ACTTION - Chemotherapy-Induced Peripheral Neuropathy (CIPN) Trial Design Considerations

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ACTTION

ANALGESIC, ANESTHETIC, AND ADDICTION CLINICAL TRIAL TRANSLATIONS, INNOVATIONS, OPPORTUNITIES, AND NETWORKS

Chemotherapy-Induced Peripheral Neuropathy (CIPN) Trial Design Considerations

Friday, March 24, 2017
8:12 a.m. to 3:20 p.m.

Westin City Center
Washington, D.C.

C O N T E N T S

P R O C E E D I N G S

(8:12 a.m.)

DR. FREEMAN: Good morning, everybody. Welcome to day 2. Before beginning the agenda, the proceedings, what I thought I would do, very briefly, is just go over what I envision as being the goals of the meeting itself.

Could I have the first slide?

Yes. Well, I suppose housekeeping is much more important than meeting goals, so I want to read this, same slide that appeared yesterday. I see check-out time is 12:00. I was told that people were not speaking closely enough to the microphone, so when you have questions and comments, please, we are, as Bob Dworkin mentioned yesterday, recording the meeting.

Next slide. My slide.

So there were a couple of questions throughout the day, what is going to come of this, why we're meeting here. And I want to outline the point that Bob made earlier on, that there will be a work product that will be a consequence of this

meeting. It may be one or more work products and those will be manuscripts.

They will be most likely first authored by Jennifer Gewandter, and all of you attending will have the opportunity, if you wish to, one, contribute and, two, be authors on that manuscript or those manuscripts.

Just to give the background to this, there have been a series of very highly cited and influential manuscripts that have come out of these ACTTION meetings, that have really changed the landscape of the territories that they have been involved in.

So we're hoping that, at the very least, this will have something that resembles the influence that those manuscripts have had. And it's worth looking, for those of you who are new to those meetings, at the ACTTION website to get some sense of the contribution to the field that the ACTTION has made.

So our goals over here are to develop a work product that outlines a road map for a clinical

Page 5

trial to evaluate disease modification of chemotherapy-induced peripheral neuropathy. And this will be primary or secondary prevention, so if you think of the slide that Pamela Horn showed, it is that bar during chemotherapy.

By primary intervention, we mean before chemotherapy is started, and secondary intervention, we mean once chemotherapy-induced peripheral neuropathy has manifested in one or other ways. And by disease modification, we mean to prevent or delay the appearance and/or slow the progression of chemotherapy-induced peripheral neuropathy.

That is somewhat different -- and I say somewhat because there is a gray zone between disease modification and symptomatic treatment, which at times we attempt to make discrete, but they're not as discrete as often as we attempt to portray, a clinical trial to evaluate symptomatic treatment of CIPN.

This is the acute treatment, so not chronic treatment. For example, that was covered in the

Page 6

manuscript published a couple of years ago by Ellen Smith. So these are the symptoms that appear, and it's not just pain, during chemotherapy, wonderfully portrayed by Joanna Brell's patient, her case study that she showed yesterday.

Then -- and this may or may not be a separate manuscript -- how to assess, how to evaluate, how to measure chemotherapy disruption, so the dose reduction, the discontinuation that occurs during chemotherapy.

Then finally, there will be areas that are unknown within 1 to 3, and those will be subject to a research agenda, areas to study. And examples of that may include the suggestions made by Scott and Mike yesterday and reinforced by Sharon about the ways to address in a combined, a composite, a synthesized measure of chemotherapy disruption and symptom modification, the example that Sharon Hertz gave to an approach to chemotherapy-induced nausea and vomiting would be.

So that territory is an example of what we might consider to be research agenda.

Page 7

So that's the landscape. That's what we would like to accomplish, at least to provide Jennifer with the components of that manuscript, and we will finalize that during the session this afternoon.

So let me hand over to my co-chair, Jennifer Gewandter.

DR. GEWANDTER: Good morning, everybody. Thank you for coming back the second day to our meeting. It's my pleasure this morning to introduce Dr. Ann O'Mara. She is the program director and head of palliative care research for the Division of Cancer Prevention.

Presentation – Ann O'Mara

DR. O'MARA: Thank you, Jennifer, and thanks for the invitation. So my task was to give an overview of the NCI's perspective on CIPN. So three goals that I have, and as you read them, I'm going to give you some background.

So I wear two hats. The first hat that I wear is I am involved in the Community Oncology Network, where we do cancer control symptom

Page 8

management trials. And I'm going to give you an overview of that, building on what Joanna Brell had talked about yesterday, but going to into a little bit more detail about that clinical trials network. And I'm going to highlight and show you some of the trials that we have done through that network.

Then the second hat that I wear is I'm also a program director for the investigator-initiated pool of research projects that come into NIH or into NCI and primarily focused on patients undergoing treatment, and the toxicities, and the psychosocial issues that patients experience, looking at both longitudinal studies in clinical trials.

Then I'm going to end with telling you a little bit about what we've learned both from these two portfolios, but more specifically what we've learned from the NCORP portfolio.

So the NCORP is comprised of three components. There is what we call the community sites, the minority underserved community sites, and the research bases. We do clinical trials

Page 9

across the cancer continuum. We do not do prevention trials. I'm sorry. We do not do disease-treatment trials. Those come from a different funding mechanism. But what we do, do is prevention, symptom toxicity, quality of life, comparative effectiveness, and screening trials, so really across the spectrum.

We also have added with this NCORP program more health services, what we call cancer care delivery. We have a high interest in disparities and the underserved population, and then we also work with the NCTNs, also known historically as the cooperative groups, but now known as the National Clinical Trials Network. Those are our old cooperative groups, SWOG, ECOG-ACRIN, et cetera.

Along these same lines, there is a very strong community, academic partnership. So what does this look like? So the way I like to explain it is that the research base, as we like to define it, is our scientific engine. This is the group. This is your SWOG, ECOG, Alliance. This is our scientific engine.

Page 10

These are the folks that design the trials, and conduct them, and actually manage the data and analyze the data. Then we have our two what I call accrual engines, the community sites which accrue participants to these trials that I highlighted in the previous slide.

We also, as I said, have a very keen interest in minority and underserved. And we actually have a number of sites where it is composed of 30 percent minority or underserved populations. So we're very, very interested in that population.

So the first bullet is wrong. It's not 12 research bases. It's seven research bases. It's five of the cooperative groups and then two cancer centers, Wake Forest and the University of Rochester.

Then we have 34 community sites and 12 minority and underserved community sites. But across that, we really have 947 components and subcomponents. So it's a really, really big network. And then we also have over 300 of what we

Page 11

call cancer care delivery components that try to do or implement health services research.

So it's really quite a big network, and this is what it looks like nationally. So it's across the country. I'm going to start backwards. So the research basis, which is in yellow, several of them are located in the Pennsylvania area in Philadelphia, University of Rochester, then Wake Forest, Alliance, and then SWOG out on the west coast. So those are the little yellow ones.

The minority and underserved is your purple, again, across most of the south and then up along the east coast, and then the community sites. And as you can see, we have both a distributive network, which means it's a component, and then there are other sites around it, and then a highly integrated system where they're using similar components.

The way they manage, the data comes to one site, whereas the distributed is more of a loose federation, as I like to think of it. And then we also have small networks, small practices across

Page 12

the country.

So it's really quite diverse in terms of how this network looks. And as you can see on the map, it's really across the country.

So over the course of a number of years -- it used to be called CCOP, now called NCORP -- we have supported 14 clinical trials and 1 natural history study. And all of them were pharmacological interventions.

As you look through that list, what you're going to see is that they're all either FDA approved, taking the agent and repurposing it, or some sort of nutritional supplement of some sort.

Four of the trials included different chemotherapies. Others targeted specific chemotherapies. Taxane, cisplatin, and oxaliplatin were the three that we had most commonly seen. Seven were prevention and seven were established CIPN, so it was evenly distributed.

Then all of the studies were negative -- that's the big take-home message from this trial -- except for duloxetine, Ellen Smith's

Page 13

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

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

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

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

Page 14

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

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

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

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

Page 15

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

So first, I want to talk about some of our funding opportunities. NIH in general is very interested in CIPN, but we're also interested in the larger issue of mechanisms of these symptoms. It is not only CIPN that is problematic for our patients, but fatigue is another one for which we have a very poor understanding of the mechanisms. Cognitive impairment is another one.

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

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

Page 16

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

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

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

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

Page 17

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

Page 18

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

Page 19

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

Page 20

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

Page 21

exactly robust. But that's NCI's interest. We're interested in everything across the cancer population, everything across patients at risk for cancer, but the actual funding of it is based on enthusiasm of peer review.

Now, that being said, I have had some success in bringing forth applications that are just shy of our pay line and bringing it to the leadership for funding by exception. I have had particular success, interestingly, in CIPN.

I've also had success in some other areas, but I have had success with applications that are just shy of the pay line. And so our interest and funding really are -- they're parallel. There's some overlap. But the actual funding is really based on the excitement of peer review.

So our interest in mechanistic studies, so it goes back to those clinical trials that I showed you that were done through NCORP and the robust negativeness of all of them.

So we have this 30-year history of funding and supporting this science, and, as I said, a lot

Page 22

of negative. But what we also learned as we looked at those studies was that many of these studies were based on empiric data, a sample size of 10 or 15. We gave just 10 or 15 patients. We found a good response. It's FDA approved for something else. Let's give it a try. That's come back to a lot of money we've spent to find out that they're negative.

Now, was that a bad thing to do? No. I don't think it was a bad thing to do. All of those agents, we can take off the list because we found that they were negative. So I try to put a positive light on this, that we've learned a lot from these negative studies, but by the same token, they weren't mechanistically based.

So we have a really very high interest in trying to understand the mechanisms of these symptoms, and so within the context of this meeting, in terms of CIPN. As was pointed out yesterday, I think by Jennifer's presentation, the natural history of symptoms and the natural history of CIPN, we do not have a good handle on. And in

Page 23

order to get I think a better handle, that's where our interest has to be.

I think you saw it in the NIH-funded studies of the very few clinical trials that we have, that the interest is primarily in longitudinal studies. And I can't talk too much about projects that were not funded, but in listening to peer review, when investigators come in with a clinical trial into peer review looking for NIH funding, if they don't have strong mechanistic underpinnings to that clinical trial, they will not receive a good score.

So I think that speaks to the 6 clinical trials that have been funded over the last 5 years, between 2011 and 2016.

This is Robert Korycinski. He was our program analyst that did this review for us. And as he read through it, one of the things he came to see was that he felt like they were operating -- our preclinical and our clinical CIPN researchers were operating in two different research paradigms, that the preclinical researchers were investigating a variety of

Page 24

biomarkers and pathways, and that our clinical researchers were examining many potential treatment methods, and there wasn't this overlap. And you saw that as I talked about our history of trials that we did through the NCORP.

They don't seem to collaborate. One of the things that we had Robert do is look not through all of them, but through a lot of the preclinical grants, and look to see if there was a clinical collaborator or a clinical consultant. And a lot of times, there wasn't. It was a group of preclinical doing this work.

So that translation gets lost. I think that's why we see so many of our models, of our animal models that were used in these studies being non-tumor-bearing.

Then the collaboration or at least frequent communication should expedite. And when we had our meeting on March 1st, we actually did bring together clinical and preclinical investigators who, from our readings and our understanding of their work, they were very close to identifying

Page 25

some interesting mechanistic underpinnings and had tested some agents within the preclinical model, and maybe these were ready for moving into the clinical arena. And then establishing CIPN research teams with both of those. And that was our goal on March 1st with that meeting.

Now, that being said, one of the interesting things that I've learned over the years -- particularly not so much in managing the NIH portfolio or NCI portfolio, investigator initiated, but more within NCORP -- as you saw, a lot of these agents are FDA approved. And I would argue, and not only for CIPN, but for many of our toxicities, that interest of pharma is much less than that interest that pharma has in our disease-treatment trials.

So engaging pharma and trying to get pharma to support these studies is very, very challenging for our investigators. It's extremely challenging. And I think that's one of the major barriers or challenges that our investigators have, is drug development.

Page 26

We have a very, very robust drug development program at NCI for disease treatment. I confess that we do not have that same drug development program. And this is not a secret or anything. We don't have it. We do not have a robust drug development.

I think it has to do with a lot of pharma's interest, or mild interest, in developing these drugs for our symptoms and toxicities. It is what it is. And so our investigators are very challenged when they bring forth protocols to us through the NCORP network of how are they going to pay for this drug, how are they going to pay for the placebo, because we don't support that through that network. That's not how our funding stream is. And drug distribution; you saw our network. You saw it across the country.

So to provide that kind of funding is a very expensive endeavor. So I would argue to you that when we get to those phase 3 trials, those are the challenges. Phase 1 may be a little bit easier. It's single institution. Maybe you can get support

Page 27

for that. But once we start moving this out to a phase 3, I would argue that's one of the biggest challenges that we have.

So questions or should we wait for the panel?

DR. GEWANDTER: Yes. I think we can have a couple.

DR. O'MARA: Joanna?

DR. BRELL: Ann, do you remember -- well, you said that there were studies to the NCORP that had functional assessments at secondary endpoints.

DR. O'MARA: Yes.

DR. BRELL: Do you remember what any of those were?

DR. O'MARA: They were primarily the functional domain and the quality-of-life measures. It wasn't anything like observing. It was more of a PRO. I think it was mostly the functional domain on either the EORTC or one of Cella's, David Cella's.

Most of them are PROs because, again, through that network, it's got to be quick and

Page 28

easy, so to do anything beyond that, it would be difficult.

DR. DWORKIN: Ann, thank you for an incredibly informing talk. I really appreciate it. But I have to take issue with one thing, and I think some people in this room are not going to be surprised. To me, a single negative trial, like for example gabapentin or amitriptyline doesn't prove that those drugs aren't efficacious in CIPN --

DR. O'MARA: I agree.

DR. DWORKIN: -- because, of course, that could be a falsely negative result.

DR. O'MARA: Based on the measure, probably.

DR. DWORKIN: Well, I don't know. And Jen just published an article examining all of those trials in detail and comes to various conclusions about that.

So I think it's essential to me, when I look at that list of trials, to kind of think about are these truly negative results or are they potentially falsely negative results? And when I

Page 29

think about that question, I think about the fact that there are about a half a dozen clinical trials now of pregabalin in painful diabetic peripheral neuropathy that are negative, but that's a drug that's FDA approved for painful DPN and that, around the world, is considered first-line.

So given half a dozen negative trials of pregabalin and DPN, my issue with your conclusion about those negative trials is could some of those be falsely negative trials?

DR. O'MARA: Oh, yeah. Let's take a look at some of them.

DR. DWORKIN: We could vote.

(Laughter.)

DR. O'MARA: I mean, yes. I agree. I agree. I think part of it, too, some of these were earlier, so we're talking 2006. And I don't have all the details, but I think in our earlier trials, it was a more mixed population.

So Charles, I'm going to pick on you. On the gabapentin one that you put in, it was more mixed, wasn't it? Wasn't it a mixed population, or

Page 30

was it all one agent?

DR. LOPRINZI: So I think it was a mixed trial, and I could double-check on that. And whether that's pro or con on it, yes. And there is an interesting story about gabapentin, going back to where it was first discovered.

It was first reported at an ASCO abstract that 7 patients who were getting FOLFOX therapy reported in 2000 at ASCO, saying they got neuropathy and they started gabapentin, 100 milligrams twice a day. And if it didn't help them, they went up to 300 milligrams a day, a whopping dose.

Everybody knows I'm really being facetious because that's a 10th of what you really can give. And all of the patients were able to get up to 14 cycles of the FOLFOX therapy.

It was never published. But that was the basis for it. And if you really go back -- and I've done this recently. If you look at the literature on this in patients with cancer, it's just -- I'd love for it to be positive. And a lot

Page 31

of people say there are some patients it helps.

My newest thought process is maybe there are some patients it helps, and maybe our trial is actually true because there are other patients it hurts, and on average, it doesn't do anything. So I'm actually planning to look back at our data to see, did we see disparity. A lot of people got better on the gabapentin, a bunch of people got worse, and the other group, the placebo group, was just right on the line.

That might help fulfill that potential thing, that it does help in some patients. And then you stop it in the patients in whom it doesn't help, and you get net benefit, and that might explain clinical.

But it would be wonderful to be able to do another trial in that area to try to solve that problem once and for all because it's utilized a lot.

DR. DWORKIN: Let me just follow up. I have a car that's 10 years old that I love. And I would bet my beloved car that if NCI gave Ellen Smith

Page 32

enough money to do a double-blind, randomized, controlled trial of, say, 300 to 450 milligrams a day of pregabalin in painful CIPN, that she'd have a positive result.

The reason I'm saying that is because you said that that kind of study can't be supported by NCI, but of course it can be because pregabalin is on the market and there are investigational pharmacies all over the country that can encapsulate pregabalin and placebo that would allow Ellen to do a definitive phase 3 trial of pregabalin and painful CIPN.

So NCI could, assuming Ellen wants to do such a study, I don't know. But Ellen could do that study, and someone could get my car if it's negative, but I think I would end up keeping my car.

DR. O'MARA: I think there's probably prejudice within NCI on doing that kind of a trial because of the negative. I think you'd have to come up with a very strong scientific argument in a very specific population of who you think would

Page 33

benefit from it, given the findings from Charles's earlier studies and the other studies --

DR. DWORKIN: We'll do that over the coffee break.

DR. EVANS: I would make one comment. I have a car that's 18 years old, so I need a new one.

(Laughter.)

DR. EVANS: I thought I'd make a comment about the sort of interpretation of negative studies, which actually we're pretty poor at, and you'll hear statisticians barking about confidence intervals all the time.

But of course, high p-values don't necessarily mean -- they mean that you couldn't rule out an effect of zero, but it may also mean that you can't rule out effects of very important magnitudes.

So that's why, looking at interval estimates and trying to figure out, can you rule out meaningful, or what you consider to be meaningful, effects with reasonable confidence rather than

Page 34

saying I've got a p-value of 0.4; therefore, there's zero effect, which is incorrect. You really have to look at interval estimates.

DR. O'MARA: Sure.

DR. GEWANDTER: Next, I would like to introduce Dr. Cavaletti. I'm not going to butcher the name of his school because I think you all know him, so here he is.

Presentation – Guido Cavaletti

DR. CAVALETTI: Thank you. Thank you very much for this invitation, although I'm not sure I can thank you for the title of my talk because PRO seems to be one of the hot topics. And what we say in Italy, a hot potato for me, because it's not so easy to have a look at this method to assess CIPN and my talk with a clear idea. So I'm sorry. I feel that we will finish my talk with more doubt than answers.

Why is the issue so complex? We need to decide which is the best way to assess our patient, and we have discussed a lot yesterday, because assessment has a clear implication not directly on

Page 35

trials, but on the way we can conduct trials to identify what is the best approach to prevent, or to limit, or to rescue our patients when they are suffering from CIPN.

So the discussion about the assessments and the assessments tool is one of the most complex in our setting, and it's one of the reasons why we don't have good data on the natural history of CIPN. And there is a clear need for such studies.

So I heard a few minutes ago that this is one of the goals of the funding bodies here in the U.S. Unfortunately, that is not the case in Europe, where wellness on CIPN probably is lower than in the U.S.

The issue of CIPN is completely different from the issue we find every day in the field of peripheral neuropathy, and one of the main reasons is that we have different actors playing a role in CIPN. Of course, the oncologist is treating the cancer, but he is inducing our problem. We as neurologists are faced with a side effect that we now know, but we have some difficulty in properly

Page 36

scoring and to find a common language with an oncologist.

Finally, but not really finally, patients, and that's why we are talking about patient-reported outcome measure because at the end of the story, we need to understand which is our best approach to their problem, and we need that feedback to understand whether our attempts are successful or not.

At the moment, the situation is like this. We as neurologists talk one language, oncologists another one, and patients even another. And unless we would be able to find a common language, we would go on like during the past years when oncology drug studies gave results, neurology-based studies another, and we learned later that patients have even another feeling.

Look at this graph. This is a comparison just to show you which is the problem in talking between neurologists and oncologists. This is a comparison between TNS, and it is a composite scale used by neurologists and that oncologists do not

Page 37

like. The other is the grading based on the NCI-CTC.

What you see in the graph is a nearly perfect correlation between the oncology score and the TNS. But this is the truth. This is what happened in the real population when we tried to make a comparison between our assessment as with a neurological tool and oncologists' assessment with the NCI-CTC.

There is a very wide distribution of the results, so it is completely meaningless using these tools and trying to make a comparison. They are talking a different language.

So which are the best ways to approach a patient? Which are the best outcome measures? We have a wide option of possible measures: clinical neurophysiological, QSD, composite scores, and PRO. Which is the best?

Probably the answer is, there is not the best or the gold standard at the moment, but we need to know exactly what we can get from each of these outcome measures. And once we have

Page 38

completely cleared what we are measuring, which is the goal of our study, we can really perform a selection and decide, among the different outcome measure types, which is the best one.

In other words, we need to consider which is the feeling of the patient, because we have learned that using instruments, neurophysiology, for instance, is completely useless.

I remember when I was much younger, that there were studies where the primary endpoint was a change in some meters per second in the conduction, velocity. It goes much easier having positive results in their studies, but unfortunately, there was no clinical relationship from that study into the clinical practice.

So the point is the quality of life of these patients, this is important to be very clear. Every time we are using a patient-reported outcome measure, we are not looking for impairment. We are looking for a change in the quality of life.

So we need to understand that if I'm visiting a patient, I can grade impairment. If I'm

Page 39

using a PRO, I am looking for something that is much more complex because there's a whole of the difficulties expressed by that patient translated into the impact in his or her quality of life.

What is extremely important in terms of planning clinical trials is how long we need to follow up on our patients to really see whether there is an effect or not because this is just an example. The literature is becoming quite full of papers looking at long-term or system impairment in patients with neurotoxic chemotherapy. And it's very clear that a substantial number of these patients years after chemotherapy still have symptoms or signs.

So this is an important point in clinical trial design. We need to look for these patients. How long we need to look after these patients? Six months after the end of chemo, one year, two years? Of course, this is a huge implication in the design of the trial, but it might be important even looking not immediately after the end of the chemotherapy, which is the outcome of the patient,

Page 40

but maybe looking at the percentage of patients who will remain persistently affected by chemotherapy. So this might be a different endpoint from the standard endpoint of clinical trials.

This of course means that we have to follow up with these patients for a long period of time. These patients have cancer, so we have to expect dropouts due to recurrence of the disease or other treatments and so on. So it is something that is very peculiar of patients with CIPN.

But what happens if we try to do another kind of comparison? Earlier, we tested neurologists against oncologists. Now we are testing neurologists against patients. It's a complex graph.

But to make it very simple, if you look at the bottom graphs, the ideal situation is having this kind of graph, very separate curves, indicating that there is a clear separation between grades when we compare the neurological assessment versus the CIPN 20 score, of course a patient-reported outcome measure, reported by the patient.

Page 41

On the left, you see this is the correlation between the NCI-CTC and the CIPN 20. That is fairly good. Lines are clearly separated, so there is a very efficient discrimination between grades across the two systems. But if we look at the other two in the center on the right, the situation is much more confused. And unfortunately, this is what happened when we made the comparison between pin perception and vibration, so two items, including the TNS. That means that our neurological examination did not correlate in terms of grading with the CIPN 20 score.

Again, one is better than the other? No. We are simply looking at two different ways to assess the same thing, but we need to be completely aware that if we include in the same trial, for instance in this case, CIPN 20, and NCI-CTC, we simply double the same result. We are looking with two different instruments, and we'll have the same result.

If we want to have two different kind of evaluations, so make the comparison between the

Page 42

patient and the real neurological assessment, we need to include something that these are a more formal neurological examination.

So why collect PRO? They are not being developed to perform clinical trials. They are being developed to assess the quality of life of the patient and to complement traditional scales.

Most of the PROs that are in use now, the most widely used, have not been developed per se. They have been developed as a complement of already-existing quality-of-life scales. We sometimes forget this aspect, but they have not been designed to be used alone, which is our advantage for the patient in our use of PRO.

Of course, they can provide us the input, so we can have feedback from the patient how these patients feel after our intervention or after chemotherapy, and we can have the independent opinion of this patient.

This is another tricky aspect of the problem. It seems from several studies that asking a patient a question or allowing the patient to

Page 43

fill in a question could produce different results, even if the domain is the same. And one of the suggestions that came up from these studies is that the patient is care to reporting side effects to the oncologist because they fear to be removed from the treatment or having reduction of the dose.

So in a sense, they try to hide the severity of the side effects. This is another interesting aspect to be considered when we are analyzing results.

We have generic PRO measurement, condition specific. That's our case. But we have also the possibility of using drug-specific patient-reported outcome measures. This should be decided because it's not so easy to design, implement, and interpret a genetic condition-specific PRO, but the limitations of drug-specific PRO are probably much higher. So the decision should be taken.

It's not so easy. We know, for instance, that there are very few oxaliplatin-specific scales, but which is the use of these scales? So we look very quickly at which might be the problem.

Page 44

We're using drug-specific PRO measurement outcomes.

The release of this kind of guidance was extremely important for the success of PRO. This is very clear. Regulatory agencies in the U.S. and also in Europe sent a message, "We want to hear the patient voice." And this was the basis of the embedding of this measurement as a primary endpoint in several studies and, probably, these PROs were not really ready for this task.

This might be one of the arguments we are taking into careful consideration when we decided to develop new tools to be used as a PRO measurement.

I took these slides from yesterday's presentation because I tried to highlight some of the points that I was impressed by yesterday. This is a position of the FDA. We need one design, placebo-controlled trials with appropriate endpoints. And we want, for symptom assessments and severity, and objective measures of functional loss. Then we want symptoms selected for studies that are validated using chemotherapy regimen in

Page 45

the disease studied.

So we need to start again from the patient. And this is crucial because, if you go back to the study population who are the basis of the currently available PRO, probably not all these issues are being properly addressed.

Not all the rules for the creation of this PRO are being published, so we still don't know exactly how these PROs have been developed. We just have the result, but we don't know exactly which was the mechanism of the basis of that result, so we cannot exclude that there was some selection bias, for instance, in the high attempts included in the pre-selection and the creation of PRO.

The big challenge is to have something that can be used in different trials across different kinds of cancer and to be the real measure of CIPN, not specific, but condition related to CIPN.

The last slide was probably a question. If we need to separate acute symptoms from chronic symptoms -- I think this is not a question; this is

Page 46

a point. We need to separate acute symptoms from chronic symptoms. There is no evidence at the moment that there is a good reason for keeping them together, although child studies on pain related to [indiscernible], our study on acute symptoms in oxaliplatin-treated patients, probably that's the indication that those patients with the most severe, acute toxicity at the end of the story tend to develop a more severe chronic neurotoxicity.

But this does not necessarily imply that the two events are pathogenetically related. This is just a clinical observation, so before using acute symptoms as an interesting endpoint, we need to be really sure that they are two events that are not by chance related, but there is a causal relationship between the two.

So that comes to the problem of how to create this PRO. This is, I think, a basic statement. We need to keep everything simple, but not too much. Otherwise, it seems to have solved the problem, but we actually have created a big problem because we are measuring something that is

Page 47

completely unpredictable.

Developing a PRO is a long process. It takes years. There is no way to produce a reliable PRO in a short period of time because the process is like a circle. We need to start from identifying which is the problem, and then talk with the patient, talk with other healthcare providers, check for the consistency of the items, go back to the patient and test whether it works, and then confirm that our new questionnaire is consistent, is reliable, is valid, in a sense. And validity of these tests is one of the most critical issues to be clearly demonstrated.

You need to use something that is able to detect changes. We need to have a movement of the score consistent with the development of the neuropathy, and this change must be as linear as possible. That means that we should be aware that once we believe we have a good questionnaire, you have to go back to test again, and to see whether it is really good in different contexts, in different settings, and probably with different

Page 48

populations. That's why it takes so long.

Now, this is what we want, of course. I'm coming from Italy, so this is perfection for me. We are not so close at the moment, I guess. And just to show that we are not perfect, I'd like to go back to this old paper, 1998, from the Dutch group, T. Postma and Aaronson, and they made this comparison. This is very, very well known.

It was the first evidence that the scales that were currently available at that time were not suitable for performing clinical trials. And what is surprising to me is that the agreement on an important score was this.

NCI-CTC, for instance, grade 3, you know much better than me, is a crucial step in the assessment of toxicity. The agreement, the exact agreement between different researchers was very, very low, definitely very low. So the authors concluded that if one would be interested in incorporating patient opinion into the assessment, something you should be implementing, 1998, and they decided that it was start on the new

Page 49

questionnaire, that eventually became the CIPN 20, to be used as a complementary tool to the EORTC-QLQ-C30 questionnaire of quality of life. Keep in mind 1998 when they started the process.

This is the QLQ-C30. That is a very, very well accepted quality-of-life scale, validated in different languages, different contexts, formally released as a validated scale by the EORTC several years ago.

This is what happened in the Dutch group. They started with a very long process, and you see that they moved across all the steps, which are formally considered the gold standard for the development of PRO. They started with selection of the items. They tested, they pre-tested, and the phase 4 that is actually the unfilled validation of this scale is still ongoing, because there is still something to be fixed in the CIPN 20 questionnaire.

They use a wide selection of cancers. The number is low because this was the very first phase of creating the questionnaire. This was the result of the job, the scale based on the mix of sensory,

Page 50

motor, and autonomic items.

Patients have 4 lines to be filled in, so they can grade from not at all up to very much from 0 to 3 or 1 to 4, 4-grade scale. The questionnaire has been tested for consistency and validity and overall is working quite efficiently.

As it worked quite efficiently, another kind of PRO is the FACT GOG. Again, this is the basic scale, the quality of life that is divided into physical, social, emotional, and functional well-being, so the typical domains you can find in a quality-of-life assessment, and this is the part dedicated to the neurotoxicities that have been added to the basic quality-of-life assessment.

The structure looks quite similar. I will go back in details and make a comparison between the two later on. But what is different is that here the patients have five grades to be used and not four. It is not trivial. This means having 25 percent more possibilities to grade something that might be good or might be trouble, and we show why it might go to be trouble. Also, the FACT

Page 51

GOG-NTx has been tested in different contexts on a wide selection of patients and, again, it works quite efficiently.

Then we have other kinds of PROs that are maybe not so efficient when they've been tested. For instance, this is the Peripheral Neuropathy Scale. That is a modification of a pre-existing scale. It's a mixture of functional scale and something that looks like the FACT GOG, actually. And this is another of these questionnaires.

They decided to keep things very simple, a completely different approach. What is the threshold for severe toxicity here is highlighted there. That means the patient reports to have some impairment in their daily-life activities, in D and E. And this might be confusing, but they added a list of activities that should be considered when you are reporting impairment. And this is very important because it's not so common in these kind of scales having a checklist of what you consider as important in terms of daily life's activities.

Just to make clear the point, if I am a

Page 52

piano player, probably my concern is different from my concern if I've been working on the road, for instance. So what does it mean, daily life activities? You need to have a list of which is the reference when you are saying it's impacting on my daily life activity.

Then we are moving to the oxaliplatin as an example of what I believe is the worst approach to a questionnaire.

(Laughter.)

DR. CAVALETTI: This is a mixture of functional neurological impairment, self-reported symptoms with a high risk of doubling results because, in this case, every time you have a positive answer in the upper limbs, it is very, very, very likely you will have a positive answer also in the lower limbs because oxaliplatin behaves like this. If I have symptoms in my hands, 99 percent of the patients will also have symptoms in the lower limbs.

What is surprising to me is that they propose this kind of questionnaire to patients, and

Page 53

you have 10 lines to be filled in by the patient. I think that, at the third line, the patient is already bored and starts making crosses here and there just to get rid of this questionnaire.

There is even a different approach. These are a very classical questionnaires, but there is something different that can be done. It's what we tried to do within our academic European, American, Australian network, that it's trying to see whether it would be possible to create a different kind of questionnaire, and we started from these assumptions.

Most of the CIPN assessments available when we started our project were based on a mix of disability and quality-of-life items. Some of them were not very, very clear, and they've not been formally tested from the clinometrics standpoint we were in 2010.

The big disadvantage of all these questionnaires is that they are based on the classic test theory. That means that moving from 1 to 2, from 2 to 3, or from 3 to 4 is exactly the

Page 54

same weight. Why, this is probably not the case, actually, because when you stay on a very low score, moving one grade from 0 to 1, probably has no impact. Moving from 3 to 4, for instance, probably the impact is much, much higher. So the mistake that sometimes can be done is using these kind of scales that are ordinal and analyze them as they are linear.

There is a theory that I'm not able to explain to you, and probably you are lucky because I tried several times to understand the details, but it's out of my capacity. This Rasch theory is a statistical theory not accepted by all the statisticians, but quite a few, that has the capacity to transform ordinal to interval scales. And based on the fact that the patient response to each item depends on the difficulty of the items, but also on the capacity of the patient to do that.

So with a rule that this is only a part of the rule, there is a way. It seems there is a way. I believe there is a way to translate these two concepts into a linear scale that can be assessed

Page 55

in a linear way. I will show you what does it mean. But again, the kick-off meeting, when we decided to start this kind of project, was in 2011, and we are not to the end of the story.

Ingemar Merkies was the leading person in this project. So we started again with a search of the items from the WHO/ICF list of items. We selected 146 items from the pre-screening selection. We tested with the patient. We go back and we prepare a pre-questionnaire. Then we tested the questionnaire in a population of cancer patients with a stable neuropathy, 281 patients with different kinds of cancer. We tried to mix up the population as much as possible in different countries, and this is the result of the analysis.

To make this very, very simple, these are 28 items with different complexity. So what you see on the blue bar is the order. That means I am able to do it without any problem. The green is, I am unable to do that. And the red is, I am able, but it's difficult for me.

You see that to get out of the bed, if you

Page 56

are not able to get out of the bed, it's very easy that the weight of your impairment is relevant in the scale, while if you are not able to run -- that is the last line at the bottom -- it's acceptable that you are not able to run, and the weight of this impairment is much lower in the context of the overall scale of some of the results that will be analyzed.

So this is a different approach to the use of PRO. In our validation phase, it was reliable. It was varied across different conditions. In this case, there is a comparison with the NCI-CTC. But what we are doing now is to test for responsiveness, because this is very important, to see whether this questionnaire is moving and to which extent it's able to replicate the changes we are observing from a neurological standpoint in our population.

We have just completed recruitment, and we are waiting for the follow-up because we planned to have a six-month follow-up after chemotherapy, and we do hope to have the results reasonably soon.

Page 57

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

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

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

Page 58

Then you have discomfort in the FACT GOG. Discomfort is a little bit generic for me. Discomfort may also include numbness and tingling. Using the CIPN 20, the question is a little bit more precise because they are asking about pain that is not clearly established in the FACT GOG.

Then cramps. You have cramps in both questionnaires, but what is very surprising to me, in the FACT GOG, you have joint pain. I'm not really sure that joint pain can be considered a sign of CIPN. In my mind, joint pain is something different.

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

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

Page 59

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

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

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

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

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

Then there are two things that are

Page 60

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

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

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

Page 61

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

Page 62

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

Page 63

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

Page 64

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

Page 65

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

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

So for instance, 40 percent, so the plurality reported only symptom measures, whereas only two trials reported only sign measures. And what you'll see here -- and this is surprising to someone who spends a lot of time in the diabetes world and another neuropathy, is that about a quarter of these trials reported a sign measure at all, and 5 percent reported functional measures. And pegboard, as I showed to Pat, was the one that was specifically mentioned in the articles, so I thought both of these seemed relatively low.

Page 66

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

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

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

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

Page 67

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

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

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

(Laughter.)

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

Page 68

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

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

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

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

Page 69

the others.
I think the first point is that most of these studies that are using a sign-based scale aren't really using a scale at all. There are only five instances of using examination scale, and I'm being very permissive because just classifying whether or not people have neuropathy based on the Toronto criteria really isn't a scale, but I included it there out of generosity.
It's much more common that either individual modalities are used, and these are often poorly defined. So we're just going to test vibration or monofilament. Sometimes, they're more precisely defined, but not always.
I was also impressed that balance and gait functional measures are now being included more frequently, which I think is a positive development, and these are obviously not sign measures, but they are at least often provider-assessed measures. And QST seems to be quite popular as well.
So I think the main point, as you can see

Page 70

from the back of the room, there's a huge bewildering array of different sign measures, and this has a number of implications for how we might interpret clinical trials.
So I wanted to switch to patient perspective. Joanna did a fantastic job starting with this. I wanted to bring it a little closer to home and just repeat some of the wisdom that Ted Burns gave us at the Foundation for Peripheral Neuropathy meeting. And a number of you were there, and many of you know Ted.
Ted is at the University of Virginia. He's a neurologist. He had a frontal sinus squamous cell carcinoma and actually developed chemotherapy-induced peripheral neuropathy. And we invited him to the foundation meeting to give us his perspective.
He not only has an interest in neuropathy generally, but he has an interest in PRO development and has developed his own scale called the CAP-PRI scale, which we're validating across multiple different centers, and we're actually

Page 71

using this in our CIPN cohort as well. He during the midst of his chemotherapy would email us his current CAP-PRI scores, which I thought was very interesting.
The take-home point I took for him is that this is a journey. It's not a point in time, and Joanna did this beautifully yesterday. In this slide, which I'll let you peruse, he thought about his goals as a patient based on the time of therapy.
Guido mentioned this, and Ted confirmed it, and this was alluded to yesterday, that he actually didn't want to tell his oncologist about his neuropathy symptoms, and actually did not do so. Even knowing all he knows about CIPN and the ultimate risk this might pose him, he did not tell them. He wanted to live, and if he lived with neuropathic pain, that beat the alternative.
It goes to the ranking discussion that we heard yesterday from our statistical colleagues. But as he survived and got further away from the turmoil and fear of his cancer and cancer therapy,

Page 72

this became more important to him.
So why do I bring this up? Well, for a couple of reasons. One, his main focus was not whether he had CIPN, but the functional deficits this caused. So do I have trouble walking, do I have pain, am I falling, and so forth, and what bearing does sign measures have on this?
This is a quote from a neurologist. And neurologists love neuropathy sign measures. Right? This is a quote from his paper about CAP-PRI in neurology. And just to emphasize, you don't have to read the whole thing, but, "At no point did I find any meaningful value in the status of my ankle reflex, toe flexion, or extension, or sural sensory amplitude," which really struck me.
This doesn't mean that these are useless measures, but from a patient perspective and a neurologist's perspective, it's somewhat surprising to me. This just graphically shows his journey, and he really didn't care about his CIPN status here.
So I think this is something we need to

Page 73

think really carefully about, because our clinical trials generally are here, not out here. And it really goes to what Guido was talking about because I suspect the performance of PROs and symptom-based scales evolve over time. We know they do because, here, Ted was denying his neuropathy.

Here, he was emailing his friends and colleagues his CAP-PRI score, and here, he cares about his CAP-PRI score. So this suggests this kind of temporal bias is really important in thinking about how we go about our measurements.

So conceptually, this is more of an investigator perspective. What are the benefits of using sign scales, and then what are the downsides of using sign scales?

This is, to some extent, veering into Roy's strawman territory because, of course, they're useful. Why are they useful? Well, they provide multi-modal information. They provide information about different fiber types, and classes, and functions, and this is important. They provide impairment-specific data and topographical data.

Page 74

And this is sort of a classic picture of distal symmetric polyneuropathy.

As I start talked about individual sign measures, one thing that's really important is to think about just a very basic neurobiology of neuropathy. That means that you can't just look at the severity of sensory abnormalities in the toe and then use that as a comprehensive metric of that modality across a neuropathy patient or group of patients.

We see this all the time with our starting residents, who will come in and say, "In my neuropathy clinic, I saw this guy. He can't feel anything in his toe. He has no vibration, no pin, no touch, and his toe is weak." Then you go, "What's the rest of his body look like? I mean, the toe isn't the problem. Or maybe it's a problem, but it's only part of the problem."

Presumably, our sign scales are less susceptible to this stage bias. And again, I apologize to the statisticians. I don't know that there is such a thing, but I made up the term in

Page 75

looking through Ted's journey through CIPN. Clearly, his report of symptoms was significantly affected by where he was in his therapeutic journey. Sign scales probably have some susceptibility to this, but probably less.

But I think, most importantly, sign measures tell us something fundamentally different, and here I will fully embrace Roy's strawman, and I'll throw up a couple of other ones, and we alluded to this yesterday.

In a neuropathic pain trial, it is possible that a positive result of an agent is because it causes neuropathy, not solves neuropathy. I don't know of any examples of this, but it's possible. This is one of the reasons that biomarkers such as nerve conduction studies are used not only as a potential efficacy measure, but also as a safety measure. So one could certainly fill up a strawman where an agent reduced symptoms, but worsened actual neuropathy by objective measures.

Perhaps a somewhat more plausible strawman is that during the period of axonal regeneration,

Page 76

it's possible that patients will have increased sensory systems. We certainly see this clinically in peripheral nerve injury patients. We see it every morning when we wake up and have to shake up our carpal tunnel syndrome.

So one can imagine, particularly in a brief trial that doesn't follow long-term outcomes, that there might be a phase of increased neuropathic symptoms with nerve regeneration. And Pat talked beautifully yesterday about spontaneously firing subepidermal, dermal growth cones.

Imagine a scenario where the tight junctions aren't the issue, and these growth cones are able to successfully reinnervate the epidermis. Well, during that phase of reinnervation, one might experience increased symptoms, but improved signs. And so I think this adds a dimensionality and is something that we really need to include.

But what are the cons? And I can think of three cons, and two are on this slide. One is, are they meaningful to patients? We need to be mindful of that. Our sign measures do have to have some

Page 77

sort of clinical meaning, but we need to think about it throughout the patient's journey, not at one specific point necessarily, and particularly in terms of long-term outcomes and functional outcomes.

Then this is a quote from one of Guido's papers. "These are frequently perceived by our oncologists as being too complicated and time consuming." And this kind of goes to the issue that's come up several times about culture and language between different specialties. I think this is not so much about oncologists' perceptions as it is about value in medicine.

There's a lot of talk about value. I think, if we have sign scales that are valuable, that were able to demonstrate value, clinical meaning, and performance in clinical trials, I don't think this is an issue. There's a little bit of communication, perhaps, but if our oncology colleagues are telling us that these scales are difficult to use, that probably means they're difficult to use, and we need to communicate about

Page 78

why that is and engage in a dialogue, because some of them are difficult to use, some of them perhaps less so.

The other thing I wanted to bring up is reproducibility in sign measures. This is a slide that I know Roy and others who live a little bit in the diabetes world had seen. This is the most surreal study I have ever participated in.

Peter Dyck, who most of you are familiar with, is at the Mayo Clinic -- and I saw Charles leaning over, making a comment -- did a study that I don't think anyone else would have the chutzpah to do or the courage. He wanted to look at reproducibility and diagnosis of neuropathy. And I was one of the people foolish enough to say, yeah, I'll do that.

So what he did is took a group of patients from the Rochester diabetic neuropathy cohort over here. This isn't the way they normally dress, but they were disguised for the first day of the visit. And they were brought in along with a group of supposed experts in diabetic neuropathy from Europe

Page 79

and North America.

It was as simple as we went through these little cubicles in the Kahler Hotel wearing voice distortion stuff. And they had sunglasses. We'd plug in, and all we had to do was talk to them. We could do anything we wanted aside from nerve conductions, QSTs. We could bring stuff with us. And we had to decide, did they have symptoms, did they have signs.

This was great. I mean, these were all my friends like Jim Albers, and James Russell, and Roy was smart enough to see that this was a trap and didn't come.

(Laughter.)

DR. G. SMITH: We went to Michael's, which is now closed, I'm told, and had a really nice steak dinner, and it was great. It was fun. And it turned out that we were terrible. In fact, there were about a quarter of us that had no statistically significant relationship between what we thought on one day versus the next day, when we did the repeat evaluation.

Page 80

We were then brought back by Peter for remediation a year later during a snow storm. And the take-home point is if you agree ahead of time on minimal criteria that one has to meet and make this somewhat structured, you do much better.

This goes back to these trials that use just 10-gram monofilament or vibration. You can't do that, even if you are an expert in the field. And I suspect the reproducibility of this as we move out maybe gets better. Maybe the non-neuropathy experts do better. I don't know.

But clearly, this has implications not only for just diagnostic reproducibility, but also how we employ signs scales and simple issues of is the vibration reduced or not. And if we don't have a discussion about what this precisely means, it's a problem.

So I wanted to show you just some scales, and then because there are not very many to talk about in CIPN, I'm going to go through each one of these in a great deal of detail, courtesy of Chris Gibbons, just so you can understand them. And I'm

Page 81

really not going to do that. I was hoping that someone would chuckle, but you guys clearly think I'm serious, and we'll just keep going forever.

(Laughter.)

DR. G. SMITH: Some of these will look familiar to you, so the Total Neuropathy Scale and so forth. I just wanted to show you three of these from the diabetes world.

But first, this is a slide. These two slides, Chris put together for the last ACTTION meeting that I was at in which he had to give this same talk, but was able to do so across all of neuropathy, so he had a lot more stuff to work with. So it was less rambling and conjectural, if that's a word in mind.

So this shows the contributions -- I'm going to point over here to this side of the room -- of different modalities, a motor sensory reflex, his cranial nerves, and general function of each scale, and the scoring. You can just get a sense of the variability in these scales of the different modalities, and score, and weighting.

Page 82

Just to give examples, this is the most commonly used scale in the diabetes world historically, which is the Neuropathy Impairment Score, Lower Leg. This hasn't really been used in CIPN trials, or at least not much to my experience. It has been used in the amyloid polyneuropathy and is being used. And I would never have predicted this would be a useful scale in familial amyloid polyneuropathy, but it turns out to be.

This just shows the scoring of it, so these are the muscle power grading, sensory grading, various modalities, and the muscle groups tested. And the points here are, no pun intended, that there are an enormous number of points that go toward muscle grading.

The way muscle strength is graded is with an expanded MRC, which I'm going to talk about as another strawman in a moment. This is the face validity of this scale for problems like diabetic neuropathy, CIPN, or frankly maybe to a less extent FAP, is relatively low because they don't cause a lot of weakness. These are kind of wasted points,

Page 83

and there are a number of other problems.

This is the Utah Early Neuropathy Scale, which I show mainly to point out that there are relatively few scales, TNS being the other one, that actually map out the distribution and severity of sensory loss, which can be useful.

But I will say that I love Guido's discussion about the complexity of putting together PROs, and I'm going to turn around and talk about Rasch analysis in a moment. But I think sign scales are put together in an even more random and haphazard way. I put this together, and I did it. It was like I had a cocktail. I was drinking a bourbon one night, and I thought, you know, "I'm going to make a scale and what's important," and we came up with this. And it turns out to be useful.

I think what's alarming is it's just as useful as the NIS-LL and other scales, which means that they're probably all really flawed. So we need to think more carefully about the clinometric of our sign scales in the same way that Guido talked about in terms of symptom scales.

Page 84

I'm just going to skip over that. So this is the Total Neuropathy Score, which everyone's familiar with. The original TNS included QST and electrophysiology. And you can see how this is scored. So their percentile scores on vibration, and distribution, and in qualitative severity descriptors across these various kind of ordinal categories.

The TNS-C, which is here, which is being more commonly used now, eliminates the electrophysiology and quantitative sensory testing, but leaves these seven domains in place.

Keep in mind my points about the potential for signs and symptoms to be divergent and the need to be mindful of this. This still is a composite scale of symptoms and signs, which has its strengths, but also has its weaknesses.

I wanted to give an example of the problem of composite scales. I couldn't think of one for symptoms and signs, so here, I'm going to show you the data from the NATHAN study.

This was actually quite an impressive trial,

Page 85

400 diabetic neuropathy patients treated with alpha-lipoic acid over four years. We talked a little bit yesterday about the expense of doing clinical trials, and this is a long one and really an impressive achievement by Dan Ziegler.

It was negative. The pre-defined primary outcome measure was a composite of the NIS-LL, which I showed you a moment ago, and an electrophysiologic parameter, so there is some normal deviance, so again, something familiar with the Mayo people.

But the reason this was negative -- and the statisticians now are cringing even more and want to take me off the stage -- is that the NIS was positive, but the electrophysiologic measures didn't change. So I'm not saying this is a positive trial. I'm not convinced alpha-lipoic acid is all that useful, but it shows you how the amalgam of nerve conduction studies with this clinical measure dragged down the clinical measure.

So one needs to at least be mindful of this risk and composite scales, and I expect there will

Page 86

be a robust discussion of that. So I can go a little more quickly through this because Guido already brought up this idea of clinometrics and types of data. But I'm not as smart, so I'm assuming that there are very few people in here who's confused about this as I am, but I'm going to go through it anyway.

These are the ranking of different types of data based on the level of information, going from nominal, which is ethnicity, religion, gender, and so forth, to ordinal, to interval, and to ratio. And as Guido pointed out, I'm going to use the MRC as a very real strawman about this.

Ordinal scales do not necessarily imply linearity. And then ratio scales, which we don't talk about a lot, are basically interval scales where there's an absolute zero, so that you can say the doubling of the scale has intrinsic meaning.

So if I say the doubling of my weight, I went from 150 to 300, that's a times-2 weight, that has some meaning to it because you know what zero weight means.

Page 87

So let's talk about the MRC scale just to give an example of why this is so important. The MRC scale, which has been around forever, and every neurologist and really every physician uses -- and someone mentioned to me in casual conversation about their MRC scale after an orthopedic problem -- is displayed here. Everyone's familiar with it.

Of course, this is the bane of existence to neurologists, particularly neuromuscular neurologists, because of the number of times we get called by the emergency department, saying, "I've got a patient who's got 4 out of 5 strength everywhere." It's amazing that we're still using it. The basic distribution of weakness in a neuromuscular clinic is here. It's around 4.

So therefore, you'll see in the NIS-LL, the strength grading is basically an MRC that's been jury-rigged to have 4 pluses, 4 minuses, 3.75s, these sorts of things to deal with the fact that this ordinal scale obviously lacks linearity. And we use this still, and I hate this scale.

Page 88

I still use this to track whether or not patients are responding to therapy, getting worse in a clinical setting. And strength scales often include characteristics, if not the MRC or an expanded MRC.

So this is a picture of Rasch, and I don't need to go through this. There are a couple of things. One, I'm appreciative of Guido for willingness to explain this, because I don't understand it at all. And Ted Burns and I were actually asked to write an editorial on this, and it scared the crap out of both of us. And we managed to muddle through without anyone laughing too hard.

So the first thing I want to say is, if you have any questions about this, Dr. Cavaletti is the person that you should be speaking with about questions of this. And then I also appreciated your recognition and admission that you didn't understand it particularly well, either. So that made me feel really good and somewhat less foolish than I normally feel.

Page 89

So to go back to the MRC, there was an effort to Rasch-transform the MRC. And I just wanted to go over this figure because I think it explains the problem in a visual way that, for me, even though I don't fully understand even this figure, is impactful.

So the top shows what an ideal kind of 5-point Rasch scale would look like. Right? And so these are basically probability of a score given a particular clinical scenario. So for a score of 5, you would see, as you transition from a true 5 to a 4, that when you're halfway there, there's a 50/50 chance that the patient is going to be scored as a 4 or 5.

You can see these probability scores. And you guys can't ask me any questions about this. It's very ordered, and then there are ordered thresholds with this.

So in this paper that I suspect Guido may have been on, they did really a herculean effort to Rasch-transform the MRC, including a very large number of patients across different neuromuscular

Page 90

disorders, and then a validation cohort, I think, in Guillain-Barre syndrome. And they did this by muscle and even down to, like, the latissimus dorsi. It's a beautiful paper, although somewhat incomprehensible to me.

But this is an example of a muscle group that had a normal kind of Rasch characteristic as it were, and it looks a lot like this. But most muscles weren't like this. So this shows the kind of ordering and thresholds of a more typical muscle.

You can tell that this is a mess and really not likely to be a very useful scale in determining when patients transition from one to the other. So they actually came up with a Rasch-transform scale that's shown here, which is a lot easier.

I talk the talk, but I don't walk the walk. I often tell my residents and fellows about this, and then they go ahead and give me the MRC score over 5 points, so maybe I'll get there. But this is now being applied, and we've already talked about CIPN RODS. And there are now a variety of

Page 91

Rasch-transform scales across neuromuscular disease and particularly inflammatory neuropathy, which is where RODS came from and MMN. And I think there's a Rasch-transformed CMT scale.

We have a Rasch-transformed TNS, which I won't go into in detail except to say that it eliminated a couple of the categories, eliminated reflexes in autonomic from the 7 domains of the TNS.

I think the last point I want to make goes back to this slide I showed of where we are in ongoing trials, which is everywhere and probably nowhere at one time in terms of sign-based outcome measures, and talk a little bit about common data elements, which is not just an NINDS effort. I think it's NIH wide.

But for some time now, there's been an effort to bring some sense of order to the various tools that we use in clinical trials. The problems are listed here, that there are no widely-used data standards, that researchers create their own data instruments. This causes problems in comparisons

Page 92

between trials or even transforming data for meta-analyses, and makes life particularly difficult for people like Jen, although it's good career stability for you. You're going to be able to do this forever. This is really a problem for data, data sharing.

One of the challenges in common data elements is these are made in a reactive way. Several of us have been to NINDS and asked to develop common data elements for neuropathy trials. And what I think was a really ironic, Escher-like [ph] response was we'll get a trial funded, and then we'll do your common data elements.

We now have a trial funded, actually, and are having that discussion. So I think working with organizations like NINDS on common data elements or NIH NCI and bringing order to this will be very useful. I think that's one of the reasons these sorts of meetings are particularly valuable, because we've got people from regulatory funding, industry, and academia here to think about this.

Page 93

So these are the conclusions. I do think sign scores provide unique value. We need to use them. They're underutilized in CIPN trials. I don't have it on this slide, but I think that part of the issue is the frequency with which we conflate pain and neuropathy.

They're not always the same, and not all CIPN patients have pain. Inclusion of sign measures in any study is probably warranted, often even in pain-focused studies. They're all over the map. We don't have well-validated, or very many well-validated sign measures for chemotherapy-induced neuropathy, and we need consensus about this.

There is I think a fairly urgent need to think of these in a clinometrically valid way. Again, Dr. Cavaletti will explain the statistical methodologies that underlie this and what we should do, but I too am sold on this idea.

I think the last thing I wanted to do was just show a slide of Ted. I don't think Ted would mind me telling this. Now, we've learned, the

Page 94

community has learned earlier this week that he's likely recurred, which is very unfortunate. He's been kind of a guiding figure for me in a number of the things that we're working on collaboratively, including in this.

So I just wanted to share that with you. Many of you know him, I know, and my thoughts and prayers are with Ted in this difficult time. And I'm hopeful that he'll marshal through and will continue to lead us in this effort. So hopefully I'm not too far over.

(Applause.)

Q&A and Panel Discussion

DR. GEWANDTER: Thank you for all of your really good talks. Does anyone have any questions they'd like to open with?

(No response.)

DR. GEWANDTER: No? Okay. I'll start then. So I guess the question for me is, you both presented for measurement that we have a lot of options and nothing is great. So what can we as a group do? What can we propose to do?

Page 95

I think Guido with the current arms study, like, where are you guys, what would be helpful that we could propose that people should be doing?

DR. CAVALETTI: We've heard this morning that there is a huge network already available for doing what we need now to test these kind of tools in a wide setting, in a community-based setting probably that will be much closer to the real-life population, and see if they work, and not stopping trying to do something better.

This is not a satisfactory position now. We are working on our questionnaire. Probably other people can work on theirs. But if we will be able to test quickly this kind of questionnaire, profiting from these kind of networks, our network, the network is much larger here, we can reduce the amount of time that is required for the validation of these tests, and we can really know if they're working or not.

So I think that this might be important as a message. We still need to get information. We have the platform where we can test these kind of

Page 96

tools. And it's not so expensive like performing an interventional trial, but can provide us all the information we are still missing.

DR. G. SMITH: I would echo that. This is easy to do if you bring community together. And the best example I can think of is Ted's CAP-PRI score. There are, I don't know, 20 sites that are validating CAP-PRI. And we're gathering data in clinic and it's exceptionally easy. In fact, I don't even need a study coordinator to do it.

We give the patient a form that the IRB says we have to give them. They look at it, throw it in the garbage. They fill out the CAP-PRI, which takes them two minutes. We fill out a RODS, which takes us a very brief period of time, and then we just send it off.

So I think building on existing communities, research communities, or clinical networks to validate particularly brief PROs is useful. And I think this goes towards the usability of our scales, and one can probably do the same thing in terms of examination scales. Most of us live in

Page 97

EMR-driven worlds, and many of these are now built into EPIC. And then that offers another opportunity to gather these during routine clinical care and leverage it for a better understanding and longitudinal cohorts.

DR. RICHARDSON: Just one comment on EPIC. You have to be very careful about that tool. We've found it problematic from the point of view of CTC grading, for example, when we tried to incorporate it. They actually put in an old version, version 3, I believe, and that was a disaster for our CLCs, as you can imagine.

DR. G. SMITH: We've built all these internally. That's a really good point, yes.

DR. RICHARDSON: Yes. That's a good point. Yes, exactly.

DR. GEWANDTER: Ellen?

DR. LAVOIE SMITH: So I'm thinking about one of the issues that came up yesterday when we were talking about should we include patients with diabetes, and if we do that, how do we evaluate baseline neuropathy in these patients, in that many

Page 98

of our trials, we've said, "Well, if they don't have any symptoms of neuropathy, then we let them in the trial." But yet a pure symptom assessment of these patients may not be enough.

But I think what I'm taking away from what you said, Dr. Smith, I'm thinking about the fact that these studies are done in oncology settings and that these patients are recruited by oncologists or an oncology team. And if getting an accurate valid sign measure is impossible for a neurologist, then it is really impossible for an oncologist.

So I'm extrapolating and thinking that, are we sort of saying that a PRO is good enough?

DR. G. SMITH: I'm not saying that. I'm actually saying something different than that. But I'll cut to the chase and say I agree with what he said yesterday in just about everything and the approach to this.

What I'm saying is, use of a sign, of a sign measure in this particular setting, would be problematic. So a diabetic patient, where you're

Page 99

trying to figure out, well, if they have sub-clinical or sign-based-only neuropathy and that's a patient we don't want to include in a trial, that would be an issue unless you pre-establish the criteria.

By and large, I don't think that's a particularly useful thing to do because subtle signs are very common. The way we became reproducible was by agreeing that we were only going to call people neuropathic from a sign perspective if they had just overt signs, really obvious stuff with age adjustment.

So I think if one wanted to do that, one can come up with criteria that are easily applied by oncologists and neurologists. I'm not convinced it's necessary. I agree with the metaphor of keeping this simple, and I actually think including diabetic patients without clinically evident neuropathy in CIPN trials is prudent, and one might even argue advantageous from an enrichment perspective.

I don't think we necessarily need to

Page 100

overcomplicate this issue. Most of us, when we see a patient who's got overt diabetic neuropathy, we know it. And I think, generally speaking, we can rely on that.

DR. GEWANDTER: Dr. Dougherty?

DR. DOUGHERTY: So I have two questions. The first question is really simple. Can someone boil down to me -- I heard that there are problems with all the tools, but what do we use today? It sounds like the CIPN 20 is where the consensus is.

Then the second part of that question, as Ann pointed out, there was a number of compounds that have been tested. Some I think without any scientific merit is pretty clear.

But with all that said of negative findings, is that a function of the lack of quality in the assessment tool, and how do we go about trying to remedy that gap, which would then still exist?

DR. CAVALETTI: My personal opinion is that, at the moment, the CIPN 20 is the best tool to be used in these kind of health studies, provided that we know that it will probably change over the next

Page 101

few years, what is most likely that would be reduced to a possibly 16-item scale.

But at the moment, for the reasons I tried to show you before, I think it is the best way to address the issue at the moment.

DR. DOUGHERTY: So let me just break in right there because that is a really important point. If there's a consensus that, today, the CIPN 20 is the best tool, shouldn't there be some sort of a consensus statement from a CIPN working group of some type to endorse that product so that that becomes propagated across studies?

As I understand and I look at the landscape, this to me is the biggest hurdle to overcome, that there's no uniformity across the landscape as to how things are being appraised.

DR. CAVALETTI: I think that oncologists should be the right persons to answer this question because, actually, the problem of using the PRO is raised mainly by the fact that they believe that they cannot assess properly the patient without an instrument. So the use of PRO in a sense is an

Page 102

answer to their request to have something they can rely on.

So I would like to have the opinion of a couple of people in the room whether they like CIPN 20 or not. And if they don't like it, what they would propose instead of the CIPN 20.

DR. LOPRINZI: I can't hold back anymore.

(Laughter.)

DR. LOPRINIZI: So what you guys said, I thought, was beautiful. I thought it was music to my ears, that sort of thing. Well, no instrument is going to be perfect. It never is going to be perfect, and there's always going to be room for improvement in things like that and that sort of thing.

The CIPN, using a PRO makes a ton of sense instead of having it interpreted by the nurse or the doctor. Okay? So that makes sense for all sorts of different things. And people have been talking about PROs for 10 years now or so. I've been doing them for 30 years in all of our trials on hot flashes, on mucositis, on anorexia-cachexia,

Page 103

and that sort of thing.

You can always validate all these. All these validation sort of things generally show that they work out or you change them moderately or mildly. So doing a PRO is necessary. And I think, Guido, I want your slide. I think you did a fabulous job of putting together why the CIPN 20 makes the most sense.

Deb Barton, a colleague of mine, first illustrated that to me on our baclofen amitriptyline ketamine trial some time ago, and we've been using it ever since that time. It's a nice thing for doing it with either oxaliplatin and with paclitaxel. It's using this exact same instrument. You can compare and contrast what you're seeing from there.

If I were in charge -- and I'm never in charge at home -- I would not change the CIPN 20 instrument. Rather, I think that not analyzing some of the data in there is plenty fine and all that, but I'd rather keep it the same so you could continue to cross-reference what you've gotten for

Page 104

other studies that have looked at it before.

There's an improvement in how you look at it, and Ellen has looked at that a lot and all those sort of things. I think you can use the individual questions that are on it, the tingliness versus numbness versus pain in hands and feet versus hands versus feet. So it makes a ton of sense from all of that sort of stuff.

I also think that using the CTCAE continues to make sense because that's an even longer historical perspective, and there are comparisons between CTCAE and CIPN 20, and we just had another paper accepted looking at that process of things.

So that makes a lot of sense. And I think what was said about the examinations, and said it's too -- we don't get much sense out of it. And I think Peter Dyck's experiment, which I was not aware of -- I know Peter Dyck well. He's the oldest staff member at Mayo, and he's still plugging along at 80-some-odd years old.

But we don't know what the references, what the reflexes are on that sort of stuff. And if it

Page 105

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

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

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

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

Page 106

DR. O'MARA: Yes, I agree.

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

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

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

DR. LOPRINZI: Yes.

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

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

DR. DOUGHERTY: It doesn't matter.

DR. LOPRINZI: Yes.

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

Page 107

this was the consensus from the meeting.

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

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

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

Page 108

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

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

DR. RICHARDSON: Yes.

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

DR. RICHARDSON: Yes.

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

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

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

Page 109

more. I think that point goes to what I think will be some of the discussion in a moment about recruitment, and culture, and how partnerships between oncology and neurology look like. And we can talk about that then, but I think that's critically important to our shared success.

But this also goes towards both a qualitative sensitivity on the part of those who are designing these sign-based scales to those who are using them. I think this goes towards Guido's quote about the scales being too complicated. And then the reflexes come up time and time again.

It's not surprising to me that in the Rasch transformation of the TNS, the two things that disappeared were autonomic and reflexes. I don't think you have to be a rocket scientist or a neurosurgeon to understand why that is.

So I think the application of clinometric tools to evaluating these measures, as well as a qualitative sensitivity to those who are actually implementing them, will be very helpful. And I totally agree with Pat that the deliverable from

Page 110

this ought to be a set of collaborative recommendations about what ought to be done here and now.

DR. DOUGHERTY: And then as well, just to follow up on my original question that we then dumped on or got away from, you then turned the perspective back on history. And of the clinical trials done so far in this indication, which used what we would recommend as the current best tools, didn't use those. So that would mean, then, that the endpoints of those studies would still be unknown.

DR. GEWANDTER: Thank you. So Daniela actually had a question a while ago.

DR. DASTROS-PITEI: Just a quick follow-up on the slides. It would be nice to have a consensus if the signs scales are needed in this clinical trial, especially for new active drugs, perhaps. And if so, what would be the minimum scale, minimum necessary?

DR. GEWANDTER: I think maybe you guys can think about that, and we can talk about that in the

Page 111

consensus part, like if you could think of one sign scale or a few would be the good ones.

DR. DASTROS-PITEI: A few or set of them? I mean, I think there was something on a slide.

DR. DOUGHERTY: Thank you for bailing me out.

(Laughter.)

DR. GEWANDTER: Jen?

DR. BRELL: So I agree that we should have a consensus to use the CIPN 20, but that doesn't mean it has to be the primary outcome or primary endpoint. So within each trial, we still can have different endpoints. Maybe we would use a PRO that's more specific for whichever drug we happen to be studying. But I think, yes, for consistency, we should have it somewhere. It should be collected somewhere in all of our trials.

I know this is a little bit off. We want to keep this simple. We want to use, and expand on, and improve on things that we're already doing. But one thing I don't think we've talked about much yet is a functional tests, and whether or not there

Page 112

are some good functional tests that we could use that have some validity that could be quickly done in the clinic, and maybe even a better way to screen our diabetics that are entering trials and people with other types of neuropathy entering the trial.

So I would like to think some more about this and maybe entertain this.

DR. GEWANDTER: I think that's a really good point. Do any of you want to say anything about functional scales or should we think about that for later, too?

DR. G. SMITH: I could just make one point. We have a couple of trials going on and soon to be a third in diabetic or pre-diabetic neuropathy, and we're really trying to look at the relationship between biomarkers and functional scales. So we're doing detailed kind of balance and mobility with many best tests timed up and go, 6-minute walks, and so forth.

I've been struck, even in just screening diabetic patients, that the limits on mobility and

Page 113

function are often driven by other things that dwarf neuropathy. And I think it's incredibly important, but it's also really challenging. I think Roy was going to say something.

DR. GEWANDTER: Roy?

DR. FREEMAN: A couple of things. With regard to patient-reported outcomes, I'd like to hear the case for actually using the CTCAE other than for AE, because just looking at it in terms of a scale, the granularity, the likelihood of responsivity, it seems to me that it just is very unlikely to be a valuable scale.

I've heard I think two speakers already this morning making the case for retaining it. I want to be more convinced. I like the fact that we're moving towards some kind of a consensus, but I'd like to flush that out a little bit more.

So that's one point. The second is -- and this is a much more general statement -- to me, one of the unfortunate aspects of developing scales is only right at the very end do we assess responsivity.

Page 114

It really strikes me as -- perhaps because Guido is sitting behind me and watching how the scale is being developed, it reminded me of a high-performance Italian car, which looks perfect, has all of the criteria that you would want in a car, and then you attempt to drive it on a cold, snowy morning in Boston, and it just doesn't do the job.

So to me, I think there are two aspects of scales. The one is to characterize, and there, I think that's relatively easy. We can characterize function. We can characterize features of an examination. But for a group like this, the most important aspect is responsivity. How does it respond to an intervention?

My concern is we only find that out after 10 years. And you're beginning to get there with your Rasch-modified scale, but I'd like us to -- and it's not necessarily part of this meeting. And I've said this many times, for example, to Ingemar when he has transformed his scale so that it has perfect psychometric or clinometric characteristics, does it actually work in the real

Page 115

world.

So that was the second point. The third point relates to the clinical exam, the signs. And Gordon was quite right. I felt that it was a set-up. And it was a set-up. And I think it's important to understand this, too. And I want us to draw the right conclusions about the neurological examination.

That scale, the NIS-LL, or the NIS, was a scale that really emanated in the ALS and chronic inflammatory demyelinating polyneuropathy world, which this is a motor world, and it was superimposed on diabetic peripheral neuropathy, which rarely works certainly initially when we are implementing clinical trials in the sensory and autonomic world.

It failed in a number of clinical trials, countless clinical trials. And one of the thoughts was that it failed, or at least the hypothesis that was behind that surreal meeting was that it failed because the clinicians could not adequately implement the trial, which may be true but

Page 116

unrelated.

It was not just neurologists. It was actually diabetologists as well who attended the meeting. And they were left, as Gordon said, to their own devices, which is never a good idea. And there was no reproducibility.

The second gathering, they were not left to their own devices, and they were trained, which is critical in any clinical trial when a PRO or a CRO is implemented and told what's normal and abnormal. And it was said, no microneurology. If it's abnormal, then it's really abnormal, and then reproducibility was actually very good.

So I actually think the message of that experiment and of clinical signs are hard to conduct a clinical trial with training for these aspects to be really reinforced.

That aside, though, I think the question of signs and utility of signs is a really very important question, how it relates to function, whether it is or is not an adequate surrogate. I think it probably is a question that is worthy of

Page 117

another meeting, but that to me is the question because signs may respond very early to an intervention long before functional measures actually change.

The implication has always been the tacit understanding is that that's why we are interested in signs. That's why we do neurophysiology, because these respond early, and the assumption -- and there are some data, but not great data to suggest that this is accurate -- is that this is a surrogate for a long-term benefit.

DR. GEWANDTER: So I think that brings up a couple really god points. The first relates to something that Gordon said, that maybe signs might be more useful potentially for early prevention, detecting early prevention or disease modifying, and then the PROs might be more useful when we're doing treatment. So I think the relative usefulness of these, we might want to consider differently for the different stages of the trials that we're doing.

One other thing that I wanted to bring up is

Page 118

this idea of responsiveness. I think when you guys talk about these and that surreal meeting, whether you could diagnose healthy patients versus patients who have diabetic neuropathy, that's a pretty big difference, though. And our trials are trying to potentially detect smaller differences and the effects of the drugs.

So is there any merit to designing your endpoint not only -- or choosing your measures not only based on CIPN and the amalgam of symptoms of CIPN and signs, but what you think your drug might actually do.

I'm not a neurologist, so this might actually be really naïve, but in treatment, at least, I think about, I'm doing an intervention that seems to help mostly for cramping, but really not for pain. So if I'm going to do the CIPN 20, there's a whole bunch of stuff in there. And am I going to cover up a response to cramping that might be really big, depending on who I include in my trial. And obviously, I think we're glossing over this idea that measurement's the only challenge in

Page 119

terms of whether a trial is inconclusive or negative.

But is a composite that includes all of these symptoms always the right choice? And I don't know if that's the right answer. Anybody?

DR. LOPRINZI: I can comment, and maybe I'm talking too much. But one, with the CTCAE, there are pros and cons. It drives my wife crazy. What are the pros and what are the cons for using it? And the cons for using it is that it's not perfect.

The pros of using it are that it's got history. We've been using it for a long time, and it'd be nice to know, as we do in the future, how we're comparing to that. It correlates very well with data from other measures such as patient-reported outcomes, such as the CIPN 20 instrument.

It's easy to do. The docs are going to do it and whatnot. It's not perfect in any way, shape, or form, but it's easy enough to do. We're used to it. We've been doing it on lots of different trials for lots of different times, even

Page 120

though it's really unproven.

Pros are going to be the primary endpoint. They're much better. They always have been better to ask it directly from the patient and have them write it down instead of have it translated by the nurse and the doctor. So that's going to be I think where your more primary is, so that it's not going to be as primary and it's not going to tap the patient-reported outcomes.

So those, as I see it, make the reason for continued use of the CTCAE. It's kind of like why you put down the pulse and the blood pressure. It's easy to do and all that sort of thing. We've been doing it for forever and a day.

But as far as the other, you said there are big differences between diabetic neuropathy and normal people, and yet you're trying to find very small ones. It makes all the more sense, more the reason why the signs are going to be very, very difficult to do. If you guys could find one that you guys could do, neurologists, to make a difference, and that us non-neurologists could do,

Page 121

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

Page 122

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

Page 123

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

Page 124

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

Page 125

So we know that, and we also have that with CTCAE, that we have that sort of thing. So they've shown that they're responsive over time in the play field that we know get neuropathy. How do we know it gets neuropathy? Because everybody tells us, and we all know that chemotherapy causes neuropathy.

But the scales do work. The CIPN 20 has been shown like that, and across a number of different drugs. So it works, not perfect.

DR. GEWANDTER: So Bob and then Ellen?

DR. DWORKIN: This conversation makes me want to ask Mike McDermott a question, which is, within Parkinson's disease trials, are patient-reported, quality-of-life outcomes more or less responsive to efficacious treatments than sign movement disorder, objective measures, across 30 years of Parkinson's disease trials?

DR. MCDERMOTT: Less.

DR. DWORKIN: So the quality-of-life patient-reported outcomes are less responsive to L-DOPA, et al. than the objective measures?

Page 126

DR. G. SMITH: Yes. I mean, one caveat for that, as a neurologist, we measure what we can, not necessarily what we ought to. And so if you look at -- and Mike probably knows this better than I. I'm not a Parkinson's doctor. But the disability and function in Parkinson's is driven, to a great extent, by non-motor phenotypes. Right? And what does L-DOPA fix? It fixes the motor phenotypes.

So the UPDRS is sensitive to motor changes and responsive to a drug that changes motor function, but what this also may mean is that the drugs that we have that are effective and do elicit a response aren't really meaningful for patients. I don't know if I stated that.

DR. McDERMOTT: But here, exactly the point, I mean, things like quality of life make up so many different things. That's why I think they tend to be less responsive to treatments that are targeted at specific things, exactly right.

DR. GEWANDTER: Is it about this?

DR. FREEMAN: It's exactly about this.

DR. G. SMITH: This is going to be on that

Page 127

Mike McDermott, a statistician, told me that I was right about something, so that's good.

(Laughter.)

DR. FREEMAN: This really reinforces the notion that we need to think of signs as potential surrogates that may be reasonably likely to predict a functional improvement. And I think the Parkinson's studies really emphasize that, that the signs may be more responsive to the intervention, but there is.

We know, after years of study, that there is a relationship between that improvement and functional outcomes even though the one is more responsive than the other. So I think this perhaps reinforces the notion. I think there's always a danger of going from one disease to another. But to some extent, this provides at least some intellectual support for the notion that signs may be a surrogate.

DR. GEWANDTER: Gordon, in your data, you'll be able to look at that. Right? Because you're going to have signs and functional data, you can

Page 128

look to see?

DR. G. SMITH: We have signs and functional data. In our CIPN cohort, I don't know. We're not getting as much functional data.

I just wanted to emphasize Roy's point in response to this concern that oncologists can't do these fancy neurology tests and the take-home from Peter Dyck's study.

It's actually I think quite simple. These are not hard to do. The ones that are hardest, we can get rid of and reflexes perhaps are that. But our ability to grade sensation or strength actually is good as long as you agree ahead of time what you're grading. I don't think it's that hard.

I think that's the take-home point, that there needs to be training and there needs to be just criteria set. And these are simple. And a year later with -- it wasn't detailed training. It was 20 minutes sitting around talking, and our reproducibility skyrocketed. And this included endocrinologists who I think everyone recognizes are not as capable as oncologists in doing these

Page 129

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

Page 130

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

Page 131

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

Page 132

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

Page 133

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

Page 134

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

Page 135

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

Page 136

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

Page 137

is that we had a simple way of evaluating the outcome that could be implemented across multiple sites without excessive training of staff, so that was important.

Then there's the issue of the intervention. So how interested are people in this intervention? How difficult is that intervention to implement? So related to how interested people were, feasibility of recruitment is also very much linked to getting people's buy-in about whether or not this is an important trial.

So as we were developing this trial, again within the cooperative group system, we were going to be potentially recruiting patients that had painful paclitaxel or oxaliplatin-induced neuropathy, so we're really targeting mainly the breast and the GI populations.

So as we were developing the study, it was important that we worked with the physicians, and the nurses, and the CRAs that manage those populations. So within the cooperative group, there is a very good mechanism for vetting when

Page 138

you're developing a study.

So you go to the breast cancer committee and you talk to the breast oncologists. You go to the GI committee and you talk to those folks. And together, it's an opportunity to employ maybe community participatory research techniques and that you're getting input from a lot of folks.

So then the next issue that is very important has to do with, again, what is your primary outcome measure, what's your target population, and as a result of those concerns, do you need to do a multi-site study or can you do a single-site study?

So this was a chronic pain study, and we've already heard that chronic pain is not as prevalent. So if only 20 to 40 percent of patients develop pain, then you have to find those patients, which means you need a multi-site approach to be able to identify them. So at some of these 100 sites, we recruited 1 patient. So they opened the trial for 1 patient.

Next, data collection methods. Again, we've

Page 139

already talked about how they have to be simple if you're going to do a multi-site study. The timing of the outcome measure needs to be aligned with when patients are coming into the clinic anyway for routine follow-up, so making certain that you're being sensible and practical in how you align your measurement.

Then there's the infrastructure. So again, we had the CALGB infrastructure to help us with this. We were able to identify dedicated recruiters, dedicated nurses that were really excited about the study, so they worked really hard at their site. So some sites recruited 50-60 people because they had a person that really spent a lot of time with it.

We ultimately had to open it up to the CTSU mechanism, which is an NCI-based mechanism that opens up the trial to not just the CALGB cooperative group, but to all the other cooperative groups, so ECOG and RTOG. So when we did that, the recruitment numbers escalated dramatically.

The last thing I'll say, and then we can

Page 140

open it up to what folks think, there's an issue that's important that has to do with training and education.

We all know that when usually you open up a study, it takes a while to get it ramped up. So people don't remember it. There are many competing trials. So here, you have a symptom intervention study that sometimes is competing with the time that an oncologist or hematologist has to give to maybe a study that's all about treating the disease. So there are those issues.

So we've found that we needed to continually educate and remind. We used the Cooperative Group Network, where everyone comes together a couple times a year to, again, go to the breast cancer group, go to the GI group, go to the nurses, go to the CRAs, say, "Remember our study? Well, here's what recruitment looks like. We're not recruiting very well. We're at risk of having to close this study. Can you do something to ramp it up, or what advice would you give me as a PI? Is there a way that I might amend this study so that we would be

Page 141

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

Page 142

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

Page 143

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

Page 144

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

Page 145

have to go through that process of review. There are non-NCI-related cooperative groups. There's the AFT and Alliance Foundation Trials Group. There's the ACCRU, A-C-C-R-U, which was developed from Mayo when we had the NCCTG, which is basically a cooperative oncology group without a government.

In the ACCRU, which I happen to chair, I'm the vice chair of that and run the symptom control part of it, so you can consider that a conflict of interest if you want. But there, we are able to do that, and we have a hundred members of ACCRU, and not everybody participates in every study, but that sort of thing.

So there are those sort of mechanisms that can be utilized. Otherwise, a pharmaceutical company could get a CRO and then get their own group there. There are advantages and disadvantages to those sort of things. The nice thing with having the group process is that they can develop protocols, or they can be drug company protocols, and they just help facilitate accrual to them. But those are different processes where that

Page 146

can work.

DR. GEWANDTER: Can you elaborate on what you mean by just help recruit to them? You said they could either run them or just help recruit to them.

DR. LOPRINZI: So there are different ways. Sometimes, a company will come to us and ask us. They have an idea. Or we've actually gone to a company and said, "Hey, we'd like to do this study of looking at apixaban versus low-molecular heparin for preventing blood clots."

Then we went to the company, and then they said, "Yes, we'll support you in terms of drug and funds for doing this thing." And then we develop the protocol, and have the whole protocol development office, and all that sort of thing, take it through IRBs, and send it out to the group members, and all that sort of thing. So we have kind of a full-service process there.

We also have a process whereby if a drug company has a trial that they're doing, that they develop, they wrote it, and they just want somebody

Page 147

to put patients on it, they can send it to us.

We will go through a review process and say do we think this is scientifically sound, do we think this is safe, et cetera, et cetera. If we buy into it, then we say, yes, we'll do that. And it's their protocol, but we'll then send it out to our members, ask them who wants to participate, and then facilitate the administrator process of making that happen. And they do it completely through ACCRU.

Then we have a situation where a drug company will have their own CRO at a bunch of institutions, and then they might also have ACCRU that used that for getting more institutions. And the nice way about that is that they don't have to contract with each of the institutions of ACCRU. They contract with ACCRU, and then we take care of the contract with the institutions.

So does that help answer your question?

DR. WEN: Some of the challenges that you have for your trials are similar to the ones we have in neurooncology. We have relatively small

Page 148

patient populations, limited resources, limited interest from industry.

There are several ways to approach this. One is to improve the efficiency of your accrual. The other is to make your trials more efficient. And one great inefficiency is that you have a control arm in each trial that's separate. So if you had a mechanism where you had a single control arm and multiple agents being tested, that would immediately cut your patient number.

So in neurooncology, we set up several platform trials where we build a mechanism. We've been working with Don Berry at MD Anderson using these Bayesian adaptive designs with the hope that we can get an answer with fewer patients.

Then because we have this mechanism, we hope that companies will have a lower threshold to come to us, to bring their agents. So that would be a slightly different way of looking at how to approach this problem.

DR. LAVOIE SMITH: Another factor has to do perhaps with concern around conflict of interest.

Page 149

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

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

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

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

Page 150

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

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

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

Page 151

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

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

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

The treatment trial, Ellen, you might say

Page 152

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

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

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

Page 153

over a thousand patients on our clinical trials with neuropathy. I think that's probably right, but close to that sort of thing over time. They had pretty good rates, too.

DR. GEWANDTER: So I'm actually surprised to hear you say that you think it's easier to recruit patients for a primary prevention study than potentially secondary because colleagues of mine have said, well, you know, at the beginning, there's so much to think about. They're deciding about what treatment they want, so it's kind of overwhelming to then add on do you want to consider this study? And it might actually be easier while they're getting their first infusion, they're just sitting there, asking them at that time.

Do any of you have any comments on that?

DR. CLEARY: Again, I think the reason his trial was successful was, if it would have been a trial of jut sign a consent form that you will or will not get calcium magnesium infusion, I don't think it would have accrued at all, because that really would have been an extra step for the

Page 154

oncologists. But the brilliance of his approach was he linked it in with the FOLFOX.

DR. GEWANDTER: So you're thinking it's more about the oncologists' time than the patient's willingness or --

DR. CLEARY: It's also where the oncologist's focus is, yes.

DR. LOPRINZI: But let me follow up on your other thing, too. So I think, actually, some of our trials have been treatment of established chemotherapy neuropathy. And nowadays, if I'm doing a treatment of established chemotherapy neuropathy, I generally don't do that in a time while they're still getting the chemotherapy. I think it's better to separate those things.

You can do it while they're getting chemotherapy. In our baclofen amitriptyline ketamine study, two people who had established chemotherapy neuropathy. They could still be getting neurotoxic chemotherapy, and a third of them still were. I think it's easier not to have that group in there, but there are plenty of people

Page 155

out there with established chemotherapy neuropathy for that.

For prevention of neuropathy, there's two ways to do it. One is to do it before they get that first dose. And that's what we did on the calcium magnesium study, and it worked pretty well.

Other times, we've actually allowed before the second dose because it's so much going on with their getting their first dose of chemotherapy, and this and that, and with that, and I'm worried about this and all that sort of stuff, to think about the neuropathy things, and sometimes before the second dose, with the rationale being that neuropathy is a cumulative sort of thing, and one dose isn't probably going to hurt you too much, but if you get 10 or 12 doses, you're going to get that and, therefore, why'd you prevent it.

But the other aspect of it is, if you want to prevent any neuropathy, maybe you should start a week prior, which is really, really hard because it doesn't fit very well. But you can put patients with established neuropathy -- they're not hard to

Page 156

accrue to studies because there are so many of them out there and about. And you send out an advertisement, anybody got chemotherapy neuropathy, and they just come flooding to your office.

DR. LAVOIE SMITH: I think, Dr. Katz, you were next, and then Dr. Brell after you.

DR. BRELL: I'm staying on this topic. I just think, in general, especially with my experience with the prevention trials at NCI, that prevention trials are harder in general to get patients on because they have to imagine having this thing you're trying to prevent, and it's hard. And neuropathy is really hard. Unless they know someone who has it, it's a concept they don't understand as well.

So of course, everything's going on when you're first trying to put them on chemotherapy. But I just think, in general, historically, it's been more difficult to accrue to those trials.

DR. RICHARDSON: I just want to add a little bit to that by saying that in the context of myeloma, obviously there is a perception amongst

Page 157

patients that it's part of the underlying disease. And the other thing is that we have very active engagement from IMF and MMRF, who are our major patient advocacy groups, and they alert patients to the fact that neuropathy is a big problem not only from the disease itself, but from therapy coming.

So when we did our sort of landmark bortezomib monotherapy study, we didn't offer an active intervention. What we offered was actually a descriptive trial. We offered a proactive approach to dose reduction and schedule change. We also integrated our complementary strategies of emollients and supplements in an organized fashion. So patients started on their supplements before they began therapy, and we introduced the emollients as well.

Our nursing team are committed to educating them, and guiding them, and monitoring them through it. We also had a commitment to IV hydration as well. We used intravenous bortezomib in that study.

That's actually one thing that I was just

Page 158

going to say that folks hadn't touched on I think in the meeting so far. And, Charles, you and I talked about it last night, this whole concept for patients as well as for us as clinicians studying neuropathy, this whole issue of route of administration, PK, and pharmacodynamic effects of the drugs we're giving, because that's an incredibly important variable to build into any trial that you do with a preventative or therapeutic agent targeting neuropathy. You have to really understand that aspect of it, just as a sidebar.

But going back to the point, when we did this study, we offered all of these things. And really, the essence of the trial was descriptive. And yet, patients were very happy to participate. We didn't have anybody unwilling to do so because of the skin biopsies, the extra nerve testing. Everyone was willing to do it.

But I think if it's just carefully explained, carefully framed, and it's understood that neuropathy is part of the territory with your

Page 159

illness and very much a part of the territory with your therapy, our accrual was not a problem at all.

DR. GEWANDTER: You had people do skin biopsies and they --

DR. RICHARDSON: We did. We did skin biopsies on the lower extremities to what we discussed with Pat yesterday.

DR. LOPRINZI: In a subset of patients.

DR. RICHARDSON: Yes, and subsequently as well. And we were able to show neurite fallout. We were able to show axonal loss across treatment, small fiber loss across treatment.

DR. GEWANDTER: Do you pay them a lot? Did you pay them a lot to do the skin biopsy?

DR. RICHARDSON: We didn't pay them at all. Why? No. I mean, IRB would absolutely put the kibosh on anything like that. We are not even allowed to offer, without IRB approval, reimbursement for travel. We're not allowed to. No, because it's considered discriminatory, because there are some people who would need it, some people who wouldn't. So it'd be viewed as an

Page 160

inducement. So we're not allowed to do that.

I mean I think that's actually slightly ridiculous because, at the end of the day, it's an expense for the patient, but they will not allow us to do that because it's an inducement. So how we get around that is we put access patients to the LLS, the Leukemia Lymphoma Society, to the chronic disease funds, and sponsors and other partners voluntarily donate to those funds. And those organizations in turn support patients. But our IRBs will not allow us to reimburse patients for anything.

DR. WEN: I think it's hard to underestimate the importance of having the oncologist be an advocate. Those trials were a success because of Paul. I mean, he went after everything. And similarly for breast cancer trials, having Charles be there probably made a huge difference.

I think, if you had someone else coming in with a trial without the contact and influence, it doesn't go nearly as well. And then having the patient advocacy groups be an important part of

Page 161

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

Page 162

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

Page 163

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

Page 164

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

Page 165

were done by drug companies for a side effect treatment.

DR. RICHARDSON: I think that's a very good point. I mean, I totally hear where Nat's coming from. I think, however, I would argue it slightly differently. I would suggest that it needs just revisiting with our pharma partners how we do this, rather than necessarily say it's an us-and-them type of situation and the division grows; rather, do it the other way.

I was reminded -- and Pat reminded me of this -- that by accident, we ran into our experience with tanespimycin, an HSP 90 inhibitor combined with bortezomib, a striking reduction in neuropathy, even by CTC criteria, which was so interesting, because, as you pointed out earlier, CTC criteria are so insensitive. But even with that tool, we saw it.

So we combined two active drugs and saw actually a reduction in neurotoxicity because the HSP 70 effect was probably important in reducing inflammation.

Page 166

I think that both drug partners there got very excited, Millennium on the one hand, and at that time, it was under Kosan before it was bought by BMS. And BMS was very excited. But unfortunately, we then ran into a drug substance problem where we couldn't get the product to where it needed to be, and batch-to-batch inconsistency killed the drug. It was a disaster, but that's a different story.

The point is that both pharma partners were very interested when the signal emerged. So pharma is interested. It's a question of how it's contextualized and how it's structured.

So Pat, maybe you can --

DR. DOUGHERTY: Along those lines, we've recruited into two longitudinal studies, and we did one small nerve protection study. We didn't have a big problem. I mean, maybe it's something about patient flow because we got gobs of patients.

The only thing that we found difficult -- and this was now four or five years ago -- was finding treatment-naïve myeloma

Page 167

patients. Now, that was a bear. But to get treatment-naïve CRC patients, we enrolled 100 and something in a little over two years' time.

I would think that in this particular case, for CIPN, if you explain to the patients that, look, this is the complication that's likely going to drive you out of therapy and this intervention may keep you on therapy if you're in the active arm. I would think that would be a huge incentive for patients to sign up, particularly if you make it easy for them.

If you make the assessments too onerous, then they're not going to be interested after a while, as we saw with the presentation earlier, because when they're in therapy, they want to survive.

But if you keep it easy, and they have a friendly face that they're used to seeing each time they come to the center -- and that they're going to have to wait to get into the clinics anyway, so to take a little extra time to meet their buddy who's going to walk them around the center and go

Page 168

about that, we didn't find it difficult. But it really is that face that meets them at the door. That I think is crucial to any of these.

DR. RICHARDSON: I think that echoes what you heard from Pat about nursing, and myself about nursing, and the team approach. But I do think also that this is a plug that really echoes with Charles and where we partner in the alliance.

The large group studies or group mechanisms can address the issue, Pat, you've touched on, which is the patient availability, newly diagnosed patients, for example, with myeloma. We have study groups that could address that, but having said that, in the broader sense, the alliance, for example, might be a great platform.

Wouldn't you agree, Charles?

DR. LOPRINZI: Yes. The patients can be accrued on either treatment or prevention trials, and through a cooperative group or a group that's not part of NCI. So they're available. Alliance is the name of a cooperative group, or now there's an alliance. Yes, so you have to be careful. Yes.

Page 169

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

Page 170

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

Page 171

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

Page 172

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

Page 173

Pat's incredibly important point, which is your patient population. You want to make sure you access who you need to you treat.

DR. LOPRINZI: Basically, you want to go to investigators who have done chemotherapy neuropathy trials, and then they can help you through the mechanism. And that might be conflict of interest because I've done more than most other people, but that's the way.

Whether you put it through -- when I talk to groups, put one through the cooperative oncology group, the nice thing about that is, it's cheaper because NCI pays for the statistics, and data management, et cetera, et cetera, or you can go through the ACCRU mechanism, which costs more money, but is quicker. But they're actually available out there.

DR. DWORKIN: Charles, just to be fanciful for a moment, could ACCRU do a 400-patient trial -- and I'm not proposing this trial -- of whether pregabalin has a preventive effect in patients initiating taxane chemotherapy?

Page 174

Is that something that, if one had the resources, the financial resources, ACCRU could actually get completed? Because that's Nat's question really, a phase 3 trial.

DR. LOPRINZI: Yes, that could be done. We just completed a randomized, placebo-controlled trial of pregabalin for trying to prevent chemotherapy -- paclitaxel-induced neuropathy.

Breast Cancer Research Foundation provided funds for me, and I ran it and I ran it through ACCRU. It was a small study because NCI wouldn't approve it before, although I tried to get that approved before. I even said Bob Dworkin said it was a great idea, and he'd bet his car on it, but they still didn't approve it back then.

So I ran this 46-patient study, 23 per arm, which has little, little power, but to see if there were pilot data to help support that we could go forward with a larger placebo-controlled trial.

What we ended up showing in that particular trial was that it looked like it actually helped to prevent the acute neurotoxicity from paclitaxel,

Page 175

the aches and pains that people get that used to call them arthralgia, myalgia, which in my mind are really neuralgia. But it didn't have any suggested benefit in terms of numbness, tingling, shooting, burning pain during the time of chemotherapy and for six months there afterwards.

So that wasn't enough for me to say, hey, I got enough pilot data to suggest that didn't need a p equals 0.5, but it would have been nice to have a split in the curves enough to do that sort of thing. So, yes. But those can be done.

DR. DASTROS-PITEI: Just a comment from an international perspective, so outside the U.S. Clinical studies, we have seen done, were done in an alliance, were done in the population, which was an adjuvant population, a CIC adjuvant. Obviously, it was easier to recruit.

But what was interesting is, in Europe, the patients need to consent to the treatment, to the chemotherapy. I don't know if it's the same in the U.S. So they come to me, so adjusting your assessments to the times needed for oncology

Page 176

assessments is very important.

We have the benefit in Europe and back in the U.K. that they need to consent two weeks before the chemo starts. So that's a good opportunity to actually consent them for the study if they're happy to start into a prevention study.

So going to the point is try to match as much as possible the oncology assessments, bearing in mind that, however, there will be some assessments which perhaps need to be done in between.

So there's some for that. We need to find a way to attract the patients and keep them engaged. And I think the nursing staff time is probably the best investment.

DR. LOPRINZI: But if you want to do a bunch of neurologic tests, and biopsies, and all that sort of stuff, you need a two-week -- yeah, you need something like that because that's just too unfriendly to do.

If you listen to the group earlier this morning that says that those tests, you probably

Page 177

don't need to get biopsies and tests like that, and we don't need to get -- we don't have the signs yet to get. We've got to work on the neurologists to figure out those signs that are easy, doable, and whatnot.

We don't have now, but we have been able to take patients who have received chemotherapy, and, oftentimes, in a day or two, and say, hey, we got this sort of thing and here's a consent form. You fill out this patient-reported outcome, or the doctor assesses neuropathy in the clinic the way they normally do. And then you go ahead and randomize to calcium magnesium versus not and do that.

So it can be done, it has been done, but if you need a bunch of tests ahead of time, that's where I say you need to make it clinically feasible and scientifically sound.

DR. LAVOIE SMITH: If you need measures in between the routine follow-up visits, it depends on what it is that you need. And patient-reported outcome measures can easily be collected via paper

Page 178

and mailed in, electronically. So that's something else to consider again so that it's a feasible approach.

DR. DASTROS-PITEI: Maybe subgroups for very intensive assessments, which would be maybe [indiscernible] assessments or others. Then maybe this subgroup analysis and the subgroup of patients are more useful, so not in the whole study, but maybe focusing on subgroup of signs.

DR. LAVOIE SMITH: Over here?

DR. G. SMITH: I was just wondering how much thought has been given to perhaps aspects of pragmatic trials that might help in some ways. There are registrational trials -- or pragmatic trials that are now submitted for registration purposes, and the idea behind can you use registries to recruit patients.

You generally simplify the data you collect to try to collect the important things. And the idea is, generally, you can hopefully improve recruitment and reduce some costs.

You are a lot more lenient on entry criteria

Page 179

in general, but I'm wondering if there might be not every aspect of that, but whether there are pockets that might be utilized to help in that regard.

DR. LAVOIE SMITH: The first thing that comes to mind for me is that it depends upon, again, what your intervention is.

So if I take us back to the duloxetine study with a norepinephrine serotonin reuptake inhibitor that can't be used with a variety of other drugs, and has black-box warning labels, and you need to make certain that people are X, Y, Z, then sometimes the intervention really precludes the ability to do that. But there probably are other circumstances where that might work.

DR. LOPRINZI: I think the English have been particularly good at this over the years. But still, it's a randomization process to A versus B, or C, or D, whatever you have in there. But on the eligibility criteria, you can have a long, long, long lists of these sort of things, and a long list of things, and all these things which really has a very, very tight group you have there, or you can

Page 180

open it up. You want safety, but you also want it to be generalizable to patients there.

So there are ways. And I think our success has been to try to be pragmatic with them. That's user friendly enough to do them and yet scientifically sound.

DR. DOUGHERTY: Charles, look at a finer grain. One of the things that struck me as we did our longitudinal studies is that the patients were so rude as to go home after receiving chemotherapy. And the critical days that I've always wanted to measure is that 3 to 5 days after each round.

When you did your assessments, didn't you get them prior? You got them the day that they were coming back for their next round prior to chemo, or did you get them in those intervals, those critical intervals, when they're generally at home?

DR. LOPRINZI: The answer is yes.

DR. DOUGHERTY: Well, I shouldn't have asked you more questions. Did you get them --

DR. LOPRINZI: I'm going to go forward a bit

Page 181

there.
So for both of the agents, we've looked at paclitaxel and for oxaliplatin. They both have chronic neuropathy that we've been talking about, and they both have acute neuropathy problems, the cold, numbness, and crampiness with oxaliplatin, the aches and pains central, that sort of thing for that.
So on each of those trials, we had patients fill out a questionnaire on day 1 before they got any chemotherapy, asking them about chronic neuropathy and acute symptoms. And then we had them fill out questionnaires daily for 7 days, a piece of paper --
DR. DOUGHERTY: At home?
DR. LOPRINZI: -- write it down, please do that, mailing it, something to mail back, that sort of thing. So we did it for 7 days, right before their next chemotherapy and afterwards.
Now, on the every-two-week oxaliplatin doses, because those are done every two weeks, then they had a week off where they didn't have to do

Page 182

anything and then they did that week after week.
On our 12-week weekly paclitaxel, they filled out questionnaires. 12 times 7 is 84 days. Is that right? Okay. They filled out questionnaires for 84 days. The ones afterwards were the acute sort of thing, and then on the day of treatment, right before treatment, we asked the chronic questions.
Then we had them fill them out once a month for six months afterwards. And our data completion is 90 percent-ish, that we get the questionnaires back. Some people have done this by iPads, and phones, and that sort of stuff, which is another way.
So it's easily doable. We've done it, reported it, so you can get that.
DR. LAVOIE SMITH: Anna?
DR. BRELL: I want to make two comment questions. One is regarding the willingness of pharmaceutical companies to be involved in these types of trials, and it's my understanding that a pharmaceutical company would probably do what it

Page 183

takes to get an FDA indication. They would probably suffer through whatever processes they have to suffer through.
But my understanding is that we still don't have good enough measures, outcome measures, for the pharmaceutical company to use to be able to go to the FDA and say, "We saw a difference. We saw a meaningful difference between arm A and arm B."
DR. DWORKIN: That's true for pain. That might have been an obstacle for peripheral neuropathy as an indication, but for pain associated with CIPN, we know how to measure it.
DR. BRELL: Then it is a process.
DR. GEWANDTER: The patients that have chronic neuropathic pain, like the people that you might be thinking about when you're talking to drug companies about a treatment for neuropathic pain, there are a lot fewer of those patients available than if you're trying to do a prevention trial.
So it would be a lot harder to get enough sites without going to the cooperative groups for that kind of study than it might be for, you want

Page 184

to enroll 400. Like Dr. Dougherty said he can 200 patients and approach the study just at his site. So I think that it depends on the population, potentially, like how hard it will be to recruit them.
DR. KATZ: Yes. The amount of suffering the company has to go through certainly depends upon the population and that depends upon the protocol, as was discussed. But the pharmaceutical companies will not go through an infinite amount of suffering to get an indication.
Let's say we're talking about neuropathic pain. There are options. I can do a painful diabetic neuropathy study. I can do a post-herpetic neuralgia study, or at least I used to be able to. And chemotherapy neuropathy, they're not going to go through an infinite amount of planning and suffering.
They've got timelines, they've got budgets, and for the pharmaceutical companies, time is the most important factor, much more important than the actual study budget in most cases. And uncertainty

Page 185

is the second most important variable. If you combine very long periods of time with a lot of uncertainty about the outcome, that's very rarely going to go in anybody's clinical development plan.

DR. BRELL: I guess I'm thinking of the times when someone's developed a drug that doesn't work in all the other indications you said, and then, oh, by the way, is there one last indication. Can we get a CIPN indication? And we see that.

But I can make another quick point about what Jennifer said about trying to learn lessons from other trials and other symptom and toxicity management trials.

It's different scales. So if you're doing a trial for dermatitis, you can measure very clearly how much of the skin was involved in a trial for this or a trial for that.

So I don't know if we can learn as many lessons going to other toxicity management trials as we can learn lessons from what our esteemed neurologist colleagues are telling us with their work in diabetes and other illnesses.

Page 186

DR. GEWANDTER: So I wasn't thinking about measuring. I was thinking about what sites do industry work with to get cancer patients who are undergoing treatment. That's what I was thinking. Where have they been able to get those patients exactly?

DR. BRELL: If it's an industry-sponsored trial, a lot of times, they do have their own networks. And so they use their own large networks to get accrual.

DR. LAVOIE SMITH: We're going to have to wrap it up here.

DR. GEWANDTER: Thank you.

DR. FREEMAN: So very quickly, some housekeeping.

Lunch is at the usual place. The session begins at 1:00. The afternoon session is the critical piece. It's the time when we try and build a consensus, agree upon what we can agree upon, disagree upon what we can't agree upon, and give Jennifer the material for her manuscript, so please be on time.

Page 187

I know people do have flights and are leaving perhaps before the scheduled end, so 1:00.

(Whereupon, at 12:05 p.m., a lunch recess was taken.)

Page 188

A F T E R N O O N S E S S I O N

(1:08 p.m.)

DR. FREEMAN: So the final round, typically, two things happen during this round. It's the most interesting, and it's the round when people start to trickle out. So we want to try and accomplish as much as we can as early as possible.

Just to focus the discussion, what I want to do is to say that this session will be done with two approaches in mind, because I now want to go from what I said were the goals initially to the focus.

The discussion will be, as we go through point by point, were a clinical trial to be done tomorrow and we have members of the audience who are contemplating doing clinical trials tomorrow, what would you recommend for eligibility, endpoints, trial design, measurements throughout the trial.

So were it to be done tomorrow, the best we've got with the understanding that these all have flaws, all have warts, but the best we've got

Page 189

for tomorrow. And then, were this trial to be done in five years' time, what's the research agenda so that a more perfect trial can be done in five years' time? So that is the approach.

One or two other things just very quickly, and that is, I think somebody asked about receipts and reimbursements. I want to make sure that everybody knows that you will get a stipend for participating in the meeting and that no receipts are necessary, at least as far as sending to the organizers.

Then because there won't be time when everybody is in the audience, I think I want to, on behalf of all of us, thank Valerie and Andrea, who aren't hearing me say this, but at least they'll hear us clap --

(Applause.)

DR. FREEMAN: -- for putting together a remarkable meeting, for organizing it so smoothly, and for getting us safely here at least and hopefully safely home.

So now, I'm going to hand over to Jen, who

Page 190

will chair this part of the meeting.

Consensus Discussion

DR. GEWANDTER: Perfect. So we are going to, in two and a half hours, try to make some decisions about, as Roy said, measures, endpoints, and eligibility criteria. So we're going to start with measures. So what do we all think?

It seemed like, during the last discussion, the EORTC CIPN 20 is what we would recommend as the best PRO for right now. Is that true? Does anyone want to maybe say something else?

(No response.)

DR. GEWANDTER: Nothing? And would you say the others are bad, are there others that you might consider -- I don't know that we want to necessarily say this is the one you should definitely use. We could say you recommend it.

Is there another one that is also potentially useful or really none?

DR. G. SMITH: So we're using the NTSS-6. Again, as a diabetes person, we're familiar with it. And it seems to work pretty well for kind of a

Page 191

quantitative symptom identification measure. I don't know if it's a good outcome measure. And it's brief, six.

DR. GEWANDTER: Cool.

DR. FREEMAN: Maybe to give some background on that, one of the challenges with many of the diseases that we are interested in is that symptoms are focused on pain. And the beauty on that questionnaire, which is not widely used or even known outside of diabetes -- and I've been a personal advocate for this instrument -- is that it deals with non-painful sensory systems, things like numbness, things like paresthesias.

It has been used and is in clinical trials trialed by Lilly, and it is a well-validated instrument. Now, I have proposed its use to a number of pharma companies, but it has not been part of chemotherapy-induced peripheral neuropathy. And I would agree, it's a short, simple, and well-validated instrument.

Now, I don't want to jump too quickly away from this discussion of CIPN 20 is the one and

Page 192

only. I think there are issues. And I think Charles made some points, and I know others are considering using some of these PROs as part of their at least secondaries or even co-primary outcomes.

So I think we should at least hear what people have to say about the other patient-reported outcome measures.

DR. GEWANDTER: So Simon?

DR. HAROUTOUNIAN: I just wanted to comment that we are using currently the Neuropathic Pain Symptom Inventory, the NPSI, in the setting of oxaliplatin- and paclitaxel-induced neuropathy. And again, it has painful descriptors and non-painful descriptors.

My experience is that we have been capturing pretty reasonably the most annoying, bothersome symptom in most of the patients. And I think it just allows you enough variability to capture the diverse type of symptoms that the patients report.

I don't know that anyone has used it in CIPN previously. In other neuropathic pain conditions,

Page 193

it is pretty common. But I think it's pretty useful, but we don't have the study results yet.

DR. GEWANDTER: It's pretty focused on pain. Right? There's only two non-pain symptoms. So the outcome would be pretty dominated by pain.

DR. HAROUTOUNIAN: Agreed.

DR. GEWANDTER: Bob?

DR. DWORKIN: So we all know that, when you make recommendations, the immediate next question is, did you do a systematic review, what is the evidence base, et cetera for the recommendations you're making.

So my question is for you, Jen, because I can't remember. It seems, whatever we suggest about the PROs will need to be consistent with what's in your muscle and nerve article, which is the systematic review. And if it's not consistent with your muscle and nerve article, then we're not going to have any way of justifying the recommendations.

DR. GEWANDTER: So we didn't make any recommendations in that review. We only looked at

Page 194

the content validity. And actually, the EORTC has one of the better content validities.

DR. DWORKIN: So that's exactly what I meant by consistency.

DR. GEWANDTER: Yes. So if we were to say that, right now, the EORTC is the best, they did some of the best work, at least published work, for content validity, that would be consistent.

DR. LOPRINZI: If I could add, I think the easy way to take care of this is that patient-reported outcomes are recommended, number one. Second sentence, the EORTC CIPN 20 was preferred. Next sentence, there are other ones that might be okay in other situations such as X, Y, Z, and Q. And then you cover the bases.

DR. GEWANDTER: Okay.

DR. FREEMAN: Be more specific. Jen is much too agreeable, and I'm far more argumentative. In other situations like what?

DR. LOPRINZI: Like what people talk about? I don't think there's a ton of differences between them, and if I saw a study that was done with FACT-

Page 195

GOG-NTX, I wouldn't disbelieve it because it wasn't done with a CIPN 20 instrument. I love Guido's slide. I asked him for it where he compared them. And I know there's some stuff in there about joints that don't have anything to do with the price of tea in China.

So you could spend a long time going through all those things. We actually do in our protocols go through why did we pick CIPN 20; we could have picked this, could have picked this, could have picked this; but it's just got the right questions, and it's not perfect. I wish the pain question wouldn't say shooting, burning, because some people say it's not, and you can supplement it with other things.

DR. GEWANDTER: Joanna, and then Pat?

DR. BRELL: I think the way I look at it is the CIPN 20 is sort of the anchor, something that we want to have somewhere in the objectives for our study for comparison's sake. But each study will have additional PROs that are related to the agent in question.

Page 196

So if it's pain, if it's other neuropathies, it'll be more specific, but I would recommend having the CIPN in all of them as a secondary endpoint at least.

DR. GEWANDTER: So what you're saying is, this would be a good general neuropathy CIPN measure, but that when necessary, adding other PRO symptom measures that are related to either your disease or your intervention would be the best.

DR. BRELL: Might be more specific to what you're studying.

DR. GEWANDTER: Sounds great.

DR. FREEMAN: So Daniela and Matt, you guys have thought about this a little. What would you say?

DR. DASTROS-PITEI: We focus on CIPN 20 just because the evidence in the literature is around it. I'm not sure about the FACT GOG, so I think we'll probably have to think about this as a special secondary.

My question is going back to pain. Are we not measuring pain at all apart from what's in the

Page 197

CIPN 20? Is this something that can be a consensus?

DR. FREEMAN: My stance would be, we are measuring pain, but we just are not only measuring pain. I think traditionally that the studies have focused on pain, and I think there is a sense that pain is, at the very least, not the only feature of chemotherapy-induced peripheral neuropathy and may be a less relevant feature for some patients, particularly later on. That would be my take.

DR. GEWANDTER: My bias, I guess because what I do, is I would always include a 0 to 10 pain scale. Why not? And then definitely not as the primary in a CIPN study, but I think Sharon has a comment.

DR. HERTZ: I actually have a question, and I've been waiting to see if anyone was going to bring this up for the whole meeting. So we use the term numbness and tingling quite a bit. I'm not sure I understand how those two are the same thing. And I notice that the terms are often used together in a lot of the instruments.

Page 198

So I'm trying to figure out what's the difference between tingling and pain, and then are there other neuropathic symptoms that we're missing, and if there are, are they even relevant in this particular realm.

So to me, paresthesias, which I will rename tingling, are painful. They may not be dysesthesias, meaning turning something not painful into painful. But when I have paresthesias just from my foot falling asleep, I consider that pretty painful.

So I guess I would like to hear what people think about those distinctions and are they just because I'm a neurologist, and I naturally think that way, and they're not meaningful distinctions?

DR. GEWANDTER: Bob and then Pat?

DR. DWORKIN: Sharon, I'll try to keep this simple. The IASP defines -- and for those of you who are IASP members know this, if I'm incorrect about this, correct me. My recollection is the IASP defines paresthesias as abnormal sensations that are neither painful nor unpleasant. They

Page 199

define dysesthesias as abnormal sensations that are unpleasant, but not painful, and pain is pain.

So in our diagnostic criteria, we've tried to adhere to that distinction of painful sensations versus non-painful paresthesias and dysesthesias. But I don't know that that's the way those terms are used in neurology. But that is I think how the IASP defines those terms.

DR. HERTZ: Can I just ask, in follow-up, can someone help me understand what's a non-painful -- what is a paresthesia if it wouldn't be considered painful? When does that happen and what do patients report? Because it seems that if they weren't painful, they wouldn't raise as much concern. But am I just again not getting it? I mean, I have not spent a lot of time in this arena, in this context.

DR. DOUGHERTY: So the numbness and the tingling, the reason they're both put together, is that when patients were given just open word descriptor lists, and there's a whole bunch of words there to describe different types of pain,

Page 200

almost always, they pick numbness and tingling.

And I mentioned yesterday that the patients will say that they have, for example, numbness and tingling in some area between pain and normal. And they say that it's not painful, but it's annoying. It's irritating.

I think pain simply is an intensification of that tingling, so that it gets to the point now, now it's gone from just tingling so that your foot's barely asleep to, now, it's downright pin pricks and it starts to morph into burning. So folks are very specific about how they describe it.

Now, once you get into the painful areas, I do agree I've never heard or rarely heard them use the word "shooting," but burning is very common. I've also heard folks have picked things like gnawing. One lady said it felt like rats were biting her on her fingers. Now, I didn't ask her what experience she had in that, but in any case, that's how she described it.

So I think that it's a gradation between no sensation bothering them, and then it's gone -- it

Page 201

feels like a fat lip, which clearly is not painful, but it's annoying right after the dentist. So that would be a paresthesia.

Now, the tingling gets into the realm bordering on dysesthesia.

DR. LOPRINZI: Just to clarify a moment, the CIPN 20 asks for numbness specifically from tingling. So it asks for numbness, another question for tingling, another one for pain in the hands and toes, hands and fingers, and separate questions. So there are six questions, separate for the toes and feet.

I've gotten to the point, when I see a lot of patients who are actually having this that were treated with Scrambler therapy and that sort of thing, the numbness and the tingling are discomforts is the word I'd put to it, not necessarily pain.

When we look at the CIPN 20 instrument, the integral patients who have numbness and tingling, it's almost on top of each other. If you look at numbness versus tingling grade, 80 percent are on

Page 202

the diagonal, where it's the same score. But pain versus tingling is 80 percent. It's above in the tingling area and not the discovery, so that they are there.

And the patients say, "It's hard for me to describe what these things are," and I always tell them, "I know it's hard for you to describe, but it's harder for me to describe it for you." And then they understand that and come up with those things.

DR. GEWANDTER: Gordon had a comment?

DR. G. SMITH: Yes. I think it's an interesting question, so a couple of points. At the risk of talking about pain in front of Bob Dworkin, I'm going to do it anyway, and it's a good thing I'm all the way across the room so I have an escape.

I think there's an affect of component to pain. Pain is whatever a patient says pain is, and I don't think it's just a matter of intensification. I think that's part of it.

All the time, we see people who say, "I've

Page 203

got terrible pins and needles." "Is it painful?" "No. It's not painful." And then I scratch my head and go, "I don't understand," but I have to respect their judgment. So I think there's that issue of personal perspective on what's pain and not.

I think another aspect of that is, I've had the same personal experience. I've never had paresthesias that I didn't find painful, but I've also never had neurotoxic chemotherapy, I don't have diabetes, and I don't know what pathologic paresthesias feel like. So I think it's important for us not to lay on our personal experience. I guess maybe one of us has a neuropathy and can speak to that.

I think the last point I'd make is, numbness is the second-least favorite word as a practicing neurologist. The first is dizziness. And because I'm a neuromuscular person, I don't have to deal with that. As soon as someone says dizzy, I go, "Go see the dizzy people."

But I'd say 10 percent of my ALS patients

Page 204

will say their first symptom was numbness. "What do you mean by numbness?" "Well, it was heavy. I couldn't move it." "You mean weak?" "No, just was numb."

So I think it's one of those terms that is even more content devoid than paresthesias. I mean, we use it to mean loss of sensation, and I think it works well in these sorts of scales.

DR. FREEMAN: I think the way neurologists think about this -- and I am including Sharon in the group -- is that we divide symptoms into positive and negative symptoms.

Positive symptoms are things like tingling, paresthesias, and negative symptoms are loss of sensation. And I agree with Gordon that I've always thought of numbness as a negative sensation, loss, a negative symptom, loss of sensation. But at least in the United States, it is a positive symptom, and patients will speak about painful numbness.

I learned to think of these as a continuum. You have a positive symptom, let's say

Page 205

paresthesias, or any positive symptom, or any positive sensation, which can be on a continuum from pleasant, and we know positive sensations that are pleasant, to unpleasant.

I think, if we look at the IASP classification of paresthesias, there are people who I'm sure would say, "If it didn't go on for a long time, I would say it was quite pleasant." And there would be people who would say that, "This is really unpleasant." And that's what IASP would classify as dysesthesias.

But I think the realm of sensory of sensation, sensory symptoms, is along that continuum, and there are some that are painful and some that are not. And I think that, to me, is a useful way of thinking about it.

DR. GEWANDTER: Matt, did you want to add something?

DR. JARPE: Yes. I just wanted to make sure that we're capturing interference items in the PRO, so Gordon's comment about mood made me think of this. I am not familiar with all the details of

Page 206

the CIPN 20. Are we capturing effect on sleep, effect on mood, effect on daily function, that kind of thing?

DR. GEWANDTER: So they're not in the CIPN 20, but I think that you could easily include in your trial a measure of sleep. And I think I would argue, actually, that it would be better to have that as a separate measure, but still very important to include.

DR. JARPE: I mean, I think the BPI captures those pretty well.

DR. GEWANDTER: The BPI captures specifically pain interference with sleep.

DR. JARPE: Right, right.

DR. GEWANDTER: Yes.

DR. JARPE: But I don't know if there's a way to do that.

DR. GEWANDTER: Right. So I think that that's actually really interesting. It's one of the things I think about a lot. And I'm not familiar with any measure that specifically says, "Tell me how your CIPN symptoms have interfered

Page 207

with your X, Y, and Z," but I think that that's something that we should work on making.

Yes?

DR. LAVOIE SMITH: I think that's why the EORTC advocates that the CIPN 20 is used along with the QLQ-30, which does evaluate the other co-occurring symptoms.

DR. GEWANDTER: But it doesn't actually say how do your symptoms affect, like do the symptoms we're interested in affect your quality of life, which I think is really important for understanding how important these things are to patients.

DR. LOPRINZI: But you could put those in a scale from 0 to 10 that's a validated instrument thing, any question you want, as long as you put the endpoints on it. You could add those into it.

DR. GEWANDTER: Yes. I think that's a good idea.

Yes, Joanna?

DR. BRELL: I'd like to hear everyone's opinion as far as other symptoms we might be missing. I hear a lot of patients talk about their

Page 208

hand and arm feeling cold. And I don't know if that's related to concomitant vascular disease or if that's something that other people hear frequently.

DR. HAROUTOUNIAN: We hear it quite a lot with oxaliplatin. At least in the study, patients are just telling their hands feel cold.

DR. DASTROS-PITEI: The cold hypersensitive is a hallmark of oxaliplatin. And I think, in fact, NTx-12, there is a question about cold-induced symptoms. And I'm not sure about CIPN 20, if there's a specific question about cold. But for NTx-12, they've added one question about the oxaliplatin.

DR. GEWANDTER: But Joanna, you're not saying cold-induced symptoms, cold-induced pain. You're just saying, just in general, when I'm standing here, my hands feel cold?

DR. BRELL: Exactly, yes, when I'm going about my daily

DR. GEWANDTER: Yes, which I don't think is in the measures very frequently, no. I don't

Page 209

remember of any. But I have actually reviewed the measures and I have checkboxes. I can look and see.

DR. FREEMAN: I can never let this go. So Guido was fairly ruthless in his dissection of FACT-GOG-NTX. Is everybody in agreement with that? It seemed to me that there was either overlap or the questions were not of value. Is there anybody who wants to advocate for this instrument?

DR. LAVOIE SMITH: The CIPN 20?

DR. GEWANDTER: The FACT.

DR. FREEMAN: The FACT.

DR. LOPRINZI: I wouldn't do both. You could just get question after question. So I wouldn't do both. I would go with the CIPN as preferred, but there are other options in there. And if a FACT group had their own study and they wanted to do it, I wouldn't want this committee to say, "That's a terrible, terrible study."

DR. DASTROS-PITEI: You would or you would not?

DR. LOPRINZI: I would not do both. I would

Page 210

not recommend both because you're getting the patient to answer too many questions. But if David Cella's group was doing a chemotherapy neuropathy trial, I wouldn't put it in a way and say, "You're crazy if you don't use the CIPN 20." I wouldn't.

DR. FREEMAN: So it sounds like we have consensus there. Then one last point that I would make, and I think probably, just in the interest of time, we should begin to include the research agenda. It seemed to me, looking at the CIPN 20, that the autonomic questions at face value were useless. I think this should be part of the research agenda.

Visual blurring is so non-specific, it's not even worth regarding this as a symptom, but the way they asked about symptoms which were meant to address all the static hypotension were not particularly good. And I'm not sure how the question that deals with erectile function in males, but that's always a challenge.

DR. DOUGHERTY: So I just want to point out before we leave the PROs that I think it was last

Page 211

year that Charlie Cleeland's group came up with another instrument that they tried to set up as specifically directed at cancer-treatment-related neuropathies. So you might want to include that potentially on a list of other PRO devices.

I think, again, just to try to draw a consensus, I think to say that CIPN 20 is a recommended PRO tool as Charles laid out in a few sentences, and here are some other options.

DR. RICHARDSON: Jennifer, do we agree on the signs or are we coming to that?

DR. GEWANDTER: We are coming. That's next.

DR. RICHARDSON: Good.

DR. GEWANDTER: Do you have an opinion?

DR. RICHARDSON: No, no. It's just, in terms of the other aspect, as we discussed earlier, not only because it's so relevant in regulatory drug trials, obviously, CTC-NCI version 4 and beyond are part of that, not necessarily for an outcome measure for this, but they would be incorporated as part of it, period, anyway.

I'm only saying that because there's a real

Page 212

disconnect between regulatory science and clinical science. You're going to have to have that until NCI-CTC change, but the FDA will absolutely require that.

So any statement we make, we recognize that that has to be also part of it, not as a primary outcome measure, but as something that's measured because, again, in oncology trials, we absolutely have to have that. If you don't have that built in IRBs, everyone will throw out their eyes with their hands.

So I think we just have to recognize that's a reality.

DR. GEWANDTER: So you mean as a safety, like an adverse event measure?

DR. RICHARDSON: Exactly. That's part of safety. The point is --

DR. FREEMAN: On the AE side.

DR. GEWANDTER: Yes, right.

DR. RICHARDSON: The point is that everything we do historically has been based upon CTC version 4 and beyond. And the reality is, we

Page 213

look at grade 2 painful neuropathy, for example, as being a cutoff, which is well established in all the therapeutic trials we've done.

To reverse that without addressing it would be a major move, which I think would require validation at least, but in any event would also be a major regulatory hurdle.

DR. GEWANDTER: Okay. Thank you.

So let's move on to signs. Let's cover all the measures, and then we'll talk about what we think we need to do for research agenda. So for sign measures, I think the TNS probably has the best or the most research done on it in CIPN.

Do you guys agree? So is that one that people think is probably, if you had to say, use one tomorrow, or are there any others that people would like to advocate for?

DR. DASTROS-PITEI: The clinical TNS.

DR. GEWANDTER: Yes, so the one that Ellen and Guido have done, like you're validated it with training people and stuff. Right? Is that the C, TNS-C?

Page 214

DR. CAVALETTI: On the clinical version.

DR. GEWANDTER: So is that the one that you would recommend using if we're going to use any sign measure? Is that a yes?

DR. LOPRINZI: Is it a sign or is it a combination of a sign and a PRO? So it's not really a sign, it's a composite.

DR. GEWANDTER: Right. That's true. It's a composite as well. Gordon, please, say something.

DR. G. SMITH: That's what I was going to say. I mean, I would say use it, but it is a composite measure.

DR. GEWANDTER: So what would you say -- so should we have a sign only that we recommend?

DR. G. SMITH: Well, I thought you were going to -- yes. I mean, I think there would be utility in having a sign-only scale. And certainly, in the diabetes world, we separate the two, and I'm not sure that there's a problem with the TNS, but I can certainly think of scenarios where one would want a pure sign measure.

So I don't know whether you take a look at

Page 215

the performance of the TNS and existing data sets by separating out the symptoms and signs. I mean, that would seem to be fairly low-hanging fruit.

DR. GEWANDTER: So what exactly you mean by that is just taking the symptoms part of the TNS, the sign part of the TNS, and just comparing what happens to them, like how well they correlate. Is that what you're saying?

DR. G. SMITH: No. I mean just in looking at the performance of the scale. I'm not sure that there's a great deal of utility of having a symptom subset. But the signs and the TNS are very similar to, like, the Toronto scale or what we've done in the UENS.

So I think having a pure sign-based measure is useful, and given that there's been a great deal of experience with the TNS-C and CIPN research and trials, we have the data. So if one wanted to look at its performance, it ought to be doable, one would think.

DR. GEWANDTER: Okay. Sounds good.

DR. FREEMAN: Since you brought it up, one

Page 216

of the weaknesses of the TNS and one of the strengths of your scale is that it gives the small fibers, your scale, examines the small fibers in a little more detail. That's the one.

The other is -- and I don't know if this part is a strength or a weakness, but the fact is that it looks at distribution. And I'm not sure how you scale it and how you measure it, but there is a proximal to distal gradient measure, which your scale has, which the TNS does not have, to my knowledge anyway. Now, there are advantages and disadvantages.

DR. G. SMITH: The TNS actually has that.

DR. FREEMAN: Does have that.

DR. G. SMITH: I think Toronto has it, the UENS has it, and TNS has it.

DR. FREEMAN: What about the small fiber question?

DR. G. SMITH: I think the TNS has it, yes. So it has pin sensibility. It's done in a different way. And so it includes -- I can look to see. I actually pulled it up. It's the pin and

Page 217

fingers, toes, wrist, ankle, elbow, knee. Ours is only lower extremity, but it does have that kind of anatomic topographical distribution.

DR. FREEMAN: So just hearing Gordon describe this, is this something the oncologists are going to be able to do, would be willing to do? I don't think we want to rush to a recommendation or consensus.

DR. RICHARDSON: Roy, I just want to say, the science testing is all about physical examination of findings with a tuning fork, and the vibration sense, et cetera. Correct? It's physical exam reflex elicitation and so forth?

DR. FREEMAN: Yes.

DR. RICHARDSON: I think with the bortezomib trials, we did this. I've got to be honest with you. My neurological examination skills are pretty rudimentary. I'm British trained, so they're not entirely hopeless, I think. But having said that, Patrick finds things that I don't, but having said that also, I'm not quite sure -- again, involving neurologists, we typically involved neurologists

Page 218

when we found issues that we were concerned about. For the upfront trial that we did with bortezomib, we did a formal neurological assessment with our partners in neurology. That did add substantial expense to the trial, no question about it, but I do think it was worth it.

So I think you could require physical examination and TNS testing as a grid by the practicing clinician, but in clinical trials, it might be reasonable to emphasize, notwithstanding that rather eccentric experience with those people in all the blue suits, recommending expert neurological involvement or neurology participation.

I mean, I don't know if that just puts all the trials out of range for cost, but it certainly seems to me reasonable. I don't know. Jim, if you want to.

DR. GEWANDTER: Jim?

DR. CLEARY: I agree with Paul. I just think, especially in terms of feasibility of trials, to ask the oncologists to do these

Page 219

exams -- they know they're not very good at it, and I'm speaking for myself, I'm not very good at them -- they're not going to be very excited about it, and I'm also worried about the reproducibility. But also, it might make the trial less attractive.

I think if you're going to do signs, make it something so simple that a research nurse could do it, because a research nurse will have a very different attitude than an oncologist with a busy waiting room who's trying to get to his patients, or as Paul suggested, just partner with a neurologist to have the exams. But having the oncologist do the signs, I don't think will be very good.

DR. GEWANDTER: I don't think it's really -- at least from my experience with the cooperative groups, if you're going to run a trial through there, it's not realistic that the oncologists are going to do it. But I think, Ellen -- I mean, I won't speak for you, but I think you and also Guido have validated the TNS in a way that you have a training video, and someone like a

Page 220

research assistant can do it with reliability.

Is that true?

DR. LAVOIE SMITH: Yes. So we've tested even a bit more abbreviated version of the TNS, where it includes the distal to proximal extension items of numbness, tingling, pain, reflexes, and vibration, and have tested that in kids and in adults.

Then specifically in a pediatric multisite, R01, we created a training video that was posted on a website, and then did a train-the-trainer approach with neurologists at individual sites, validating skill once someone learned how to do it.

We've used this training mechanism at multiple sites around the county and have been able to validate that the assessor can be trained in a way that is appropriate, and that neurologist assessment of that person confirms that.

DR. GEWANDTER: Have you done anything to see if there's any inter-grader reliability?

DR. SMITH: Yes. So we tested inter-rater reliability with the person that we trained. And

Page 221

the people that we trained were nurses, fellows, physical therapists, med students, and then had their exams repeated by a neurologist to evaluate the correlation, and it was good. I mean, reflexes are tricky.

DR. GEWANDTER: So it's interesting because I'm doing a small study right now, and I have a research assistant who's actually using the UENS and a neurologist. And the sample size is really small, so I can't do any statistics on it, but she gets pretty close to the neurologist, except for reflexes.

DR. SMITH: We eliminated the strength item just because we don't see that very often.

DR. GEWANDTER: Well, maybe it's possible.

DR. LOPRINZI: So listening to Gordon -- I think that Ellen's been able to show that, yes, you can do that and it correlates very well. But when I listen to Gordon, it turned out that it didn't seem to make much difference in diabetes and the other.

DR. GEWANDTER: I don't think that's what he

Page 222

said. He said that when they were trained, it did make a big difference.

DR. G. SMITH: I completely agree, and I wasn't articulate enough. If you take a bunch of neurologists, put them in a room, and say, "Figure out if this person has signs of neuropathy," we aren't particularly reproducible.

If you sit down with us ahead of time and say, "Here are what we consider signs," we do incredibly well. And it's not because we're neurologists. We see this I think in endocrinology. And really, this has always baffled me, because our endocrinology colleagues do this just fine, and they don't have any more neurology training or no neurology mojo, and certainly less neurology mojo than any British-trained physician has.

We also have our study coordinators actually trained to do the UENS, but the only thing that's really difficult is reflexes. And I'll go to the Rasch-transformed TNS, which got rid of the autonomic questions and got rid of the reflex

Page 223

assessment.

I think reflexes are hard, but they're not only hard for oncologists. The beautiful thing about being an attending is you always disagree with the residents about the reflexes, and you're right. And when you're a resident, you're wrong.

So I think this is actually a lot easier than we're making it. And I think this is one of these communication and cultural issues that I have full confidence that every oncologist in this room could be trained to do the TNS perfectly well in a way that wouldn't be terribly obtrusive, and that we just haven't done a good job of doing that. That's just my perspective

DR. LOPRINZI: We haven't shown yet that it provides value added to the patient-reported outcomes.

DR. G. SMITH: I think there's face validity that it tells us something different. I suppose you're right that we haven't. But we haven't really used it very extensively, and I think the literature right now is dominated by symptom-based

Page 224

trials. As we're thinking about prevention trials and looking at actual disease prevention as opposed to symptom prevention, then it makes sense that it would be useful.

DR. FREEMAN: So maybe just to frame this discussion a little, I think the utility of the examination is twofold. The first is diagnostic, to make sure that there is a greater likelihood that the patient in front of you has the neuropathy and doesn't have arthritis or something of that nature. That's one.

In disease modifying, it has a different dimension, and one of the ways that at least this has -- and we'll talk about the special investigation -- been used in the past, not successfully as of yet, although perhaps at least in Europe, successfully as far as amyloid peripheral neuropathy goes, the way it has been used is as a surrogate measure for the important feels, functions, and survives type questions.

I think it's important to consider, as we think about this, is the examination -- and here,

Page 225

it's obviously very important to here, both today and even more so in the future when companies go to the FDA, would the exam -- and it has been in diabetic peripheral neuropathy, either standing alone or as part of a composite, is it considered a potential surrogate perhaps for approval under subpart H for what really matters, the way the patient feels, functions, and survives.

So I really want to say that the exam actually is potentially important.

DR. LOPRINZI: So it's a research question.

DR. FREEMAN: No.

DR. LOPRINZI: If it's potentially important, then I think that --

DR. FREEMAN: I don't want to say potentially. I mean if the FDA accepts for chemotherapy-induced peripheral neuropathy that this is a surrogate measure for approval, then it is important. The potential lies in the hands of whether the pharmaceutical industry can make a case to the FDA as to the importance of this as a potential surrogate measure for approval under

Page 226

subpart H, which is to say that an additional trial needs to be done in the future.

DR. RICHARDSON: Right. And Roy, if I may, in that same context, to echo the point that Jim made and Charles as well as the oncologists, I totally agree with Dr. Smith's comment earlier.

Having said that, I think that if you do an oncology assessment, say, with each cycle, if you're in an approval setting with regulatory approval, it makes sense that a neurologist validates the finding because at the end of the day, that will add strength to it. It's what we found with our own experience hands on.

In reality, however well trained we are, our neurologists differed. They found things differently than we did, and that's okay. I mean, I just think that if you're designing a study, why wouldn't you have the oncologists assess every one to two weeks, or every visit, or clinician every visit -- because we do that with bortezomib, for example, routinely anyway -- but then have a neurologist validate the finding at a different

Page 227

period, say, every two or three cycles, because again, that adds an internal control that I think would make us feel more comfortable.

I mean, what do you think, Jim? Because it was very nice of Dr. Smith to say what he did, but I think at the same time, the reality is, in a busy clinic, we take shortcuts, don't we?

DR. CLEARY: Yes. And I just worry because they're going to be so busy that the data won't be that good. I do think if you could show that nurses could do it, they have a very different attitude than the oncologists will have. They'll view that as their job. They'll take it very seriously, whereas the oncologist will just try to go very, very quickly.

DR. GEWANDTER: I think that Ellen and Guido's work has shown that that is possible, and also Gordon's, too.

DR. DOUGHERTY: In this same context, really, the QST could be brought in underneath the signs category instead of over there someplace out on a peninsula. But if you have a well-trained

Page 228

post doc, they can do a lot of these assays quite effectively.

The important thing about some sort of quantitative sign or other measure is as long as you include one for A beta fibers, A delta fibers, and C fibers, an important outcome of any potential clinical study, you may end up only impacting a subgroup of fibers, you can maintain pain with either A or C fibers.

So to understand the results of your clinical trial as potentially impacting one group of fibers but not another, you could still have pain, and that metric won't move. But you could still get a positive result out of your trial, nevertheless.

DR. GEWANDTER: So it's already 1:48, so I wonder if we should try to decide on a sign measure that we would all agree on. I don't know that we're going to be able to agree today that you should or shouldn't include a sign measure in your CIPN trials, but maybe what we could agree on is, if so, which one would be the best.

Page 229

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

Page 230

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

Page 231

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

Page 232

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

Page 233

that is reliable and reproducible, because if it's going to be a surrogate, it's one step removed.

So that's not answering your question, and I'm sorry. But I will say that in the context of therapy that we think might actually improve function, we would be willing to consider a functional outcome, especially if it is expected to greatly pre-date the PRO-measured outcome. So considering a surrogate for the primary in a subpart H-type thing is certainly a possibility.

For any of you who have been involved in disease-modifying neuropathy studies that have come through the agency, we ask for nerve conduction studies. And then someone says, "But nobody walks into the office complaining that my nerve conduction velocity has declined by 2 meters per second," and that's true. But at least it's an objective measure.

Whether or not it's relevant, for instance, in a diabetic, for instance, is that going to ultimately result in fewer or longer delay until there are foot ulcers and amputation, well, that's

Page 234

a long-term commitment to follow-up. That would be part of a subpart H approval, but it would at least provide time to get on the market, and then fund additional studies that way for a commercial development program.

DR. GEWANDTER: Thank you.

So it's 2:00, so do we care about getting a sign consensus on the sign measure? So can we try to get a consensus on, if you were going to include a sign measure, which one would it be? Any suggestions? Gordon?

DR. G. SMITH: Can I ask a different question? Sorry. I think the problem with that is most of us probably don't know anything about most of those sign measures. And I wonder if there might be consensus that in a trial that is intended to prevent neuropathy or alter the disease course, not primarily to manage symptoms, that a sign measure ought to be included. And I wonder whether our ability to render a judgment about which of these is appropriate might be best served by having everyone look at them and provide feedback after

Page 235

the meeting.

DR. GEWANDTER: That sounds good. And I agree with you that face valid-wise, it seems more important to have the sign measure in the early prevention studies than potentially after you've already had the symptoms and you're trying to treat those symptoms.

DR. FREEMAN: In that context, I want to just say that, at the moment, Chris Gibbons and Jennifer are in the middle of a project looking at these quantified neurological examinations. And if anybody has any views, feels that their particular instrument should be include, that we may have left those out, please, before it's too late, let us know.

DR. GEWANDTER: Okay. So the only thing left on the list is skin biopsy, and I know we've talked a lot about how that could potentially be a barrier to recruitment. So I guess the question is, is there anyone who wants to really strongly champion the idea that we should include skin biopsies in our studies and see if the FDA

Page 236

potentially would be willing to make them a surrogate endpoint.

Sharon, do you have anything to say?

DR. HERTZ: The easy part for me is to say, as long as it fits the criteria that I just described.

DR. GEWANDTER: So for that criteria, how much evidence do you need that a decrease in intraepidermal nerve fiber density correlates with potentially long-term deficit in neuropathy or something? What kind of evidence do you want for that?

DR. HERTZ: So in terms of what it takes to make a surrogate sufficient to stand alone and no longer be part of a subpart H approval is kind of the question there. So initially, changes in blood pressure were really surrogates because nobody again walks in saying, "I think my blood pressure is up 5 millimeters." They'd walk in with a heart attack or a stroke, kidneys stop working, and those are the important downstream correlations.

But over time, it was determined that

Page 237

certain amounts of improvement in blood pressure can translate reliably into these clinical benefits. So now, any hypertensive trials really don't require these long-term clinical benefits.

So here, for nerve fiber density or any other sign that is potentially a surrogate for some type of bigger outcome, it's kind of a two-stage process.

If there's enough data to show that there's a very good correlation between changes in the sign and the desired endpoint, you would dump all of that into your application. Not dump. You would assemble all of that in a nice, logical conversation to describe why your measure is capable of serving for your study, and in the absence of that would be an argument for why it's a reasonable surrogate, again with a longer-term follow-up that would be needed to then ultimately support that.

Because the next question is, how much difference, right? So I don't know. Is 2 meters per second less slowing in a DPN patient in the

Page 238

course of a year ever going to translate into anything? I don't know. But that's why there's these added commitments to those kinds of things. Is that better than nothing? It might be. It might be the equivalent of nothing.

So when we do these kinds of surrogate approvals, there are all kinds of language that says this is what was found, and we don't know if it's going to translate yet. But presumably, at the time the decision is made, there will be a good argument to support a positive decision to accept it.

DR. GEWANDTER: Okay.

DR. FREEMAN: So Gordon, as part of your studies on skin biopsy, have you looked in the same way that others have looked at the relationships among sural nerve biopsy, nerve fiber density, motor conduction velocity meters per second, and changing the clinical examination over time?

Because one of the issues with this is that we are dealing in the small-fiber realm in many of the neuropathies that we are interested in, and

Page 239

nerve conduction studies are not particularly helpful.

DR. G. SMITH: So we have a lot of data in diabetes. And one of the challenges, as you know, is it doesn't change very much. And so looking at the relationship between change and measures hasn't been particularly productive because they don't change much, except skin biopsy and every study we've done seems to change.

All the natural history data is of decline, and our studies have thus far really been focused on lifestyle-based intervention, one sees an effect. And I don't know whether that's clinically meaningful or not yet. I think in the IGTN study, there was a weak correlation in a very small sample size between change in INFD and change in pain.

Cross-sectionally, it correlates beautifully in our hands with actually pain with examination scores and with nerve conduction studies. These all, in a cross-sectional fashion, seem to relate to one another.

We're trying to answer this in a cohort of

Page 240

patients who are getting paclitaxel. And what's interesting is that we are having a hard time convincing people to have skin biopsies, I think mainly because this is an oncology setting. I don't think we've fully sold our oncology colleagues on it. But we get nerve conduction studies on everyone, and we're finding that nerve conduction studies are often normal in patients who have clinically obvious neuropathy, which is interesting.

Of the people who have had skin biopsy, which is probably about -- and we're only doing this in people who have neuropathy -- maybe 10 percent are abnormal or something. It's really remarkable how often they're normal.

So we don't have those data, but our hope is we've got a proposal in the process to try to answer this question with CIPN, where I think we have a better hope of understanding at least the relationship in change in both nerve conduction studies and INFD.

Again, this is non-glabrous distal leg INFD

Page 241

and PROs. And we're not really looking at function in this population, but one could. We are doing that in diabetes, and we're doing that in our lifestyle base and are soon to start an intervention study to try and get at this.

DR. FREEMAN: So clearly, this is research agenda material and quite critical research agenda material.

DR. GEWANDTER: So if nobody has any other things to say about that, I think we should move on to our next challenge.

DR. EVANS: Can I just make one comment? I just thought I'd throw this out there. But surrogacy is a very high bar, and it's much higher than most people realize. It's certainly further beyond correlation. Correlation is fairly weak as a bar.

Some of the cancer folks may relate to this because even the most famous surrogate in cancer being progression of some type is frequently questioned about how good of a surrogate it is. It's supposed to be a surrogate for improving

Page 242

survival, and half the time, it doesn't play out. And there's a lot in the literature even questioning things like that, that they really have to be predictive, which is a much higher bar than most people think it is.

DR. MCDERMOTT: Just to add to that, it's also treatment specific. You can imagine treatments that have an effect on the surrogate but don't ultimately have an effect on the clinical endpoint and vice versa, which makes it even more of a minefield.

I would suggest couching this in terms of these measures might be useful for proof-of-concepts sorts of studies or early leads types of things rather than thinking about it in terms of surrogate approval.

DR. GEWANDTER: Yes, Joanna?

DR. BRELL: Before we move on, I just want to make sure, if we're listing research agenda topics, to further assess more functional testing.

DR. GEWANDTER: Yes. Thank you for reminding me. And maybe Drs. Dougherty and Gordon

Page 243

can help me with a list of functional endpoints to propose since we didn't really talk about it too much here, like the things that you're doing with diabetes and stuff. That would be great.

So moving on, I'm not really sure -- I don't know if we account really make a choice right now or come up with a research agenda of how to -- so we have to decide how to measure CIPN, but once we measure the severity, what do we want to do with that?

So after hearing my presentation and Mike and Scott's presentations, do we have a consensus of what might be the best endpoints to use. Any thoughts?

DR. LOPRINZI: So you're asking for prevention trials?

DR. GEWANDTER: Yes.

DR. LOPRINZI: If you're doing a prevention of chemotherapy neuropathy, which is different than a treatment established, so you're talking about chemo.

DR. GEWANDTER: We're not covering treatment

Page 244

of established chemo after --

DR. LOPRINZI: So this is prevention. Okay. So it's prevention --

DR. GEWANDTER: Yes, yes.

DR. LOPRINZI: Then I like what we've heard from statisticians of area under the curve seems to make a lot of sense to me as opposed at 1 month, or 3 months, or 6 months, or 12 months, area under the curve during the time of treatment.

I think it's important if you're doing a prevention trial and you're using your prevention drug, that you follow them for six months afterwards and make sure that the neuropathy doesn't get really bad once you stop the drug and the drug actually was not preventing the neuropathy, but rather was masking it.

So it'd be very important to know that after you stop the drug, you didn't get all bad neuropathy and even worse than you would have before, because you were continuing chemotherapy through that whole time and just treating it with an opioid-type medication for there. But I think

Page 245

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

Page 246

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

Page 247

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

Page 248

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

Page 249

to a very large phase 3 effort that is then -- especially as we've heard, the sensitivity of our tools can be so variable, please don't forget that piece of it is my only point.

DR. GEWANDTER: Okay.

DR. DASTROS-PITEI: With the cumulative dose of the drug, sometimes it's related to the individual patient. And I think what's also important to understand is the interruptions or discontinuations, what are these due to? So are they due to neuropathy or hematology adverse events, or other adverse events?

This is I think important to be captured to put it in the context, so you know what much damage is due to neuropathy per se on the chemotherapy that the patient was supposed to receive.

So if there's a percentage of the theoretical dose, the patient should receive it. There are different ways to calculate, but the most common is the total cumulative dose.

DR. LOPRINZI: I think both are important. The simplest way to do it and what we utilized

Page 250

before is looking at the area under the curve and looking at that, we use that as our primary endpoint.

Then separate from that, looking at the dose of chemotherapy, the average dose, or when people quit taking full dose, or whatever on those things. And if they both go along with each other, that's fine.

If there is some sort of interaction, again, that somebody continued a full dose like this and people got more neuropathy, but they added a bigger dose, as Patrick said, it's per dose that they got, then you sort through that. So you can put up some statistical rules to that sort of thing. So think of them separate, and then combine them together if need be.

DR. GEWANDTER: Can we let Mike comment?

DR. MCDERMOTT: Yes. I think that the biggest message from Scott's talk yesterday was just the opposite, that you need to take these things together and analyze them together in the same patient, somehow.

Page 251

Now, the operationalization of this is the part that's tricky. The one way that was suggested yesterday was, well, if they have to modify their dose, call them the worst endpoint. You can do finer gradations than that if you want to based on how much dose you receive or something like that. That needs more thought. But I think that looking at these things separately, I don't think that that is -- I don't think that's a good idea.

DR. LOPRINZI: I think you have to think about them separately, but figure out how to marry them together. It's just easier to think about them separately, and then with some statistical rule, you can marry them together by going by dose instead of time.

DR. DASTROS-PITEI: But are you thinking of a composite of this?

DR. MCDERMOTT: I think you have to.

DR. DASTROS-PITEI: -- or an analysis, which takes into account the --

DR. GEWANDTER: He's saying a composite for each patient, so each patient, they received at

Page 252

least 75 percent of their planned chemo and they didn't get worse than X neuropathy. That's a very simple dichotomous way to combine them, but then Mike also proposed this ranking system where you can maybe have a little bit more than just two options.

So I think this is a very complicated discussion that might be hard for us to talk about here, and it might be easier if we put together some proposals. Like I could do this with the help of Mike and Scott, and obviously Bob and Roy, and then maybe we could send that around.

Maybe a better use of our time right now would be to go back to the inclusion/exclusion criteria for right now if you think that's reasonable, and then we can come back to this if we have time.

DR. FREEMAN: Yes. I'd like to hear a little more discussion about this before we leave it to us to do this in small session, because the challenge with this territory is that there are several moving parts. There's the chemotherapeutic

Page 253

regimen, there's the neuropathy, and there's also the drug, which different drugs will have different mechanisms of action, different times when they worked. So I think we should maybe just air the issues related to each one of these territories.

So with respect to the neuropathy, there are different ways in which we can assess it. We can assess the time to an event, whichever we decide, what we decide the appearance of a neuropathy is.

We can look at the severity of the neuropathy, and we can look at that at a fixed time point or we can look at the area under the curve. And before we jump to the beauty of area under the curve, which obviously has its appeal, to some extent, whether this is going to be a sensitive measure will depend on the nature of the intervention.

The problem with area under the curve is that if there is useless data in the beginning, if there's noise, if there is acute toxicity from specific drugs, which is unrelated to what we're going to see six months later, the effect of a drug

Page 254

may be washed out.

So I think it's really important to dissect out separately the individual components, to dissect out also the nature of what I call the disruption of the chemotherapeutic regimen, because this takes several points as well and also how frequently that occurs, because in certain regimens, it occurs more frequently than others. And then finally, and this is the challenge, to come up with some novel way, if we need to, that combines these.

So what I would like to hear is just if anybody can elaborate on what I've said, if anybody has a different view of this, I'd like to hear it to help us think about this in a more quiet session.

DR. LOPRINZI: At the risk of talking too much, I think you look at all of these issues. I sent you a protocol on our calcium magnesium study and look at that. We have a chart of the 8 or 10 things we look at. And you look at the time, the area under the curve. You look at the time to

Page 255

grade 1 neuropathy, to grade 2, to grade 3 neuropathy. You look at the dose, all those different things, and you can set up your statistical rules, how you put those things together.

But you have to look at them I think individually, like you're putting out there during the time of chemotherapy and there afterwards, and then work with a statistician to say how do we marry these things together?

DR. HAROUTOUNIAN: I'd just add one comment. I think while thinking about the mechanisms of neurotoxicity with most of the agents, I think we don't really even know whether the neurotoxicity is related to peak plasma concentrations, trough plasma concentrations over time, total AUC, and even same patients getting the 85-milligrams per meters squared oxaliplatin, their individual PK profile might be quite different, which might affect their development of neuropathy or not.

The question is, do we add individual pharmacokinetics as a research agenda, at least

Page 256

something to think about? I'm not saying we need to take full PK profile of each of the chemotherapy drugs and to compare, but maybe there are certain key parameters such as peak plasma concentration or some kind of trial for something to try to relate to the individual differences.

DR. LOPRINZI: All that stuff gets I think sorted out initially when you figure out how to give the drug, and the toxicities, and all those sorts of things. So we're talking about people who are getting the drug all the same way, over 20 minutes, over an hour. That's something that's determined ahead of time.

DR. HAROUTOUNIAN: That's correct.

DR. LOPRINZI: That's something that someone might want to do to help figure out if that affects neuropathy. And they've done that at times where they used to give paclitaxel over one hour versus 24 hours and all that sort of stuff.

But assume all that is done, and it's all given in the same way. So that takes care of a lot of that PK thing. That's another thing to figure

Page 257

out, which one's worse, the peak effect or the area under the curve of the drug for that?

Let me just get in here one more part of it, if I can. So then the individual variability -- and there is individual variability. We've looked at that, and we can look at the area under the curve for the neuropathy thing and show that that's related to Charcot-Marie-Tooth type gene, and then people look at other things. A lot of things, we don't understand.

That takes good care of the randomization process in the balance of patients for that. So that's why you have groups of patients. You can't do a study with two patients, one who got and one who didn't, because of all these variations for that aspect.

DR. HAROUTOUNIAN: I'm just wondering if there is a drug that is targeting peak plasma concentration-related toxicity, which might be above a certain point in a certain subset of the population with drug -- again, I'm not saying this is something that we should do to every patient in

Page 258

a study, but this is something to keep in mind if we want to look more specifically into the mechanism.

DR. GEWANDTER: So that's what I was going to say. It could help explain potentially why it didn't work in some patients and worked in others potentially.

So I think one thing that might be useful is if the oncologists could help us. If we did want to make -- I think that Dr. Richardson clearly enunciated that it's complicated operationalizing how to quantify discontinuations and disruptions.

So can you guys give us some tips on what we would need to consider if we wanted to turn discontinuation or disruption of chemotherapy into an endpoint? Like what things do we need to consider? How could we start to try to think about that?

DR. LOPRINZI: So you asked for oncologists. So what you do is you ask how much drug did each person get at each day. So that will help establish whether they got the drug and whether it

Page 259

was 100 percent, so all that sort of thing. And the other thing you could add in, if they didn't get 100 percent drug, why not? Was it because blood count was low or was it because of neuropathy?

Then having that information, then you know how much drug everybody got over time, or was it just a change because it was somebody's birthday and they decided to wait a week, whatever, how much they got over time and why they didn't get 100 percent of dose?

DR. GEWANDTER: Dr. Cleary, do you have a thought on that?

DR. CLEARY: I agree with what he said. These things are done very standardly on oncology clinical trials, so I don't think it will be very hard for the oncology sites to do that, because we're used to having this sort of data entry. And I think that it can give you data about why people miss doses, as he said, and also give you a cumulative dose.

DR. GEWANDTER: So you're saying maybe

Page 260

having the information on cumulative dose would be useful.

DR. CLEARY: Yes, but also if a dose reduction happened, why did it happen, because another reason someone might dose-reduce oxaliplatin has nothing to do with neuropathy. Maybe the person's cell counts were low that day. So you have to know if they did dose-reduce, why did they do it?

DR. GEWANDTER: Joanna, do you have a thought?

DR. BRELL: I think that would be relatively easy to capture. But I also think PKs on some of these drugs and their association with the neuropathy might help inform this as well.

DR. RICHARDSON: Yes. And the way you tackle that, Jen, just to give you practical aspects of it, is you do subsets. So you do it at centers that can do it. You don't have to do it across the trial, but you want to maybe do it at centers that can do it. And the reason why is because then you can provide to the regulatory

Page 261

authorities that's got a nice correlative population, base data, or whatever you want to do. Also, you might want to do that in the context of more exploratory, early-phase data as well.

DR. GEWANDTER: So part of the research agenda.

DR. FREEMAN: So I just want to be clear on this, that if the statistician is going to work out this novel endpoint, that in some way normalizes the neuropathy for dose of chemotherapy received, you're recommending that they take into account the cumulative dose.

DR. LOPRINZI: Yes, but not just the cumulative dose, the cumulative dose over time. If they get a dose now and a dose a year later, that's two doses versus two doses a week later. So I'm being facetious, I know, but cumulative dose over time.

DR. FREEMAN: Over time. So what you're saying is, then, the dose and dose -- let's call it dose intensity, so --

DR. LOPRINZI: No. We'll just -- yes.

Page 262

DR. FREEMAN: -- so this is -- then Paul has made and Joanna also introduced the notion that the dose may be less relevant than actually the pharmacokinetic profile of the dose. How strongly do people feel about that?

DR. LOPRINZI: The pharmacokinetic profile I think is figuring out if that affects how the drug causes neuropathy over time. It has nothing to do with what drug you're giving to try to prevent. I think that stuff gets figured out in the phase 1 study and the phase 2 study, early on there.

But in the clinical trial, where you're looking at X versus Y, X versus placebo, the pharmacokinetics, yes, might help determine whether it's a peak or area under the curve. And I think it fits with -- first of all, to what Pat said before, too. It's not necessarily the effect over time, but the effect per dose. It's actually both.

DR. RICHARDSON: Yes. So I agree with you, Charles, it's a mix of exploratory versus confirmatory. I mean, the only reason I say it is because that I guess would be addressed

Page 263

appropriately in the phase 2 as we get proof of principle trial sets.

My only point is that the population-based PK studies as part of phase 3, we do. We do, do those, and we do do those for the noxious agents. So the point is, it's not impossible, and that probably would be a very nice discussion with the agency as to how much they would need and what they would want, to just understand variance between patient populations so that you don't lose the ability to at least evaluate the impact of the neurotoxic drug and how that interacts with your intervention.

I'm kind of thinking out loud a bit here, but the reason I'm doing it is because I'm struck by everything that was said by Nat earlier that, literally, to date, intervention trials and CIPN have failed. And the question is why.

The point is, I think one of the huge variables that have occurred to me, listening over the last two days, is the variance that we see in what we give in terms of our agents that drive the

Page 264

neurotoxicity, and then the beautiful presentation by Pat yesterday of the complexity of the biology.

So all I'm trying to do is help give you ideas to think about how you can correct for all these confounders.

DR. FREEMAN: Can I ask Sharon just a question? So if we somehow come up with this novel endpoint that drug X diminishes neuropathic burden per unit chemotherapeutic agent received, however we define neuropathic burden and however we define chemotherapeutic agent received, does that look like a label that --

DR. HERTZ: I don't even know how to answer that.

DR. FREEMAN: Yes. That's what bothers me about it.

DR. HERTZ: I would say -- this one's a little harder than some of the other areas because of the nexus with receiving enough of your chemo. So I wouldn't say anything's off the table.

DR. DOUGHERTY: So following to that and listening to this entire conversation, I think

Page 265

we've complicated things a bit by conflating two endpoints, and that's why we're struggling.

The first endpoint is, does this agent X given with chemotherapy Y, help them get through chemotherapy without such a heavy symptom burden that they have to drop out?

Number two -- and this could be a separate drug -- a year after your chemotherapy, deemed successful, whatever that criteria is, do you have less neuropathy at that point?

So there's during the treatment and then there's how does it impact your ultimate outcome. I think those are potentially two separate endpoints.

DR. LOPRINZI: This is very, very confusing as we're trying to look at each individual part together. And I understand why Sharon's saying what she's saying. It's just how do you put this little piece into the overall picture?

So I hadn't thought about this before, but one thing that I think would be interesting to do, and I might threaten to do it on myself anyway if

Page 266

Sharon would allow me, is to say, "Why am I sending to you, the FDA, my calcium magnesium clinical trial that was done, and all that sort of stuff, and have you look at it and say, 'Yeah, this was a good trial,' or, 'No, we'd need X, Y, Z, and Q,'" or anything like that?

But that way, that's sort of a process. I'm not asking for FDA approval on it or anything; in fact, it was a negative study. But is that sort of a protocol that would make sense?

The other sort of thing could be done as your duloxetine trial, treatment trial, to say does this make sense or how would people recommend you ought to have changed these two things?

Those are two different types of trials we're talking about, and then you could say how do we make these trials better? There were some terrible trials. But that would make more sense I think than trying to pick off each of these individual things alone.

DR. HERTZ: I can't imagine how we could give you that kind of feedback, because it's always

Page 267

so situationally dependent. And it could be the absolutely perfect trial for that drug and not serve another one quite well. So I really would be reluctant to commit to doing something like that.

I think it makes more sense to have this body decide if this makes sense, or for any given drug and any given intent of that drug's action, why does that particular study make sense is really the question.

The reality is, there's not going to be one answer for every -- there are so many variables. There's so many unknowns. I could imagine this being a situation in which we get two similar-type programs with different researchers involved and very different approaches, and both being acceptable. That's why it's very hard for us to commit to giving that kind of feedback.

DR. LOPRINZI: And something like that doesn't mean that you would have to say everything has to be done like this. But the other way of potentially doing it is the group take one of these protocols, or take two of these protocols and say

Page 268

everybody shoot at this and see how do we build upon this as opposed to looking at each individual thing to say, look -- because there are a lot of people in here who have never developed a protocol and don't see these particular patients. So anyway --

DR. FREEMAN: Let's move on to the next phase of this.

DR. GEWANDTER: I just want to say one thing relating to what Pat said. I totally agree with you that I think that they're two separate objectives. And I think that the objective of trying to prevent neuropathy, like six months after you've finished chemo, doesn't necessarily have to deal with some of these other issues as much as if you want to look at the neuropathy at the end of chemo or throughout chemo, and how do we deal with how discontinuations affect that severity.

I think in the paper, we will say that there are these different kinds of study objectives. And for this study objective in particular, meaning the one where do we want to consider, make a composite,

Page 269

that one I think is probably the most complicated. So I think that we will just point out that they're separate objectives, and there will be separate endpoints depending on the objective.

So I want to recognize like we didn't really address what you said and that I totally agree. I think that's a really important differentiation to make, and we'll make it in the paper.

DR. FREEMAN: So before we move on to the next phase, I think listening to this discussion, it's clear that there are a number of issues that are going to be challenging to resolve in a very clear-cut way. And I do want to say that, as we've said all throughout the meeting, there will be a publication from this. It will require everybody's participation.

I don't think it's going to be one of those that everybody will sign off on immediately. I want to be sure that everybody recognizes that this will be a participatory process, and that, please, in your areas of expertise, commit to being very involved in the writing process.

Page 270

DR. GEWANDTER: We talked a lot about this yesterday, which is why I put it last. But I think we want to kind of go back to some of these and just see if my read of the consensus was correct and if anyone has anything else to say.

So for the first one, for localized and metastatic cancers, I think what I was hearing yesterday was, if we need more data on safety, so obviously anything that has a new mechanism, we need to start in metastatic cancers from the FDA's perspective for a safety reason. But then in terms of ideally for efficacy trials and actually proving efficacy, actually sticking to earlier-stage cancers would actually be better.

Was I right in hearing that or does anyone have anything to say about that?

DR. DASTROS-PITEI: My understanding from yesterday was that metastatic cancers, yes, perhaps for proof-of-concept study, just to give a sense of the safety. But I think it was recognized that measuring safety -- I mean, impact on the chemotherapy effect of the drug, of the active

Page 271

drug, it's actually quite difficult because, obviously, it implies long-term follow-up looking at DFS, or PFS, or overall survival, which will not happen in a proof-of-concept study.

So I think we need to understand a little bit better. Although it makes sense that the metastatic cancer population is the one which is probably more vulnerable and more fragile, is this the one really which is going to give that safety measure quickly?

DR. GEWANDTER: So are you saying that because it's going to take a long time, that we should be doing efficacy at the same time in that population? Is that what you're saying?

DR. DASTROS-PITEI: Safety, so I guess the early studies, for immediate -- I guess for biomarkers of safety like hematology platelets, I don't know, neutrophils and so on, probably this does makes sense. But I don't know if it's correlated necessarily with the metastatic population.

I'm just concerned, how long would these

Page 272

studies need to be in order to show that there's an effect on safety, if you know?

DR. GEWANDTER: Sharon, do you want to comment? No? Okay.

Joanne?

DR. BRELL: I hate to put off making decisions and seeming wishy-washy, but I think it depends on whether or not we use localized or metastatic cancers depends on the cancer and depends on the chemo they received.

So first-line, even second-line metastatic breast and metastatic colon, these patients are usually very fit, and they can live for years with metastatic disease and live really good lives. So they would be good subjects to follow while still being in a metastatic situation.

DR. GEWANDTER: So Sharon, would those people be -- I don't know. Maybe you can't answer from this, but the people that have the metastatic cancer as she was just describing that live for like three years, would they be in the group of people for the higher-risk interventions?

Page 273

DR. HERTZ: From the consults that we get from our oncology group about selecting the patient population, the concern is -- I remember one particular IND that came in where the treatment for the neuropathy specifically targeted the mechanism of action of the chemo, so we were all very nervous about that because it seemed, yes, it would work. So would dose reduction. You know what I mean? It seemed very nerve-racking to give that to somebody who would potentially have a cure without it.

So the thinking is are you going to -- the concern is will there be a negative impact on the survival of an individual because of the intervention for the neuropathy?

So if somebody doesn't have a chance for a cure, that's sort of the first cutoff. And then, in terms of whether somebody who's got a fairly good longer prognosis, but not a cure, then it's going to depend on are you giving the drug during chemo or after chemo, are you giving it before? So there's all these different considerations.

I'm trying to think of what we've seen, and

Page 274

I don't have that kind of clear grasp for the details like some of the others in my group. So I wouldn't say that's not a population that could be studied, but why the risk to that population is acceptable should come in with the protocol, any considerable risk, whatever the risk might be.

DR. BRELL: I would think, before we would come forward with anything, we would have studied whether or not there was an effect. I mean, of course, long-term data is the best, but I think we would have looked at that before we even bring it forward.

DR. GEWANDTER: When you say we would have looked at that, do you mean preclinically or what do you mean by that?

DR. BRELL: Yes, preclinically, and maybe graphically, and then a longer-term follow-up depending on the cancer and the natural history of the cancer. But we have to decide -- we have to make sure we've eliminated to the best of our ability any loss of efficacy with the treatment that we would give, a loss of efficacy of

Page 275

chemotherapy with any treatment we would give. But we would look at that way before.

DR. HERTZ: Well, you know, that sounds very obvious to you and perhaps everyone else in this group, but I can tell you it is not obvious to everyone submitting an IND. So that's why those consultations have really focused a lot on those, because we often don't get a well-considered evaluation of that risk.

DR. GEWANDTER: So as far as the paper goes, I think we could say that, at first, if there is no good understanding of the risk of the new agent in terms of the effects on chemotherapy, that starting in a more advanced cancer with less curative potential is recommended, or you should consider that. I think that's maybe where we would end our recommendation on that.

Do you have anything to say about that? Okay.

Moving on, I think everyone agreed it seemed like the one thing was that we should do one type of chemotherapy at a time, so oxaliplatin

Page 276

separately from taxane separately from bortezomib. But there was still a little bit of question about one cancer type, so I think we had a discussion of, can GI go with pancreatic if they're getting the same type of chemo? So I just wanted to open that back up for discussion a little bit. Yes?

DR. CLEARY: When you said one or multiple chemotherapies, I think for preventative, it should be one chemo, but for one where people already have neuropathy, I think it could be preventative.

DR. GEWANDTER: So we're not talking about people who already have neuropathy after chemo like Ellen's study, but do you think that is true even for acute symptoms? If you're trying to treat established acute symptoms during chemotherapy, do you also think it could be more than one type of chemotherapy, or at that point still?

DR. CLEARY: I think it should say one type, but I would say --

DR. GEWANDTER: During chemotherapy, one type.

DR. CLEARY: -- it can be multiple cancer

Page 277

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

Page 278

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

Page 279

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

Page 280

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

Page 281

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

Page 282

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

Page 283

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

Page 284

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

Page 285

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

Page 286

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

Page 287

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

Page 288

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

Page 289

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

Page 290

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

Page 291

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

Page 292

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

Page 293

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

Page 294

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

Page 295

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

Page 296

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

Page 297

signs. So why don't you lay out some sign options, and then we can come up -- if we all agree on a set of signs, we can then come up, well, what level should that sign be at baseline in order to be acceptable. But right now, it's such a void as to what we're talking about when we get into the sign category, that --

DR. GEWANDTER: Can't make that choice here.

DR. FREEMAN: Yes. I think that's very reasonable.

DR. GEWANDTER: I think also, what Bob mentioned before, I think, Gordon, taking from the diabetes literature, if there are some cutoffs that have some sensitivity and specificity worked out, that we could potentially propose them. But proposing a cutoff just because it's what we think is good and we don't have any data for might be a little tenuous.

DR. DOUGHERTY: That's what I'm saying. Go ahead, lead with your chin, and then we'll find out once you lay something out.

DR. GEWANDTER: Or it could be also a

Page 298

research agenda to find what could that be.

DR. G. SMITH: I would say that requiring your PRO to be zero may be unrealistic. It depends on the PRO. I mean, on any given day, I probably fulfill at least one criteria of most PROs depending on how much sleep and coffee I've had in the morning.

I would be cautious about making a blanket statement that the PRO has to be zero. I think it probably depends on the PRO and the specific items and characteristics of the instrument, which is wishy-washy.

DR. GEWANDTER: Well, we'll think about that, I think.

DR. LAVOIE SMITH: And I would just caution that -- I mean, I don't disagree that a TNS cutoff or some kind of sign cutoff might be a good idea. But when we think about having to administer a PRO or to do a TNS exam prior to determining if someone's eligible in a busy onc clinic, is just a bit challenging, for feasibility.

DR. GEWANDTER: That's good feedback. Thank

Page 299

you.

DR. FREEMAN: Yes. So maybe just before we jump from this thing, Daniela, what are you doing, what are you considering doing? Matt, what are you considering doing?

DR. DASTROS-PITEI: At the moment, we're looking at the CTNS, but maybe I've heard so much about reflexes that we may need to reconsider it to make sure that it's reliably done. If we do it by training, or not doing them, then --

DR. FREEMAN: This is as an inclusion criteria. You are excluding patients with neuropathy and you are using some kind of cutoff for doing that.

Matt, have you thought it through thus far?

DR. JARPE: We haven't really set up a prevention trial, so it's not really relevant.

DR. GEWANDTER: Do you know what the cutoff is going to be? I mean, you don't have to tell me, but how did you choose it?

DR. DASTROS-PITEI: Yes. We looked at the age related, so we were careful about those which

Page 300

may be affected by age.

DR. FREEMAN: That's fine. Yes. I think that's fine.

DR. GEWANDTER: But I think what Ellen said is important. We'll have to think about that.

DR. DASTROS-PITEI: The question is, do we use the money for eligibility and then we don't use them anymore, or we use them at the beginning, screening and baseline, and then at the very end.

DR. GEWANDTER: Maybe in Europe, it might not be as -- because you said you have that consent two weeks before, like maybe it won't be as hard as it would be in America to do that.

DR. DASTROS-PITEI: So you see, if you get them at the beginning, at least two weeks before, yes, because you automatically do all the tests you need to do for chemotherapy as well at that point, all the labs and everything else. So it's a good time to move, as the time.

DR. GEWANDTER: So I think there are previous neurotoxic treatments. I was convinced at our talk yesterday that we want to exclude these

Page 301

people because they could be the people who are just lucky enough to never get neuropathy, and so putting them in a prevention trial is a bad idea.

Does anyone disagree with that statement?

DR. SIMON: Do you refer to neurotoxic chemotherapy or any neurotoxic potential drugs?

DR. GEWANDTER: I was thinking chemotherapy.

DR. LAVOIE SMITH: Any neurotoxic.

DR. SIMON: Because these drugs are popping up. I think there are recent studies on fluoroquinolones causing peripheral neuropathy potentially, and 90 percent of people would have gotten fluoroquinolones at a certain point in time.

Where do we make a cutoff of drugs that are causing neurotoxicity at a higher prevalence or higher severity versus metronidazole or something like that?

DR. DASTROS-PITEI: Within the previous exclusion criteria, which is the neuropathy, pre-existing neuropathy, wouldn't that get rid of some of this if there's been neurotoxic injury and it's still persistent?

Page 302

DR. FREEMAN: No. But this is the exposure.

DR. GEWANDTER: Yes.

DR. DASTROS-PITEI: So on the exposure if it really was clinically relevant or not?

DR. GEWANDTER: So I think that's what you're saying. Right? Like, which drugs are we talking about, and how severe, and how often do they cause neuropathy, and how good is the evidence kind of thing.

DR. SIMON: To me, it makes sense to exclude neurotoxic chemotherapy.

DR. BRELL: Or if they're adjuvant therapy, they should be chemo naïve, and we couldn't do this trial unless they're chemo naïve.

DR. DASTROS-PITEI: Not metastatic.

DR. BRELL: I mean, they might have had chemo for other cancers, so did we exclude anyone who's had a prior cancer, which is really common in treatment studies.

DR. DASTROS-PITEI: Chemo naïve, it's a really good definition, though.

DR. BRELL: So you can make a list of all

Page 303

the known CIPN-causing chemotherapy agents, but you can't make a list of all the probably thousands of other agents that could be related to neuropathy as well.

DR. SIMON: Vitamin B6 could cause neuropathy.

DR. BRELL: Yes. I mean, the list could be endless.

DR. GEWANDTER: I think we want things that are very well agreed upon to cause neuropathy as exclusions. I mean, we can't get crazy and start excluding everything, because, like you said, if you exclude something where 90 percent of the population has had it, you don't have a study. But I think that's a good point that we'll have to think about when we're writing.

So there's no one who feels strongly that we should include people who have had previous neurotoxic chemotherapies and things that are very well known to be neurotoxic? No. Good.

So allowing concomitant treatments that are thought to help neuropathy, what do people think?

Page 304

I think for prevention and treatment, it may be different, so let's talk about prevention first. So we should not allow? Should?

DR. BRELL: Well, if we don't want someone coming in with an existing, active, difficult-to-treat neuropathy, they're already excluded.

DR. GEWANDTER: So what would that list of drugs be? Yes. So what would that list of drugs be, you think?

DR. DASTROS-PITEI: Above empty noise as a summary?

DR. BRELL: For the list of drugs that we treat neuropathy with.

DR. DOUGHERTY: Yesterday, we had this discussion, and it was quite clear. If we're excluding people that had neuropathy, then they're probably not getting a drug for neuropathy. But if they're on something like -- and we talked about depression. There are a number of patients who have cancer that are depressed and are on an anti-depressant.

So if it's an SSRI, then they're probably

Page 305

okay. If they're on desipramine or something like that, then maybe that's not good.

DR. GEWANDTER: So I guess the question is, what are you basing that distinction on, like what data?

DR. DOUGHERTY: Well, because other neuropathic pains are treated with the tricyclics, but they're not treated with the SSRIs.

DR. GEWANDTER: So you're basing it on neuropathic pain.

DR. DOUGHERTY: Right.

DR. DASTROS-PITEI: So any drugs for neuropathic pain, I guess.

DR. FREEMAN: No. I think the point Bob made was that if there's any component of your assessment that involves neuropathic pain, then you do not want the patients to be on a drug that treats neuropathic pain.

DR. G. SMITH: I can present a real strawman. This is a real, live strawman. So I don't know what you call that, but it exists. And that's the trial that Joanna and I are working on,

Page 306

which is a disease prevention trial.

It's a phase 2, using electrophysiology as a primary outcome measure and the secondary, the TNS, but there's no pain measure as certainly one of the main outcomes. And perhaps it's buried in the long list and would therefore make no sense to preclude a patient taking, I don't know, gabapentin, for something else during the course of the trial. It's not going to contaminate any of the measures. Right?

So that's a great strawman. Right? So there, you wouldn't really need to worry about this.

If that patient was going to start taking -- I can't think of a potentially effective disease-altering neuropathy-preventing drug, but if there were one, then that would pose a problem. But that's a true strawman because I don't know that that exists.

DR. HAROUTOUNIAN: And I think if we exclude anyone who is on opioids, or NSAIDs, or tramadol, we are going to exclude quite a lot of people,

Page 307

considering that just 30 percent of the adult population have some kind of chronic pain.

DR. GEWANDTER: So what I'm hearing is if pain is a major part of your outcome measure, we exclude drugs for neuropathic pain. If your outcome measure doesn't have pain -- so if it's one of the sign measures, then you wouldn't necessarily want to exclude those patients.

Is that what I'm hearing?

DR. LAVOIE SMITH: It all depends on if we believe all the negative trials. That's the challenge.

DR. GEWANDTER: So are you saying that we don't know if these pain drugs could work for these other neurological symptoms and signs?

DR. DASTROS-PITEI: I think we're saying that studies which were done before may not have been big enough to show an effect of this type.

DR. GEWANDTER: For CIPN, you mean.

DR. DASTROS-PITEI: Yes.

DR. GEWANDTER: But I think a lot of those drugs would be covered under they work for other

Page 308

pain conditions.

DR. HERTZ: Jen?

DR. GEWANDTER: Yes?

DR. HERTZ: I think that even the ones that might work that, I mean, have had negative studies, do we really think that anything is so good, we just haven't realized it yet, that it would completely mask neuropathy?

So I think it could add to the background noise, but unless you really think there is something very, very symptom minimizing, it'll be some background noise. But hopefully they will overall randomize out, and it won't really necessarily have a huge effect on detecting a signal.

So I think it sort of depends. I mean, if somebody comes up with something and it looks like it has a pretty substantial symptomatic effect, you're going to target that much more than duloxetine, even though we knew it works a bit. How much do you have to cut it out is depending on how much of a signal you think you can detect, and

Page 309

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

Page 310

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

Page 311

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

Page 312

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

Page 313

necessarily, but the pain related with cancer. And I think that requires its own -- obviously, opioids is what some of these patients get.

DR. LAVOIE SMITH: I'm having a hard time hearing you.

DR. DASTROS-PITEI: I'm saying this population will get cancer pain, some of them, not CIPN pain, but cancer pain. And that obviously needs addressing and measuring very carefully. And it's not rescue release, the treatment for the baseline disease, in a way, but it needs to be taken into account.

DR. GEWANDTER: Right.

DR. DASTROS-PITEI: But the randomization should take care of it, I think.

DR. GEWANDTER: Yes. It just adds noise. That's all.

DR. BRELL: If we're studying the adjuvant patients, they should have minimal cancer pain, maybe a little bit of post-op pain. That shouldn't be as much of an issue at all. And then I don't know what lessons we can take from other pain

Page 314

trials and how they managed rescue pain, a rescue analgesic for pain.

DR. SIMON: I think if it's mastectomies with breast cancer, we need to consider a persistent post-mastectomy pain because 20, 30 percent of patients might develop pain that might require treatment with anti-neuropathic medications or analgesics. Just again, some noise that could be added to that cohort.

DR. BRELL: Again, it depends on the outcome. The outcome is pain.

DR. DASTROS-PITEI: That's a neuropathic-type pain.

DR. SIMON: Sorry?

DR. DASTROS-PITEI: The chronic post-surgical persistent pain, it's a neuropathic-type pain.

DR. SIMON: Yes, that's what I'm --

DR. DASTROS-PITEI: And I think that is a confounder for the CIPN, then, because the CIPN -- yes. I think this probably is worth thinking about in moving.

Page 315

DR. FREEMAN: We hope to have excluded those patients.

DR. DASTROS-PITEI: Yes.

DR. GEWANDTER: Actually, that's a good point because specifically excluding those patients might be a new exclusion criteria than what we've talked about already, because if you ask people to think about their hands and their feet when they're filling out their PROs for peripheral neuropathy, you might not capture that in the exclusion that we've talked about so far.

So if we wanted to exclude people because they have post-op mastectomy pain, we have to say that specifically. And what will that do to recruitment?

DR. BRELL: Depends on what we're studying. A lot of patients, there's less post-mastectomy pain if you've only had a lumpectomy. So maybe we'll be okay even though we exclude the mastectomies.

DR. G. SMITH: So Roy, can I ask a question? I guess this would also be a statistical question.

Page 316

You've mentioned several times the worry about acute pain syndromes creating an issue in an area-under-the-curve analysis. But couldn't you just say we're going to start the area under the curve one month after initiation of chemotherapy, or at some time point where you expect to be beyond this common and fairly predictable side effect?

DR. GEWANDTER: The acute is associated with each cycle. Right?

DR. G. SMITH: Right. So yes, that's a fair point.

(Crosstalk.)

DR. GEWANDTER: So it would have to be after you finish chemo completely --

DR. G. SMITH: Yes.

DR. GEWANDTER: -- which that is a really probably --

DR. SMITH: Fair point.

DR. GEWANDTER: -- clinically meaningful endpoint. It's just you have to have a lot of people in your trial because not that many people are going to end up with chronic, so it's a huge

Page 317

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

Page 318

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

Page 319

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

Page 320

thing soon. So thank you very, very much.
DR. LAVOIE SMITH: Thank you for pulling it together.
(Applause.)
(Whereupon, at 3:20 p.m., the meeting was adjourned.)

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