F				
fabulous (2) 103:7;121:6				
face (6) 82:18;167:18;168:2; 210:11;223:18;235:3				
faced (2) 35:21;149:9				
facetious (2) 30:14;261:17				
facilitate (3) 145:21;147:8;163:7				
FACT (32) 13:20;14:12;29:1; 50:8,22;51:9;54:16; 57:12;58:1,6,9,20;60:1, 9;65:6;79:18;87:20; 96:9;98:6;101:20; 107:13;113:15;157:5; 196:18;208:10;209:11, 12,17;216:6;229:4; 266:9;279:18				
FACT- (1) 194:22				
FACT-GOG-NTX (1) 209:6				
factor (3) 136:22;148:21;184:21				
factors (4) 135:18,20,22;136:15				
failed (4) 115:17,19,20;263:18				
fair (4) 18:21;293:14;316:10, 18				
fairly (9) 41:3;93:15;209:5; 215:3;232:13;241:16; 273:17;291:14;316:7				
falling (2)				

72:6;198:10 fallout (1) 159:10 falls (1) 20:21 falsely (3) 28:13,22;29:10 familial (2) 82:8;230:10 familiar (9) 78:9;81:6;84:3;85:10; 87:7;190:21;205:22; 206:21;317:16 famous (1) 241:19 fanciful (1) 173:18 fancy (1) 128:7 fantastic (3) 64:7;70:6;287:8 fantastically (1) 62:8 FAP (1) 82:21 far (15) 94:11;110:8;120:15; 158:2;189:10;194:18; 207:21;224:17;239:11; 275:10;296:17,21; 299:15;315:11;317:7 Farrell (1) 286:4 fascinating (1) 66:15 fashion (2) 157:13;239:20 faster (2) 171:2,8 fat (1) 201:1 fatigue (1) 15:11 favorite (1) 203:17 FDA (28) 12:11;22:5;25:12; 29:5;44:17;57:4,7; 107:4,6;121:8,17,22; 183:1,7;212:3;225:3,16, 21;229:14,16;230:21; 231:4;235:22;266:2,8; 286:1,20;287:5 FDA's (1) 270:10 fear (2) 43:5;71:22 feasibility (7) 134:18;136:3;137:9; 162:1,5;218:21;298:21 feasible (5) 162:6;163:8;164:14; 177:17;178:2	feature (2) 197:7,9 features (3) 67:4,4;114:11 federation (1) 11:21 feedback (7) 36:8;42:16;142:9; 234:22;266:22;267:17; 298:22 feel (15) 34:17;42:17;59:18,18; 60:3;74:13;88:21,22; 108:21;172:5;203:12; 208:7,18;227:3;262:5 feeling (6) 36:17;38:6;59:5;62:9, 16;208:1 feels (6) 201:1;224:20;225:8; 230:22;235:12;303:17 feet (7) 57:19,20;60:3;104:6, 7;201:12;315:8 fellows (2) 90:18;221:1 felt (3) 23:18;115:4;200:17 few (14) 13:17;23:4;35:10; 43:20;54:14;65:1;67:7; 83:4;86:5;101:1;111:2, 3;129:15;211:8 fewer (5) 64:15;148:15;164:5; 183:18;233:21 fiber (6) 73:20;159:12;216:17; 236:9;237:5;238:17 fibers (8) 216:3,3;228:5,5,6,8,9, 12 field (5) 4:19;16:6;35:16;80:8; 125:4 FIELDS (1) 61:18 figure (17) 33:20;89:3,6;94:3; 99:1;123:10,11;161:17; 164:16;177:4;198:1; 222:5;251:11;256:8,16, 22;293:17 figured (1) 262:10 figuring (1) 262:7 fill (9) 43:1;75:18;96:13,14; 151:18;177:10;181:10, 13;182:9 filled (4) 50:2;53:1;182:3,4	filling (1) 315:9 final (1) 188:3 finalize (1) 7:4 finally (6) 6:11;36:3,3;123:21; 132:4;254:9 financial (2) 143:12;174:2 find (15) 22:7;35:16;36:1,13; 50:11;72:13;114:15; 120:17,20;138:17; 168:1;176:12;203:9; 297:20;298:1 finding (4) 166:22;226:11,22; 240:7 findings (6) 18:16;19:6;33:1; 68:20;100:15;217:11 finds (1) 217:20 fine (6) 103:20;222:14;250:8; 278:7;300:2,3 finer (2) 180:7;251:5 fingers (3) 200:18;201:10;217:1 finish (5) 34:17;124:18,21; 316:14;319:4 finished (1) 268:14 firing (1) 76:10 first (42) 3:8;4:3;7:20;10:13; 13:22;15:6;30:6,7;48:9; 49:20;57:6;62:13;66:12; 68:13;69:2;78:20;81:9; 88:15;100:7;103:9; 117:13;123:9;135:22; 136:3;141:19;153:14; 155:5,9;156:17;179:4; 203:18;204:1;224:7; 230:8;262:16;265:3; 270:6;273:16;275:11; 286:7;287:21;304:2 first-line (2) 29:6;272:11 fit (3) 68:22;155:21;272:13 fits (2) 236:5;262:16 five (7) 10:15;50:18;69:5; 142:2;166:21;189:2,3 five-year (1) 19:12	fix (1) 126:8 fixed (3) 49:18;253:11;312:8 fixes (1) 126:8 flag (1) 295:7 flashes (1) 102:22 flattered (1) 67:14 flavor (1) 66:3 flawed (1) 83:19 flaws (1) 188:22 flexion (1) 72:14 flights (1) 187:1 flooding (1) 156:4 flow (1) 166:19 fluoroquinolones (2) 301:11,13 flush (1) 113:17 focus (7) 72:3;154:7;188:8,12; 196:16;231:11;246:11 focused (10) 8:10;15:15;63:8; 66:17,17;191:8;193:3; 197:6;239:11;275:7 focusing (1) 178:9 fold (1) 172:6 FOLFIRONOX (1) 277:10 FOLFOX (28) 30:8,17;150:18,20,20; 151:4,5,11,11;154:2; 277:10,12,20;278:4,20; 279:8,13,17;281:19; 282:2,12;284:8,8;288:1, 12,14,20;290:5 folks (9) 10:1;138:4,7;140:1; 158:1;200:12,16; 241:18;285:8 follow (9) 31:20;39:7;40:5;57:6; 76:7;110:5;154:8; 244:12;272:15 following (1) 264:21 follow-up (12) 56:20,21;110:15; 139:5;177:20;199:9;	234:1;237:18;271:2; 274:17;287:18,21 foolish (2) 78:15;88:21 foot (3) 59:15;198:10;233:22 foot's (1) 200:10 Forest (2) 10:16;11:9 forever (5) 81:3;87:3;92:5; 120:14;123:8 forget (3) 42:12;249:4;295:5 fork (1) 217:11 form (5) 96:11;119:20;150:18; 153:19;177:9 formal (2) 42:3;218:3 formally (3) 49:7,13;53:17 former (1) 15:22 forth (10) 21:7;26:11;64:5;72:6; 81:7;86:11;112:20; 124:2;217:13;293:15 forward (11) 68:7;107:8,16,19; 141:10;143:4;174:19; 180:22;274:8,12;287:14 found (15) 17:3,3;22:4,11;61:3; 97:8;140:12;166:20; 218:1;226:13,15; 232:15;238:8;287:3; 310:3 Foundation (5) 70:9,16;145:3;170:18; 174:9 Four (7) 12:14;15:14;50:19; 85:2;123:20;149:20; 166:21 fragile (1) 271:8 frame (2) 224:5;229:20 framed (1) 158:21 frankly (3) 82:20;282:18;293:20 FREEMAN (58) 3:3;113:6;126:21; 127:4;133:4;149:6; 186:14;188:3;189:18; 191:5;194:17;196:13; 197:3;204:9;209:4,12; 210:6;212:18;215:22; 216:14,17;217:4,14;
---	---	--	--	---

<p>224:5;225:12,15; 229:20;235:8;238:14; 241:6;252:18;261:7,19; 262:1;264:6,15;268:7; 269:9;277:19;278:1,10; 290:10;291:1,5;296:9; 297:9;299:2,11;300:2; 302:1;305:14;311:15; 312:2;315:1;317:2; 319:1,4,20 frequency (2) 65:10;93:5 frequent (1) 24:17 frequently (8) 19:17;69:17;77:7; 208:4,22;241:20;254:7,8 Friday (1) 1:12 friendly (4) 167:18;170:19;180:5; 286:11 friends (2) 73:7;79:11 front (2) 202:14;224:9 frontal (1) 70:13 fruit (2) 149:10;215:3 frustrating (1) 169:14 fulfill (2) 31:11;298:5 full (10) 39:9;223:10;245:8; 247:21;248:4,4;250:6, 10;256:2;291:3 full-service (1) 146:19 fully (3) 75:8;89:5;240:5 fun (1) 79:17 function (15) 81:19;100:16;113:1; 114:11;116:20;121:22; 126:6,11;206:2;210:19; 230:16;232:11,22; 233:6;241:1 functional (31) 14:15;27:11,16,18; 44:20;50:10;51:8;52:12; 65:19;68:12;69:16;72:4; 77:4;111:22;112:1,11, 17;117:3;121:9,11,19; 127:7,13,22;128:2,4; 230:7;231:20;233:7; 242:20;243:1 functions (4) 73:21;224:20;225:8; 230:22 fund (1)</p>	<p>234:3 fundamental (1) 284:2 fundamentally (1) 75:7 funded (6) 17:3,5;23:7,13;92:13, 15 funder (1) 105:14 funders (1) 105:19 funder's (1) 105:13 funding (14) 9:4;15:7;20:18;21:4,9, 14,15,21;23:9;26:15,18; 35:11;92:21;105:16 funds (5) 144:7;146:14;160:8,9; 174:10 further (3) 71:21;241:15;242:20 future (4) 119:13;131:2;225:2; 226:2</p>	<p>103:3;154:13;178:18, 20;180:17;279:13 generated (1) 107:4 generic (3) 43:11;58:2;284:11 generosity (1) 69:9 genetic (2) 18:22;43:16 gets (11) 24:13;80:10;123:13, 13;125:5;200:8;201:4; 221:11;256:7;262:10; 280:14 Gewandter (174) 4:4;7:7,8;27:6;34:5; 61:15,19;94:14,18; 97:17;100:5;105:11; 108:15;110:13,21; 111:8;112:9;113:5; 117:12;121:20;122:3; 125:11;126:20;127:20; 129:2;133:1,7,13;146:2; 153:5;154:3;159:3,13; 164:20;183:14;186:1, 13;190:3,13;191:4; 192:9;193:3,7,21;194:5, 16;195:16;196:5,12; 197:11;198:16;202:11; 205:17;206:4,12,15,18; 207:8,17;208:15,21; 209:11;211:12,14; 212:14,19;213:8,19; 214:2,8,13;215:4,21; 218:19;219:15;220:19; 221:6,15,22;227:16; 228:16;234:6;235:2,16; 236:7;238:13;241:9; 242:17,21;243:17,22; 244:4;246:16;247:16; 248:11;249:5;250:17; 251:21;258:4;259:12, 22;260:10;261:5;268:9; 270:1;271:11;272:3,17; 274:13;275:10;276:11, 20;277:2,6,11,18,22; 278:13;279:1,6,15; 280:9,13;281:2;282:5; 283:17;287:15;288:22; 289:5;290:7;294:2,12; 295:19;296:4,7,19; 297:8,11,22;298:13,22; 299:18;300:4,10,20; 301:7;302:2,5;303:9; 304:7;305:3,9;307:3,13, 19,21;308:3;309:13; 310:7,14,18;311:2; 313:13,16;315:4;316:8, 13,16,19;317:19;318:7, 15;319:2,17 GI (8) 134:3;137:17;138:4;</p>	<p>140:16;276:4;283:5,14; 285:15 giant (1) 141:2 Gibbons (2) 80:22;235:9 given (17) 29:7;33:1;68:14;89:9; 178:12;199:20;215:16; 232:4;245:6;247:5; 248:16;256:21;265:4; 267:6,7;279:17;298:4 gives (1) 216:2 giving (9) 18:1,3,10;158:7; 246:10;262:9;267:17; 273:19,20 glossing (1) 118:21 gnawing (1) 200:17 goal (2) 25:6;38:2 goals (8) 3:7,10;4:21;7:18; 13:13;35:11;71:9; 188:11 gobs (1) 166:19 god (1) 117:13 goes (15) 14:1;21:18;38:12; 71:19;73:3;77:9;80:6; 91:10;96:20;107:8; 109:1,7,10;224:18; 275:10 GOG (10) 50:8;51:9;57:12;58:1, 6,9,20;60:1,9;196:18 GOG-NTx (2) 51:1;195:1 gold (2) 37:20;49:13 Good (91) 3:3;7:8;22:5,22;23:11; 35:8;41:3;46:3;47:19, 21;50:21;61:7;62:17; 64:4;65:5;88:21;92:3; 94:15;97:14,15;98:14; 108:18;111:2;112:1,9; 116:5,13;124:18;127:2; 128:13;129:13;133:1,10, 15;135:9;137:22;143:1, 153:4;165:3;176:4; 179:16;183:5;191:2; 196:6;202:15;207:17; 210:18;211:13;215:21; 219:1,2,14;221:4; 223:13;227:10;235:2; 237:10;238:10;241:21; 251:9;257:11;266:5;</p>	<p>272:14,15;273:18; 275:12;278:1;280:5,21; 281:8;283:17;289:8,15; 293:5,7;297:17;298:17, 22;300:18;302:8,21; 303:15,20;305:2;308:6; 309:13,14;310:19; 315:4;319:1,3 Gordon (20) 62:2,5;108:15;115:4; 116:4;117:14;127:20; 202:11;204:15;214:9; 217:4;221:16,19; 234:11;238:14;242:22; 282:5;287:16;296:13; 297:12 Gordon's (2) 205:21;227:18 government (1) 145:6 gradation (1) 200:21 gradations (1) 251:5 grade (11) 38:22;48:14;50:3,20; 54:3;128:12;201:22; 213:1;255:1,1,1 graded (1) 82:16 grades (3) 40:20;41:4;50:18 gradient (1) 216:9 grading (10) 37:1;41:12;82:11,11, 15;87:18;97:9;128:14; 131:4,14 grain (1) 180:8 grants (8) 17:3,7,14,20;18:17,18; 19:20;24:9 granularity (1) 113:10 graph (4) 36:18;37:3;40:15,18 graphically (2) 72:19;274:17 graphs (1) 40:17 grap (1) 274:1 gray (1) 5:15 great (21) 15:2;79:10,17;80:21; 94:21;107:21;117:10; 121:12;123:17;126:6; 148:6;163:2;168:15; 174:14;196:12;215:11, 16;243:4;279:15;284:3; 306:11</p>
--	---	---	---	---

<p>greater (1) 224:8</p> <p>greatly (2) 229:5;233:8</p> <p>green (1) 55:19</p> <p>grid (1) 218:8</p> <p>grooved (1) 68:22</p> <p>ground (1) 60:3</p> <p>group (64) 9:20;24:11;31:9,9; 48:7;49:10;57:7;74:9; 78:17,21;90:6;94:22; 101:11;105:21;106:18, 22;114:12;134:22; 137:13,21;139:19; 140:13,16,16;141:3; 142:13,19;144:1,5,11, 21;145:3,6,17,19; 146:17;149:2;154:22; 168:9,9,19,19,21; 169:10;170:8;172:7,9; 173:12;176:21;179:22; 204:11;209:17;210:3; 211:1;228:11;267:21; 272:21;273:2;274:2; 275:5;286:3,11;310:5,6</p> <p>grouped (1) 68:19</p> <p>groups (19) 9:13,15;10:15;82:12; 139:20;142:16;145:2; 157:4;160:22;164:2; 168:13;169:5;170:6; 173:11;183:21;219:17; 257:13;292:10;310:1</p> <p>grows (1) 165:9</p> <p>growth (2) 76:11,13</p> <p>guess (16) 48:4;94:19;124:4; 143:7;185:5;197:11; 198:12;203:14;235:19; 262:22;271:15,16; 277:19;305:3,13;315:22</p> <p>guidance (2) 44:2;295:2</p> <p>guide (1) 286:22</p> <p>guidelines (1) 163:19</p> <p>guiding (3) 94:3;121:17;157:18</p> <p>Guido (16) 34:9;62:18;71:11; 73:3;83:21;86:2,12; 88:8;89:19;95:1;103:6; 106:5;114:2;209:5; 213:20;219:21</p>	<p>Guido's (7) 63:4;77:6;83:7; 109:10;195:2;227:17; 295:16</p> <p>Guillain-Barre (1) 90:2</p> <p>guy (1) 74:13</p> <p>guys (16) 81:2;89:16;95:2; 102:9;110:21;118:1; 120:20,21;172:1,2; 196:13;213:14;258:13; 289:14;290:14;294:5</p> <p style="text-align: center;">H</p> <p>half (7) 29:2,7;64:14;68:8; 162:9;190:4;242:1</p> <p>halfway (1) 89:12</p> <p>hallmark (1) 208:9</p> <p>hand (5) 7:6;152:17;166:2; 189:22;208:1</p> <p>handle (2) 22:22;23:1</p> <p>hands (14) 52:18;57:19,19;104:6, 7;201:10,10;208:7,18; 212:11;225:19;226:13; 239:18;315:8</p> <p>hanging (1) 149:11</p> <p>haphazard (1) 83:12</p> <p>happen (10) 111:14;145:7;147:9; 188:4;199:12;260:4; 271:4;278:15,18;291:22</p> <p>happened (6) 37:6;41:8;49:10; 130:16;247:12;260:4</p> <p>happens (5) 40:11;215:7;248:17, 18;281:6</p> <p>happy (5) 130:22;150:14; 158:16;176:6;290:19</p> <p>hard (25) 62:15;88:14;105:8; 116:15;128:10,14; 139:12;152:2;155:20, 22;156:12,13;160:13; 184:4;202:5,7;223:2,3; 240:2;252:8;259:17; 267:16;287:9;300:12; 313:4</p> <p>harder (4) 156:10;183:20;202:8; 264:18</p>	<p>hardest (1) 128:10</p> <p>HAROUTOUNIAN (8) 192:10;193:6;208:5; 255:11;256:14;257:17; 306:20;312:15</p> <p>hashing (1) 287:7</p> <p>hat (2) 7:20;8:7</p> <p>hate (2) 87:22;272:6</p> <p>hats (1) 7:20</p> <p>head (3) 7:12;162:10;203:3</p> <p>health (4) 9:9;11:2;16:22;100:21</p> <p>healthcare (1) 47:7</p> <p>healthy (1) 118:3</p> <p>hear (20) 19:16;33:12;44:5; 61:18;113:8;149:17; 153:6;165:4;189:16; 192:6;198:12;207:20, 22;208:3,5;252:18; 254:12,14;283:12; 311:15</p> <p>heard (23) 20:2,3,22;35:10; 71:20;95:4;100:8; 107:20;113:13;121:8; 133:21;138:15;149:9; 162:7;168:5;200:14,14, 16;244:5;246:8;249:2; 295:20;299:7</p> <p>hearing (13) 58:18;59:1,2;149:7; 164:10;189:15;217:4; 243:11;270:7,15;307:3, 9;313:5</p> <p>heart (3) 161:8;236:19;277:14</p> <p>heavy (2) 204:2;265:5</p> <p>heck (1) 229:9</p> <p>help (33) 30:11;31:11,12,14; 63:4;118:16;121:21; 139:9;145:21;146:3,4; 147:19;152:4;161:17; 173:6;174:18;178:13; 179:3;199:10;243:1; 252:10;254:15;256:16; 258:5,9,21;260:15; 262:14;264:3;265:4; 291:3;303:22;319:12</p> <p>helped (4) 15:1;135:20;163:19; 174:21</p>	<p>helpful (7) 95:2;109:21;231:22; 239:2;286:21;289:20; 290:8</p> <p>helps (5) 31:1,3;150:22;151:7,7</p> <p>hematologist (1) 140:9</p> <p>hematology (2) 249:11;271:17</p> <p>heme (1) 283:6</p> <p>heparin (1) 146:10</p> <p>herculean (1) 89:20</p> <p>Here's (3) 62:12;140:17;177:9</p> <p>heroics (1) 141:15</p> <p>herpettic (1) 184:15</p> <p>Hershman (1) 163:20</p> <p>Hertz (15) 6:18;122:2,5;197:16; 199:9;231:7;236:4,13; 264:13,17;266:21; 273:1;275:3;308:2,4</p> <p>Hey (4) 67:9;146:9;175:7; 177:8</p> <p>Hi (1) 141:13</p> <p>hide (1) 43:7</p> <p>high (8) 9:10;22:16;33:14; 45:13;52:13;241:14; 247:15;293:12</p> <p>high- (1) 114:3</p> <p>higher (8) 43:18;54:5;241:14; 242:4;278:16;288:16; 301:15,16</p> <p>higher-risk (1) 272:22</p> <p>high-grade (1) 246:2</p> <p>highlight (2) 8:5;44:15</p> <p>highlighted (2) 10:5;51:13</p> <p>highly (6) 4:9;11:16;64:8;170:8; 172:7;232:16</p> <p>highly-defined (1) 285:20</p> <p>high-risk (1) 287:12</p> <p>historical (2) 104:11;132:6</p>	<p>historically (4) 9:12;82:3;156:18; 212:21</p> <p>history (14) 12:8;21:21;22:21,21; 24:4;35:8;110:7;119:12; 123:12;124:7,13,15; 239:10;274:18</p> <p>hold (1) 102:7</p> <p>home (6) 70:8;103:18;180:10, 18;181:15;189:21</p> <p>honest (1) 217:16</p> <p>honestly (1) 281:7</p> <p>hope (7) 56:22;148:14,16; 240:16,19;315:1;319:21</p> <p>hopeful (1) 94:9</p> <p>hopefully (4) 94:10;178:20;189:21; 308:12</p> <p>hopeless (1) 217:19</p> <p>hoping (3) 4:14;81:1;169:15</p> <p>Horn (1) 5:4</p> <p>hot (4) 34:13,14;60:7;102:22</p> <p>Hotel (1) 79:3</p> <p>hour (3) 133:9;256:12,18</p> <p>hours (2) 190:4;256:19</p> <p>housekeeping (2) 3:9;186:15</p> <p>HSP (2) 165:13,21</p> <p>H-type (1) 233:10</p> <p>huge (10) 39:19;70:1;95:5; 105:17;160:18;167:9; 263:19;308:14;316:22; 318:18</p> <p>human (3) 17:18;18:3,12</p> <p>hundred (2) 135:5;145:11</p> <p>hundreds (1) 152:22</p> <p>hurdle (2) 101:14;213:7</p> <p>hurt (1) 155:15</p> <p>hurts (1) 31:5</p> <p>hydration (2)</p>
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157:19;246:4 hypersensitive (1) 208:8 hypertensive (1) 237:3 hypotension (1) 210:17 hypothesis (1) 115:19 hypothesis-generating (1) 172:21	IMF (1) 157:3 immediate (3) 62:14;193:9;271:16 immediately (3) 39:21;148:10;269:18 immunological (1) 283:22 impact (10) 39:4;54:4,5;247:12; 263:11;265:12;270:21; 273:12;284:18;290:21 impactful (1) 89:6 impacting (3) 52:5;228:7,11 impacts (2) 136:5;281:14 impairment (10) 15:13;38:19,22;39:10; 51:15,18;52:12;56:2,6; 82:3 impairment-specific (1) 73:22 implement (6) 11:2;43:15;115:22; 137:7;149:18;317:17 implemented (4) 19:22;116:10;137:2; 150:2 implementing (3) 48:21;109:21;115:15 implication (3) 34:22;39:19;117:5 implications (2) 70:3;80:12 implies (1) 271:2 imply (2) 46:10;86:14 importance (4) 131:7;160:14;225:21; 248:22 important (72) 3:10;33:17;38:17; 39:5,15,20;44:3;48:13; 51:19,21;56:14;60:4; 61:8;62:10;72:1;73:10, 21;74:4;83:15;87:2; 95:20;101:7;109:6; 113:3;114:13;115:6; 116:20;121:5;137:4,11, 19;138:9;140:2;158:8; 160:22;163:5;165:21; 171:12;173:1;176:1; 178:19;184:21,21; 185:1;203:12;206:9; 207:11,12;224:19,21; 225:1,10,14,19;228:3,6; 235:4;236:21;244:10, 17;247:3;249:9,13,21; 254:2;269:7;278:4; 281:21;286:15;295:14;	300:5;312:16 importantly (3) 75:6;172:16;246:1 impossible (4) 98:10,11;105:7;263:6 impressed (2) 44:16;69:15 impressive (2) 84:22;85:5 improve (4) 111:20;148:4;178:20; 233:5 improved (1) 76:16 improvement (5) 102:14;104:2;127:7, 12;237:1 improves (1) 230:21 improving (1) 241:22 inability (1) 135:19 incentive (1) 167:9 Incidence (4) 318:5,7,11,16 incident (1) 67:2 incidents (1) 317:21 include (23) 6:14;16:9;41:16;42:2; 58:3;76:18;88:4;97:20; 99:3;118:20;136:18; 197:12;206:5,9;210:9; 211:4;228:5,20;234:9; 235:13,21;281:10; 303:18 included (9) 12:14;45:14;58:17; 69:9,16;84:3;128:20; 132:2;234:19 includes (4) 119:3;216:21;220:5; 246:19 including (8) 41:10;64:22;89:21; 94:5;99:17;169:18; 204:10;287:19 Inclusion (2) 93:8;299:11 inclusion/exclusion (1) 252:14 incomprehensible (1) 90:5 inconclusive (1) 119:1 inconsistency (1) 166:7 incorporate (1) 97:9 incorporated (1)	211:21 incorporating (1) 48:20 incorrect (2) 34:2;198:19 increase (1) 310:12 increased (3) 76:1,8,16 incredibly (8) 28:4;113:2;123:5; 158:8;169:6;171:12; 173:1;222:10 IND (2) 273:4;275:6 independent (1) 42:18 indicating (1) 40:19 indication (8) 46:7;110:8;183:1,11; 184:11;185:8,9;285:7 indications (1) 185:7 indirect (1) 17:9 individual (15) 69:10;74:3;104:5; 220:12;249:8;254:3; 255:18,21;256:6;257:4, 5;265:16;266:20;268:2; 273:13 individually (1) 255:7 induced (3) 70:15;93:13;162:4 inducement (2) 160:1,5 inducing (1) 35:20 industry (7) 92:22;148:2;164:13; 170:19;186:3;225:20; 319:14 industry- (1) 143:6 industry-funded (1) 161:9 industry-sponsored (3) 163:11;164:19;186:7 inefficiency (1) 148:6 inefficient (1) 169:7 INFD (3) 239:16;240:21,22 inference (1) 291:16 infinite (2) 184:10,17 inflammation (1) 165:22 inflammatory (2)	91:2;115:11 inflates (1) 60:18 influence (3) 4:16;134:18;160:20 influenced (1) 135:18 influential (1) 4:10 inform (1) 260:15 information (9) 60:6,19;73:19,19; 86:9;95:21;96:3;259:6; 260:1 informative (1) 62:8 informed (1) 172:1 informing (1) 28:4 infrastructure (3) 139:8,9;163:6 infusion (2) 153:14,20 Ingemar (2) 55:5;114:19 inhibitor (2) 165:13;179:8 initial (2) 142:1;151:4 initially (4) 115:14;188:11; 236:16;256:8 initiated (2) 25:11;141:16 initiating (1) 173:22 initiation (1) 316:5 initiatives (1) 171:5 injury (3) 76:3;285:4;301:21 inner (1) 68:1 INNOVATIONS (1) 1:4 input (2) 42:15;138:7 insensitive (1) 165:17 insight (1) 231:4 instance (14) 38:8;41:17;43:19; 45:13;48:14;51:6;52:3; 54:4;57:18;65:12;68:22; 169:9;233:19,20 instances (1) 69:5 instead (7) 57:12;102:6,17;120:5;
---	--	--	---	--

<p>227:21;251:15;293:3 Institute (2) 16:20;162:21 institution (3) 26:22;67:9;143:22 institutions (5) 135:6;147:13,14,16,18 instrument (18) 101:22;102:11; 103:15,19;119:17; 130:21;191:11,16,20; 195:2;201:19;207:14; 209:9;211:2;235:13; 295:5;296:18;298:11 instruments (4) 38:7;41:19;91:22; 197:22 integral (1) 201:20 integrated (2) 11:17;157:12 integrity (1) 293:21 intellectual (1) 127:18 intended (2) 82:13;234:16 intensification (2) 200:7;202:21 intensity (2) 261:21;290:18 intensive (1) 178:5 intent (1) 267:7 interaction (1) 250:9 interacts (1) 263:12 interest (22) 9:10;10:8;16:12; 20:18;21:1,13,17;22:16; 23:2,5;25:14,15;26:8,8; 61:15;70:18,19;145:10; 148:2,22;173:7;210:8 interested (30) 10:11;15:8,8;16:18, 21,21;19:18;20:4,7,8,13, 17;21:2;48:19;117:6; 121:8;122:5;137:6,8; 149:17;161:13;166:11, 12;167:13;171:17; 191:7;207:10;238:22; 311:15;317:9 interesting (25) 15:5;25:1,7;30:5;43:8; 46:13;60:6;71:4;149:6, 8;150:3,17;165:16; 175:18;188:5;202:13; 206:19;221:6;240:2,10; 265:21;283:11;310:18; 311:3;319:20 Interestingly (3)</p>	<p>13:21;16:5;21:10 interests (1) 61:20 interfered (1) 206:22 interference (2) 205:20;206:13 inter-grader (1) 220:20 internal (1) 227:2 internally (1) 97:14 international (1) 175:13 interpret (2) 43:16;70:4 interpretation (2) 33:10;296:11 interpreted (1) 102:17 inter-rater (1) 220:21 inter-related (1) 319:8 interruptions (2) 245:9;249:9 intersection (1) 63:17 interval (7) 33:19;34:3;54:15; 86:11,16;318:19,20 intervals (3) 33:13;180:16,17 intervention (25) 5:6,8;42:17;114:14; 117:3;118:15;127:9; 137:5,6,7;140:7;151:3; 157:9;167:7;179:6,12; 196:9;230:5,12;239:12; 241:5;253:17;263:13, 17;273:14 interventional (1) 96:2 interventions (5) 12:9;19:15;20:6,8; 272:22 into (60) 8:3,9,10;14:4;17:15; 19:8;23:8;25:3;38:14; 39:4;44:11;48:20;50:9; 54:22;68:19,22;73:16; 91:6;97:2;123:2;131:10, 20;132:6,8,13,21;139:4; 147:5;158:8;165:12; 166:5,16;167:20; 170:21;172:19;176:6; 198:9;200:11,13;201:4; 204:11;207:16;232:12; 233:15;237:2,12;238:1; 251:20;258:2,15; 261:11;265:19;286:16; 291:9,11,17;292:1;</p>	<p>293:4;297:6;313:12 intraepidermal (1) 236:9 intravenous (1) 157:20 intrinsic (1) 86:18 introduce (4) 7:11;34:6;62:2;133:15 introduced (2) 157:15;262:2 introductions (1) 133:20 Inventory (1) 192:12 investigating (1) 23:22 investigation (1) 224:15 investigational (1) 32:8 investigator (3) 25:10;63:15;73:13 investigator-initiated (3) 8:8;14:20;164:17 investigators (10) 17:13;18:5;19:17; 20:12;23:8;24:20;25:19, 21;26:10;173:5 investment (2) 170:14;176:15 invitation (2) 7:16;34:11 invited (1) 70:15 inviting (1) 62:11 involved (13) 4:13;7:21;17:14;66:9, 9,10,13;182:20;185:16; 217:22;233:11;267:14; 269:22 investment (1) 218:13 involves (1) 305:16 involving (1) 217:21 iPads (1) 182:12 IRB (3) 96:11;159:16,18 IRBs (3) 146:17;160:11;212:10 ironic (1) 92:11 irrespective (2) 277:20;280:1 irritating (1) 200:6 issue (35) 14:10;15:9;18:7;28:5; 29:8;34:19;35:15,16;</p>	<p>61:2;76:13;77:9,18; 93:5;99:4;100:1;101:5; 122:19,20;123:4; 129:14;134:13;137:5; 138:8;140:1;158:5; 161:7;168:10;169:5; 203:5;311:12;312:11,16, 21;313:21;316:2 issues (24) 8:12;45:5;47:13; 80:14;97:19;140:11; 149:12;163:3;169:11; 192:1;218:1;223:9; 230:4;238:20;245:11; 253:5;254:18;268:15; 269:11;286:12;289:19; 317:14;319:8,9 Italian (1) 114:4 Italy (2) 34:14;48:3 item (2) 54:17;221:13 items (16) 41:9;47:8;49:15;50:1; 53:15;54:17;55:7,7,8,17; 130:9,14;205:20;220:6; 295:8;298:10 iterations (1) 65:3 IV (2) 157:19;245:17</p>	<p>207:19;208:15;242:17; 260:10;262:2;305:22 Joanne (1) 272:5 job (9) 15:2;49:22;61:7;70:6; 103:7;114:7;123:10; 223:13;227:13 joint (4) 58:9,10,11,14 joints (1) 195:4 Jose (1) 171:1 journey (5) 71:6;72:19;75:1,4; 77:2 judgment (2) 203:4;234:20 jump (3) 191:21;253:13;299:3 junctions (1) 76:12 jury-rigged (1) 87:19 justifying (1) 193:19 jut (1) 153:19</p>
K				
<p>Kahler (1) 79:3 KATZ (5) 141:13;156:5;161:6; 164:10;184:6 keen (1) 10:7 keep (16) 46:19;49:4;51:11; 66:1;81:3;84:13;103:21; 111:19;132:17;167:8, 17;176:13;198:17; 258:1;311:5;312:7 keeping (8) 32:16;46:3;99:17; 132:5,8,12,21;141:6 ketamine (2) 103:11;154:18 key (2) 107:22;256:4 kibosh (1) 159:17 kick-off (1) 55:2 kidding (1) 62:21 kidneys (1) 236:20 kids (1) 220:7 killed (1)</p>				

166:8 kind (60) 26:18;28:20;32:6,19; 40:12,18;41:21;44:2; 50:7;51:19;52:22;53:10; 54:7;55:3;60:5;61:22; 68:9;73:10;77:9;82:22; 84:7;89:7;90:7,9;94:3; 95:6,14,15,22;100:21; 112:18;113:16;120:11; 130:13;141:8;144:12; 146:19;153:11;183:22; 190:22;206:2;217:2; 236:11,15;237:7; 246:18;256:5;263:14; 266:22;267:17;270:3; 274:1;286:18;290:17; 294:7;298:17;299:13; 302:9;307:2;319:22	ladies (1) 286:1 lady (1) 200:17 laid (1) 211:8 landmark (1) 157:7 landscape (4) 4:12;7:1;101:13,15 language (6) 36:1,11,13;37:13; 77:11;238:7 languages (1) 49:7 large (11) 89:21;99:6;134:22; 143:11;149:2;168:9; 170:13;186:9;249:1; 295:6;318:4 larger (4) 15:9;95:16;171:9; 174:19 last (24) 16:1;23:13;45:20; 56:4;63:17;66:13;81:10; 91:10;93:20;129:3; 132:14;136:2;139:22; 158:3;162:11;163:4; 185:8;190:8;203:16; 210:7,22;246:8;263:21; 270:2 late (1) 235:14 late-phase (1) 287:8 later (13) 13:18;36:16;50:17; 80:2;112:12;128:18; 129:12;152:7;162:14; 197:10;253:22;261:15; 16 latissimus (1) 90:3 laugh (1) 282:7 laughing (1) 88:13 Laughter (12) 29:14;33:8;52:10; 62:20;67:18;79:14;81:4; 102:8;111:7;127:3; 133:3,6 launching (1) 172:18 LAVOIE (27) 97:18;129:4;133:19; 134:6;141:22;143:15; 148:21;156:5;177:19; 178:10;179:4;182:17; 186:11;207:4;209:10; 220:3;280:3,7;298:15; 301:8;307:10;309:15;	310:3,9,20;313:4;320:2 lay (3) 203:13;297:1,21 L-carnitine (1) 13:4 L-DOPA (2) 125:22;126:8 lead (4) 94:10;248:22;286:7; 297:20 leadership (2) 16:8;21:9 leading (1) 55:5 leads (1) 242:14 leaning (1) 78:11 learn (3) 185:11,18,20 learned (14) 8:16,18;22:1,13;25:8; 36:16;38:6;93:22;94:1; 204:21;220:13;245:16; 287:9;319:21 learning (1) 18:13 least (41) 4:14;7:2;24:17;60:13, 21;63:11;65:8;69:19; 82:5;85:21;115:19; 118:15;121:18;127:17; 184:15;189:10,15,20; 192:4,6;194:7;196:4; 197:7;204:18;208:6; 213:6;219:16;224:13, 16;233:17;234:2; 240:19;252:1;255:22; 263:11;283:1;298:5; 300:15;309:9;317:10; 319:7 leave (7) 61:2,12;62:8;210:22; 252:19;287:2;289:1 leaves (1) 84:12 leaving (1) 187:2 led (1) 286:3 left (7) 41:1;116:4,7;172:5; 235:13,17;286:1 Leg (2) 82:4;240:22 legitimate (1) 317:2 length (1) 66:11 lengthy (1) 162:12 lenient (1) 178:22	less (25) 25:14;74:19;75:5; 78:3;81:14;82:20;88:21; 125:16,19,21;126:18; 133:21;197:9;219:5; 222:15;237:22;262:3; 265:10;275:14;281:20; 282:12,13;284:5;312:6; 315:17 lessons (4) 185:11,19,20;313:22 Leukemia (1) 160:7 level (5) 60:22;86:9;142:11,13; 297:3 levels (1) 278:20 leverage (1) 97:4 lies (1) 225:19 life (12) 9:5;38:16,20;39:4; 42:6;49:3;50:9;52:3,6; 92:2;126:16;207:10 life's (1) 51:21 lifestyle (1) 241:4 lifestyle-based (1) 239:12 light (1) 22:13 likelihood (3) 113:10;224:8;282:8 likely (11) 4:3;52:16;90:13;94:2; 101:1;127:6;141:1; 167:6;282:12,13;285:7 Lilly (4) 142:3,6;143:9;191:15 limbs (3) 52:15,17,20 limit (1) 35:3 limitations (1) 43:17 limited (2) 148:1,1 limiting (1) 312:18 limits (1) 112:22 line (7) 20:22,22;21:8,13; 31:10;53:2;56:4 linear (4) 47:17;54:8,22;55:1 linearity (2) 86:15;87:21 lines (6) 9:16;15:16;41:3;50:2;	53:1;166:15 linked (3) 136:4;137:9;154:2 linking (1) 151:3 lip (1) 201:1 list (19) 12:10;13:6,14;22:11; 28:20;51:17;52:4;55:7; 179:20;211:5;235:17; 243:1;302:22;303:2,7; 304:7,8,12;306:6 listed (1) 91:20 listen (3) 176:21;221:19;247:19 listening (5) 23:7;221:16;263:20; 264:22;269:10 listing (1) 242:19 lists (2) 179:20;199:21 literally (1) 263:17 literature (8) 30:21;39:9;64:13; 196:17;223:22;242:2; 295:3;297:13 little (48) 8:3,16;11:10;14:11, 19;26:21;58:2,4;63:16, 21;64:2,14;67:13;70:7; 77:18;78:6;79:3;85:3; 86:2;91:14;111:18; 113:17;122:8;142:14; 156:20;167:3,21;174:17, 17;196:14;216:4;224:6; 229:22;245:8;252:5,19; 264:18;265:19;271:5; 276:2,6;278:16;284:18; 287:13;290:12;297:18; 313:20;319:3 live (7) 71:17;78:6;96:22; 272:13,14,20;305:20 lived (1) 71:17 liver (1) 288:20 lives (1) 272:14 LLS (1) 160:7 lobby (1) 141:3 localized (2) 270:6;272:8 located (1) 11:7 logical (1) 237:13
L				
lab (1) 123:2 label (4) 136:9;264:12;285:18; 286:16 labels (1) 179:10 labs (1) 300:18 lack (1) 100:16 lacks (1) 87:21 laden (1) 291:15				

<p>long (32) 39:6,17;40:6;47:2; 48:1;49:11;85:4;117:3; 119:12;128:13;141:20; 144:18;170:12;179:19; 19,20,20;185:2;195:7; 205:8;207:15;228:4; 236:5;271:12,22; 279:21;281:11;284:8,8; 294:9;306:5;309:12</p> <p>longer (6) 104:10;172:10; 233:21;236:15;273:18; 281:13</p> <p>longer-term (2) 237:17;274:17</p> <p>longitudinal (9) 8:13;18:19;23:5;97:5; 122:13;124:7;129:10; 166:16;180:9</p> <p>long-term (9) 39:10;76:7;77:4; 117:11;234:1;236:10; 237:4;271:2;274:10</p> <p>look (71) 9:18;12:10;14:15; 19:8;24:7,9;28:19; 29:11;30:20;31:6;34:3, 15;36:18;39:16,17; 40:16;41:5;43:22;57:5; 63:12;74:6,16;78:13; 81:5;89:8;96:12;101:13; 104:2;106:6;107:19; 109:4;112:16;124:2,17; 126:3;127:21;128:1; 167:6;180:7;195:17; 201:19,21;205:5;209:2; 213:1;214:22;215:18; 216:21;232:17;234:22; 248:7;253:10,11,12; 254:18,20,21,21,22; 255:2,6;257:6,9;258:2; 264:11;265:16;266:4; 268:3,16;275:2;296:9</p> <p>looked (15) 13:15;22:1;68:2; 104:1,3;174:21;181:2; 193:22;232:15;238:15, 16;257:5;274:11,14; 299:21</p> <p>looking (34) 4:17;8:13;18:21;23:9; 33:19;38:19,20;39:1,10, 21;40:1;41:14,18;75:1; 104:13;113:9;146:10; 148:19;210:10;215:9; 224:2;232:21;235:10; 239:5;241:1;250:1,2,4; 251:7;262:13;268:2; 271:2;299:7;309:7</p> <p>looks (9) 11:4;12:3;50:15;51:9; 90:8;114:4;140:18;</p>	<p>216:7;308:17</p> <p>loose (1) 11:20</p> <p>LOPRINIZI (1) 102:9</p> <p>LOPRINZI (58) 30:2;102:7;105:19; 106:2,15,18,21;108:3,6, 12;119:6;121:10; 124:12;144:12;146:6; 151:8;154:8;159:8; 161:2;163:12;168:17; 169:3;172:8,15;173:4; 174:5;176:16;179:15; 180:19,22;181:16;194:9, 20;201:6;207:13; 209:13,22;214:5; 221:16;223:15;225:11, 13;229:2;243:15,18; 244:2,5;249:21;251:10; 254:17;256:7,15; 258:19;261:13,22; 262:6;265:15;267:18</p> <p>lose (2) 246:12;263:10</p> <p>loss (10) 44:21;83:6;159:11,12; 204:7,14,17,17;274:21, 22</p> <p>lost (1) 24:13</p> <p>lot (66) 21:22;22:7,13;24:8, 10;25:12;26:7;30:22; 31:7,19;34:21;59:12; 62:15;63:22;65:16; 66:22;77:14;81:13; 82:22;86:16;90:8,16; 94:20;104:3,14;122:6; 123:15;138:7;139:15; 143:3,18;159:13,14; 169:11;178:22;183:18, 20;185:2;186:8;197:22; 199:16;201:13;206:20; 207:22;208:5;223:7; 228:1;231:7;235:18; 239:3;242:2;244:7; 256:21;257:9;268:3; 270:1;275:7;288:3; 290:4;295:17;306:22; 307:21;315:17;316:20; 317:14;319:21</p> <p>lots (4) 105:9;119:21,22; 280:22</p> <p>loud (1) 263:14</p> <p>loudly (1) 282:8</p> <p>love (6) 30:22;31:21;72:9; 83:7;195:2;287:5</p> <p>lovely (1)</p>	<p>63:7</p> <p>low (15) 17:22;48:18,18;49:20; 54:2;65:22;82:21; 149:11;259:4;260:7; 288:15,15;292:17,18; 293:11</p> <p>lower (10) 35:13;52:17,20;56:6; 82:4;148:17;159:6; 217:2;245:17,17</p> <p>low-hanging (2) 149:10;215:3</p> <p>low-molecular (1) 146:10</p> <p>lucky (3) 15:22;54:10;301:2</p> <p>lumpectomy (1) 315:18</p> <p>lumping (2) 288:7,11</p> <p>Lunch (3) 186:16;187:3;245:5</p> <p>Lymphoma (4) 160:7;282:20;283:1,9</p>	<p>163:8;193:12;207:2; 223:8;272:6;277:13; 278:3;298:8;317:18</p> <p>MALE (1) 280:12</p> <p>males (1) 210:20</p> <p>malignancies (5) 134:3;283:7,14; 287:20;288:8</p> <p>malignancy (2) 282:15;285:16</p> <p>manage (4) 10:2;11:19;137:20; 234:18</p> <p>managed (2) 88:13;314:1</p> <p>management (5) 8:1;173:14;185:13,19; 231:14</p> <p>managing (1) 25:9</p> <p>manifested (1) 5:9</p> <p>manner (1) 231:20</p> <p>mantle (3) 282:20;283:1,8</p> <p>manual (1) 130:17</p> <p>manuscript (6) 4:6;6:1,7;7:3;186:21; 319:10</p> <p>manuscripts (4) 4:2,7,10,16</p> <p>many (31) 16:6;18:12,13;22:2; 24:2,14;25:13;70:11; 80:19;93:11;94:7;97:1, 22;112:19;114:19; 126:16;140:6;152:16; 156:1;161:4;185:18; 191:6;210:2;238:21; 267:11,12;293:16; 312:1;316:21;318:20; 319:8</p> <p>map (5) 4:22;12:3;63:2;83:5; 93:11</p> <p>March (4) 1:12;18:9;24:19;25:6</p> <p>market (2) 32:8;234:3</p> <p>marry (3) 251:11,14;255:10</p> <p>marshal (1) 94:9</p> <p>mask (1) 308:8</p> <p>masking (1) 244:16</p> <p>massive (2) 172:19;287:11</p>	<p>mastectomies (2) 314:3;315:20</p> <p>mastectomy (1) 315:13</p> <p>match (1) 176:7</p> <p>material (3) 186:21;241:7,8</p> <p>Matt (5) 196:13;205:17;299:4, 15;311:16</p> <p>matter (7) 106:20;107:13; 202:20;229:10,12; 278:5;295:9</p> <p>matters (3) 225:7;246:6,11</p> <p>max (1) 294:20</p> <p>may (43) 4:1;6:6,6,14;26:21; 33:16;58:3;89:19;98:4; 107:12;115:22;117:2; 126:11;127:6,9,18; 149:3,21;164:18;167:8; 171:22;197:8;198:7; 226:3;228:7;235:13; 241:18;245:16;246:14; 248:7,10;254:1;262:3; 283:2;292:16,18;298:3; 299:8;300:1;304:1; 307:17;312:22;317:16</p> <p>maybe (73) 25:3;26:22;31:2,3; 40:1;51:5;59:12;74:17; 80:10,10;82:20;90:20; 105:2;110:21;111:13; 112:3,8;117:14;119:6; 121:21;129:2;133:21; 138:5;140:10;141:9,11; 144:5,9;152:6;155:19; 161:7;162:13;164:17, 20;166:14,18;178:4,5,6, 9;190:11;191:5;203:14; 221:15;224:5;228:21; 229:20;240:13;242:22; 252:5,12,13;253:4; 256:3;259:22;260:7,20; 272:18;274:16;275:16; 289:16;291:10;292:20; 299:2,7;300:10,12; 305:2;313:20;315:18; 317:6,11,20</p> <p>Mayo (5) 78:10;85:11;104:19; 107:13;145:5</p> <p>McDermott (10) 125:13,19;126:15; 127:1;242:6;250:18; 251:18;290:20;291:4,12</p> <p>MD (1) 148:13</p> <p>mean (80)</p>
---	---	---	---	--

<p>5:6,8,10;29:15;33:15, 15,16;52:3;55:2;60:14; 72:16;74:16;79:10; 105:22;106:19;107:9; 110:10;111:4,10; 121:22;122:1;123:1; 126:1,11,16;141:9; 142:21;143:16;146:3; 159:16;160:2,16;165:4; 166:18;169:13;171:20; 199:16;204:2,3,7,7; 206:10;212:14;214:11, 16;215:2,4,9;218:15; 219:20;221:4;225:16; 226:16;227:4;246:16; 247:7;248:14,21; 262:21;267:19;270:21; 273:8;274:9,14,15; 277:7,8;286:2;298:4,16; 299:19;302:16;303:7, 11;307:19;308:5,16; 309:19;311:12;318:13</p> <p>meaning (7) 61:5;77:1,16;86:18, 21;198:8;268:21</p> <p>meaningful (11) 33:21,21;66:3;72:13; 76:21;126:13;130:2; 183:8;198:15;239:14; 316:19</p> <p>meaningless (1) 37:11</p> <p>means (15) 11:15;40:5;41:10; 47:18;50:19;51:14; 53:21;55:18;74:6;77:21; 80:16;83:18;86:22; 106:17;138:18</p> <p>meant (3) 142:4;194:3;210:16</p> <p>measure (74) 6:8,17;28:14;36:5; 38:4,19;40:22;45:18; 64:15;65:9,11,18;66:21; 67:11;68:9,15;75:17,18; 85:7,20,20;98:10,21; 105:16;121:19;126:2; 138:10;139:3;180:12; 183:12;185:15;191:1,2; 196:7;206:6,8,21; 211:20;212:7,15;214:4, 12,21;215:15;216:8,9; 224:19;225:18,22;228:4, 17,20;229:13;230:15; 231:6;232:11;233:18; 234:8,10,19;235:4; 237:14;243:8,9;246:19; 253:16;271:10;290:17; 292:5;295:22;306:3,4; 307:4,6</p> <p>measured (2) 13:19;212:7</p> <p>measurement (7)</p>	<p>43:11;44:1,7,13; 94:20;136:18;139:7</p> <p>measurements (3) 73:11;129:20;188:18</p> <p>measurement's (1) 118:22</p> <p>measures (63) 14:7;27:16;37:15,16, 22;43:14;44:20;63:1,8; 64:12,21;65:10,13,14, 19;67:1,5;68:12;69:16, 19,20;70:2;72:7,9,17; 74:4;75:6,20;76:22; 78:5;85:15;91:14;93:9, 12;109:19;117:3;118:9; 119:15;123:7;125:17, 22;136:18,19;177:19,22; 183:5,5;190:5,7;192:8; 196:8;208:22;209:2; 213:10,12;230:7,11; 234:15;239:6;242:13; 288:6;306:9;307:7</p> <p>measuring (11) 14:9;19:1;38:1;46:22; 186:2;196:22;197:4,4; 231:18;270:21;313:9</p> <p>mechanism (25) 9:4;45:11;137:22; 139:17,17;144:2,2,9; 148:8,12,16;169:15; 170:4,7,17;171:3,10,12; 172:22;173:7,15; 220:14;258:3;270:9; 273:5</p> <p>mechanisms (10) 15:9,12,17;16:3,13; 22:17;145:14;168:9; 253:3;255:12</p> <p>mechanistic (3) 21:17;23:10;25:1</p> <p>mechanistically (1) 22:15</p> <p>med (1) 221:2</p> <p>medical (2) 134:2;152:3</p> <p>medication (2) 244:22;312:17</p> <p>medications (2) 311:5;314:8</p> <p>Medicine (3) 16:20,22;77:13</p> <p>meet (2) 80:4;167:21</p> <p>meeting (36) 3:7,10,16,20;4:1;7:10; 18:8,10;22:19;24:19; 25:6;55:2;67:7;68:11; 70:10,16;81:11;107:1; 114:18;115:20;116:4; 117:1;118:2;134:16; 141:3;149:13;158:2; 164:14;189:9,19;190:1;</p>	<p>197:18;235:1;269:14; 319:22;320:5</p> <p>meetings (6) 4:11,18;62:7;92:20; 161:20;319:6</p> <p>meets (1) 168:2</p> <p>member (1) 104:19</p> <p>members (5) 145:11;146:18;147:7; 188:15;198:19</p> <p>men (1) 106:10</p> <p>mentally (1) 150:2</p> <p>mentioned (9) 3:15;65:21;71:11; 87:5;172:9;200:2;245:7; 297:12;316:1</p> <p>Merck (1) 143:9</p> <p>merged (1) 135:1</p> <p>merit (2) 100:14;118:8</p> <p>Merkies (1) 55:5</p> <p>mess (1) 90:12</p> <p>message (5) 12:21;44:5;95:21; 116:14;250:19</p> <p>messy (1) 64:13</p> <p>met (1) 13:12</p> <p>meta- (1) 92:1</p> <p>metaphor (1) 99:16</p> <p>metastasizes (1) 288:20</p> <p>metastatic (15) 270:7,10,18;271:7,20; 272:9,11,12,14,16,19; 284:20,21;285:6;302:15</p> <p>meters (5) 38:11;233:16;237:21; 238:18;255:18</p> <p>method (1) 34:15</p> <p>methodological (1) 163:3</p> <p>methodologies (1) 93:18</p> <p>methods (4) 24:3;136:4;138:22; 291:13</p> <p>metric (2) 74:8;228:13</p> <p>metrics (1) 124:8</p>	<p>metronidazole (1) 301:16</p> <p>mic] (2) 61:17;278:13</p> <p>Michael's (1) 79:15</p> <p>Michigan (2) 133:17;295:4</p> <p>microneurology (1) 116:11</p> <p>microphone (1) 3:14</p> <p>middle (3) 105:4;161:8;235:10</p> <p>midst (1) 71:2</p> <p>might (82) 6:22;31:11,14;39:20; 40:3;43:22;44:10;50:21, 21,22;51:16;59:3;64:4; 70:3;71:16;76:8,15; 95:20;99:19;117:14,17, 19;118:11,13,19;132:2; 140:22;147:13;150:21; 151:22;153:13;164:7; 168:15;173:7;178:13; 179:1,3,14;183:10,16, 22;190:14;194:14; 196:10;207:21;211:4; 218:10;219:5;231:5,10, 15;232:11;233:5; 234:16,21;238:4,5; 242:13;243:13;246:12; 252:8,9;255:19,19; 256:16;257:19;258:8; 260:5,15;261:3;262:14; 265:22;274:6;297:17; 298:17;300:10;302:16; 308:5;314:6,7;315:6,10</p> <p>Mike (10) 6:15;125:13;126:4; 127:1;243:11;247:19; 250:17;252:4,11;280:19</p> <p>mild (1) 26:8</p> <p>mildly (1) 103:5</p> <p>Millennium (1) 166:2</p> <p>milligrams (4) 30:11,12;32:2;279:4</p> <p>millimeters (1) 236:19</p> <p>million (1) 17:8</p> <p>mind (15) 49:4;58:11;60:13; 66:1;81:15;84:13;93:22; 132:4;175:2;176:9; 179:5;188:10;245:10; 246:9;258:1</p> <p>mindful (3) 76:21;84:15;85:21</p>	<p>mine (2) 103:9;153:8</p> <p>minefield (1) 242:11</p> <p>minimal (2) 80:4;313:19</p> <p>minimizing (1) 308:11</p> <p>minimum (2) 110:19,20</p> <p>minority (5) 8:21;10:8,10,19;11:11</p> <p>minuses (1) 87:19</p> <p>minutes (5) 35:10;96:14;128:19; 256:12;319:3</p> <p>miss (2) 259:20;279:18</p> <p>missing (3) 96:3;198:4;207:22</p> <p>mistake (1) 54:6</p> <p>mix (6) 49:22;53:14;55:13; 105:14;262:20;286:19</p> <p>mixed (4) 29:19,22,22;30:2</p> <p>mixture (2) 51:8;52:11</p> <p>MMN (1) 91:3</p> <p>MMRF (1) 157:3</p> <p>MNSI (2) 295:4,11</p> <p>mobility (2) 112:18,22</p> <p>modalities (4) 69:11;81:18,22;82:12</p> <p>modality (1) 74:9</p> <p>mode (1) 105:4</p> <p>model (1) 25:2</p> <p>models (3) 17:15;24:14,15</p> <p>moderate (1) 134:7</p> <p>moderately (1) 103:4</p> <p>modest (1) 13:2</p> <p>modification (6) 5:1,10,16;6:18;51:7; 282:13</p> <p>modifications (2) 151:13,15</p> <p>modify (1) 251:3</p> <p>modifying (3) 117:16;224:12;230:6</p>
--	---	--	---	--

<p>mojo (2) 222:15,16</p> <p>molecular (1) 16:2</p> <p>moment (17) 36:10;37:20;46:3; 48:4;82:18;83:10;85:8; 100:20;101:3,5;109:2; 130:12;173:19;201:6; 235:9;286:1;299:6</p> <p>money (5) 22:7;32:1;143:18; 173:16;300:7</p> <p>monitoring (1) 157:18</p> <p>monofilament (2) 69:13;80:7</p> <p>monotherapy (1) 157:8</p> <p>month (8) 135:11;182:9;244:7; 312:8;316:5;317:9,9,9</p> <p>months (17) 39:18;124:20;135:9; 175:6;182:10;244:8,8,8, 12;253:22;268:13; 277:9;312:9;317:22; 318:6,8,11</p> <p>mood (2) 205:21;206:2</p> <p>more (126) 3:10;4:1;8:4,17;9:9; 11:20;14:4,7,7;15:16; 25:11;27:17;29:19,21; 34:17;39:2;41:7;42:2; 46:9;50:20;58:5;59:20; 60:13;64:1;66:16;69:10, 13,16;72:1;73:12;75:21; 81:13;83:11,20;84:10; 85:13;86:2;90:10;108:6; 109:1;111:14;112:7; 113:15,17,19;117:15,17; 120:7,18,18;124:20; 125:15;127:9,13; 131:17;133:21;141:1; 142:14;143:13,16; 144:13;147:14;148:5; 149:16,22;150:10,14; 154:3;156:19;163:17; 170:19;173:8,15;178:8, 22;180:21;184:21; 189:3;194:17,18;196:2, 10;204:6;216:4;220:4; 222:14;225:2;227:3; 235:3;242:10,20;245:9, 22;248:7,10;250:11; 251:7;252:5,19;254:8, 15;257:3;258:2;261:4; 266:18;267:5;270:8; 271:8,8;275:14;276:16; 281:3,10,13,19;282:12, 12;283:6;287:6;290:4; 291:21;308:19;310:4,</p>	<p>12;312:5;319:5</p> <p>morning (11) 3:3;7:8,10;76:4;95:4; 113:14;114:7;176:22; 230:1;245:4;298:7</p> <p>morph (1) 200:11</p> <p>most (51) 4:3;11:12;12:17; 14:12;27:21;35:6;42:8, 9;46:7;47:12;53:13; 64:22;65:2,8;68:10; 69:2;75:6;78:7,9;82:1; 90:8;96:22;100:1;101:1; 103:8;106:2,7;114:12; 121:4;169:20;172:16; 173:8;184:21,22;185:1; 188:4;192:17,18; 213:13;230:12;234:14, 14;241:15,19;242:5; 249:19;255:13;269:1; 279:13;282:6;298:5</p> <p>mostly (3) 27:18;118:16;232:20</p> <p>motor (8) 50:1;59:16;81:18; 115:12;126:8,9,10; 238:18</p> <p>move (19) 14:19;57:2;61:20; 80:9;130:6;141:10; 143:3;204:3;213:5,9; 228:13;229:3;241:10; 242:18;268:7;269:9; 290:13;300:19;319:21</p> <p>moved (4) 14:4,4;15:19;49:12</p> <p>movement (2) 47:15;125:17</p> <p>moves (1) 287:14</p> <p>moving (15) 25:3;27:1;52:7;53:21; 54:3,4;56:15;113:16; 171:8;243:5;252:22; 275:20;312:13;314:22; 317:14</p> <p>MRC (12) 82:17;86:12;87:1,3,6, 18;88:4,5;89:1,2,21; 90:19</p> <p>much (83) 3:9;13:10;23:6;25:9, 14;34:11;38:9,12;39:2; 41:7;43:17;46:20;48:15; 50:3;54:5,5;55:14;56:6; 57:8,17;60:13;69:10; 77:12;80:5;82:5;95:8, 16;104:16;106:9; 111:21;113:19;119:7; 120:3;128:4;137:9; 153:10;155:8,15;159:1; 163:16;170:19,19;171:2,</p>	<p>6,8,9;176:8;178:11; 184:21;185:16;188:7; 194:17;199:14;221:20; 236:8;237:20;239:5,8; 241:14;242:4;243:3; 246:20,22;248:10; 249:14;251:6;254:18; 258:20;259:7,9;263:8; 268:15;284:11;287:9; 298:6;299:7;308:19,21, 22;309:1;311:22; 313:21;320:1</p> <p>mucositis (1) 102:22</p> <p>muddle (1) 88:13</p> <p>multi-modal (1) 73:19</p> <p>multiple (14) 18:10;70:22;134:16; 137:2;144:3;148:9; 161:15;220:15;276:7, 22;277:2;283:12; 292:13;294:3</p> <p>multisite (1) 220:9</p> <p>multi-site (4) 138:12,18;139:2; 143:17</p> <p>muscle (9) 82:11,12,15,16;90:3,6, 11;193:16,18</p> <p>muscles (1) 90:9</p> <p>music (1) 102:10</p> <p>must (1) 47:17</p> <p>myalgia (1) 175:2</p> <p>myeloma (13) 107:3,4,13;156:22; 166:22;168:12;171:4; 282:20;283:8,13; 285:19;286:5,7</p> <p>myself (5) 161:12;162:22;168:5; 219:2;265:22</p> <p>myth (2) 19:16;20:3</p> <p>myths (1) 19:16</p>	<p>84:21</p> <p>National (1) 9:13</p> <p>nationally (1) 11:4</p> <p>Nat's (3) 165:4;171:16;174:3</p> <p>natural (10) 12:8;22:21,21;35:8; 123:12;124:7,13,15; 239:10;274:18</p> <p>naturally (1) 198:14</p> <p>nature (4) 108:13;224:11; 253:16;254:4</p> <p>nausea (1) 6:19</p> <p>NCCTG (1) 145:5</p> <p>NCI (28) 8:10;15:20;16:7,18; 18:2;20:13,17;25:10; 26:2;31:22;32:7,13,19; 92:18;142:20;143:14; 144:22;156:9;163:13; 168:20;169:5,15;170:11, 21;171:9,11;173:13; 174:11</p> <p>NCI-based (1) 139:17</p> <p>NCI-CTC (13) 37:2,9;41:2,17;48:14; 56:12;64:22;132:4,5,8, 13,18;212:3</p> <p>NCI-funded (1) 164:18</p> <p>NCI's (3) 7:17;20:18;21:1</p> <p>NCORP (9) 8:18,19;9:8;12:7; 21:19;24:5;25:11;26:12; 27:10</p> <p>NCTNs (1) 9:12</p> <p>nearly (2) 37:3;160:21</p> <p>necessarily (21) 33:15;46:10;65:5; 66:2;77:3;86:14;99:22; 105:20;114:18;126:3; 161:2;165:8;190:16; 201:18;211:19;262:17; 268:14;271:20;307:7; 308:14;313:1</p> <p>necessary (6) 60:18;99:16;103:5; 110:20;189:10;196:7</p> <p>need (92) 33:6;34:19;35:9;36:6, 7;37:21;38:5,21;39:6,16, 17;41:15;42:2;44:17; 45:2,21;46:1,13,19;47:5,</p>	<p>14,15;52:4;57:5;58:15; 72:22;76:18,21;77:1,22; 83:20;84:14;88:7;93:2, 13,15;95:6,21;96:10; 99:22;121:18;123:11; 127:5;130:19;132:19; 138:12,18;141:8; 149:22;159:21;170:3; 173:3;175:8,19;176:3, 10,12,18,19;177:1,2,16, 17,19,21;179:10;193:15; 213:11;236:8;250:16, 20;254:10;256:1; 258:14,16;263:8;266:5; 270:8,10;271:5;272:1; 287:12;288:20;292:4,5; 299:8;300:17;306:12; 309:10;314:4;318:21; 319:12</p> <p>needed (5) 110:17;140:12;166:7; 175:22;237:18</p> <p>needles (1) 203:1</p> <p>needs (12) 60:16;85:21;128:16, 16;139:3;165:6;226:2; 230:20;245:8;251:7; 313:9,11</p> <p>negative (28) 12:21;22:1,8,12,14; 28:7,13,21,22;29:4,7,9, 10;32:16,20;33:10;85:6, 12;100:15;119:2; 204:12,14,16,17;266:9; 273:12;307:11;308:5</p> <p>negativeness (1) 21:20</p> <p>neither (2) 105:14;198:22</p> <p>nerve (23) 16:15;75:16;76:3,9; 79:6;85:19;158:18; 166:17;193:16,18; 232:12,22;233:13,15; 236:9;237:5;238:17,17; 239:1,19;240:6,7,20</p> <p>nerve-racking (1) 273:9</p> <p>nerves (1) 81:19</p> <p>nervous (1) 273:6</p> <p>net (1) 31:14</p> <p>Network (19) 7:22;8:4,6;9:14;10:22; 11:3,15;12:3;26:12,15, 16;27:22;53:9;95:5,15, 16;134:22;140:14;149:3</p> <p>NETWORKS (6) 1:5;11:22;95:15; 96:18;186:9,9</p>
		N		
		<p>naïve (6) 118:14;169:8;282:6; 302:13,14,20</p> <p>name (2) 34:7;168:21</p> <p>Nat (3) 171:21;172:18;263:16</p> <p>NATHAN (1)</p>		

<p>neuralgia (2) 175:3;184:15</p> <p>neurite (1) 159:10</p> <p>neurobiology (1) 74:5</p> <p>neuroimmune (1) 283:21</p> <p>neuroleptics (1) 309:16</p> <p>neurologic (2) 176:17;231:22</p> <p>neurological (14) 37:8;40:20;41:11; 42:1,3;52:12;56:17; 115:8;217:17;218:3,13; 231:5;235:11;307:15</p> <p>neurologist (23) 66:20;70:13;72:8; 87:4;98:11;118:13; 126:2;134:5;150:11,15; 152:1,6,9;185:21; 198:14;203:18;219:12; 220:17;221:3,9,11; 226:10,22</p> <p>neurologists (23) 35:21;36:11,20,22; 40:13,14;72:9;87:10,11; 99:15;105:1;108:20; 116:2;120:21;177:3; 204:9;217:22,22; 220:12;222:5,11; 226:15;319:14</p> <p>neurologist's (1) 72:18</p> <p>neurology (13) 62:3;66:16;72:11; 109:4;128:7;142:7; 152:7;199:7;218:4,13; 222:14,15,16</p> <p>neurology-based (1) 36:15</p> <p>neuromuscular (5) 87:10,16;89:22;91:1; 203:19</p> <p>NeuroNEXT (1) 67:7</p> <p>neurooncology (3) 147:22;148:11;169:14</p> <p>neuropathic (22) 71:18;75:11;76:8; 99:10;161:14,17;183:15; 17;184:12;192:11,22; 198:3;264:8,10;305:7, 10,13,16,18;307:5; 309:8,11</p> <p>neuropathic- (1) 314:12</p> <p>neuropathic-type (1) 314:16</p> <p>neuropathies (4) 105:3;196:1;211:4; 238:22</p>	<p>Neuropathy (177) 1:8;5:2,9,13;29:4; 30:10;35:17;47:17;51:6; 55:12;65:17;66:5,16; 67:2,11;69:7;70:10,15, 18;71:14;72:9;73:6; 74:6,9,13;75:13,13,20; 78:14,18,22;81:6,13; 82:3,20;83:2;84:2;85:1; 91:2;92:10;93:6,13; 97:22;98:2;99:2,19; 100:2;105:6;112:5,15; 113:2;115:13;118:4; 120:16;123:5,18;125:4, 5,7;131:19,20;132:1; 137:16;150:7,13,22; 153:2;154:11,13,19; 155:1,3,12,13,19,22; 156:3,13;157:5;158:5, 10,22;161:11,19;162:4; 163:22;165:15;173:5; 174:8;177:11;181:4,5, 12;183:11;184:14,16; 191:18;192:13;196:6; 197:8;203:14;210:3; 213:1;222:6;224:9,18; 225:4,17;232:17,18; 233:12;234:17;236:10; 240:9,13;243:19;244:13, 16,19;246:2,20;249:11, 15;250:11;252:2;253:1, 6,9,11;255:1,2,20; 256:17;257:7;259:5; 260:6,15;261:10;262:8; 265:10;268:13,16;273:5, 14;276:10,12;283:13; 285:9,9;289:12;290:16; 292:16,17;293:6;294:8, 9,13;295:5,7,15;299:13; 301:2,11,19,20;302:8; 303:3,6,10,22;304:6,13, 16,17;308:8;312:14; 315:9</p> <p>neuropathy-preventing (1) 306:16</p> <p>neurophysiological (1) 37:17</p> <p>neurophysiology (2) 38:7;117:7</p> <p>neurosciences (2) 17:1,5</p> <p>neurosurgeon (1) 109:17</p> <p>neurotoxic (20) 39:11;154:20;203:10; 245:5;246:14;247:6,13; 263:12;281:17;283:2, 10;284:9;300:21;301:5, 6,8,21;302:11;303:19,20</p> <p>neurotoxicities (2) 50:13;311:9</p> <p>neurotoxicity (11) 46:9;57:12;165:20;</p>	<p>174:22;245:19;255:13, 14;264:1;285:4;301:15; 312:5</p> <p>neurotoxin (2) 246:11;248:6</p> <p>neutrophils (1) 271:18</p> <p>nevertheless (1) 228:15</p> <p>new (14) 4:17;19:1;33:6;44:12; 47:10;48:22;110:18; 172:4,5,6,20;270:9; 275:12;315:6</p> <p>newest (1) 31:2</p> <p>newly (1) 168:11</p> <p>Next (18) 3:17;34:5;79:21; 100:22;133:16;136:17; 138:8,22;156:6;180:15; 181:19;193:9;194:13; 211:12;237:20;241:11; 268:7;269:10</p> <p>nexus (1) 264:19</p> <p>nice (15) 79:16;103:13;106:3; 110:16;119:13;141:15; 144:21;145:18;147:15; 173:12;175:9;227:5; 237:13;261:1;263:7</p> <p>nicely (1) 106:5</p> <p>nicotinamide (1) 19:6</p> <p>night (3) 66:13;83:14;158:3</p> <p>NIH (10) 8:9;15:7;19:11,17; 20:3,7;23:9;25:10; 91:16;92:18</p> <p>NIH-funded (1) 23:3</p> <p>NINDS (3) 91:15;92:9,17</p> <p>NIS (2) 85:14;115:9</p> <p>NIS-LL (4) 83:18;85:7;87:17; 115:9</p> <p>nobody (4) 106:4;233:14;236:17; 241:9</p> <p>noise (9) 253:20;304:10; 308:10,12;309:1; 313:16;314:8;317:6,10</p> <p>nominal (1) 86:10</p> <p>non- (2) 192:14;199:10</p>	<p>None (3) 15:15;163:22;190:19</p> <p>non-glabrous (1) 240:22</p> <p>non-motor (1) 126:7</p> <p>non-NCI-related (1) 145:2</p> <p>non-neurologists (1) 120:22</p> <p>non-neuropathy (1) 80:10</p> <p>non-pain (1) 193:4</p> <p>non-painful (2) 191:12;199:5</p> <p>nonsense (1) 132:15</p> <p>non-specific (1) 210:14</p> <p>non-tumor-bearing (1) 24:16</p> <p>nor (2) 105:14;198:22</p> <p>norepinephrine (1) 179:8</p> <p>normal (7) 85:10;90:7;116:10; 120:17;200:4;240:8,15</p> <p>normalizes (1) 261:9</p> <p>normally (5) 78:19;88:22;151:14; 152:9;177:12</p> <p>North (1) 79:1</p> <p>notch (1) 286:4</p> <p>note (1) 133:1</p> <p>notice (2) 65:1;197:21</p> <p>notion (4) 127:5,15,18;262:2</p> <p>notwithstanding (1) 218:10</p> <p>Novartis (1) 143:9</p> <p>novel (3) 254:10;261:9;264:7</p> <p>nowadays (1) 154:11</p> <p>nowhere (1) 91:13</p> <p>noxious (1) 263:5</p> <p>NPSI (1) 192:12</p> <p>NSAIDs (1) 306:21</p> <p>NTSS-6 (1) 190:20</p> <p>NTx (1)</p>	<p>13:20</p> <p>NTx-12 (2) 208:10,13</p> <p>nuance (1) 296:15</p> <p>numb (1) 204:4</p> <p>number (32) 10:9;12:5;17:11; 18:22;39:12;49:20;61:4; 70:3,10;82:14;83:1; 87:11;89:22;94:3; 100:12;115:17;125:9; 148:10;161:21;171:4; 191:17;194:11;265:7; 269:11;278:3,6,8,9; 279:10;283:14;289:22; 304:19</p> <p>numbers (3) 61:5;139:21;277:13</p> <p>numbness (22) 14:14;57:19;58:3; 104:6;175:4;181:6; 191:13;197:19;199:18; 200:1,3;201:7,8,16,20, 22;203:16;204:1,2,16, 20;220:6</p> <p>nurse (5) 102:17;120:6;131:7; 219:7,8</p> <p>nurses (7) 131:7;137:20;139:11; 140:16;161:3;221:1; 227:11</p> <p>nursing (6) 17:1;157:17;161:5; 168:5,6;176:14</p> <p>nutritional (1) 12:13</p> <hr/> <p style="text-align: center;">O</p> <hr/> <p>objective (10) 44:20;75:20;125:17, 22;231:20;232:10; 233:18;268:12,21;269:4</p> <p>objectives (4) 195:19;268:12,20; 269:3</p> <p>objects (1) 59:5</p> <p>observation (1) 46:12</p> <p>observed (1) 293:15</p> <p>observing (2) 27:17;56:17</p> <p>obstacle (1) 183:10</p> <p>obtrusive (1) 223:12</p> <p>obvious (5) 99:12;231:2;240:9;</p>
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<p>275:4,5 obviously (19) 69:18;87:21;107:10; 118:21;136:3;156:22; 175:16;211:18;225:1; 248:16;252:11;253:14; 270:9;271:2;286:22; 313:2,8;317:7;319:5 occasions (1) 135:15 occur (1) 288:5 occurred (1) 263:20 occurring (1) 248:20 occurs (3) 6:10;254:7,8 off (18) 22:11;61:17;63:5; 64:6;85:14;96:16; 111:18;181:22;229:8; 264:20;266:19;269:18; 272:6;278:13;288:20; 289:3;310:4,10 offer (3) 157:8;159:18;285:19 offered (3) 157:9,10;158:14 offers (1) 97:2 office (5) 58:13;146:16;152:3; 156:4;233:15 official (2) 130:14;131:4 often (18) 5:18;13:19;20:10; 69:11,19;88:3;90:18; 93:9;113:1;197:21; 221:14;240:8,15;275:8; 287:5,13,14;302:7 oftentimes (1) 177:8 old (7) 9:14;13:8;31:21;33:6; 48:6;97:10;104:20 oldest (1) 104:19 O'Mara (14) 7:11,14,15;27:8,12,15; 28:11,14;29:11,15; 32:18;34:4;105:13; 106:1 onc (1) 298:20 once (15) 5:8;27:1;31:18;37:22; 47:19;61:3;131:9; 141:16;182:9;200:13; 220:13;243:8;244:14; 283:22;297:21 oncologic (1)</p>	<p>248:3 oncologist (17) 35:19;36:2;43:5; 66:19;71:13;98:12; 134:2;140:9;150:10,19; 151:14;160:14;162:19; 219:9,13;223:10;227:14 oncologists (26) 36:11,20,22;40:13; 77:8;98:9;99:15;101:17; 123:1;128:6,22;138:3; 149:18,21;154:1;217:5; 218:22;219:19;223:3; 226:5,18;227:12;248:9; 258:9,19;319:13 oncologist's (1) 154:7 oncologists' (3) 37:8;77:12;154:4 Oncology (22) 7:21;36:15;37:4; 77:19;98:7,9;109:4; 142:7;145:6;152:3; 164:22;173:11;175:22; 176:8;212:8;226:8; 240:4,5;259:15,17; 273:2;282:7 one (216) 4:1,5;5:9;11:19;14:1, 22;15:11,13,18;16:14; 18:15;19:16;23:17;24:6; 25:7,20;27:2,19;28:5; 29:21;30:1;33:5,7; 34:13;35:6,7,11,17; 36:11,12;38:4;39:18; 41:13;43:2;44:10,17; 47:12;48:19;54:3;57:21; 58:13,17;60:1;63:13; 64:8;65:1,8,20;66:9,12; 67:1,8;72:3;74:4;75:15, 18;76:6,15,20;77:3,6; 78:15;79:21;80:4,20; 83:4,14;84:19;85:4,21; 88:8;90:14;91:13;92:7, 19;96:21;97:6,18;99:13, 13,19;105:11;106:9,16; 108:19;111:1,21; 112:13;113:18,19; 114:9;115:18;117:22; 119:7;120:20;121:7; 122:14;126:1;127:13, 16;132:5;136:1,22; 142:11;148:4,6;155:4, 14;157:22;164:8;166:2, 17;173:11;174:1;180:8; 182:19;185:8;189:5; 190:16,18;191:6,22; 194:2,12;200:17;201:9; 203:14;204:5;206:19; 208:13;210:7;213:14,16, 19;214:2,21;215:18,19, 22;216:1,4;223:8; 224:11,13;226:18;228:5,</p>	<p>11,22;230:4;231:2,10; 232:2,3;233:2;234:10; 238:20;239:4,12,21; 241:2,12;251:2;253:5; 255:11;256:18;257:3,14, 14;258:8;263:19; 265:21;267:3,10,21; 268:9,22;269:1,17; 270:6;271:7,9;273:3; 275:21,21;276:3,7,9,9, 16,18,20;277:10,15; 279:18;280:5,21; 281:10;286:7;288:3,4, 10;289:9;294:18,19; 296:2;298:5;303:17; 306:4,17;307:6;311:19; 312:8;316:5;317:4,19; 319:5 onerous (1) 167:12 ones (15) 11:10;75:9;111:2; 120:18;128:10;147:21; 162:7;164:4,5;170:2; 182:5;194:13;229:7,9; 308:4 one's (2) 257:1;264:17 one-year (1) 309:7 ongoing (4) 49:17;63:11;91:12; 129:7 only (53) 15:10;18:15;25:13; 54:19;64:16;65:13,14, 14;67:6;68:14;69:4; 70:18;74:18;75:16; 80:12;99:9;106:9; 113:21;114:15;118:9,10, 22;132:5,12;133:8; 135:10;138:16;143:2; 150:21;157:5;166:20; 192:1;193:4,22;197:4,7, 211:17,22;214:14; 217:2;222:19;223:3; 228:7;235:16;240:12; 245:3;248:4;249:4; 262:21;263:3;282:15; 315:18;318:11 open (11) 94:16;135:5,12; 139:16;140:1,4;141:11; 144:2;180:1;199:20; 276:5 opened (1) 138:20 opening (1) 279:6 opens (1) 139:18 operating (2) 23:19,20</p>	<p>operationalization (2) 248:15;251:1 operationalize (1) 248:13 operationalizing (1) 258:11 operator (1) 232:16 opinion (6) 42:19;48:20;100:19; 102:3;207:21;211:14 opinions (1) 296:10 opioids (5) 306:21;309:18;310:1, 4;313:2 opioid-type (1) 244:22 OPPORTUNITIES (2) 1:5;15:7 opportunity (5) 4:5;97:3;124:6;138:5; 176:4 opposed (6) 149:2;152:5;224:2; 244:7;268:2;310:6 opposite (1) 250:20 option (3) 37:16;294:20,20 options (7) 94:21;184:13;209:16; 211:9;252:6;294:17; 297:1 order (7) 23:1;55:18;91:18; 92:18;121:16;272:1; 297:4 ordered (2) 89:17,17 ordering (1) 90:10 ordinal (6) 54:7,15;84:7;86:11, 14;87:21 organizations (2) 92:17;160:10 organized (1) 157:13 organizers (1) 189:11 organizing (1) 189:19 original (2) 84:3;110:5 orthopedic (1) 87:6 Others (15) 12:15;69:1;78:6; 124:1;133:22;178:6; 190:14,14;192:2; 213:16;232:14;238:16; 254:8;258:6;274:2</p>	<p>Otherwise (2) 46:20;145:15 ought (8) 64:3;110:1,2;126:3; 215:19;234:19;266:14; 277:19 Ours (1) 217:1 ourselves (1) 247:7 out (118) 4:10;11:9;13:1,2;14:6, 11;15:20;16:18;18:2,6, 8;22:7,19;27:1;33:16,17, 20,20;54:12;55:22;56:1; 64:9;67:22;69:9;73:2; 79:18;80:10;82:9;83:3, 5,16;86:12;87:13;88:12; 96:13,14;99:1;100:12; 103:4;104:16;106:5,13, 14;111:6;113:17; 114:15;123:10,11; 134:19;141:6;144:18; 146:17;147:6;149:10; 151:16,19;152:18; 155:1;156:2,2;161:17; 163:19;164:15,17; 165:16;167:7;172:5; 173:17;177:4,10;181:10, 13;182:3,4,9;188:6; 198:1;210:21;211:8; 212:10;215:2;218:16; 221:19;222:6;227:21; 228:14;235:14;241:13; 242:1;247:20;251:11; 254:1,3,4;255:7;256:8,8, 16;257:1;261:8;262:7, 10;263:14;265:6;269:2; 280:2;287:7;289:1; 291:16;292:19;293:17; 297:1,14,20,21;308:13, 21;315:9 outcome (56) 14:16;36:5;37:15,22; 38:3,18;39:22;40:22; 43:14;63:1;64:11,15,20; 65:9,9,11;66:3,21;67:1, 5;85:7;91:13;111:11; 121:9,11,14;136:19,20; 137:2;138:10;139:3; 177:10,22;183:5;185:3; 191:2;192:8;193:5; 211:20;212:7;228:6; 231:20;233:7,8;237:7; 246:15;265:12;288:6; 291:18;293:10;295:21; 306:3;307:4,6;314:11,11 outcomes (21) 14:16;44:1;65:7;76:7; 77:4,5;113:7;119:16; 120:9;121:4;125:15,21; 127:13;192:5;194:11; 223:17;281:15;293:6,13,</p>
--	---	---	--	---

16;306:5 outline (3) 3:20;135:17,22 outlines (1) 4:22 outside (3) 169:11;175:13;191:10 over (58) 3:6;4:21;7:6;10:22; 12:5;23:13;25:8;32:9; 33:3;59:18;63:21;64:14, 21;73:5;78:11,18;81:17; 84:1;85:2;89:3;90:20; 93:10;94:11;100:22; 107:11;118:21;124:17; 125:3;132:14;136:2; 144:17;150:15;153:1,3; 163:4;167:3;178:10; 179:16;189:22;227:21; 230:17;236:22;238:19; 246:8;255:16;256:11,12, 18;259:7,10;261:14,17, 19;262:8,17;263:20; 278:10;279:22 overall (6) 50:6;56:7;265:19; 271:3;281:15;308:13 overcome (1) 101:14 overcomplicate (1) 100:1 overestimating (1) 131:6 overlap (4) 21:15;24:3;63:3;209:7 overt (2) 99:11;100:2 overview (2) 7:17;8:2 overwhelming (1) 153:12 own (15) 70:20;91:21;107:12; 116:5,8;123:13;145:16; 147:12;162:10;186:8,9; 209:17;226:13;292:6; 313:2 oxaliplatin (27) 12:16;52:7,17;60:4; 103:13;124:14,19;181:3, 6,20;208:6,9,14;248:18; 255:18;260:6;275:22; 277:8,8;278:20,21; 279:4;284:9;285:3,17; 286:15;309:4 oxaliplatin- (1) 192:13 oxaliplatin-induced (1) 137:15 oxaliplatin-specific (1) 43:20 oxaliplatin-treated (1) 46:6	P packaged (1) 150:17 packaging (1) 282:4 paclitaxel (9) 103:14;124:13,21; 137:15;174:22;181:3; 182:2;240:1;256:18 paclitaxel-induced (2) 174:8;192:13 page (1) 67:22 pain (100) 6:3;14:13,17;46:4; 58:5,9,10,11,14;64:18; 66:2,3,5;71:18;72:6; 75:11;93:6,8;104:6; 118:17;136:20;138:14, 15,17;161:14,17;175:5; 183:9,11,15,17;184:13; 191:8;192:11,22;193:3, 5;195:12;196:1,21,22; 197:4,5,6,7,12;198:2; 199:2,2,22;200:4,7; 201:9,18;202:1,14,19, 19,19;203:5;206:13; 208:16;220:6;228:8,13; 239:16,18;305:10,13,16, 18;306:4;307:2,4,5,6,14; 308:1;309:8,11;311:22; 312:22;313:1,7,8,8,19, 20,22;314:1,2,5,6,11,13, 16,17;315:13,18;316:2 pain-focused (1) 93:10 painful (30) 29:3,5;32:3,12; 137:15;169:7;171:17; 184:13;192:14,15;198:7, 8,9,11,22;199:2,4,11,12, 14;200:5,13;201:1; 203:1,2,9;204:19; 205:14;213:1;232:17 pains (3) 175:1;181:7;305:7 palliative (1) 7:12 Pamela (1) 5:4 pancreatic (10) 276:4;283:15;284:7; 288:2,15,17;289:17,20, 22;290:4 panel (5) 27:5;61:22;94:13; 133:18;149:18 paper (15) 48:6;64:7;72:10; 89:19;90:4;104:13; 177:22;181:14;268:19;	269:8;275:10;289:15; 294:4;312:16;318:2 papers (4) 39:10;64:9,14;77:7 paradigms (1) 23:21 parallel (1) 21:14 parameter (1) 85:9 parameters (1) 256:4 paresthesia (2) 199:11;201:3 paresthesias (11) 191:13;198:6,9,21; 199:5;203:9,12;204:6, 14;205:1,6 Parkinson's (6) 125:14,18;126:5,6; 127:8;230:1 part (40) 29:16;50:12;54:19; 60:22;74:18;93:4; 100:11;109:8;111:1; 114:18;145:9;157:1; 158:22;159:1;160:22; 168:20;190:1;191:18; 192:3;202:21;210:12; 211:19,21;212:6,16; 215:5,6;216:6;225:5; 234:2;236:4,15;238:14; 251:2;257:3;261:5; 263:4;265:16;307:4; 319:15 participants (2) 10:5;135:4 participate (4) 136:11;147:7;158:16; 309:19 participated (1) 78:8 participates (1) 145:12 participating (3) 135:6;189:9;319:16 participation (2) 218:14;269:16 participatory (2) 138:6;269:20 particular (18) 13:5;20:13;21:10; 89:10;98:21;136:10; 143:20;167:4;170:8; 174:20;198:5;231:8; 232:22;235:12;267:8; 268:5,21;273:4 particularly (19) 25:9;76:6;77:3;87:10; 88:20;91:2;92:2,20; 96:19;99:7;167:10; 179:16;197:10;210:18; 222:7;239:1,7;311:19;	312:11 partner (3) 168:8;169:1;219:11 partners (5) 160:8;165:7;166:1,10; 218:4 partners' (1) 286:10 partnership (1) 9:17 partnerships (1) 109:3 parts (4) 245:14;252:22; 312:13;317:14 passion (1) 245:18 past (4) 19:20;36:14;68:8; 224:15 Pat (15) 65:20;76:9;107:2; 109:22;159:7;165:11; 166:14;168:5,10; 195:16;198:16;262:16; 264:2;268:10;286:14 pathogenetically (1) 46:11 pathologic (1) 203:11 pathophysiology (1) 284:2 pathway (1) 171:7 pathways (3) 17:12,16;24:1 patient (83) 6:4;34:20;37:15;38:6, 22;39:3,22;40:22;42:1,7, 14,16,19,22,22;43:4; 44:6;45:2;47:7,9;48:20; 51:14;53:1,2;54:16,18; 55:9;60:2,4;63:13;70:5; 71:9;72:17;74:9;87:13; 89:13;96:11;98:22;99:3; 100:2;101:21;120:4; 131:17,19,21;132:1; 136:13;138:20,21; 141:19;148:1,10;152:3; 157:4;160:4,22;166:19; 168:11;173:2;202:19; 210:2;224:9;225:8; 230:22;237:22;247:5; 249:8,16,18;250:22; 251:22,22;257:22; 263:10;273:2;279:20; 292:19;293:5,5;294:9; 306:7,14;317:8 patient- (2) 36:4;40:21 patient-reported (15) 38:18;43:13;113:7; 119:16;120:9;121:4,14;	125:15,21;136:19; 177:10,21;192:7; 194:11;223:16 patients (165) 8:10,12;15:11;17:16; 21:3;22:4;30:8,16,21; 31:1,3,4,12,13;35:3; 36:3,12,16;38:17;39:7, 11,13,16,17;40:1,6,7,10, 14;42:17;46:6,7;50:2, 18;51:2;52:19,22;55:12, 12;58:13;60:20;61:9,9; 74:10;76:1,3,21;78:17; 85:1;88:2;89:22;90:14; 93:8;97:20,22;98:4,8; 99:18;105:5;112:22; 118:3,3;123:15;126:13; 129:10;131:10,16; 135:11;136:6,11; 137:14;138:16,17; 139:4;147:1;148:15; 150:11,12,14;152:12,12, 22;153:1,7;155:21; 156:11;157:1,4,14; 158:4,16;159:8;160:6, 10,11;163:1;164:22; 166:19;167:1,2,5,10; 168:12,17;173:22; 175:19;176:13;177:7; 178:7,17;180:2,9;181:9; 183:14,18;184:2;186:3, 5;192:18,20;197:9; 199:13,20;200:2;201:14, 20;202:5;203:22; 204:19;207:12,22; 208:6;219:10;229:5,6; 240:1,8;255:17;257:12, 13,14;258:6;268:5; 272:12;279:10;281:12; 283:8,9;287:20;289:20; 290:4;295:6,15;299:12; 304:19;305:17;307:8; 309:11,17;312:7;313:3, 19;314:6;315:2,5,17 patient's (2) 77:2;154:4 patient-to-patient (1) 245:12 Patrick (3) 134:4;217:20;250:12 Pat's (2) 173:1;285:15 Paul (5) 160:16;218:20; 219:11;262:1;283:12 Paul's (1) 283:19 pay (10) 20:22,22;21:8,13; 26:13,13;144:7;159:13, 14,15 pays (2) 144:22;173:13
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<p>peak (5) 255:15;256:4;257:1,18;262:15</p> <p>peculiar (1) 40:10</p> <p>pediatric (1) 220:9</p> <p>peer (5) 20:20;21:5,16;23:7,9</p> <p>pegboard (2) 65:20;68:22</p> <p>peninsula (1) 227:22</p> <p>Pennsylvania (1) 11:7</p> <p>people (103) 3:13;28:6;31:1,7,8;66:15;67:20;69:7;78:15;85:11;86:5;92:3,21;95:3,13;99:10;102:4,19;105:15,21,22;106:3;108:3;112:5;120:17;124:9;131:11;132:18;137:6,8;139:14;140:6;141:6;150:7;154:18,22;159:3,21,22;162:17;173:8;175:1;179:11;182:12;183:15;187:1;188:5;192:7;194:20;195:13;198:12;202:22;203:21;205:6,9;208:3;213:15,16,21;218:11;221:1;240:3,11,13;241:15;242:5;247:20;250:5,11;256:10;257:9;259:19;262:5;266:13;268:4;272:18,19,22;276:9,12;277:11;278:16;279:13,17;281:19;289:6;292:9;294:13;295:13;301:1,1,12;303:18,22;304:16;306:22;310:4;315:7,12;316:21,21;318:9,20</p> <p>people's (1) 137:10</p> <p>per (12) 38:11;42:9;135:11;174:16;233:16;237:22;238:18;249:15;250:12;255:17;262:18;264:9</p> <p>perceived (1) 77:7</p> <p>perceives (1) 164:13</p> <p>percent (26) 10:10;50:20;52:19;65:12,19;138:16;144:16,20;162:13;163:12;201:22;202:2;203:22;240:14;252:1;259:1,3,11;295:13;301:12;303:13;307:1;310:13;</p>	<p>314:6;318:8,11</p> <p>percentage (7) 17:22;40:1;245:7;248:4;249:17;295:6,6</p> <p>percentile (1) 84:5</p> <p>percent-ish (1) 182:11</p> <p>perception (2) 41:9;156:22</p> <p>perceptions (1) 77:12</p> <p>perfect (18) 20:19;37:4;48:5;60:15;61:3;102:12,13;108:17;114:4,21;119:10;19:124:5;125:10;189:3;190:3;195:12;267:2</p> <p>perfection (1) 48:3</p> <p>perfectly (1) 223:11</p> <p>perform (3) 38:2;42:5;131:11</p> <p>performance (6) 73:4;77:17;114:4;215:1,10,19</p> <p>performing (2) 48:11;96:1</p> <p>perhaps (23) 66:4;75:21;77:19;78:2;110:19;114:1;122:22;127:14;128:11;134:14;135:10,17;148:22;149:3;176:10;178:12;187:2;224:16;225:6;270:18;275:4;285:1;306:5</p> <p>period (10) 14:21;17:6;40:6;47:4;75:22;96:15;211:21;227:1;281:13;310:11</p> <p>periods (1) 185:2</p> <p>Peripheral (28) 1:8;5:2,9,12;16:15;29:3;35:17;51:6;70:9,15;76:3;115:13;131:18,20;161:10,19;162:4;183:10;191:18;197:8;224:18;225:4,17;292:15,17;293:6;301:11;315:9</p> <p>permissive (1) 69:6</p> <p>persistent (3) 301:22;314:5,16</p> <p>persistently (1) 40:2</p> <p>person (11) 55:5;88:17;139:14;150:19;190:21;203:19;220:18,22;222:6;258:21;286:21</p>	<p>personal (5) 100:19;191:11;203:5,8,13</p> <p>personally (1) 172:3</p> <p>persons (1) 101:18</p> <p>person's (1) 260:7</p> <p>perspective (19) 7:17;63:14,14;70:6,17;72:17,18;73:13;99:11,21;104:11;105:13;110:7;122:22;175:13;203:5;223:14;270:11;309:6</p> <p>perspectives (2) 15:5;63:13</p> <p>peruse (1) 71:8</p> <p>Peter (5) 78:9;80:1;104:17,18;128:8</p> <p>Pfizer (1) 143:9</p> <p>PFS (1) 271:3</p> <p>pharma (10) 19:21;25:14,15,17,17;165:7;166:10,11;191:17;286:10</p> <p>pharmaceutical (11) 19:19;145:15;163:7,9;171:16;182:20,22;183:6;184:9,20;225:20</p> <p>pharmacies (1) 32:9</p> <p>pharmacodynamic (1) 158:6</p> <p>pharmacokinetic (2) 262:4,6</p> <p>pharmacokinetics (2) 255:22;262:14</p> <p>pharmacological (2) 12:9;161:14</p> <p>pharma's (1) 26:7</p> <p>phase (23) 26:20,21;27:2;32:11;49:16,20;56:10;76:8,15;170:1,13;171:6;172:19;174:4;249:1;262:10,11;263:1,4;268:8;269:10;287:11;306:2</p> <p>phenomenon (1) 68:7</p> <p>phenotypes (2) 126:7,8</p> <p>Philadelphia (1) 11:8</p> <p>phones (1) 182:13</p> <p>photon (2)</p>	<p>19:5;20:5</p> <p>physical (5) 50:10;217:10,13;218:7;221:2</p> <p>physician (2) 87:4;222:16</p> <p>physicians (2) 137:19;161:3</p> <p>PI (1) 140:21</p> <p>piano (1) 52:1</p> <p>pick (7) 29:20;122:7;195:9;200:1;266:19;277:10;278:21</p> <p>picked (6) 66:20;135:10;195:10,11;200:16</p> <p>picture (3) 74:1;88:6;265:19</p> <p>piece (6) 161:5;181:14;186:18;249:4;265:19;287:3</p> <p>pieces (2) 231:8;293:4</p> <p>pilot (2) 174:18;175:8</p> <p>pin (5) 41:9;74:14;200:10;216:20,22</p> <p>pins (1) 203:1</p> <p>PK (6) 158:6;245:11;255:18;256:2,22;263:4</p> <p>PKs (1) 260:13</p> <p>place (4) 58:15;84:12;107:11;186:16</p> <p>placebo (9) 26:14;31:9;32:10;130:3;142:4;144:7;229:7;262:13;310:6</p> <p>placebo-controlled (5) 13:11;44:18;135:3;174:6,19</p> <p>places (1) 319:10</p> <p>plan (6) 64:17;185:4;281:1,5,7,10</p> <p>planned (5) 56:20;252:1;278:9;280:9,15</p> <p>planning (6) 18:10;31:6;39:6;67:10;131:9;184:17</p> <p>plasma (4) 255:15,16;256:4;257:18</p> <p>platelets (1)</p>	<p>271:17</p> <p>platform (4) 95:22;148:12;168:15;170:11</p> <p>plausible (1) 75:21</p> <p>play (3) 125:3;242:1;319:15</p> <p>player (1) 52:1</p> <p>playing (1) 35:18</p> <p>pleasant (3) 205:3,4,8</p> <p>please (14) 3:15;132:21;133:14;142:9,10;181:16;186:22;214:9;235:14;249:3;269:20;280:19;282:5,7</p> <p>pleasure (3) 7:10;62:2,7</p> <p>plenty (2) 103:20;154:22</p> <p>plug (2) 79:5;168:7</p> <p>plugging (1) 104:20</p> <p>plurality (1) 65:13</p> <p>pluses (1) 87:19</p> <p>pm (4) 1:13;187:3;188:2;320:5</p> <p>pockets (2) 143:10;179:2</p> <p>point (95) 3:21;14:10;16:17;18:15;19:10,12;38:16;39:15;46:1;51:22;62:18;68:13;69:2,22;71:5,6;72:12;77:3;80:3;81:17;83:3;91:10;97:8,14,15;101:8;107:10;108:1;109:1;112:10,13;113:18;115:2,3;121:15;126:15;128:5,15;130:4,22;132:20;141:21;142:17;158:13;165:4;166:10;172:18;173:1;176:7;185:10;188:14,14;200:8;201:13;203:16;210:7,21;212:17,20;226:4;247:4;248:5,9,21;249:4;253:12;257:20;263:3,6,19;265:10;269:2;276:17;278:2;280:5,21;285:21,22;286:2,9,10,13;289:8;300:17;301:13;303:15;305:14;309:14;310:19;315:5;316:6,11,18;</p>
--	--	--	--	--

<p>317:3,18 pointed (10) 13:1,1;14:6;18:2,5; 22:19;86:12;100:12; 106:13;165:16 points (11) 44:16;82:13,14,22; 84:13;90:20;117:13; 192:2;202:13;254:6; 319:5 political (1) 162:12 polyneuropathy (5) 74:2;82:6,9;115:11; 230:11 pool (1) 8:9 poor (3) 15:12;33:11;293:5 poorly (1) 69:11 popping (1) 301:9 popular (1) 69:21 population (40) 9:11;10:12;17:18; 18:14;20:14,16,16;21:3; 29:19,22;32:22;37:6; 45:4;55:11,14;56:18; 95:9;123:17;138:11; 173:2;175:15,16;184:3, 8;241:2;257:21;261:2; 271:7,14,21;273:3; 274:3,4;282:1;285:20; 303:14;307:2;311:19; 312:21;313:7 population-based (1) 263:3 populations (7) 10:11;48:1;129:17; 137:17,21;148:1;263:10 portfolio (6) 8:18;14:20;15:4; 25:10,10;143:3 portfolios (1) 8:17 portray (1) 5:19 portrayed (1) 6:4 pose (2) 71:16;306:17 posed (1) 20:10 position (2) 44:17;95:11 positive (23) 22:13;30:22;32:4; 38:12;52:15,16;69:17; 75:12;85:15,17;134:8; 163:22;164:9;204:12,13, 18,22;205:1,2,3;228:14;</p>	<p>238:11;295:8 possibilities (1) 50:20 possibility (4) 43:13;171:19;233:10; 294:15 possible (13) 37:16;47:18;53:10; 55:14;75:11,14;76:1; 132:3;169:9;176:8; 188:7;221:15;227:17 possibly (1) 101:2 post (1) 228:1 post- (2) 184:14;314:15 posted (1) 220:10 poster (1) 141:2 posters (1) 141:2 Postma (1) 48:7 post-mastectomy (2) 314:5;315:17 post-op (2) 313:20;315:13 potato (1) 34:14 potential (13) 24:2;31:11;75:17; 84:13;127:5;172:19; 225:6,19,22;228:6; 275:15;288:7;301:6 potentially (34) 28:22;117:15;118:6; 122:14;129:6;135:12; 137:14;153:8;184:4; 190:19;211:5;225:10,13, 16;228:11;231:14; 235:5,18;236:1,10; 237:6;246:18;248:6; 258:5,7;265:13;267:21; 273:10;280:15;291:7; 297:15;301:12;306:15; 311:9 power (2) 82:11;174:17 PQ (1) 16:10 PQ-12 (1) 15:20 PQ-9 (2) 15:19;16:2 practical (2) 139:6;260:17 practice (1) 38:15 practices (1) 11:22 practicing (2)</p>	<p>203:17;218:9 pragmatic (3) 178:13,14;180:4 prayers (1) 94:8 precise (3) 14:8;58:5;60:13 precisely (2) 69:13;80:16 precision (1) 14:8 preclinical (10) 17:10,13;18:5,14; 23:19,21;24:8,12,20; 25:2 preclinically (2) 274:14,16 preclude (1) 306:6 precludes (1) 179:12 pre-date (1) 233:8 pre-define (1) 131:16 pre-defined (4) 64:14;85:6;295:16,21 pre-diabetic (1) 112:15 predict (1) 127:6 predictable (2) 123:12;316:7 predicted (1) 82:7 predictive (1) 242:4 predictor (1) 289:14 predictors (1) 289:10 pre-establish (1) 99:5 pre-existing (3) 51:7;294:7;301:20 prefer (2) 59:20;60:11 preferred (3) 57:9;194:13;209:16 pregabalin (8) 29:3,8;32:3,7,10,12; 173:21;174:7 prejudice (1) 32:19 prepare (2) 55:10;229:21 prepared (1) 287:11 preplanned (1) 133:4 pre-questionnaire (1) 55:10 pre-screening (1)</p>	<p>55:8 pre-selection (1) 45:14 present (1) 305:19 Presentation (8) 7:14;22:20;34:9; 44:15;62:5;167:14; 243:11;264:1 presentations (1) 243:12 presented (1) 94:20 prespecified (1) 64:17 pressure (4) 120:12;236:17,18; 237:1 Presumably (2) 74:19;238:9 pre-tested (1) 49:15 pretty (21) 13:9;33:11;57:17; 62:17;100:14;118:4; 129:13;153:4;155:6; 190:22;192:17;193:1,1, 3,5;198:10;206:11; 217:17;221:11;284:11; 308:18 prevalence (1) 301:15 prevalent (1) 138:16 prevent (12) 5:11;35:2;105:6; 155:17,19;156:12; 163:21;174:7,22; 234:17;262:9;268:13 preventative (5) 158:9;246:12;247:9; 276:8,10 preventing (2) 146:11;244:15 prevention (36) 5:3;7:13;9:2,5;12:18; 117:15,16;121:3; 149:13;153:7;155:3; 156:9,10;168:18;176:6; 183:19;224:1,2,3;229:8; 231:13;235:5;243:16, 18;244:2,3,11,11;277:4; 299:17;301:3;304:1,2; 306:1;311:8;318:10 preventive (1) 173:21 previous (5) 10:6;131:3;300:21; 301:18;303:18 previously (1) 192:22 price (1) 195:5</p>	<p>pricks (1) 200:11 primarily (7) 8:10;14:16;17:22; 18:20;23:5;27:15; 234:18 primary (29) 5:3,6;13:18,19;14:1,2, 13,16;38:10;44:7;64:15, 20;66:20;85:6;111:11, 11;120:2,7,8;136:20; 138:10;149:13;153:7; 197:14;212:6;233:9; 250:2;306:3;318:10 principle (2) 172:21;263:2 prior (7) 136:17;155:20; 180:14,15;298:19; 302:18;310:11 PRO (46) 27:18;30:4;34:12; 37:17;39:1;42:4,14; 43:11,16,17;44:1,3,12; 45:5,8,15;46:18;47:2,4; 49:14;50:8;56:10;57:2, 9;70:19;98:14;101:19, 22;102:16;103:5; 111:13;116:9;121:16; 190:10;196:7;205:20; 211:5,8;214:6;294:19; 296:17;298:3,4,9,10,18 proactive (1) 157:10 probability (2) 89:9,15 probably (78) 20:19;28:14;32:18; 35:13;37:19;43:17;44:8; 45:5,20;46:6;47:22; 52:1;54:1,3,5,10;57:9, 21;58:15,21;59:4,7; 60:10,15,17,22;64:19; 66:20;75:4,5;77:21; 83:19;91:12;93:9;95:8, 12;96:21;100:22; 116:22;121:17;126:4; 131:2;133:19;134:7; 135:4,9;142:21;144:20; 153:2;155:15;160:18; 163:16;165:21;176:14, 22;179:13;182:22; 183:2;196:19;210:8; 213:12,15;234:14; 240:12;263:7;269:1; 271:8,18;291:19;298:4, 10;303:2;304:17,22; 309:9;311:12;314:21; 316:17 problem (34) 31:18;35:20;36:7,19; 42:21;43:22;46:17,21, 22;47:6;55:19;74:17,18,</p>
--	---	---	---	--

18;80:17;84:18;87:7; 89:4;92:5;101:19;130:1, 2,7;148:20;152:11; 157:5;159:2;166:6,18; 214:19;234:13;253:18; 292:9;306:17	233:8	proving (1) 270:12	QLQ-30 (1) 207:6	quote (4) 72:8,10;77:6;109:11
problematic (4) 15:10;97:8;98:22; 135:13	promptly (1) 133:8	provocative (2) 15:21;16:2	QLQ-C30 (2) 49:5;130:16	R
problems (9) 14:8;57:1;82:19;83:1; 91:19,22;100:8;181:5; 291:21	proof (2) 172:20;263:1	proximal (2) 216:9;220:5	QSD (1) 37:17	
proceedings (1) 3:5	proof-of- (1) 242:13	prudent (1) 99:19	QST (5) 68:20;69:20;84:3; 227:20;232:15	R01 (1) 220:10
process (25) 31:2;47:2,4;49:4,11; 104:13;144:19;145:1, 19;146:19,20;147:2,8; 149:15,19;163:8,20; 179:17;183:13;237:8; 240:17;257:12;266:7; 269:20,22	proof-of-concept (2) 270:19;271:4	psychometric (2) 114:21;129:7	QSTs (1) 79:7	radically (1) 283:10
processes (4) 142:5;145:22;183:2; 293:1	propagated (1) 101:12	psychosocial (1) 8:12	qualitative (3) 84:6;109:8,20	raise (1) 199:14
produce (2) 43:1;47:3	properly (4) 35:22;45:6;101:21; 231:21	publication (1) 269:15	quality (11) 9:5;38:16,20;39:4; 42:6;49:3;50:9;67:17; 100:16;126:16;207:10	raised (3) 101:20;134:15;136:1
product (6) 3:22;4:22;101:11; 106:14,16;166:6	proposal (2) 240:17;295:1	publications (1) 19:9	quality-of-life (8) 27:16;42:11;49:6; 50:12,14;53:15;125:15, 20	rambling (1) 81:14
productive (1) 239:7	proposals (1) 252:10	published (7) 6:1;19:7;28:16;30:18; 45:8;142:2;194:7	quantified (1) 235:11	ramp (1) 140:20
products (1) 4:1	propose (7) 52:22;94:22;95:3; 102:6;243:2;294:15; 297:15	pulled (1) 216:22	quantify (2) 232:1;258:12	ramped (1) 140:5
professor (1) 62:3	proposed (2) 191:16;252:4	pulling (1) 320:2	quantitative (3) 84:11;191:1;228:4	ran (8) 150:5,5,7;165:12; 166:5;174:10,10,16
profile (4) 255:19;256:2;262:4,6	proposing (2) 173:20;297:16	pulse (1) 120:12	quarter (2) 65:18;79:19	random (1) 83:11
profiting (1) 95:15	PROs (23) 27:21;42:8;44:8;45:9; 51:4;63:17;73:4;83:9; 96:19;102:20;117:17; 119:8,9,11;120:2;192:3; 193:15;195:21;210:22; 241:1;288:6;298:5; 315:9	pun (1) 82:13	questionnaire (21) 47:10,19;49:1,3,18,21; 50:4;52:9,22;53:4,11; 55:11;56:15;60:14;61:1, 4;95:12,14;129:19; 181:10;191:9	randomization (7) 179:17;257:11; 280:18;291:22;292:2; 293:22;313:14
prognoses (1) 288:10	prospective (1) 129:10	pure (3) 98:3;214:21;215:15	questionnaires (12) 51:10;53:6,20;57:16, 18,21;58:8;151:19; 181:13;182:3,5,11	randomized (4) 177:13;293:13,22; 308:13
prognosis (3) 273:18;287:22;288:4	protection (1) 166:17	purple (1) 11:11	quick (3) 27:22;110:15;185:10	randomized (8) 13:10;32:1;135:2; 171:6;174:6;246:15; 247:8;289:21
program (14) 7:11;8:8;9:8;14:22; 17:2,7;18:16;19:8; 20:11,11;23:16;26:2,4; 234:5	protects (1) 292:6	purposes (1) 178:16	quicker (3) 170:19;173:16;281:13	range (1) 218:16
programs (1) 267:14	protocol (14) 141:16,18;142:8; 146:15,15;147:6; 151:12;184:8;232:13; 254:19;266:10;268:4; 274:5;281:22	put (41) 22:12;29:21;62:17; 81:10;83:11,12;97:10; 106:5;120:12;147:1; 151:5;152:4,6,16,22,22; 155:21;156:17;159:16; 160:6;161:7;173:10,11; 199:19;201:17;207:13, 15;210:4;222:5;229:22; 248:3;249:14;250:13; 252:9;255:4;265:18; 270:2;272:6;294:4; 311:3,11	quickly (11) 43:22;86:2;95:14; 112:2;170:3;186:14; 189:5;191:21;227:15; 246:17;271:10	rarely (3) 115:14;185:3;200:14
progression (4) 5:12;122:14;241:20; 290:6	protocols (6) 26:11;145:20,21; 195:8;267:22,22	puts (1) 218:15	quiet (1) 254:15	Rasch (6) 54:12;83:10;88:6; 89:8;90:7;109:13
prohibitive (1) 279:11	prove (1) 28:9	putting (7) 83:8;103:7;152:17; 189:18;255:7;301:3; 318:1	quietly (1) 282:7	Rasch-built (1) 129:18
project (7) 20:13,20;53:14;55:3, 6;235:10;287:14	provide (12) 7:2;26:18;42:15; 73:18,19,21;93:2;96:2; 142:9;234:3,22;260:22	p-value (1) 34:1	quit (1) 250:6	Rasch-modified (1) 114:17
projects (2) 8:9;23:6	provided (3) 100:21;142:4;174:9	p-values (1) 33:14	quite (28) 11:3;12:2;13:17;39:9; 50:6,7,15;51:3;54:14; 59:4;60:6;69:21;84:22; 115:4;128:9;129:22; 141:10;197:19;205:8; 208:5;217:21;228:1; 241:7;255:19;267:3; 271:1;304:15;306:22	Rasch-transform (4) 89:2,21;90:15;91:1
PRO-measured (1)	provider-assessed (1) 69:20	Q	Q' (1) 266:5	Rasch-transformed (3) 91:4,5;222:21
	providers (1) 47:8	Q&A (1) 94:13		rates (1) 153:4
	provides (3) 127:17;223:16;229:18			rather (12) 33:22;67:17;103:19, 21;165:8,9;218:11; 242:15;244:16;245:5; 248:9;291:18

<p>rats (1) 200:17</p> <p>RCTs (1) 13:10</p> <p>reacting (1) 292:12</p> <p>reaction (3) 62:13,14,15</p> <p>reactive (1) 92:8</p> <p>read (7) 3:11;7:18;23:17; 68:16;72:12;270:4; 294:6</p> <p>readings (1) 24:21</p> <p>ready (2) 25:3;44:9</p> <p>real (15) 37:6;42:1;45:18; 86:13;114:22;132:12; 163:5;211:22;230:20; 245:20;288:21;305:19, 20;312:11,12</p> <p>realistic (1) 219:18</p> <p>reality (6) 212:13,22;226:14; 227:6;246:1;267:10</p> <p>realize (2) 241:15;288:19</p> <p>realized (2) 62:17;308:7</p> <p>real-life (1) 95:8</p> <p>really (171) 4:11;9:7;10:20,21,21; 11:3;12:2,4;13:2,7;15:2, 15;16:17;20:9;21:14,15; 22:16;28:4;30:14,15,19; 34:3;36:3;38:2;39:7; 44:9;46:14;47:21;58:10; 61:8;62:14;63:8;64:6,8; 66:16;67:20,21;68:22; 69:4,8;72:15,20;73:1,3, 10;74:4;76:18;79:16; 81:1;82:4;83:19;85:4; 87:4;88:21;89:20;90:12; 92:5,11;94:15;95:18; 97:14;98:11;99:11; 100:7;101:7;105:15; 106:12;112:9,16;113:3; 114:1;115:10;116:12,17, 19;117:13;118:14,16,20; 120:1;122:17,20; 126:13;127:4,8;133:10; 135:12;136:1,5;137:16; 139:11,12,14;141:8; 149:6,17;150:16;151:3; 153:22;155:20,20; 156:13;158:11,15;168:2, 7;174:4;175:3;179:12, 21;190:19;205:10;</p>	<p>206:19;207:11;214:7; 219:16;221:9;222:12, 20;223:21;225:7,9; 227:20;229:12;231:19; 235:20;236:17;237:3; 239:11;240:14;241:1; 242:3;243:2,5,6;244:14; 247:20;254:2;255:14; 267:3,8;269:5,7;271:9; 272:14;275:7;277:13; 280:5;281:14,21;283:11, 20;285:14;286:9; 287:12;290:7;293:2; 299:16,17;302:4,18,21; 306:12;308:6,10,13; 316:16;317:3,8;319:8,20</p> <p>realm (4) 198:5;201:4;205:12; 238:21</p> <p>reason (22) 32:5;46:3;60:20; 85:12;120:10,19;132:5, 8,12;153:17;161:9; 162:4;171:1;199:19; 260:5,21;262:21; 263:15;270:11;281:6; 284:19;289:17</p> <p>reasonable (8) 33:22;132:7;144:20; 218:10,17;237:17; 252:16;297:10</p> <p>reasonably (3) 56:22;127:6;192:17</p> <p>reasons (10) 35:7,17;59:12;72:3; 75:15;92:19;101:3; 132:6;162:7;289:12</p> <p>reassured (1) 287:21</p> <p>recall (2) 107:12;142:22</p> <p>receipts (2) 189:6,9</p> <p>receive (4) 23:11;249:16,18; 251:6</p> <p>received (7) 177:7;246:21;251:22; 261:10;264:9,11;272:10</p> <p>receiving (2) 180:10;264:19</p> <p>recent (1) 301:10</p> <p>recently (2) 30:20;291:13</p> <p>recess (2) 133:11;187:3</p> <p>recognition (1) 88:19</p> <p>recognize (3) 212:5,12;269:5</p> <p>recognized (2) 170:10;270:20</p>	<p>recognizes (2) 128:21;269:19</p> <p>recollection (1) 198:20</p> <p>recommend (10) 110:9;188:17;190:9, 17;196:2;210:1;214:3, 14;229:16;266:13</p> <p>recommendation (4) 121:15;217:7;275:17; 295:20</p> <p>recommendations (5) 110:2;193:9,11,20,22</p> <p>recommended (4) 121:19;194:11;211:8; 275:15</p> <p>recommending (2) 218:12;261:11</p> <p>reconsider (1) 299:8</p> <p>recording (2) 3:16;312:18</p> <p>recruit (14) 135:19;136:6,22; 141:1;146:3,4;153:6; 162:18,22;164:22; 175:17;178:17;184:4; 318:9</p> <p>recruited (5) 98:8;135:3;138:20; 139:13;166:16</p> <p>recruiters (1) 139:11</p> <p>recruiting (6) 135:8,10;137:14; 140:18;141:7,7</p> <p>recruitment (13) 56:19;109:3;133:9; 134:18;135:9;137:9; 139:21;140:18;141:4; 162:16;178:21;235:19; 315:15</p> <p>rectal (4) 282:11;283:15;288:2, 12</p> <p>recurred (1) 94:2</p> <p>recurrence (1) 40:8</p> <p>recurrent (2) 284:20;288:14</p> <p>red (1) 55:20</p> <p>reduce (3) 95:16;178:21;317:15</p> <p>reduced (4) 59:19;75:19;80:15; 101:2</p> <p>reducing (2) 165:21;245:18</p> <p>reduction (8) 6:9;43:6;157:11; 165:14,20;260:4;273:8;</p>	<p>282:9</p> <p>reductions (3) 280:22;283:15;284:10</p> <p>refer (1) 301:5</p> <p>reference (1) 52:5</p> <p>references (1) 104:21</p> <p>refined (2) 60:17;107:20</p> <p>reflect (1) 108:18</p> <p>reflected (1) 66:8</p> <p>reflection (1) 66:6</p> <p>reflex (5) 72:14;81:18;217:13; 222:22;229:12</p> <p>reflexes (12) 91:8;104:22;109:12, 15;128:11;220:6;221:4, 12;222:20;223:2,5; 299:8</p> <p>refrain (1) 293:16</p> <p>regard (2) 113:7;179:3</p> <p>regarding (2) 182:19;210:15</p> <p>regeneration (2) 75:22;76:9</p> <p>regimen (12) 44:22;253:1;254:5; 277:5,6,7,15;279:17; 282:10,14;288:2;312:14</p> <p>regimens (1) 254:8</p> <p>regiment (2) 278:6;279:8</p> <p>registration (1) 178:15</p> <p>registrational (1) 178:14</p> <p>registries (1) 178:17</p> <p>regulations (1) 151:10</p> <p>Regulatory (10) 44:4;92:21;108:1; 169:11;211:17;212:1; 213:7;226:9;260:22; 286:20</p> <p>reimburse (1) 160:11</p> <p>reimbursement (1) 159:19</p> <p>reimbursements (1) 189:7</p> <p>reinforced (2) 6:15;116:17</p> <p>reinforces (2)</p>	<p>127:4,15</p> <p>reinnervate (1) 76:14</p> <p>reinnervation (1) 76:15</p> <p>relate (3) 239:20;241:18;256:5</p> <p>related (17) 45:19;46:4,11,15; 136:15,17;137:8; 195:21;196:8;208:2; 249:7;253:5;255:15; 257:8;299:22;303:3; 313:1</p> <p>relates (3) 115:3;116:20;117:13</p> <p>relating (1) 268:10</p> <p>relationship (7) 38:14;46:16;79:20; 112:16;127:12;239:6; 240:20</p> <p>relationships (1) 238:16</p> <p>relative (1) 117:18</p> <p>relatively (9) 65:1,22;82:21;83:4; 114:10;147:22;169:19; 260:12;291:13</p> <p>release (3) 44:2;130:12;313:10</p> <p>released (3) 49:8;130:15;131:5</p> <p>relevant (11) 56:2;60:21;134:17; 197:9;198:4;211:17; 233:19;262:3;299:17; 302:4;312:6</p> <p>reliability (4) 220:1,20,22;295:12</p> <p>reliable (4) 47:3,11;56:10;233:1</p> <p>reliably (2) 237:2;299:9</p> <p>relied (1) 232:8</p> <p>religion (1) 86:10</p> <p>reluctant (2) 232:16;267:4</p> <p>rely (2) 100:4;102:2</p> <p>remain (2) 40:2;107:22</p> <p>remarkable (2) 189:19;240:15</p> <p>remediation (1) 80:2</p> <p>remedy (1) 100:18</p> <p>remember (8) 27:9,13;38:9;140:6,</p>
--	---	--	---	---

<p>17;193;14;209;1;273;3 remind (1) 140:13 reminded (3) 114:3;165:11,11 reminding (1) 242:22 removed (2) 43:5;233:2 rename (1) 198:6 render (1) 234:20 renewing (1) 16:8 repeat (2) 70:8;79:22 repeated (1) 221:3 repetitively (1) 123:19 replicate (1) 56:16 report (3) 75:2;192:20;199:13 reported (11) 30:7,9;36:5;40:22,22; 65:8,13,14,18,19;182:16 reporting (2) 43:4;51:18 reports (1) 51:14 reproducibility (8) 78:5,14;80:9,13; 116:6,13;128:20;219:4 reproducible (3) 99:9;222:7;233:1 repurposing (1) 12:12 request (1) 102:1 require (9) 212:3;213:5;218:7; 229:16;237:4;269:15; 310:7,9;314:7 required (3) 95:17;162:12;310:10 requires (3) 131:8;229:14;313:2 requiring (1) 298:2 rescore (1) 131:3 rescue (9) 35:3;311:10,17,22,22; 312:17;313:10;314:1,1 research (35) 6:13,22;7:12;8:9,22; 9:19;10:14,14;11:2,6; 13:7;17:14;23:21;25:5; 96:18;138:6;174:9; 189:2;210:9,13;213:11, 13;215:17;219:7,8;</p>	<p>220:1;221:8;225:11; 241:6,7;242:19;243:7; 255:22;261:5;298:1 researchers (7) 17:8;23:20,22;24:2; 48:17;91:21;267:14 research-type (1) 229:18 resembles (1) 4:15 resident (1) 223:6 residents (3) 74:12;90:18;223:5 resistant (1) 285:10 resolution (1) 131:13 resolve (1) 269:12 resources (6) 143:12;148:1;170:15; 172:2;174:2,2 respect (4) 172:1;203:4;253:6; 292:3 Respectfully (1) 279:16 respond (3) 114:14;117:2,8 responding (1) 88:2 response (15) 20:14;22:5;54:16; 92:12;94:17;107:5,9,11; 118:19;126:13;128:6; 129:17;190:12;283:21; 294:11 responsive (9) 123:7;125:3,16,21; 126:10,18;127:9,14; 129:6 responsiveness (10) 56:14;118:1;122:6,20; 124:3,10;129:21;130:1, 5;131:14 responsivity (3) 113:11,22;114:13 rest (1) 74:16 restrict (1) 279:10 result (14) 28:13;32:4;41:18,20; 45:10,12;49:21;55:15; 59:7;75:12;132:10; 138:11;228:14;233:21 results (18) 28:21,22;36:15;37:11; 38:13;43:1,10;52:13; 56:7,22;59:2;130:8; 131:4;132:11;142:2; 149:4;193:2;228:10</p>	<p>retaining (1) 113:14 reuptake (1) 179:8 reverse (1) 213:4 review (19) 20:20;21:5,16;23:7,9, 16;63:6;64:10;142:5,8, 11,12;145:1;147:2; 193:10,17,22;289:10; 318:17 reviewed (1) 209:1 reviewers (1) 105:15 reviewing (1) 64:6 revisited (1) 246:5 revisiting (1) 165:7 reword (1) 291:10 RFA (2) 15:22;16:8 RFAs (1) 15:20 riboside (1) 19:6 RICHARDSON (34) 97:6,15;107:2;108:5, 11;156:20;159:5,9,15; 161:5;165:3;168:4; 170:5;172:4,13,16; 211:10,13,15;212:16,20; 217:9,15;226:3;245:2; 247:2;248:1,14;258:10; 260:16;262:19;282:17; 285:13,22 rid (6) 53:4;128:11;170:2; 222:21,22;301:20 ridiculous (1) 160:3 ridiculously (1) 318:3 right (66) 31:10;41:6;57:13; 58:15;64:18,18;72:9; 89:8;101:7,18;113:21; 115:4,7;119:4,5;122:1; 124:21,22;126:7,19; 127:2,21;143:19;153:2; 161:8;181:18;182:4,7; 190:10;193:4;194:6; 195:11;201:2;206:14,14, 18;212:19;213:21; 214:8;221:7;223:6,20, 22;226:3;237:21;243:6; 252:13,15;270:15;279:1, 3;288:9;292:18;293:9; 295:20;297:5;302:6;</p>	<p>305:11;306:10,11; 311:4;312:2;313:13; 316:9,10;319:2 ringing (2) 58:21,22 risk (16) 20:17;21:3;52:13; 67:2;71:16;85:22; 140:19;202:14;254:17; 274:4,6,6;275:9,12; 279:6;288:21 RO3 (1) 129:7 road (3) 4:22;52:2;63:2 roadblocks (1) 170:21 Robert (2) 23:15;24:7 robust (5) 21:1,19;26:1,5;86:1 Rochester (3) 10:17;11:8;78:18 rocket (1) 109:16 RODS (4) 90:22;91:3;96:14; 129:18 role (1) 35:18 room (11) 28:6;64:18;70:1; 81:17;102:4,13;108:6; 202:16;219:10;222:5; 223:10 root (1) 248:16 round (5) 180:12,15;188:3,4,5 route (1) 158:5 routine (3) 97:3;139:5;177:20 routinely (1) 226:21 Roy (16) 62:11,12,19;78:6; 79:11;105:11;106:13; 108:15;113:4,5;190:5; 217:9;226:3;252:11; 296:15;315:21 Roy's (3) 73:16;75:8;128:5 RTC (2) 130:12,15 RTOG (1) 139:20 rude (1) 180:10 rudimentary (1) 217:18 rule (7) 33:16,17,20;54:19,20;</p>	<p>251:14;291:20 rules (4) 45:7;151:10;250:14; 255:4 run (7) 56:3,5;145:8;146:4; 170:21;219:17;232:11 rush (1) 217:7 Russell (1) 79:11 ruthless (1) 209:5</p>
S				
			<p>safe (1) 147:4 safely (2) 189:20,21 safety (13) 75:17;180:1;212:14, 17;270:8,11,20,21; 271:9,15,17;272:2;285:6 sake (1) 195:20 same (61) 3:11;9:16;14:21; 16:11;22:14;26:3;41:15, 16,18,19;43:2;54:1; 57:17,20;59:4;81:12; 83:21;93:7;96:21; 103:14,21;106:3;132:11, 13;170:20;175:20; 197:20;202:1;203:8; 226:4;227:6,19;238:15; 245:3;248:19;250:22; 255:17;256:11,21; 271:13;276:5;277:1,3,5, 6,7,15;279:8,13,19,21; 281:1,5,7,12;282:9,14; 283:10,14;288:1;289:22 sample (4) 22:3;221:9;239:15; 317:20 sat (1) 161:15 satisfactory (1) 95:11 satisfying (1) 230:21 saw (14) 23:3;24:4;25:11; 26:16,17;62:12;74:13; 78:10;165:18,19; 167:14;183:7,7;194:22 saying (42) 30:9;32:5;34:1;52:5; 58:14;85:16;87:12; 98:14,15,16,20;107:6; 131:1,2;156:21;196:5; 208:16,17;211:22; 215:8;236:18;246:17,21,</p>	

22;247:2;248:2,3; 251:21;256:1;257:21; 259:22;261:20;265:17; 18;271:11,14;278:14; 297:19;302:6;307:13, 16;313:6	score (22) 23:11;37:4;40:21; 41:12;47:16;48:13;54:3; 60:19;73:8,9;81:22; 82:4;84:2;89:9,10; 90:19;96:7;130:8,18; 131:17;202:1;295:11	24:6;215:3;221:20; 239:20	sent (3) 44:5;67:12;254:19	134:14;135:14;136:2; 148:3,11;252:22;254:6; 316:1
scale (69) 13:20;14:17;36:21; 49:6,8,17,22;50:4,9; 51:7,8,8;54:22;56:3,7; 64:4;67:14,17;69:3,4,5, 8;70:20,21;81:6,19;82:2, 8,19;83:2,15;84:16; 86:18;87:1,3,6,21,22; 89:8;90:13,15;91:4; 101:2;110:20;111:2; 113:10,12;114:3,17,20; 115:9,10;122:11,19; 130:1,6;132:14;171:9; 172:17;197:13;207:14; 214:17;215:10,13;216:2, 3,8,10;295:17	scored (2) 84:5;89:13	seemed (7) 65:22;190:8;209:7; 210:10;273:7,9;275:20	sentence (2) 194:12,13	severe (4) 46:8,9;51:13;302:7
scales (50) 14:5;42:7,11;43:21, 21;48:9;51:20;54:7,15; 63:20;64:1;67:21;68:21; 73:5,14,15;74:19;75:4; 77:15,20;80:14,18; 81:21;83:4,11,18,21,22; 84:19;85:22;86:14,15, 16;88:3;91:1;96:21,22; 109:9,11;110:17;112:11, 17;113:20;114:9;122:8, 12;125:8;131:6;185:14; 204:8	scores (8) 37:17;71:3;84:5; 89:15;93:2;124:18; 130:17;239:19	seeming (1) 272:7	sentences (1) 211:9	severity (11) 43:7;44:20;66:5;74:7; 83:5;84:6;243:9;246:19; 253:10;268:18;301:16
scared (1) 88:12	scoring (6) 36:1;81:20;82:10; 130:11,13;131:4	seems (15) 34:13;42:21;46:20; 54:20;69:20;113:11; 118:16;190:22;193:14; 199:13;218:17;235:3; 239:9;244:6;283:20	separate (18) 6:7;40:18;45:21;46:1; 148:7;154:15;170:16; 201:10,11;206:8; 214:18;250:4,15;265:7, 13;268:11;269:3,3	shake (1) 76:4
scarier (1) 288:3	Scott (2) 6:14;252:11	sees (1) 239:12	separated (1) 41:3	shape (2) 59:5;119:20
scenario (2) 76:12;89:10	Scott's (2) 243:12;250:19	selected (2) 44:21;55:8	separately (6) 251:8,11,13;254:3; 276:1,1	share (1) 94:6
scenarios (1) 214:20	Scrambler (1) 201:15	selecting (1) 273:2	separating (1) 215:2	shared (1) 109:6
schedule (2) 157:11;281:18	scratch (1) 203:2	selection (6) 38:3;45:13;49:14,19; 51:2;55:9	separation (1) 40:19	sharing (1) 92:6
scheduled (1) 187:2	screen (3) 112:4;131:21;169:10	self-reported (1) 52:12	series (3) 4:9;15:20;16:1	Sharon (14) 6:15,18;121:21; 197:14;198:17;204:10; 229:21;236:3;264:6; 266:1;272:3,17;296:4,6
school (1) 34:7	screening (5) 9:6;112:21;131:15; 295:5;300:9	self-select (1) 292:9	serious (1) 81:3	Sharon's (1) 265:17
science (8) 20:9;21:22;108:14; 212:1,2;217:10;286:19, 20	se (2) 42:9;249:15	send (10) 66:11;96:16;146:17; 147:1,6;150:11;152:1,5; 156:2;252:12	seriously (1) 227:14	shoot (1) 268:1
scientific (10) 9:20,22;32:21;100:14; 132:7,15,16;142:5,11,12	search (1) 55:6	sending (2) 189:10;266:1	serotonin (1) 179:8	shooting (3) 175:4;195:13;200:15
scientifically (5) 147:3;152:13,20; 177:18;180:6	second (15) 7:9;8:7;38:11;62:14; 100:11;113:18;115:2; 116:7;155:8,12;185:1; 194:12;233:17;237:22; 238:18	sensation (8) 128:12;200:22;204:7, 15,16,17;205:2,13	serve (1) 267:3	short (2) 47:4;191:19
scientist (1) 109:16	secondaries (1) 192:4	sensations (4) 198:21;199:1,4;205:3	served (1) 234:21	shortcuts (1) 227:7
scope (1) 169:8	secondary (12) 5:3,7;14:14;27:11; 65:9;67:1,5;149:14; 153:8;196:3,20;306:3	sense (42) 4:19;43:7;47:11; 81:20;91:18;101:22; 102:16,18;103:8;104:8, 10,14,16;106:2,7,9,11; 107:18,21;120:18; 168:14;197:6;217:12; 224:3;226:10;244:7; 246:7;266:10,13,18; 267:5,6,8;270:19;271:6, 19;278:1;291:2;295:18; 296:3;302:10;306:6	services (2) 9:9;11:2	shorter (1) 163:16
	second-least (1) 203:17	sensibility (1) 216:20	session (8) 7:4;133:16;134:7; 186:16,17;188:9; 252:20;254:16	short-term (1) 309:3
	second-line (1) 272:11	sensible (1) 139:6	set (15) 110:1;111:3;128:17; 148:11;151:9,9,12; 152:13;163:6;169:9; 211:2;255:3;288:4; 297:2;299:16	shoulders (1) 319:11
	second-to-last (1) 17:20	sensitive (3) 126:9;230:12;253:15	sets (2) 215:1;263:2	show (24) 8:5;36:19;48:5;50:21; 55:1;57:14;80:18;81:7; 83:3;84:20;93:21;101:4; 103:3;159:10,11;162:6; 170:1;221:17;227:10; 237:9;257:7;272:1; 287:10;307:18
	secret (1) 26:4	sensitivity (5) 109:8,20;249:2;295:9; 297:14	setting (15) 35:7;88:3;95:7,7; 98:21;150:8,8;192:12; 226:9;240:4;246:15; 247:8;284:4,13,18	showed (9) 5:4;6:5;13:3;21:18; 65:20;85:8;91:11;141:4; 292:14
	section (1) 60:18	senior (13) 49:22;66:21;72:14; 74:7;76:2;81:18;82:11; 83:6;84:11;115:15; 191:12;205:12,13	settings (2) 47:22;98:7	showing (1) 174:20
	seeing (4) 103:16;152:9;167:18; 246:2		set-up (2) 115:5,5	shown (7) 90:16;125:3,9;132:10; 223:15;227:17;229:17
	seek (1) 57:6		seven (4) 10:14;12:18,18;84:12	shows (7) 72:19;81:16;82:10; 85:18;89:7;90:9;124:17
	seeking (1) 105:15		several (16) 11:6;13:1;42:21;44:8; 49:8;54:11;77:10;92:9;	shy (2) 21:8,13
	seem (4)			side (8)

<p>35:21;43:4,8;81:17; 165:1;212:18;248:3; 316:7 sidebar (1) 158:12 sideways (1) 284:1 sign (67) 58:11;59:16;63:8; 65:2,14,18;67:10,16; 68:9,11,15;69:18;70:2; 72:7,9;73:14,15;74:3,19; 75:4,6;76:22;77:15; 78:5;83:10,21;93:2,8,12; 98:10,20,20;99:10; 111:1;121:6,19;122:2; 125:16;136:18;153:19; 167:10;213:12;214:4,5, 6,7,14,21;215:6;228:4, 17,20;234:8,8,10,15,18; 235:4;237:6,10;269:18; 296:22;297:1,4,6; 298:17;307:7 signal (4) 166:11;283:2;308:15, 22 sign-based (7) 63:1,18;64:4;69:3; 91:13;109:9;215:15 sign-based-only (1) 99:2 significant (1) 79:20 significantly (2) 75:2;164:9 sign-only (1) 214:17 signs (44) 39:14;76:16;79:9; 80:14;84:14,16,20;99:8, 11;108:19;110:17; 115:3;116:15,19,19; 117:2,7,14;118:11; 120:19;121:22;127:5,9, 18,22;128:2;177:2,4; 178:9;211:11;213:9; 215:2,12;219:6,13; 222:6,9;227:21;231:21; 232:22;296:21;297:1,3; 307:15 similar (8) 11:17;50:15;68:6; 144:10;147:21;149:2; 172:9;215:12 similarly (1) 160:17 similar-type (1) 267:13 Simon (8) 192:9;301:5,9;302:10; 303:5;314:3,14,18 simple (20) 40:16;46:19;51:11;</p>	<p>55:16;79:2;80:14;99:17; 100:7;111:19;128:9,17; 131:8;137:1;139:1; 191:19;198:18;219:7; 248:10;252:3;318:21 simplest (1) 249:22 simplify (2) 178:18;318:2 simplistic (1) 248:5 simply (7) 41:14,18;59:1;130:13; 152:15;171:22;200:7 single (5) 26:22;28:7;143:21; 148:8;162:2 single-site (1) 138:13 sinus (1) 70:13 sit (2) 133:14;222:8 site (4) 11:20;139:13;184:2; 232:2 sites (23) 8:21,21;10:4,9,18,19; 11:13,16;96:7;135:5,7, 12;137:3;138:20; 139:13;143:14;144:3; 152:21;183:21;186:2; 220:12,15;259:17 sitting (4) 114:2;128:19;153:15; 287:6 situation (8) 36:10;40:17;41:6; 60:12;147:11;165:9; 267:13;272:16 situationally (1) 267:1 situations (3) 172:9;194:14,19 six (9) 19:3;39:17;175:6; 182:10;191:3;201:11; 244:12;253:22;268:13 six-month (1) 56:21 size (4) 22:3;221:9;239:16; 317:20 skill (1) 220:13 skills (1) 217:17 skin (12) 124:2;158:18;159:3,5, 14;185:16;235:17,21; 238:15;239:8;240:3,11 skip (3) 57:10;84:1;246:16</p>	<p>skyrocketed (1) 128:20 sleep (4) 206:1,6,13;298:6 slide (20) 3:8,11,17,17;5:4;10:6; 15:18;45:20;68:10;71:8; 76:20;78:5;81:9;91:11; 93:4,21;103:6;111:4; 195:3;311:4 slides (5) 44:14;57:5;68:18; 81:10;110:16 slightly (4) 64:15;148:19;160:2; 165:5 slow (2) 5:11;169:7 slowing (1) 237:22 slowly (1) 123:6 small (17) 11:22,22;59:5;120:18; 147:22;159:12;164:17; 166:17;172:17;174:11; 216:2,3,17;221:7,10; 239:15;252:20 smaller (2) 118:6;171:14 small-fiber (1) 238:21 smart (2) 79:12;86:4 Smith (79) 6:2;31:22;62:3,5,6,21; 67:19;79:15;81:5;96:4; 97:13,18;98:6,15; 108:17;112:13;122:21; 126:1,22;128:2;129:4; 133:15,19;134:6; 141:22;143:15;148:21; 156:5;177:19;178:10, 11;179:4;182:17; 186:11;190:20;202:12; 207:4;209:10;214:10, 15;215:9;216:13,15,19; 220:3,21;221:13;222:3; 223:18;227:5;234:12; 239:3;280:3,7,11;282:6; 287:18;295:2;296:2,5, 15;298:2,15;301:8; 305:19;307:10;309:2, 15;310:3,9,16,20;311:1; 313:4;315:21;316:10,15, 18;320:2 Smith's (4) 12:22;61:21,22;226:6 smoothly (1) 189:19 snow (1) 80:2 snowy (1)</p>	<p>114:6 social (1) 50:10 Society (1) 160:7 sold (2) 93:19;240:5 solid (1) 284:5 solution (1) 170:6 solve (2) 31:17;291:21 solved (1) 46:20 solves (1) 75:13 somebody (7) 146:22;189:6;250:10; 273:9,15,17;308:17 somebody's (1) 259:8 somehow (2) 250:22;264:7 someone (20) 32:15;65:16;81:2; 87:5;100:7;133:21; 156:14;160:19;199:10; 203:20;219:22;220:13; 233:14;256:15;260:5; 278:17;280:14;282:11; 288:12;304:4 someone's (2) 185:6;298:20 someplace (1) 227:21 sometimes (9) 42:12;54:6;66:4; 69:13;140:8;146:7; 155:12;179:12;249:7 somewhat (9) 5:14,15;72:18;75:21; 80:5;88:21;90:4;124:5; 150:6 somewhere (4) 111:16,17;135:4; 195:19 soon (6) 56:22;112:14;129:13; 203:20;241:4;320:1 sophisticated (1) 245:22 sorry (10) 9:2;34:16;105:12; 169:7;233:4;234:13; 281:3;287:1;295:19; 314:14 sort (65) 12:13,13;33:10;63:2, 14;74:1;77:1;98:14; 101:10;102:11,14;103:1, 3;104:4,8,22;108:7; 120:13;125:2;141:5;</p>	<p>144:18,19;145:13,14,18; 146:16,18;151:15,16; 153:3;155:11,14;157:7; 161:6;162:9;163:13,17; 164:15;170:20;171:13; 175:10;176:18;177:9; 179:20;181:7,17;182:6, 13;195:18;201:15; 228:3;229:9,15;250:9, 13,14;256:19;259:1,18; 266:3,7,9,11;273:16; 308:16 sorted (1) 256:8 sorts (8) 68:6;87:20;92:20; 102:19;129:1;204:8; 242:14;256:10 sound (6) 147:3;152:13,20; 177:18;180:6;296:4 sounds (8) 100:10;123:14; 196:12;210:6;215:21; 235:2;275:3;288:3 south (1) 11:12 space (1) 67:16 speak (5) 149:7;203:15;204:19; 219:20;283:5 speakers (1) 113:13 speaking (8) 3:13;88:17;100:3; 149:20;219:2;247:7; 279:13;286:3 speaks (1) 23:12 special (3) 196:20;224:14;283:20 specialize (1) 134:2 specialties (1) 77:11 specific (20) 12:15;14:7;32:22; 43:12;45:19;77:3; 111:14;126:19;194:17; 196:2,10;200:12; 208:12;242:7;248:11; 253:21;282:18;285:16; 286:16;298:10 specifically (13) 8:17;65:21;129:8; 151:9;201:7;206:13,21; 211:3;220:9;258:2; 273:5;315:5,14 specificity (2) 295:10;297:14 spectrum (1) 9:7</p>
---	---	---	--	--

spend (3) 169:22;195:7;287:6	208:18;225:4	270:13	80:5;166:13	111:15;158:4;161:13; 196:11;231:16;313:18; 315:16
spends (1) 65:16	standpoint (4) 53:17;56:17;60:11; 132:15	still (32) 39:13;45:8;49:17,17; 60:16;84:15;87:14,22; 88:1;95:21;96:3;100:18; 104:19;108:12;110:11; 111:12;121:3;154:14,19, 21;174:15;179:17; 183:4;206:8;228:12,14; 246:2;272:15;276:2,17; 284:15;301:22	struggling (2) 123:3;265:2	stuff (20) 68:21;79:4,7;81:13; 99:12;104:8,22;118:18; 155:11;163:13;176:18; 182:13;195:4;213:21; 243:4;256:7,19;262:10; 266:3;286:18
spent (4) 22:7;123:19;139:14; 199:16	start (29) 11:5;27:1;45:2;47:5; 48:22;55:3;63:5;64:6; 74:3;94:18;124:22; 133:8,20;155:19;162:9, 11;176:6;188:5;190:6; 229:7;241:4;258:17; 270:10;279:5;287:12; 292:8;303:11;306:14; 316:4	stipend (1) 189:8	stuck (2) 229:15;284:15	sub-clinical (1) 99:2
spinning (1) 162:10	started (13) 5:7;13:22;15:21; 30:10;49:4,11,14;53:11, 14;55:6;123:9;133:13; 157:14	stop (7) 31:13;141:9;236:20; 244:14,18;290:5;310:21	students (1) 221:2	subcomponents (1) 10:21
split (2) 65:3;175:10	starting (4) 13:8;70:6;74:11; 275:13	stopping (1) 95:9	studied (3) 45:1;274:4,8	subepidermal (1) 76:11
spoke (1) 230:1	starts (3) 53:3;176:4;200:11	storm (1) 80:2	studies (81) 8:13;12:20;18:20; 20:4;21:17;22:2,2,14; 23:3,5;24:15;25:18; 27:10;33:2,2,11;35:9; 36:15,16;38:10,13; 42:21;43:3;44:8,21; 46:4;65:8;68:4,14;69:3; 75:16;85:19;93:10;98:7; 100:21;101:12;104:1; 110:11;122:13;124:7; 127:8;143:2,17;144:10; 152:12;156:1;161:9; 163:11,20;164:13,17,18, 19,21;166:16;168:9; 175:14;180:9;197:5; 232:13;233:12,14; 234:4;235:5,22;238:15; 239:1,11,19;240:7,8,21; 242:14;263:4;271:16; 272:1;285:18;301:10; 302:19;307:17;308:5	subject (2) 6:12;232:3
spoken (1) 284:17	stated (1) 126:14	story (6) 30:5;36:6;46:8;55:4; 134:12;166:9	studying (7) 6:5,13;12:8;13:21; 32:6,14,15;38:2,14;45:4; 46:5;57:12;78:8,11; 84:21;93:9;95:1;96:10; 124:13,14;127:11; 128:8;129:8,10,18; 134:13;135:5,14; 136:10;137:18;138:1,12, 13,14;139:2,12;140:5,8, 10,17,20,22;141:4; 143:2,10,20;144:3,4; 145:12;146:9;152:5,6; 153:7,13;154:18;155:6; 157:8,21;158:14; 161:18;162:3,14,18; 166:17;168:12;174:11, 16;176:5,6;178:8;179:7; 183:22;184:2,14,15,22; 193:2;194:22;195:20, 20;197:14;208:6; 209:17,19;221:7; 222:18;226:17;228:7; 231:16;232:4;237:15; 239:8,14;241:5;254:19; 257:14;258:1;262:11, 11;266:9;267:8;268:20, 21;270:19;271:4; 276:13;282:21;289:21; 303:14;309:12;311:8; 318:9,10	subjects (1) 272:15
sponsor (1) 287:10	statement (9) 46:19;65:5;101:10; 105:21;113:19;212:5; 285:14;298:9;301:4	straw (1) 124:15	study (113) 6:5,13;12:8;13:21; 32:6,14,15;38:2,14;45:4; 46:5;57:12;78:8,11; 84:21;93:9;95:1;96:10; 124:13,14;127:11; 128:8;129:8,10,18; 134:13;135:5,14; 136:10;137:18;138:1,12, 13,14;139:2,12;140:5,8, 10,17,20,22;141:4; 143:2,10,20;144:3,4; 145:12;146:9;152:5,6; 153:7,13;154:18;155:6; 157:8,21;158:14; 161:18;162:3,14,18; 166:17;168:12;174:11, 16;176:5,6;178:8;179:7; 183:22;184:2,14,15,22; 193:2;194:22;195:20, 20;197:14;208:6; 209:17,19;221:7; 222:18;226:17;228:7; 231:16;232:4;237:15; 239:8,14;241:5;254:19; 257:14;258:1;262:11, 11;266:9;267:8;268:20, 21;270:19;271:4; 276:13;282:21;289:21; 303:14;309:12;311:8; 318:9,10	submitted (2) 64:7;178:15
sponsored (1) 143:7	States (2) 129:16;204:18	strategies (3) 157:12;247:11;293:12	submitting (1) 275:6	subgroup (5) 13:3;178:7,7,9;228:8
sponsoring (1) 149:1	static (1) 210:17	strategy (2) 287:12;291:17	subgroups (1) 178:4	subgroups (1) 178:4
sponsors (1) 160:8	statistical (8) 54:13;60:10;71:20; 93:17;250:14;251:13; 255:4;315:22	straw (1) 124:15	subject (2) 6:12;232:3	subgroups (1) 178:4
spontaneously (1) 76:10	statistically (1) 79:20	strawman (10) 73:17;75:8,18,21; 82:18;86:13;305:20,20; 306:11,18	subjects (1) 272:15	submitted (2) 64:7;178:15
spot (1) 229:22	statistician (3) 127:1;255:9;261:8	stream (1) 26:15	submitted (2) 64:7;178:15	submitting (1) 275:6
squamous (1) 70:13	statisticians (8) 33:12;54:14;74:21; 85:13;244:6;290:11; 317:13;319:14	strength (11) 59:19;82:16;87:13,18; 88:3;128:12;216:6; 221:13;226:12;230:13, 13	submitting (1) 275:6	subpart (6) 225:7;226:1;230:19; 233:10;234:2;236:15
squared (1) 255:18	statistics (3) 144:22;173:13;221:10	strengths (3) 57:3;84:17;216:2	subQ (2) 245:16;246:3	subpart (6) 225:7;226:1;230:19; 233:10;234:2;236:15
SSRI (1) 304:22	status (2) 72:13,20	strikes (1) 114:1	subsequently (1) 159:9	subQ (2) 245:16;246:3
SSRIs (1) 305:8	stay (2) 54:2;289:16	striking (1) 165:14	subset (3) 159:8;215:12;257:20	subsequently (1) 159:9
stability (1) 92:4	stayed (1) 151:16	stringent (1) 136:10	subsets (1) 260:18	subset (3) 159:8;215:12;257:20
stable (5) 55:12;309:18,19; 310:8,10	staying (1) 156:7	stroke (1) 236:20	substance (1) 166:5	subsets (1) 260:18
staff (5) 18:2;104:19;137:3; 176:14;232:4	steak (1) 79:17	strong (4) 9:17;23:10;32:21; 230:18	substance (1) 166:5	subsets (1) 260:18
stage (2) 74:20;85:14	step (3) 48:15;153:22;233:2	strongly (3) 235:20;262:4;303:17	substantial (3) 39:12;218:4;308:18	subsets (1) 260:18
stages (1) 117:20	steps (1) 49:12	struck (4) 72:15;112:21;180:8; 263:15	substantially (3) 39:12;218:4;308:18	subsets (1) 260:18
stairs (1) 230:16	sticking (1)	structure (1) 50:15	substrate (1) 284:6	subsets (1) 260:18
stance (2) 197:3;231:3		structured (2)	subtle (2) 99:7;230:6	subsets (1) 260:18
stand (2) 60:2;236:14			succeeding (1) 123:22	subsets (1) 260:18
standard (6) 37:20;40:4;49:13; 108:2;290:15;311:22			success (8) 21:7,10,11,12;44:3; 109:6;160:15;180:3	subsets (1) 260:18
standardize (1) 279:2			successful (8) 36:9;135:17,21; 153:18;170:8;172:7,14; 265:9	subsets (1) 260:18
standardly (1) 259:15			successfully (4) 16:7;76:14;224:16,17	subsets (1) 260:18
standards (2) 91:21;105:22			sudden (1) 288:19	subsets (1) 260:18
standing (2)			suffer (2) 183:2,3	subsets (1) 260:18

35:4;184:6,10,18; 317:8 sufficient (1) 236:14 suggest (5) 117:10;165:6;175:8; 193:14;242:12 suggested (3) 175:3;219:11;251:2 suggesting (2) 130:10;286:14 suggestions (4) 6:14;43:3;234:11; 248:12 suggests (1) 73:9 suitable (1) 48:11 suits (1) 218:12 sum (2) 130:8,16 summarize (2) 15:3;134:14 summarized (1) 63:7 summary (1) 304:11 sunglasses (1) 79:4 superimposed (1) 115:13 supplement (2) 12:13;195:14 supplements (2) 157:13,14 support (11) 25:18;26:14,22; 127:18;142:3;144:10; 146:13;160:10;174:18; 237:19;238:11 supported (3) 12:7;13:9;32:6 supporting (1) 21:22 supportive (2) 245:15;285:17 suppose (4) 3:9;143:18;223:19; 295:9 supposed (3) 78:22;241:22;249:16 sural (3) 66:21;72:14;238:17 Sure (30) 34:4,11;46:14;58:10; 67:21;129:22;130:6; 142:22;173:2;189:7; 196:18;197:20;205:7; 19:208:11;210:18; 214:19;215:10;216:7; 217:21;224:8;242:19; 243:5;244:13;269:19;	274:20;279:15;293:14; 295:20;299:9 surgical (1) 314:16 surprised (3) 28:7;67:13;153:5 surprising (7) 48:12;52:21;58:8; 65:15;66:19;72:18; 109:13 surreal (3) 78:8;115:20;118:2 surrogacy (1) 241:14 surrogate (22) 116:21;117:11; 127:19;224:19;225:6,18, 22;230:15;231:6;232:9; 233:2,9;236:2,14;237:6, 17;238:6;241:19,21,22; 242:8,16 surrogates (2) 127:6;236:17 survival (3) 242:1;271:3;273:13 survive (1) 167:16 survived (1) 71:21 survives (3) 224:20;225:8;230:22 susceptibility (1) 75:5 susceptible (1) 74:20 suspect (3) 73:4;80:9;89:19 switch (2) 70:5;292:21 switched (1) 292:19 SWOG (3) 9:15,21;11:9 symmetric (1) 74:2 sympathetic (1) 317:18 symptom (31) 6:18;7:22;9:5;44:19; 59:21;60:5;65:13;83:22; 98:3;140:7;145:8; 162:18;172:12;185:12; 191:1;192:12,18;196:8; 204:1,17,19,22;205:1; 210:15;215:11;224:3; 231:13;265:5;294:19; 295:4;308:11 symptomatic (4) 5:16,19;149:15; 308:18 symptom-based (3) 63:18;73:4;223:22 symptoms (59)	6:2;15:9,17;22:18,21; 26:9;39:14;44:21;45:21, 22;46:1,2,5,13;52:13,18, 19;60:17,21;71:14;75:2, 19;76:9,16;79:8;84:14, 16,20;98:2;118:10; 119:4;181:12;191:7; 192:20;193:4;198:3; 204:11,12,13,14;205:13; 206:22;207:7,9,9,21; 208:11,16;210:16;215:2, 5;234:18;235:6,7; 276:14,15;294:18,21; 307:15 syndrome (3) 76:5;90:2;161:18 syndromes (1) 316:2 synthesized (1) 6:17 system (8) 11:17;39:10;130:12, 18;131:14;137:13; 169:19;252:4 systematic (4) 193:10,17;289:10; 318:17 systems (3) 41:5;76:2;191:12	85:2;90:21;111:21; 136:4;139:1;158:3; 235:18;247:19;270:1; 293:3;304:18;315:7,11 talking (24) 29:17;36:4,19;37:13; 66:12;73:3;97:20; 102:20;119:7;128:19; 150:20;181:4;183:16; 184:12;202:14;243:20; 254:17;256:10;266:16; 276:11;294:2;297:6; 302:7;311:4 talks (1) 94:15 tanespimycin (1) 165:13 tangible (1) 66:6 tap (1) 120:8 target (2) 138:10;308:19 targeted (3) 12:15;126:18;273:5 targeting (3) 137:16;158:10;257:18 task (2) 7:16;44:9 Taxane (3) 12:16;173:22;276:1 tea (1) 195:6 team (4) 98:9;157:17;161:4; 168:6 teams (1) 25:5 tease (1) 291:16 techniques (1) 138:6 Ted (9) 70:8,11,12;71:11; 73:6;88:10;93:21,21; 94:8 Ted's (2) 75:1;96:6 telling (6) 8:15;77:20;93:22; 185:21;208:7;296:6 tells (2) 125:5;223:19 temporal (1) 73:10 tend (2) 46:8;126:17 tenuous (1) 297:18 term (2) 74:22;197:19 terms (28) 12:2;14:8;22:19;39:5;	41:11;51:21;77:4;83:22; 91:13;96:22;113:9; 119:1;146:13;163:21; 175:4;197:21;199:6,8; 204:5;211:16;218:21; 236:13;242:12,15; 263:22;270:11;273:17; 275:13 terrible (6) 79:18;150:13;203:1; 209:19,19;266:18 terribly (1) 223:12 territories (2) 4:12;253:5 territory (5) 6:21;73:17;158:22; 159:1;252:21 test (10) 19:19;47:9,20;53:21; 56:13;69:12;95:6,14,22; 129:20 tested (16) 20:7;25:2;40:12; 49:15;50:5;51:1,5; 53:17;55:9,10;82:12; 100:13;148:9;220:3,7,21 testing (10) 19:1;40:14;65:4; 84:11;129:19;151:6; 158:18;217:10;218:8; 242:20 tests (12) 19:1;47:12;95:18; 111:22;112:1,19;128:7; 176:17,22;177:1,16; 300:16 thanks (6) 7:15;62:6;133:10; 141:13;290:7;319:17 that'll (1) 63:4 theirs (1) 95:13 theoretical (1) 249:18 theory (4) 53:21;54:9,12,13 therapeutic (6) 75:3;122:7,17;158:10; 172:13;213:3 therapies (1) 122:9 therapists (1) 221:2 therapy (24) 16:4,16;19:5;20:6; 30:8,17;66:14;71:10,22; 88:2;124:19;150:12; 157:6,15;159:2;167:7,8, 15;201:15;233:5; 279:19;282:22;292:21; 302:12	
T					
<table border="1"> <tr> <td> table (4) 161:16;232:19; 264:20;287:7 tacit (1) 117:5 tackle (1) 260:17 tackling (1) 123:3 take-away (1) 287:1 take-home (5) 12:21;71:5;80:3; 128:7,15 talk (52) 14:19;15:6;23:6;28:4; 34:12,16,17;36:11;47:6; 7;61:21,22;62:22;63:3,4, 10,17,20;64:2;66:7; 77:14;79:5;80:19;81:12; 82:17;83:9;86:16;87:1; 90:17,17;91:14;107:19; 109:5;110:22;118:2; 138:3,4;141:17;150:19; 152:4;173:10;194:20; 207:22;213:10;224:14; 243:2;250:19;252:8; 287:5,13;300:22;304:2 talked (21) 8:3;14:11;16:14;18:8; 24:4;74:3;76:9;83:22;</td> </tr> </table>					table (4) 161:16;232:19; 264:20;287:7 tacit (1) 117:5 tackle (1) 260:17 tackling (1) 123:3 take-away (1) 287:1 take-home (5) 12:21;71:5;80:3; 128:7,15 talk (52) 14:19;15:6;23:6;28:4; 34:12,16,17;36:11;47:6; 7;61:21,22;62:22;63:3,4, 10,17,20;64:2;66:7; 77:14;79:5;80:19;81:12; 82:17;83:9;86:16;87:1; 90:17,17;91:14;107:19; 109:5;110:22;118:2; 138:3,4;141:17;150:19; 152:4;173:10;194:20; 207:22;213:10;224:14; 243:2;250:19;252:8; 287:5,13;300:22;304:2 talked (21) 8:3;14:11;16:14;18:8; 24:4;74:3;76:9;83:22;
table (4) 161:16;232:19; 264:20;287:7 tacit (1) 117:5 tackle (1) 260:17 tackling (1) 123:3 take-away (1) 287:1 take-home (5) 12:21;71:5;80:3; 128:7,15 talk (52) 14:19;15:6;23:6;28:4; 34:12,16,17;36:11;47:6; 7;61:21,22;62:22;63:3,4, 10,17,20;64:2;66:7; 77:14;79:5;80:19;81:12; 82:17;83:9;86:16;87:1; 90:17,17;91:14;107:19; 109:5;110:22;118:2; 138:3,4;141:17;150:19; 152:4;173:10;194:20; 207:22;213:10;224:14; 243:2;250:19;252:8; 287:5,13;300:22;304:2 talked (21) 8:3;14:11;16:14;18:8; 24:4;74:3;76:9;83:22;					

<p>therefore (4) 34:1;87:17;155:17; 306:6</p> <p>thinking (25) 66:7,18;73:11;97:18; 98:6,13;108:20;154:3; 183:16;185:5;186:1,2,4; 205:16;224:1;242:15; 251:16;255:12;263:14; 273:11;287:19;295:3; 301:7;312:10;314:22</p> <p>third (7) 53:2;62:15;64:16; 112:15;115:2;154:20; 170:22</p> <p>though (15) 17:5;89:5;116:18; 118:5;120:1;121:7; 127:13;164:1;169:6; 279:3;283:9,19;302:21; 308:20;315:19</p> <p>thought (30) 3:5;15:3;31:2;33:9; 65:22;67:19;71:3,8; 79:21;83:14;102:10,10; 123:10,14;149:8; 178:12;196:14;204:16; 214:15;241:13;245:4; 251:7;259:13;260:11; 265:20;288:18;293:18; 299:15;303:22;311:16</p> <p>thoughts (4) 94:7;105:10;115:18; 243:14</p> <p>thousand (1) 153:1</p> <p>thousands (1) 303:2</p> <p>threaten (1) 265:22</p> <p>threatening (1) 135:13</p> <p>three (11) 7:18;8:19;12:17; 76:20;81:7;124:19; 143:22;149:20;227:1; 272:21;317:22</p> <p>threshold (3) 51:13;131:21;148:17</p> <p>thresholds (2) 89:18;90:10</p> <p>throughout (6) 3:19;77:2;136:2; 188:18;268:17;269:14</p> <p>throw (6) 75:8;96:12;134:19; 212:10;241:13;247:20</p> <p>thus (2) 239:11;299:15</p> <p>tight (2) 76:12;179:22</p> <p>tightly (1) 20:18</p>	<p>timed (1) 112:19</p> <p>timelines (1) 184:19</p> <p>times (19) 5:17;24:11;54:11; 77:10;87:11;114:19; 119:22;134:16;140:15; 155:7;161:4,15;175:22; 182:3;185:6;186:8; 253:3;256:17;316:1</p> <p>times-2 (1) 86:20</p> <p>timing (1) 139:2</p> <p>tingliness (1) 104:5</p> <p>tingling (22) 14:14;57:18;58:3; 175:4;197:19;198:2,7; 199:19;200:1,4,8,9; 201:4,8,9,16,20,22; 202:2,3;204:13;220:6</p> <p>tips (1) 258:13</p> <p>title (2) 16:17;34:12</p> <p>TNS (34) 36:21;37:5;41:10; 65:3;67:1,22;83:4;84:3; 91:5,9;109:14;131:7,14; 213:12,18;214:20;215:1, 5,6,12;216:1,10,13,16, 19;218:8;219:21;220:4; 222:21;223:11;294:21; 298:16,19;306:3</p> <p>TNS-C (4) 84:9;131:12;213:22; 215:17</p> <p>today (6) 100:9;101:8;107:21; 122:16;225:1;228:19</p> <p>toe (6) 72:14;74:7,14,15,17; 230:13</p> <p>toes (3) 201:10,12;217:1</p> <p>together (26) 24:20;46:4;81:10; 83:8,11,12;96:5;103:7; 138:5;140:14;189:18; 197:21;199:19;250:15, 21,21;251:12,14;252:9; 255:5,10;265:17; 282:21;288:8,11;320:3</p> <p>token (1) 22:14</p> <p>told (6) 3:12;64:10;68:16; 79:16;116:10;127:1</p> <p>tolerate (1) 292:20</p> <p>tomorrow (5)</p>	<p>188:15,16,20;189:1; 213:16</p> <p>ton (3) 102:16;104:7;194:21</p> <p>took (11) 44:14;66:11;67:22; 71:5;78:17;135:8; 141:20,22;142:21,22; 310:1</p> <p>tool (12) 35:6;37:8;49:2;97:7; 100:17,20;101:9; 121:16;129:21;132:17; 165:18;211:8</p> <p>tools (12) 37:12;44:12;91:19; 95:6;96:1;100:9;109:19; 110:9;123:18,22; 245:21;249:3</p> <p>top (4) 89:7;201:21;286:4; 318:19</p> <p>topic (2) 62:12;156:7</p> <p>topics (2) 34:13;242:20</p> <p>topographical (2) 73:22;217:3</p> <p>Toronto (3) 69:8;215:13;216:15</p> <p>Total (5) 81:6;84:2;249:20; 255:16;278:8</p> <p>totaling (1) 17:8</p> <p>totally (6) 107:2;109:22;165:4; 226:6;268:10;269:6</p> <p>touch (2) 63:16;74:15</p> <p>touched (3) 158:1;168:10;245:4</p> <p>tough (1) 136:16</p> <p>toward (1) 82:15</p> <p>towards (4) 96:20;109:7,10; 113:16</p> <p>toxicities (7) 8:11;16:4,13;20:1; 25:14;26:9;256:9</p> <p>toxicity (8) 9:5;46:8;48:16;51:13; 185:12,19;253:20; 257:19</p> <p>track (1) 88:1</p> <p>traditional (1) 42:7</p> <p>traditionally (1) 197:5</p> <p>train (1)</p>	<p>131:11</p> <p>trained (9) 116:8;217:18;220:16, 22;221:1;222:1,19; 223:11;226:14</p> <p>training (12) 116:16;128:16,18; 131:8;137:3;140:2; 213:21;219:22;220:10, 14;222:15;299:10</p> <p>train-the-trainer (1) 220:11</p> <p>trajectory (1) 18:21</p> <p>tramadol (1) 306:21</p> <p>transcript (1) 68:17</p> <p>transform (1) 54:15</p> <p>transformation (1) 109:14</p> <p>transformed (1) 114:20</p> <p>transforming (1) 92:1</p> <p>transition (2) 89:11;90:14</p> <p>translate (4) 54:21;237:2;238:1,9</p> <p>translated (2) 39:3;120:5</p> <p>translation (2) 18:12;24:13</p> <p>translational (1) 17:15</p> <p>TRANSLATIONS (1) 1:4</p> <p>trap (1) 79:12</p> <p>travel (1) 159:19</p> <p>treat (5) 173:3;235:6;276:14; 304:6,13</p> <p>treated (5) 85:1;201:15;282:2; 305:7,8</p> <p>treating (4) 35:19;140:10;244:21; 280:1</p> <p>treatment (51) 5:16,20,21,22;8:11; 24:2;26:2;43:6;117:18; 118:14;121:3;131:15; 149:16;151:4,22; 153:11;154:10,12; 159:11,12;164:6;165:2; 168:18;175:19;182:7,7; 183:17;186:4;229:6; 242:7;243:20,22;244:9; 265:11;266:12;273:4; 274:21;275:1;280:16;</p>	<p>289:3;290:20;291:3,6; 292:4,10,19,20;302:19; 304:1;313:10;314:7</p> <p>treatment-naïve (2) 166:22;167:2</p> <p>treatments (10) 40:9;122:18;125:16; 126:18;161:10,14; 169:10;242:8;300:21; 303:21</p> <p>treats (1) 305:18</p> <p>trees (1) 246:13</p> <p>tremendous (2) 245:12;247:14</p> <p>TRIAL (140) 1:4,9;5:1,19;12:22; 13:1,5;19:11;23:8,11; 28:7;30:3;31:3,17;32:2, 11,19;39:16,20;41:16; 61:6;63:19;66:18;67:12; 75:11;76:7;84:22;85:17; 92:12,15;96:2;98:3; 99:4;103:11;110:18; 111:12;112:6;115:22; 116:9,16;118:21;119:1; 131:10,10,20;132:2,6,8, 13,21;134:8,9,9,17,21; 135:3;136:7;137:11,12; 138:21;139:18;143:7, 14;146:21;148:7;149:1, 7;150:4,5,6,16;151:1,6, 8,22;153:18,19;157:10; 158:9,15;160:20;173:20, 20;174:4,7,19,21; 183:19;185:15,16,17; 186:8;188:14,18,19; 189:1,3;206:6;210:4; 218:2,5;219:5,17;226:1; 228:11,14;230:20; 234:16;244:11;247:3; 248:21;256:5;260:20; 262:12;263:2;266:3,12, 12;267:2;285:6;289:6; 293:9,9;295:17;299:17; 301:3;302:14;305:22; 306:1,8;309:3,3,7,16; 310:11;312:7,13; 316:21;317:15,15</p> <p>trial' (1) 266:5</p> <p>trialed (1) 191:15</p> <p>trialist (1) 248:2</p> <p>trialists (1) 319:13</p> <p>trials (147) 8:1,4,6,14,22;9:2,3,6, 14;10:1,5;12:7,14;13:6, 9,16,18,22;14:3,13,15; 15:4;18:9,20;19:3;</p>
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<p>21:18;23:4,13;24:4; 25:16;26:20;28:17,20; 29:2,7,9,10,18;35:1,1; 39:6;40:4;42:5;44:18; 45:17;48:11;63:9,11; 65:14,18;66:1,2,8;68:3, 12;70:4;73:2;77:17; 80:6;82:5;85:4;91:12; 19;92:1,10;93:3;98:1; 99:19;102:21;105:2,3; 110:8;111:17;112:4,14; 115:15,17,18;117:20; 118:5;119:22;121:3; 124:13;125:14,18;134:3, 12;140:7;145:3;147:21; 148:5,12;150:4,4;153:1; 154:10;156:9,10,19; 160:15,17;164:8; 168:18;169:10;170:1,13, 18;171:14;172:12,14,22; 173:6;178:13,14,15; 181:9;182:21;185:12,13, 19;188:16;191:14; 211:18;212:8;213:3; 215:18;217:16;218:9,16, 22;224:1,1;228:21; 230:11;237:3;243:16; 259:16;263:17;266:15, 17,18;270:12;285:15; 307:11;311:17;314:1; 317:22</p> <p>tribulations (1) 134:13</p> <p>trickle (1) 188:6</p> <p>tricky (3) 42:20;221:5;251:2</p> <p>tricyclics (1) 305:7</p> <p>tried (10) 37:6;44:15;53:8; 54:11;55:13;97:9;101:3; 174:12;199:3;211:2</p> <p>tripping (1) 230:16</p> <p>trivial (2) 50:19;61:10</p> <p>trouble (11) 50:21,22;58:18;59:3, 9,10,13,15;72:5;232:12; 292:1</p> <p>trough (1) 255:15</p> <p>true (16) 19:19;20:5;31:4; 68:20;89:11;115:22; 122:1;183:9;190:10; 214:8;220:2;231:20; 233:17;276:13;290:2; 306:18</p> <p>truly (1) 28:21</p> <p>truth (1)</p>	<p>37:5</p> <p>try (27) 11:1;22:6,12;31:17; 40:11;43:7;152:16; 161:16;164:15;176:7; 178:19;180:4;186:18; 188:6;190:4;198:17; 211:6;227:14;228:17; 234:8;240:17;241:5; 256:5;258:17;262:9; 291:16;292:11</p> <p>trying (43) 17:17;22:17;25:17; 33:20;37:12;53:9;95:10; 99:1;100:17;105:6; 108:22;112:16;118:5; 120:17;122:7;123:3,19; 156:12,17;162:18,22; 163:21;174:7;183:19; 185:11;198:1;219:10; 235:6;239:22;264:3; 265:16;266:19;268:13; 273:22;276:14;291:18, 21;292:8,22;293:4,17; 317:12,13</p> <p>tumor (2) 18:7;284:5</p> <p>tumor-bearing (1) 17:21</p> <p>tumors (2) 169:17,21</p> <p>tuning (1) 217:11</p> <p>tunnel (1) 76:5</p> <p>turmoil (1) 71:22</p> <p>turn (4) 83:9;160:10;231:9; 258:14</p> <p>turned (3) 79:18;110:6;221:19</p> <p>turning (1) 198:8</p> <p>turns (3) 82:9;83:16;149:10</p> <p>twice (2) 30:11;277:8</p> <p>twisted (1) 292:22</p> <p>two (81) 4:6;7:20;8:17;10:3,15; 17:14,17;19:3,4,5;23:20; 39:18;41:5,6,9,14,19,21; 46:11,14,16;50:17; 54:21;57:16,17,20;59:8, 19,22;61:6;63:13;65:14; 76:20;81:9;96:14;100:6; 109:14;113:13;114:8; 129:17;142:6;143:22; 150:4;152:14;154:18; 155:3;162:8;165:19; 166:16;167:3;176:3;</p>	<p>177:8;181:21;182:18; 188:4,10;189:5;190:4; 193:4;197:20;214:19; 226:19;227:1;246:8; 252:5;257:14;261:16, 16;263:21;265:1,7,13; 266:14,15;267:13,22; 268:11;282:21;300:12, 15;312:8</p> <p>twofold (1) 224:7</p> <p>two-stage (1) 237:7</p> <p>two-week (2) 176:18;310:11</p> <p>two-year (1) 309:7</p> <p>type (26) 65:11;101:11;121:18; 136:12;149:3;161:17; 165:9;192:20;224:20; 232:10;237:7;241:20; 257:8;275:21;276:3,5, 16,18,21;277:3,7;278:5; 279:9;283:21;307:18; 314:13</p> <p>types (13) 38:4;73:20;86:4,8; 112:5;182:21;199:22; 242:14;266:15;277:1,3; 278:19;294:3</p> <p>typical (2) 50:11;90:10</p> <p>typically (5) 18:15;143:1;170:12; 188:3;217:22</p>	<p>10;316:4</p> <p>underestimate (3) 160:13;247:11;248:22</p> <p>undergoing (2) 8:11;186:4</p> <p>underlie (1) 93:18</p> <p>underlying (3) 16:3;157:1;277:20</p> <p>underneath (1) 227:20</p> <p>underpinnings (3) 15:16;23:10;25:1</p> <p>underserved (6) 8:21;9:11;10:8,10,19; 11:11</p> <p>understood (1) 158:21</p> <p>undertaking (1) 317:1</p> <p>under-the-curve (1) 316:3</p> <p>underutilized (1) 93:3</p> <p>undervalued (1) 108:21</p> <p>unfilled (1) 49:16</p> <p>unfortunate (2) 94:2;113:20</p> <p>Unfortunately (6) 35:12;38:13;41:7; 57:9;68:7;166:5</p> <p>unfriendly (1) 176:20</p> <p>uniform (1) 107:6</p> <p>uniformity (1) 101:15</p> <p>unique (1) 93:2</p> <p>unit (1) 264:9</p> <p>United (1) 204:18</p> <p>University (4) 10:16;11:8;62:4;70:12</p> <p>unknown (2) 6:12;110:12</p> <p>unknowns (1) 267:12</p> <p>unless (10) 36:12;61:16;99:4; 121:5;156:13;163:5; 164:12,16;302:14; 308:10</p> <p>unlikely (1) 113:12</p> <p>unpleasant (4) 198:22;199:2;205:4, 10</p> <p>unpredictable (1) 47:1</p>	<p>unproven (1) 120:1</p> <p>unrealistic (1) 298:3</p> <p>unrelated (2) 116:1;253:21</p> <p>unwilling (1) 158:17</p> <p>up (95) 11:12;15:19;30:12,16; 31:20;32:16,21;39:7; 40:6;43:3;50:3;55:13; 67:9;72:2;74:22;75:9, 18;76:4,4;77:10;78:4; 83:16;86:3;90:15;97:19; 99:14;105:14;106:6; 109:12;110:5;112:19; 117:12,22;118:19; 121:18;122:6,19;124:18, 20,22;126:16;135:10; 139:16,18;140:1,4,5,20; 141:11;148:11;151:9,9, 12;152:13;154:8; 161:20;163:6;164:8,18; 167:10;169:9;174:20; 180:1;186:12;197:18; 202:9;211:1,2;215:22; 216:22;228:7;230:7,16; 236:19;243:7;250:13; 254:10;255:3;264:7; 276:6;277:13;279:6; 283:19;284:1;292:11; 294:15;297:2,3;299:16; 301:10;308:17;310:13; 311:2,11;316:22</p> <p>updated (1) 141:6</p> <p>UPDRS (1) 126:9</p> <p>upfront (1) 218:2</p> <p>upon (10) 179:5;184:7,8;186:19, 20,20,20;212:21;268:2; 303:10</p> <p>upper (1) 52:15</p> <p>urgent (1) 93:15</p> <p>usability (1) 96:20</p> <p>us-and-them (1) 165:8</p> <p>use (67) 42:8,14;43:21;47:14; 49:19;56:9;57:11;58:19; 64:4;74:8;77:21,22; 78:2;80:6;86:12;87:22; 88:1;91:19;93:2;98:20; 100:9;101:22;104:4; 105:17;106:3,19; 107:18;110:10;111:10, 13,19;112:1;120:11;</p>
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122:12;131:1,13,15,21; 132:14,18;144:1,8; 178:16;183:6;186:9; 190:17;191:16;197:18; 200:14;204:7;210:5; 213:15;214:3,11; 243:13;250:2;252:13; 272:8;279:13;282:18; 291:5;295:21;296:12; 300:7,7,8;312:1	108:21;140:4;272:13 Utah (2) 62:4;83:2 utility (4) 116:19;214:17; 215:11;224:6 utilized (4) 31:18;145:15;179:3; 249:22	56:11 variety (4) 23:22;90:22;179:9; 231:10 various (9) 28:17;64:11;65:3; 68:11;82:12;84:7;91:18; 142:16;161:13 vary (1) 229:5 vascular (1) 208:2 veering (1) 73:16 velocity (3) 38:12;233:16;238:18 versa (1) 242:10 version (6) 97:10,11;211:18; 212:22;214:1;220:4 versus (23) 40:21;79:21;104:6,6, 7,7;118:3;121:3;146:10; 151:17;177:13;179:17; 199:5;201:22;202:2; 256:18;261:16;262:13, 13,20;282:20;288:2; 301:16 vet (1) 142:8 vetting (1) 137:22 via (2) 129:9;177:22 vibration (9) 41:9;65:4;69:12; 74:14;80:7,15;84:5; 217:12;220:7 vice (2) 145:8;242:10 video (2) 219:22;220:10 view (6) 97:8;108:2;227:13; 248:9;254:14;286:10 viewed (2) 149:4;159:22 views (1) 235:12 Virginia (1) 70:12 visit (3) 78:20;226:19,20 visiting (1) 38:22 visits (1) 177:20 visual (2) 89:4;210:14 vital (1) 161:5 Vitamin (1)	303:5 voice (3) 44:6;79:3;280:12 void (1) 297:5 volume (2) 246:3,6 voluntarily (1) 160:9 vomiting (1) 6:20 vote (1) 29:13 vulnerable (2) 170:20;271:8	165:10;171:1,11;173:9; 176:13;177:11;182:14; 185:8;193:19;194:10; 195:17;198:15;199:6; 202:16;204:9;205:16; 206:17;210:4,15; 216:21;219:21;220:17; 223:12;224:18;225:7; 229:11;230:22;234:4; 238:16;249:22;251:2; 252:3;254:10;256:11, 21;260:16;261:9;266:7; 267:20;269:13;275:2; 287:9;289:18;291:11, 12;293:2,18;294:1; 311:21;313:11;317:4, 16;318:3
used (54) 12:6;14:17;17:21; 20:5;24:15;36:22;42:9, 13;44:12;45:17;49:2; 50:18;63:9;65:11;67:15, 22;68:12;69:11;75:16; 82:2,4,6,7;84:10;100:21; 108:1;110:8;119:21; 136:19,20;140:13; 147:14;151:20;157:20; 167:18;169:17;175:1; 179:9;184:15;191:9,14; 192:21;197:21;199:7; 207:5;220:14;223:21; 224:15,19;245:21; 246:4;256:18;259:18; 282:20	V	validates (1) 226:11 validating (3) 70:21;96:8;220:13 validation (9) 49:16;56:10;90:1; 95:17;103:3;108:7,7,7; 213:6 validities (1) 194:2 validity (7) 47:12;50:5;82:19; 112:2;194:1,8;223:18 valid-wise (1) 235:3 valuable (3) 77:15;92:20;113:12 value (9) 72:13;77:13,14,16; 93:2;209:8;210:11; 223:16;229:18 variability (8) 81:21;192:19;245:12; 246:13;257:4,5;284:3; 318:18 variable (4) 136:20;158:8;185:1; 249:3 variables (3) 263:20;267:11;279:22 variance (4) 247:14;263:9,21; 283:4 variances (1) 248:17 variations (1) 257:15 varied (1)	wait (3) 27:4;167:20;259:9 waiting (3) 56:20;197:17;219:10 Wake (3) 10:16;11:8;76:4 walk (5) 90:17,17;167:22; 230:17;236:19 walking (1) 72:5 walks (3) 112:19;233:14;236:18 wants (5) 32:13;106:13;147:7; 209:9;235:20 warm (1) 60:8 warning (2) 136:9;179:10 warranted (1) 93:9 warrants (1) 245:14 warts (1) 188:22 washed (1) 254:1 Washington (1) 1:18 wasted (1) 82:22 watching (1) 114:2 way (89) 9:18;11:19;34:20; 35:1;47:3;54:20,20,21; 55:1;63:12;78:19;82:16; 83:12,21;89:4;92:8; 93:16;99:8;101:4;112:3; 119:19;122:10,14; 130:14;131:4;132:3; 133:5;137:1;140:21; 143:19,21;147:15; 148:19;149:4;151:6,21;	ways (13) 5:10;6:16;37:14; 41:14;146:6;148:3; 155:4;178:13;180:3; 224:13;249:19;253:7; 293:16 weak (7) 59:11,18,18;74:15; 204:3;239:15;241:16 weakness (3) 82:22;87:15;216:6 weaknesses (3) 57:3;84:17;216:1 wear (3) 7:20,21;8:7 wearing (1) 79:3 website (4) 4:18;68:18,18;220:11 week (8) 94:1;152:7;155:20; 181:22;182:1,1;259:9; 261:16 weekly (1) 182:2 weeks (8) 67:7;129:11;176:3; 181:21;226:19;277:9; 300:12,15 weight (6) 54:1;56:2,5;86:19,20, 22 weighting (2) 81:22;130:14 Welcome (1) 3:4 well- (2) 50:10;191:19 well-considered (1) 275:8 wellness (1) 35:13 well-trained (1) 227:22 well-validated (3) 93:11,12;191:15
useful (26) 60:19;61:1;73:18,18; 82:8;83:6,16,18;85:18; 90:13;92:19;96:19;99:7; 106:16;117:15,17; 132:16;178:8;190:19; 193:2;205:16;215:16; 224:4;242:13;258:8; 260:2 usefulness (1) 117:19 useless (4) 38:8;72:16;210:12; 253:19 user (1) 180:5 uses (2) 87:4;293:7 using (55) 11:17;37:11;38:7,18; 39:1;43:13;44:1,22; 46:12;54:6;58:4;60:11; 67:10;68:9,15;69:3,4,5; 71:1;73:14,15;87:14; 101:19;102:16;103:12, 14;104:9;109:10;113:8; 119:9,10,11,12;123:22; 130:7,8,13;148:13; 150:5;190:20;192:3,11; 214:3;221:8;244:11; 246:14;288:1;290:15; 295:16,17,22;299:13; 306:2;312:3,8 usual (1) 186:16 usually (3)			W	

<p>Wen (5) 134:4,4;147:20; 160:13;169:5</p> <p>weren't (4) 22:15;90:9;199:14; 245:22</p> <p>west (1) 11:9</p> <p>Westin (1) 1:17</p> <p>whatnot (2) 119:19;177:5</p> <p>what's (17) 63:5,10,21;74:16; 83:15,17;107:18; 116:10;138:10;189:2; 193:16;196:22;198:1; 199:10;203:5;240:1; 249:8</p> <p>whereas (5) 11:20;65:13;227:14; 288:15;295:12</p> <p>whereby (1) 146:20</p> <p>Whereupon (3) 133:11;187:3;320:5</p> <p>whichever (2) 111:14;253:8</p> <p>whistles (1) 152:17</p> <p>WHO/ICF (1) 55:7</p> <p>whole (11) 39:2;72:12;118:18; 146:15;158:3,5;178:8; 197:18;199:21;244:21; 310:8</p> <p>whopping (1) 30:13</p> <p>who's (10) 86:6;87:13;100:2; 162:3;167:22;219:10; 221:8;273:17;289:6; 302:18</p> <p>why'd (1) 155:17</p> <p>wide (6) 37:10,16;49:19;51:2; 91:16;95:7</p> <p>widely (2) 42:9;191:9</p> <p>widely-used (1) 91:20</p> <p>wife (1) 119:8</p> <p>willing (4) 158:19;217:6;233:6; 236:1</p> <p>willingness (3) 88:9;154:5;182:19</p> <p>wisdom (1) 70:8</p> <p>wiser (1)</p>	<p>291:19</p> <p>wish (2) 4:5;195:12</p> <p>wishy-washy (3) 272:7;296:12;298:12</p> <p>within (20) 6:12;15:1;17:17; 20:21;22:18;25:2,11; 32:19;53:8;111:12; 125:14;137:13,21; 142:18;144:4;231:8; 279:17;281:19;283:14; 301:18</p> <p>without (15) 55:19;60:19;88:13; 99:18;100:13;101:21; 137:3;145:6;159:18; 160:20;183:21;213:4; 265:5;273:10;295:7</p> <p>wonder (7) 141:14,16;150:8; 171:15;228:17;234:15, 19</p> <p>wonderful (2) 31:16;121:11</p> <p>wonderfully (1) 6:4</p> <p>wondering (4) 122:12;178:11;179:1; 257:17</p> <p>wood (1) 246:12</p> <p>word (7) 81:15;141:6;199:20; 200:15;201:17;203:17; 284:13</p> <p>wording (1) 16:11</p> <p>words (4) 38:5;172:17;199:22; 246:10</p> <p>work (42) 3:22;4:1,21;9:12; 24:12,22;66:15;81:13; 95:9,13;103:4;114:22; 122:10;124:16;125:8; 132:9,17;146:1;163:1, 15;169:22;170:2,3; 177:3;179:14;185:7,22; 186:3;190:22;194:7,7; 207:2;227:17;230:9; 255:9;258:6;261:8; 273:7;296:7;307:14,22; 308:5</p> <p>worked (9) 50:7;137:19;139:12; 155:6;162:20;253:4; 258:6;287:4;297:14</p> <p>working (20) 50:6;52:2;59:9,10,13, 15;92:16;94:4;95:12,19; 101:10;130:20,20; 132:19,20,22;148:13;</p>	<p>161:12;236:20;305:22</p> <p>works (9) 47:9;51:2;115:14; 122:11;123:6;125:10; 130:10;204:8;308:20</p> <p>world (13) 29:6;63:22;65:17; 78:7;81:8;82:2;115:1, 11,12,16;214:18;282:3; 293:18</p> <p>worlds (1) 97:1</p> <p>world's (1) 282:6</p> <p>worms (1) 279:7</p> <p>worried (3) 155:10;219:4;290:3</p> <p>worry (5) 66:4;227:8;288:7; 306:12;316:1</p> <p>worse (10) 31:9;88:2;123:13; 124:19;172:20;229:8; 244:19;252:2;257:1; 288:4</p> <p>worsened (2) 13:4;75:19</p> <p>worst (2) 52:8;251:4</p> <p>worth (4) 4:17;210:15;218:6; 314:21</p> <p>worthwhile (1) 164:15</p> <p>worthy (1) 116:22</p> <p>wow (1) 62:14</p> <p>wrap (1) 186:12</p> <p>wrist (1) 217:1</p> <p>write (3) 88:11;120:5;181:16</p> <p>writing (2) 269:22;303:16</p> <p>wrong (2) 10:13;223:6</p> <p>wrote (2) 142:1;146:22</p>	<p>39:13,18;47:3;49:9; 85:2;101:1;102:20,21; 104:20;106:4;114:16; 123:9;125:18;127:11; 132:14,18;142:3; 161:15;162:9,21; 166:21;172:11;179:16; 232:15;272:13,21;286:8</p> <p>years' (3) 167:3;189:2,4</p> <p>yellow (2) 11:6,10</p> <p>yesterday (42) 3:11,16;6:5,15;8:3; 14:2,6,12;22:20;34:21; 44:16;63:7;64:10;71:7, 12,20;75:10;76:10;85:3; 97:19;98:18;121:8,17; 131:22;159:7;200:2; 247:19;250:19;251:3; 264:2;270:2,8,18; 285:12;290:12;292:14; 293:3;294:7,14;296:17; 300:22;304:14</p> <p>yesterday's (1) 44:14</p> <p>younger (1) 38:9</p>
Z			
<p>zero (7) 33:16;34:2;86:17,21; 296:18;298:3,9</p> <p>Ziegler (1) 85:5</p> <p>zone (1) 5:15</p>			
Y			
<p>year (14) 39:18;80:2;128:18; 140:15;143:1;144:14, 17;161:15;162:13; 163:17;211:1;238:1; 261:15;265:8</p> <p>years (35) 6:1;12:6;13:21;23:13; 25:9;31:21;33:6;36:14;</p>			