

*IMPACT XVIII - Initiative on Methods, Measurement, and
Pain Assessment in Clinical Trials*

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*A Matter of Record
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1 your phone's not working -- your phone's not
 2 working -- microphone isn't working. It's just
 3 that there are other people in the queue ahead of
 4 you. As people get off, then you'll be able to get
 5 back into the queue at 6. It's a little bit
 6 awkward, but I think you'll find it works quite
 7 well.

8 Today's lunch will be held in the Buchanan
 9 Room, which I can read. It's located next to the
 10 room. Speakers, you're going to find this out, if
 11 you can't see the screen, it's really hard to see.

12 So the luncheon is next to a meeting room.
 13 Please note tonight's dinner has been moved to The
 14 Nest located on the mezzanine level, so they can
 15 find The Nest.

16 Check-out time on Friday is 12 o'clock noon.
 17 Restrooms are located by the board room, which
 18 means right outside where we had breakfast. If you
 19 go outside the breakfast room, they're right
 20 outside there, the important information.

21 For departures, the airport, train stations,
 22 taxis will be available in front of the hotel.

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1 Please sign up for the taxis. Valorie and Andrea
 2 will have sign-up sheets that you can use. If you
 3 need any assistance, please stop by the
 4 registration desk. If you haven't picked up
 5 your -- haven't signed or if you haven't picked up
 6 your tent card with your name on it, please do.
 7 They should be on the side over here.

8 Let's see. Any other housekeeping details
 9 for you? Not really.

10 One other announcement though, if anyone of
 11 you are having trouble seeing the slides, it's
 12 because we found your glasses last night at the
 13 reception.

14 (Laughter.)

15 DR. TURK: So if it happens to be you and
 16 you're having difficulty, we may have your glasses.
 17 Valorie and/or Andrea will have those at the
 18 registration desk, so hopefully you will be able to
 19 pick those up.

20 That's the basic details. We encourage you
 21 to get involved, get active, talk to your friends,
 22 your colleagues, new people. There are some of you

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1 who are alumni who have been to IMMPACT meetings in
 2 the past. We've learned over time, that alumni
 3 come back and want to come back. And some of you
 4 that are new people are here. We hope that you'll
 5 have an opportunity to meet each other, to talk to
 6 each other.

7 The greatest amount of what we do with
 8 IMMPACT and ACTION is learning to communicate, to
 9 speak with each other, not just formally. But what
 10 we found we intentionally do is lots of breaks,
 11 lots of dinners, lots of opportunities for you to
 12 speak with each other, because often what's more
 13 important than what goes on during the formal
 14 session is what happens when you're talking among
 15 yourselves and discussing things. And many of you
 16 have noticed that. The alumni have seen that
 17 happen.

18 So what's this particular meeting? Since
 19 the 18th when I got started doing this with
 20 Dr. Dworkin, he and I both had black hair. Things
 21 have changed in 18 years. The title for this
 22 particular meeting is Ensuring Data Quality and

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1 Clinical Trials of Pain Treatment: Considerations
 2 for Study Execution and Conduct. We really are
 3 addressing a fundamentally important issue for all
 4 of us, for all of you, and for the field in
 5 general, how to, in fact, ensure the quality of the
 6 data.

7 We can have the best scientific questions.
 8 We can have the best understanding of the anatomy
 9 and the physiology, and the biochemistry. If in
 10 fact, we don't gather the data appropriately,
 11 correctly, accurately and validly, then we can't
 12 draw any reasonable conclusions in these studies.

13 So this is a fundamental, probably should
 14 have been the first IMMPACT meeting, or first one
 15 or two IMMPACT meetings, that began back in 2002,
 16 was the first meeting, I believe.

17 I want to acknowledge the support from a
 18 number of pharmaceutical companies. For those that
 19 are new to IMMPACT, what you may not know is that
 20 when we have people attending from the
 21 pharmaceutical companies, every company that
 22 supports us is allowed to have one person here. We

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1 encourage, strongly encourage, that the people here
 2 from industry not be viewed as marketing people,
 3 but rather they're here as scientists who
 4 understand the kinds of issues we are talking about
 5 and that hopefully they will be talking about
 6 things that are meaningful, in general, that's
 7 broadly relevant not just to their particular
 8 companies. But we do thank these particular
 9 companies.

10 If for some reason the logo of your company
 11 isn't there -- there were some things changed right
 12 at the last minute -- and the same thing will be
 13 true when I show you of who's present. I
 14 apologize, but I had to leave Seattle. I'm from
 15 Seattle. I left Seattle early yesterday, so things
 16 have changed, and I've tried to keep things up to
 17 date. But if for some reason I've messed up let me
 18 know, and we'll fix it on the slides.

19 So what IMMPACT is not. For those again,
 20 the alumni can immediately turn this off. It's not
 21 the International Micronutrient Malnutrition and
 22 Prevention and Control Program, in case you were

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1 wondering. If you're for that meeting you're in
 2 the wrong room. This is not it.

3 It's not the Interactive Massive Model
 4 Proximity and Collision Tester. And these are, by
 5 the way, all accurate from the Web; these are real
 6 organizations that you can look up, but we're not
 7 them.

8 We're not the IMMigrants Public Action
 9 Coalition of Trenton, New Jersey. If you're here
 10 for that meeting, again, you're in the wrong place.
 11 We're not the International Maine Maritime Potato
 12 Action Team.

13 (Laughter.)

14 Sometimes it feels that way. And we're also
 15 not the Double Impact Tae Kwon Do for those that
 16 are in to martial arts, although at times, it may
 17 feel to you as if this meeting is like that and —

18 (Laughter.)

19 DR. TURK: -- we have to find ways to try to
 20 keep the meeting organized, and sometimes it feels
 21 like that. But that's not the meeting you're at.
 22 What is IMMPACT? Well, it's the Initiative

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1 on Methods, Measurement, and Pain Assessment in
 2 Clinical Trials, I-M-M-P-A-C-T. If you go to the
 3 Web, make sure you have the double M's in there,
 4 and it'll ask you, do you really want to say one M?
 5 No, you want both M's so you can see everything
 6 about the IMMPACT.org.

7 It's an international consortium, and by
 8 international, I want to especially thank of our
 9 colleagues who have come from the other side of the
 10 pond that have given generously of their time, not
 11 only to be here at the meeting but who traveled a
 12 great distance. And then there are those of us who
 13 are from Seattle like Mark Jensen and myself who
 14 also donated a huge amount of time in having
 15 traveled across country.

16 It's an international consortium of academic
 17 research, governmental agencies -- and different
 18 agencies are listed there -- industry, consulting,
 19 research organizations. And I don't like the word
 20 "consumer advocate," but I know from Penney
 21 Cowan -- I don't want to say "patient advocate," so
 22 I haven't come up what the best term to use; those

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1 groups that support people who have pain problems.
 2 Penney, is that okay? Did I say that
 3 reasonably well?

4 We're part of the Analgesic, Anesthetic, and
 5 Addiction Clinical Trials, Translation,
 6 Innovations, Opportunities and Networks, or ACTION
 7 Public-Private Partnership with the Food and Drug
 8 Administration.

9 Now, you'll notice throughout that there are
 10 a lot of acronyms. I want to thank my colleague,
 11 Dr. Dworkin, who was awarded a special honorary
 12 degree from the Society for Acronyms when he has
 13 come up with many of these acronyms, but it's
 14 helpful. And the reason -- you may wonder why all
 15 these double letters and double TT's, and why is
 16 IMMPACT only one M.

17 Well, if you want to go to Google and find
 18 out about IMMPACT, if you type in I-M-P-A-C-T, you
 19 will find a huge amount of information irrelevant
 20 to what you're looking for. Having the double
 21 letters sometimes helps you find who we are.
 22 The same for ACTION. If you type in

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1 A-C-T-I-O-N, you're going to get a whole range of
 2 different organizations and meetings, and
 3 everything you want to know, but not about us.
 4 So one of the reasons, although there are
 5 others as well, for the double letters are to try
 6 to help people find us if they want to know about
 7 us.
 8 Our mission is to suggest methods for
 9 improving the design, execution, and interpretation
 10 of clinical trials and treatments for pain. They
 11 are all about a better research designs, better
 12 studies, so that in fact we can draw better
 13 conclusions about the kinds of treatments that we
 14 are offering to patients, which is the ultimate
 15 end-user of anything that we do.
 16 The whole mission is can we find more
 17 effective and efficient ways to make sure that
 18 treatments get evaluated, and those that have
 19 turned out to be appropriate to be able to get into
 20 the hands of the providers as soon as possible.
 21 Who is IMMPACT? Well, over the 18 meetings,
 22 we've had 200 different participants. Usually

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1 meetings run anywhere from 35 to 50 people. This
 2 is one of the larger ones at this particular
 3 meeting. Some of you have attended multiple ones,
 4 as I have said before. Some of the other people
 5 have been at multiple ones.
 6 Academic and related participants from 12
 7 different countries have been attending these
 8 meetings over time, and the countries are listed
 9 there if you just kind of curious about where they
 10 come from. We are short on Asia, so will do the
 11 best we can in the future to make sure we have
 12 opportunities for our Asian colleagues.
 13 Over 85 different academic institutions have
 14 had people who have attended these particular
 15 meetings. Participants from government agencies at
 16 DOD, DEA, EMA, FDA, NIH, SAMHSA, VA; some of you
 17 are all here from some of those organizations as
 18 well.
 19 We try to make sure we bring together
 20 academics, government people, industry and people
 21 who have pain problems have their representation.
 22 The idea is to try to have people in the same room

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1 who are addressing the same kinds of issues but
 2 maybe with some different perspectives, and that's
 3 the real purpose of why we're here.
 4 We've had 45 different pharmaceutical
 5 companies over the history of the 18 years. Some
 6 of which have been multiple ones; some of which are
 7 new. And they will come and go depending upon the
 8 nature of the meeting or where they are in their
 9 development stages on the way.
 10 But as you can see, we've had a lot of
 11 people. Obviously, we don't have all those people
 12 in the room at one time, different people and
 13 different organizations are here for different
 14 meetings.
 15 We've also had, as I've mentioned consumer
 16 advocacy representatives. Again, I don't like the
 17 word "consumer," but okay. And we've had five
 18 different organizations involved and 1 and
 19 three-quarters are here today because people are
 20 sort of transitioning from one to another. So
 21 we're happy to have all of you attend in case
 22 you're wondering.

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1 These are the different organizations that
 2 have been involved from the government in case
 3 you're wondering about what institutions have been
 4 involved. Some of them are participants and some
 5 of them are observers. And what I mean by that is
 6 that, depending upon the charge from certain
 7 governmental agencies, some people just sat and
 8 observed and didn't have anything that they wanted
 9 to add; they wanted to learn from us. Others have
 10 been intricately involved in the discussions.
 11 What do we do? Well, as I mentioned, it's
 12 been 18 IMMPACT meetings, and I'm sure you can't
 13 read these, especially in the back, but this is
 14 just giving you an idea the kinds of topics. These
 15 are up through the first 14; the next slide will
 16 show you the next few. But these are the kinds of
 17 topics we cover, everything from outcome domains to
 18 statistical models to ways of improving the design
 19 of studies to have to interpret to multiple
 20 endpoints, et cetera.
 21 Again, I know you can't read them all, but
 22 you can find them easily on our website, which is

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1 either IMMPACT.org or you can go to ACTION -- is
 2 it ACTION.org, Bob? ACTION.org. Again, the most
 3 recent meetings, and as I said, the one that you're
 4 here for is this particular one.
 5 So these are the meetings. We've tried to
 6 be as transparent about these meetings so that on
 7 our website for both IMMPACT and ACTION, we've
 8 included speakers, the topics, background
 9 presentations. We ask all speakers who have slide
 10 presentations to make those available to us and
 11 remove any slides that they are not comfortable
 12 with for proprietary reasons, but to put them on
 13 the website so that anybody can, in fact, get
 14 access to those.
 15 The more recent meetings are being
 16 transcribed, so those become available. So if
 17 anybody wants to know what we're doing -- those of
 18 you that are familiar with IMMPACT and ACTION know
 19 that we try to have every one of these meetings
 20 arrive at some type of considerations, discussions,
 21 ways to help people improve their studies. But
 22 obviously it's not just for the people here, so we

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1 try to publish these in mainstream journals,
 2 typically in the Pain journals, to try to make sure
 3 that information get out as soon as possible.
 4 All of you will be invited to the authors of
 5 those papers. What typically happens, if you're
 6 wondering, is that some couple of people will draft
 7 up an initial version, and we will often come back
 8 to speakers and ask them to look at the section or
 9 to give us a section from their presentation. We
 10 then craft a draft, it gets circulated, you get a
 11 chance to put comments on those.
 12 With the number of people in this room,
 13 50-plus people, you can imagine that it takes an
 14 awful lot of time. We plead with you if you get
 15 this and you are considering being an author, that
 16 you turn things around in a reasonably timely
 17 fashion. Sometime papers are dragged out for much
 18 more time than we want them to, and we get
 19 pressured, how come you're not faster? It's
 20 because we can only turn things around as quickly
 21 as the authors are willing to do that.
 22 Welcome, Dr. Hertz, who just snuck in the

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1 back.
 2 So you'll be asked. And for those of you
 3 who are from companies, I know that there have been
 4 times when they've had to have their legal
 5 departments look at anything that's we're doing,
 6 and that can take some time. So to the extent that
 7 you can expedite that, we appreciate that. The
 8 goal is within at least a year, hopefully less, is
 9 to try to get these manuscripts out. The idea is
 10 to disseminate the information. If it's just us
 11 talking to ourselves, that's fine, but we really
 12 want to go beyond that.
 13 What does IMMPACT do? In addition to the
 14 meetings from ACTION and IMMPACT that we've been
 15 talking about, we commission review papers and
 16 conduct scientific studies. So in addition to the
 17 presentations and the papers that come out of these
 18 meetings, we've also contracted some studies to be
 19 conducted on certain things. For example, one of
 20 the contracted papers was to do a study which
 21 involved patients, and they were patients who had
 22 different types of pain problems, to be in focus

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1 groups for discussions about the important
 2 meaningful outcomes were for them, what bothers
 3 them, what's not getting picked up.
 4 So because that came up in one of our
 5 meetings and we didn't have enough input and enough
 6 knowledge about what those people experiences were,
 7 to try to make sure that we included them, so we
 8 contracted a study in that.
 9 We've also contracted some background papers
 10 on the pediatric aspects of pain because one of the
 11 things we felt was there wasn't sufficient
 12 information out there about pediatric pain
 13 assessment. So those are some of the things we've
 14 tried to do, and there are a number of others.
 15 Again, if you're interested in any of these
 16 things, you can ask me, ask Bob, or go to the
 17 website and find out more about those. Everything
 18 we do we try to get published. The idea is to get
 19 the information out there.
 20 Articles have been cited, and we always toot
 21 our horns. So last I went to a Google scholar
 22 4,100 times in over 600 scientific journals

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1 published in 14 different countries. So somehow or
 2 another, people are getting access to these and
 3 learning about these things.
 4 The journals are running anywhere from
 5 addiction medicine, women's health, to my favorite
 6 veterinary medicine. Somehow or another, what
 7 we're saying has something important for veterinary
 8 medicine, so that's good. And that's the kind of
 9 things we do.
 10 If you're just kind of interested over the
 11 time, first meeting was in 2002. I think the first
 12 publication came out in 2003. And that's just
 13 showing you -- this is unique citations, so
 14 sometimes more than one article will get published,
 15 which is where the 4,000 number comes from. But
 16 this is just showing you over time, and that's up
 17 through about mid-May-ish the last time I went to
 18 look to see where we are.
 19 So you can see it's been going up steadily
 20 over time. It doesn't appear to be that it's going
 21 down in any way. I want to thank the editors of
 22 one of the journals who's sitting here who has

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1 published some of our papers, Mark Jensen, and
 2 we've helped the IMMPACT factor of his particular
 3 journal tremendously.
 4 (Laughter.)
 5 DR. TURK: So therefore he's begging us for
 6 our favors but we fight him off.
 7 (Laughter.)
 8 DR. TURK: Here's the website I mentioned,
 9 IMMPACT.org, if you want to go. This is the old
 10 website that's now been imbedded within the ACTTION
 11 website, but you can see the information that's
 12 there, who's on the steering committees, the
 13 publications, one of the instruments that we
 14 supported, the development of the Short Form-McGill
 15 Pain Questionnaire 2. There's also the other
 16 information.
 17 So if you get interested in any of the
 18 things you've heard, or if you just happen to be
 19 browsing and see some particular meeting that that
 20 topic was interesting, gee, I wish I had been
 21 there, you can go to the website and you can
 22 actually download the information, the

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1 presentations, as much as possible, the background
 2 articles, the citations. So you find out as much
 3 as you want about us. Again, the idea is to make
 4 this as transparent and as available to anyone who
 5 wants to.
 6 ACTTION, which I have mentioned to you what
 7 it stands for. Notice that there are two
 8 additional A's in there, and we were asked by the
 9 Food and Drug Administration to expand what was
 10 originally analgesic to also include anesthetic and
 11 addiction products. So now we try to bring all
 12 that information in as much as possible to this
 13 public-private partnership.
 14 Mission of ACTTION, it's a public-private
 15 partnership with the U.S. Food and Drug
 16 Administration to identify, prioritize, sponsor,
 17 coordinate, promote innovative activities with a
 18 special interest in optimizing clinical trials that
 19 will expedite the discovery and development of
 20 improved analgesic, anesthetic and addiction
 21 treatments for the benefit of the public health.
 22 That's what we are here to do. That's what you are

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1 here to do. And you're here to help us do that.
 2 ACTTION.org, there it is. If you want to go
 3 to their website, remember there are two T's in
 4 ACTTION and two M's in IMMPACT.
 5 Here's the people who are here at last I
 6 knew, which was about two days ago. If for some
 7 reason there's been some shifting or changing and
 8 who is coming are not coming, I apologize, but this
 9 is the best I can do. I have highlighted in yellow
 10 those people who are either speakers or they're
 11 moderators, or they're discussants on different
 12 projects. So if you see your name there -- and any
 13 misspellings, it's totally Bob's fault. I have
 14 nothing to do with this. This is what he gave me.
 15 So that's who's here.
 16 Now, the best way to know who's here, and
 17 we'll do this shortly, is to let you go around and
 18 just tell us in 30 seconds or less who you are, but
 19 mostly so people get the a name with a face as they
 20 are sitting around. You all should have your name
 21 tags as well.
 22 What are the objectives? I've told you

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1 these are ready, to discuss important
 2 considerations and provide suggestions regarding
 3 the execution and conduct of clinical trials to
 4 improve data quality. That's what this meeting is
 5 all about. That's what we're going to be talking
 6 about for the next two days.

7 We want to disseminate these considerations,
 8 observations, suggestions, and research agenda by
 9 publication of peer-view articles. The end of
 10 tomorrow, when we'll know this is a successful
 11 meeting, is when we sit back as we say, okay, was
 12 there enough discussion, did we get enough
 13 interesting input, ideas, that we, in fact, can
 14 come up with some suggestions, considerations,
 15 recommendations, that can be considered by people
 16 doing their clinical trials.

17 Let me caution with the word "considered."
 18 We have no authority to require anybody to do
 19 anything. That's all we can do is to put the
 20 information out there of our discussions of an
 21 informed group of people who are thinking about
 22 these issues. What people choose to do with the

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1 information we put out there is totally up to them.

2 So we don't have any regulatory authority,
 3 we don't have any control, we can't require them to
 4 do anything. All we can do is say, this is our
 5 opinion. People who are here from the government
 6 agencies who end up being authors, and they can
 7 decide to be or not, they are not speaking for the
 8 government agency when they endorse one of our
 9 papers. What they are basically saying is their
 10 personal opinion from their experience is relevant
 11 to this particular topic, and they agree
 12 sufficiently.

13 Consensus, by the way, does not mean
 14 unanimity; doesn't mean every exact person agrees
 15 with every word in here. It means there was a
 16 consensus or there was a group discussion that led
 17 to an agreement that this was reasonably close to
 18 what they feel comfortable signing off on.

19 As I said, all of you will be invited to be
 20 authors. You can have commentary on that. We do
 21 our best when the manuscripts come back to
 22 take -- you can imagine 50 authors, the comments.

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1 We then tried to integrate the comments. It's
 2 always interesting when we've done is, when we've
 3 have three people all of whom want the sentence
 4 written in different ways and how do we make it
 5 work for them. So then we go to Mark Jensen and
 6 say, you're an editor, you know how to do this, and
 7 we asked him for his consultation.

8 So that's what our objectives are. In order
 9 to accomplish this, we sort of have to do some
 10 herding of you. And because of the time pressure,
 11 you will find that we tend to do a good bit of
 12 pushing. It's all Bob Dworkin who does the
 13 pushing. I'm this gentle guy who just sits back
 14 and lets it happen."

15 So how do you herd participants? Well, some
 16 notes for you in the gentle art of herding IMMPACT
 17 participants that we've learned over the last
 18 18 years. Participants don't like to be herded.
 19 In fact, you can't really hurt IMMPACT
 20 participants, but that doesn't stop us from trying.

21 Participants prefer to herd themselves, but
 22 they're not very good at it, so sometimes you need

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1 a little assistance.

2 Participants understand that they sometimes
 3 need to be herded; however that doesn't make it any
 4 easier to herd them even though you don't realize
 5 it.

6 Harsh herding has negative consequences, so
 7 we don't coerce. We don't try to do any herding
 8 negatively. However, Bob does do a little bit of
 9 herding, and there see him in action of what he's
 10 trying to accomplish.

11 In case you don't know Bob Dworkin, that is
 12 him without his glasses.

13 Okay. Very simply what I want to do now and
 14 quickly -- first of all, let me do this. Any
 15 questions, any comments, either about the
 16 housekeeping details; about the purpose of the
 17 meeting; about anything I've presented in the
 18 background about IMMPACT and ACTION that you feel
 19 you'd like to know? And any questions, Bob will be
 20 happy to answer them for you.

21 (No response.)

22 DR. TURK: No questions? Okay.

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1 What I want to do quickly, and I know this
2 is a big room, and you can say this is going to
3 take some time, but I do think -- and Bob and I
4 talked about this, that we felt that it might be
5 useful, just so people will have the name with a
6 face, with who's around them, so when they see
7 them, they can talk to them and they will know a
8 little bit about them.

9 So Kushang, why don't we start with you?
10 12.5 seconds you have to tell us who you are and
11 where you're from.

12 MR. PATEL: Kushang Patel. I'm a research
13 assistant professor at the University of
14 Washington. Do you want other background
15 information?

16 DR. TURK: I think that's going to be
17 enough.

18 Oh. Bob wants more. Bob wants more
19 background -- Bob doesn't want more. Okay.

20 MS. CHEN: My name is Crystal Chen from
21 Biogen, Cambridge, Massachusetts.

22 DR. TURK: And your background is what?

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1 MS. CHEN: I'm a trained physician but a
2 medical director now with Biogen.

3 DR. TURK: I'm glad you're not an untrained
4 physician. Okay.

5 DR. CHEN: Thank you.

6 DR. TURK: Nat?

7 DR. KATZ: I'm Nathaniel Katz. I'm a
8 neurologist from Boston, and I'm at a company call
9 Analgesic Solutions and Tufts University School of
10 Medicine.

11 DR. TURK: Amy?

12 MS. KIRKWOOD: I'm Amy Kirkwood. I'm a
13 statistician from the Cancer Trials Center in the
14 UK, and we are part of the UCL cancer research.
15 I'm going to talk about central statistical
16 monitoring this afternoon.

17 DR. TURK: And you're originally from
18 Georgia or Alabama?

19 (Laughter.)

20 DR. TURK: I heard an accent.

21 MS. KIRKWOOD: Yeah.

22 MS. DOYLE: I'm Mittie Doyle. I am a

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1 rheumatologist and vice president of clinical
2 research at Flexion Therapeutics, which is a small
3 company outside of Boston.

4 DR. TURK: Thank you. Mark?

5 DR. JENSEN: Mark Jensen, University of
6 Washington, clinical psychologist by training.

7 DR. TURK: Wen?

8 MS. NEIBLER: Wendy Neibler. I'm a
9 neurologist by training, and I'm with Egalet
10 Corporation, a small pharmaceutical company based
11 outside of Philadelphia, focused on developing
12 abuse-deterrent opioids.

13 DR. MARKMAN: Good morning. My name is
14 John Markman, and I'm a neurologist from the
15 University of Rochester in Rochester, New York.

16 DR. VANHOVE: Trudy Vanhove. I'm a VP
17 medical affairs, Jazz Pharmaceuticals.

18 DR. FREEMAN: Roy Freeman, neurologist,
19 Boston Beth Israel Deaconess Medical Center,
20 Harvard University.

21 DR. TURK: Mike?

22 DR. McDERMOTT: I'm Mike McDermott, a

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1 biostatistician at the University of Rochester.

2 DR. EDWARDS: Rob Edwards. I'm a clinical
3 psychologist at Brigham and Women's Hospital in
4 Boston.

5 DR. VRIJENS: Bernard Vrijens from Belgium.
6 I'm a statistician by training and specialized in
7 medication adherence.

8 DR. SCHUETTE: This is the statistician
9 row. Paul Schuette, statistician, Office of
10 Biostatistics in the Center for Drug Evaluation and
11 Research, FDA.

12 DR. TURK: We put Bob Edwards back with you
13 guys as a psychologist just to make sure things
14 were okay.

15 (Laughter.)

16 DR. TURK: Now, I'm going to have trouble
17 seeing in the back, so I'm just going to sort of
18 point. I'm sorry if I can't call your names.

19 DR. KERNS: Bob Kerns, VA. I'm a
20 psychologist, VA Connecticut Health Care System;
21 Yale University.

22 DR. ROWBOTHAM: Mike Rowbotham, neurologist

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1 at UCSF and scientific director at the CPMC
 2 Research Institute in San Francisco; part of Sutter
 3 Health.
 4 DR. TURK: Jim?
 5 DR. CAMPBELL: Jim Campbell. I'm a
 6 neurosurgeon by training from Hopkins, and I
 7 represent a company called Centrexion, which is in
 8 the field of pain therapeutics.
 9 DR. JACOBS: I'm David Jacobs. I'm a
 10 clinician, Daiichi-Sankyo Pharmaceuticals.
 11 DR. TURK: Ajay, you want to go back to
 12 you?
 13 DR. WASAN: I'm Ajay Wasan. I'm a pain
 14 physician at the University of Pittsburg.
 15 DR. SKLJAREVSKI: And I'm Vladamir
 16 Skljarevski, neurologist and neurosurgeon by
 17 training, working for Eli Lilly and Company,
 18 overseeing late-stage pain trials.
 19 DR. RICE: Andrew Rice. I'm professor of
 20 pain research, Imperial College, London.
 21 DR. MALAMUT: Hi. And I'm Rick Malamut,
 22 neurologist and therapeutic area of pain at Teva

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1 Pharmaceuticals.
 2 DR. MULIA: Good morning. I'm Sohail
 3 Mulla. I'm a clinical epidemiologist at McMaster
 4 University in Canada.
 5 DR. HERTZ: Sharon Hertz. I'm a
 6 neurologist by training, and I am currently the
 7 director for the review division that covers
 8 analgesics at FDA.
 9 MS. BURKE: Laurie Burke, Lora Group,
 10 University of Maryland, School of Pharmacy, and
 11 formerly FDA, where I established the SEALD staff.
 12 DR. KOVACS: Sarrit Kovacs, reviewer with
 13 the clinical assessment staff at FDA, which was
 14 formerly the SEALD Study Endpoints Team.
 15 DR. TURK: You've changed your name; is
 16 that correct?
 17 DR. KOVACS: We did.
 18 DR. FIELDS: Ellen Fields, clinical team
 19 leader in Sharon's division at the FDA.
 20 DR. CONAGHAN: Philip Conaghan, professor
 21 of musculoskeletal at the University of Leeds and a
 22 member of the OMERACT executive.

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1 DR. HEWITT: I'm David Hewitt. I'm a
 2 neurologist by training, and I'm vice president of
 3 neuroscience and pain at inVentive, which is a CRO,
 4 and vice president of Medical and Scientific
 5 Affairs at inVentive.
 6 DR. EVANS: Good morning. Scott Evans,
 7 biostatistics, Harvard University.
 8 DR. CARR: Dan Carr, a physician and
 9 professor at Tufts University where I direct their
 10 program on pain research, education, and policy.
 11 DR. TURK: Lee?
 12 DR. SIMON: Good morning. Lee Simon, a
 13 rheumatologist, a member of the OMERACT Exec and
 14 some other involvement, and a consultant in
 15 clinical drug development.
 16 DR. TURK: Lee, why don't you mention what
 17 OMERACT is, just because some people may not know
 18 the acronym.
 19 DR. SIMON: So there's something called
 20 OMERACT, which stands for Outcomes Measurements in
 21 Rheumatology, and it's been in existence since
 22 1992. They have had every-other-year meetings

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1 since then.
 2 We have 54 working groups all from below,
 3 meaning everybody who wants to work in an outcome
 4 measurements system, in any disease state in
 5 rheumatology, proposes to us. We're a
 6 non-membership organization.
 7 They have certain criteria about how to get
 8 this done, the evidence that needs to be done.
 9 Every-other-year meetings are consensus meetings
 10 leading to Adelphi process for certifying or giving
 11 approval to whatever is proposed based on evidence
 12 We have 975 publications. I think you may have
 13 beat us in number of publications, but we only have
 14 one area as opposed to yours.
 15 Our next meeting is in Whistler in May of
 16 2016, and then after that it's in Australia
 17 sometime in 2018. We have a group of people from
 18 all over the world, and we are delighted to
 19 continue to work with IMMPACT/ACTTION in coming up
 20 with outcome measures in pain.
 21 DR. TURK: Thank you. The reason I asked
 22 Lee to give you that background other than just

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1 because of the acronym was at the last meeting that
2 we had for IMMPACT was jointly with the OMERACT
3 group, which was the physical function as outcome
4 measurements and clinical trials. Last year,
5 roughly at this time, we had that meeting.
6 Yes, Judy?
7 DR. TOCKARSHEWSKY: Good morning. Tina
8 TockarsheWSky.
9 DR. TURK: Tina.
10 MS. TOCKARSHEWSKY: Good morning. I have,
11 the past several years, nearly a decade, been
12 serving as the presidency of the Neuropathy
13 Association. Recent years, I've also been a member
14 of the Interagency Pain Research Coordinating
15 Committee.
16 My time with the association is winding
17 down in the next couple of weeks, and I'm winding
18 up on my own consultancy of working on strategic
19 communications, such as patient community
20 engagement, advocacy work, continuing in the health
21 care sector. And I've also been working on future
22 articles for industry trade magazines.

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1 DR. TURK: Thank you.
2 DR. COSTELLO: Good morning. I'm Ann
3 Costello. I'm trained as an oral-maxillofacial
4 surgeon. I'm with the FDA Center for Devices and
5 Radiological Health, and I'm the pain expert for
6 our center.
7 DR. JUGE: I'm Dean Juge. I'm a
8 pharmacist. I'm a regional medical director at
9 Horizon Pharma. Most recently I was involved in
10 patient-reported outcomes research for a company
11 and also associate professor at University of
12 Alabama, Birmingham, in biotechnology.
13 DR. CHEUNG: Good morning. Raymond Cheung,
14 clinician from Pfizer in New York.
15 DR. SINGLA: Hi. I'm Neil Singla. I'm an
16 anesthesiologist by training, and I work with Lotus
17 Clinical Research, which is an analgesic research
18 site and CRO.
19 MS. COWAN: Hi. Penney Cowan, founder and
20 executive director of the American Chronic Pain
21 Association for the last 35 years.
22 DR. KOPECHY: Good morning. Ernest

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1 Kopechy. I'm a pediatric clinical pharmacologist
2 by training, and I'm the head of clinical
3 development at Collegium Pharmaceutical.
4 DR. DEVINE: Hi. I'm Eric Devine. I'm a
5 clinical psychologist at Boston University where I
6 do clinical trials for addiction.
7 DR. SESSLER: Morning. Nelson Sessler from
8 Purdue Pharma. I'm a pharmacist in the medical
9 affairs group and recently focused a lot on risk
10 management and pharmacovigilance.
11 DR. UPMALIS: Good morning. I'm David
12 Upmalis. I'm with Janssen research and
13 development. I'm a physician by training.
14 DR. ALLEN: I am Rob Allen. I'm a
15 neurologist by training. I do clinical consulting
16 with drug development and currently working with
17 inVentiv Health.
18 DR. GILRON: Hi. Ian Gilron. I'm a
19 professor of anesthesiology and director of
20 clinical pain research at Queen's University in
21 Kingston, Canada.
22 DR. FARRAR: Good morning. I'm John

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1 Farrar. I'm a neurologist and epidemiologist,
2 clinical epidemiologist, at the University of
3 Pennsylvania, interested in pain and clinical trial
4 design for many years.
5 DR. WITTER: Good morning. Jim Witter.
6 I'm a rheumatologist and medical officer at the
7 rheumatic diseases section of the National
8 Institutes of Arthritis and Musculoskeletal and
9 Skin Diseases. I'm also the chief science officer
10 for PROMIS.
11 DR. TURK: Which stands for?
12 DR. WITTER: Patient Reported Outcome
13 Measurement Information System.
14 DR. TURK: Thank you.
15 DR. DWORKIN: Hi. I'm Bob Dworkin at the
16 University of Rochester. And please, please,
17 please don't believe a single thing Dennis says
18 about me.
19 (Laughter.)
20 DR. TURK: Bob is one of the nicest guys
21 I've ever met.
22 (Laughter.)

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1 DR. TURK: Totally ethical, intellectual
2 giant in the field.
3 (Laughter.)
4 DR. TURK: As you heard as we went around,
5 this is really an impressive group, impressive in a
6 number of different ways. In the range of
7 healthcare disciplines, from dentistry to
8 neurosurgery to pharmacology to neurology, women's
9 health. We've covered I think rheumatology, one of
10 the largest ranges I've heard. We have
11 psychologists, epidemiologists, biostatisticians.
12 We've got multiple companies involved. We've got
13 advocacy representatives.
14 I think this is really a wonderful group of
15 people. I'm awed at the qualifications and status,
16 the knowledge base that people bring to this. I'm
17 really looking forward tremendously to this
18 particular meeting. I think it's going to be
19 extremely exciting.
20 We are going to do a little bit of herding,
21 so I apologize for that, but to keep things on
22 target, we'll try to move things along. We'll try

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1 to have lots of discussion sessions.
2 By the end of the day tomorrow, you're
3 going to love Bob. He's going to be really sweet.
4 He's going to really work with you to help you
5 craft the beginnings of this manuscript that we're
6 going to circulate. And now I want to turn this
7 offer to Bob.
8 For the person who isn't seeing the slides,
9 remember, the glasses have been found and we have
10 those available to you.
11 Bob?
12 DR. DWORKIN: Thanks, Dennis. Welcome, all
13 of you. I just want to reiterate Dennis' welcome.
14 It's really a great pleasure to introduce our first
15 speaker, who is Dr. Sharon Hertz. As she
16 mentioned, she recently became director of the
17 FDA's division of Anesthesia, Analgesia and
18 Addiction Products, and that enormously pleased
19 many of in the room and elsewhere when she was
20 appointed the director of the division at the FDA.
21 The other I have to say about Sharon is to
22 acknowledge that from the very beginning of IMMPACT

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1 and ACTION, she's been a steadfast, stalwart
2 supporter, and Dennis and I have greatly
3 appreciated that. Also her mentorship in this
4 whole — what is now over 12-year-saga. And so
5 thank you very much, Sharon.
6 Her first lecture — her presentation is
7 going to be called, A Regulatory Perspective on
8 Threats to the Integrity of Analgesic Clinical
9 Trial Efficacy Data.
10 Presentation – Sharon Hertz
11 DR. HERTZ: Good morning. Can I have the
12 next slide, please?
13 I could say that — oh, always the
14 disclaimer. So, here it is. I don't know why
15 you'd want me here if I wasn't with FDA, but these
16 opinions are mine and not those of my agency. On a
17 serious note, I will say, for the record, that
18 there will be no conversations about any particular
19 product or development program. There will be no
20 advice given or sought from me or to me. This will
21 simply be a scientific discussion, and that is my
22 purpose for being here, to participate in that.

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1 Next slide, please. So you can see I'm no
2 good at acronyms. I'm going to have to leave that
3 to Bob. But this is just a quote from one of the
4 articles that were a part of the background
5 message.
6 (Pause.)
7 DR. HERTZ: It's the article by Colin
8 Baigent, and it just describes the concern
9 regarding safety when there are errors in the
10 design conduct, data collection, or analysis of
11 trial data; potential safety issues for the person
12 in the study but also for the future recipients of
13 the drug product. But beyond that potential -- you
14 know, safety is always first and foremost, but
15 really there are a lot of threats beyond that.
16 The ability to demonstrate efficacy is
17 really the threat that I've seen manifested mostly
18 commonly when they're having problems with clinical
19 trial integrity, or data integrity, because that's
20 the setting in which my experience has been in
21 terms of catching those problems. And this has, in
22 fact, resulted in substantially increased time to

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1 get new products to market.
 2 So it's also, simply put, a waste of
 3 resources. It's not easy to get these clinical
 4 studies done. We do have a lot of patients with
 5 pain in this country, but as you all know, they're
 6 not limitless. So there are many reasons why it's
 7 important for us to get this right from the start.
 8 So just in terms of describing some of the
 9 forms of threats to the integrity of analgesic
 10 clinical trial efficacy data, there's of course,
 11 inadequate study design. If the study can't
 12 produce useful information, then none of the data
 13 is useful.
 14 We try very hard to work at catching
 15 problems early before clinical trials are started,
 16 but resources being what they are, the
 17 responsibility really comes from whoever is writing
 18 the protocol, as well as, to the extent we can, our
 19 ability at the agency to provide input.
 20 Sloppy study conduct is extremely
 21 frustrating for us to see. And I know that this
 22 first item, the training of clinical trial sites is

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1 a big pocket that's being discussed. We've
 2 discussed it in this setting. One of our former
 3 directors for the Office of Biostatistics, that was
 4 like one of his primary concerns, Bob O'Neill, is
 5 to get these clinical trials site staff, the
 6 investigators, all the way down to everyone
 7 participating, well trained so that they know the
 8 protocol, they know what to do, they know how to
 9 collect the data, the know how to record the data,
 10 everything, and to train the patients. And that's
 11 another topic that's being discussed here.
 12 Then the kind of stupid protocol violations
 13 by the staff and study patients, patients who
 14 really do forget things or make mistakes, and same
 15 thing with study staff. And then sloppiness as it
 16 relates to unverifiable data and poor audit trails,
 17 when things are not well recorded and managed.
 18 So while this is frustrating, this
 19 downright puts us over the top when we find that
 20 there were intentional actions that negatively
 21 affect data integrity. These are issues that we
 22 see in analgesic studies, but really all of our

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1 therapeutic areas in the division, but they're not
 2 specific to our therapeutic areas. These are broad
 3 concepts.
 4 Deceptive subjects; that's one of the
 5 articles, the professional subject. Or the subject
 6 who simply really wants to get into the study for
 7 whatever reason.
 8 Fraudulent data, and I'm going to give you
 9 an example of what we suspect was fraudulent data.
 10 Intentional failure to adhere to a protocol. Yeah,
 11 I got an example for you. And improper handling of
 12 data. I got one of those for you too. And
 13 deviation from prespecified analyses. Well, you
 14 all are going to smirk because I know how many of
 15 you want to do that at the end of the day. But we
 16 can fix that one as long as the data has been
 17 collected properly and locked properly. That one
 18 can always be fixed.
 19 So this is a question. We've never been
 20 able to prove it, but I think this is an example of
 21 investigator fraud. And I've left out all details
 22 about the drug product because it's really

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1 irrelevant to the story, and I don't want to put
 2 anyone on the spot.
 3 But we had a submission come in with three
 4 efficacy studies. They had very similar design;
 5 two were successful, one failed. Ha. Slam-dunk,
 6 right? You've replicated your finding of efficacy,
 7 so there really shouldn't be too much of a
 8 question.
 9 We started looking at this, though, and we
 10 started noticing some things that were a little
 11 funny. First of all, the two positive studies were
 12 not in the U.S., and the U.S. study was an abysmal
 13 failure to differentiate from placebo.
 14 Well, okay, it happens. But we also
 15 started looking -- I know what this drug is. It's
 16 not its first in class, so we have a history of how
 17 this type of product behaves. And gee, that's a
 18 really good effect size. Change from placebo of
 19 30 on a VAS? How many people have actually ever
 20 seen that happen except perhaps with a single dose
 21 opioid post-op study or something really
 22 phenomenal? I mean, 30 points. Wow. So we were

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1 really impressed by this, but also a little
 2 concerned.
 3 Then we noticed one other thing, which
 4 is -- I didn't highlight it, so I don't know if any
 5 of you have picked up on it already, but lo and
 6 behold, oh, man, very little placebo effect.
 7 Well, this happens to be a clinical
 8 setting, which is known for an extremely troubling
 9 placebo effect, and we can see that that was
 10 potentially part of the problem with the U. S.
 11 study. The placebo effect had a pretty good sized
 12 change, pain intensity difference was 30 points.
 13 So we decided we needed to look over all
 14 what we were seeing. So we had a very large effect
 15 size, larger than inspected. Yeah. The successful
 16 studies had a higher baseline pain intensity, yet
 17 it worked better. All right. Sometimes that's
 18 helpful for sensitivity.
 19 But, ha, they had a higher pain sensitivity
 20 and didn't use rescue or any of the non-drug
 21 treatments that were available. And there was less
 22 of a placebo response with no placebo patients; not

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1 one having a meaningful change, meaningful onset of
 2 pain relief.
 3 Well, it started to sound a little too good
 4 to be true. So we checked the study demographics
 5 looking for things that could explain it. We
 6 looked to see if there was a particular site
 7 driving the effect. The two foreign studies had
 8 the same clinical sites.
 9 Then we started doing an analysis of were
 10 we remembering things correctly, so we started
 11 looking at other programs that had similar studies,
 12 similar drug products. Yeah, we didn't see anyone
 13 else who had a similar placebo response, one that
 14 low, nor anything close to similar effect size. We
 15 even had prior studies of this drug.
 16 So we always do routine site inspections.
 17 We have a couple of algorithms we use to check
 18 sites. Some of them are pretty basic. Site
 19 enrolls a whole lot of people, we're going to check
 20 it out and make sure they were doing things
 21 properly. There are some other factors that can go
 22 in based on the site if somebody's been -- if we've

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1 been concerned that an investigative site has been
 2 doing things a little funny in the past, we may go
 3 double check that.
 4 This was simply based on high enrollment
 5 numbers. And the first site, one of the first
 6 things the inspector found was that all of the
 7 source data had been transcribed from the primary
 8 investigator for legibility, and then destroyed.
 9 Well, that's a problem with that. That's no-no.
 10 Never do that.
 11 This site enrolled 21 subjects in both
 12 studies. The study involved people who had an
 13 injury. Well, 14 of these 21 subjects who were in
 14 both studies, at least a month apart, were injured
 15 on the same day twice and were enrolled on the same
 16 day twice. You can see this is a pretty good
 17 enrollment from this site, 55 in the first study,
 18 35 in the second.
 19 Then the investigator started seeing common
 20 surnames and addresses. There were pairs and
 21 triplets who were injured with the same injury, on
 22 the same day, in the same home, and were enrolled

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1 in the study on the same day. Some of them that
 2 happened in both studies.
 3 We just excluded that site from the
 4 analysis. I mean, after that first bullet, it
 5 really didn't even matter what was going on
 6 afterwards. But we already had a lot of questions
 7 about this program, so we went and looked for other
 8 patterns that were similar, and they were there:
 9 same-day enrollment with related subjects, or
 10 subjects sharing an address, multiple subjects
 11 enrolled with the same issue in both studies.
 12 We asked the applicant, "Didn't this make
 13 you wonder?" And they said they spoke with the
 14 investigators, and they felt that multiple members
 15 of the same family or household could sustain the
 16 same injury on the same day, and because people in
 17 this country were more active than people in the
 18 U.S.
 19 (Laughter.)
 20 DR. HERTZ: You guys are laughing, but we
 21 were having -- this was serious at the time. We
 22 were about to disrupt a major program that had come

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1 in for a marketing application. It just so happens
2 that if this had been U.S. sites, we would have
3 actually tried to verify the existence of these
4 people. We can't do that in this particular
5 country. There are privacy laws that precluded
6 verifying the existence of individual subjects. So
7 we had to just end the study, end the inspection at
8 this point.

9 So we never proved fraud. And it was
10 suspected that there may be a problem, and that's
11 why there's a question mark; there's no proof. But
12 all of these factors and the comparison to the U.S.
13 site was enough so that this didn't go through.
14 And honestly, I got to believe that somebody in the
15 company knew this was coming. They pushed back as
16 hard as they could; I don't blame them. I was a
17 lot of money spent on this, but we couldn't use
18 that data.

19 This is another product. This is an
20 unusual situation because there was one study site
21 for two studies. That's probably not a good
22 approach. Well, on inspection we found that there

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1 was a failure to record key safety variables
2 because the investigator felt that the protocol
3 asked for too much, so he just didn't do it, even
4 though there was a research assistant present
5 specifically to monitor dosing. So it's not like
6 this with a particular burdensome request. And
7 they didn't have the equipment that was mandated by
8 the protocol to establish a baseline parameters.

9 Well, once you see this for a safety data,
10 you are also going to start to question the
11 efficacy data. We requested some additional data
12 and found more and more problems as it unfolded,
13 and we just basically -- we couldn't characterize
14 the safety of this product, and it's still not on
15 market.

16 This is a long, very frustrating story for
17 everyone involved, and this product had routine
18 inspections on the first review cycle, found a
19 number of problems. There were problems with
20 protocol deviation. There was a problem with
21 failing to report those violations in the study
22 report. We found them on inspection. That's a

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1 no-no. And then there was also what appeared to be
2 some accidental unblinding at the sites.

3 So this was not approved for a cycle. So
4 after a lot of discussion, another study was
5 conducted. Again, we routinely inspected two of
6 the sites. This time we also inspected the
7 applicant because there have been some issues with
8 that prior study report.

9 Lo and behold, statisticians had extracted
10 data to create some SAS data sets. Unfortunately
11 they did that before the study database was locked,
12 and it turned out there was an important variable
13 that was unblinded; it was the treatment
14 assignment.

15 (Laughter.)

16 DR. HERTZ: Well, the company caught wind
17 of this, and I think what they probably did what
18 was appropriate. I think they immediately blinded
19 the variable. They got rid of the data sets, not
20 the data, the SAS data sets that had been created,
21 and they interviewed the people involved. And it
22 looked as if, in fact, most of the people who

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1 potentially had access didn't really even get to
2 it, get to look at the data, nor did they have
3 interaction with the sites or the critical outcome
4 data.

5 Unfortunately, when this happened, it was
6 about a year before the NDA came in, and we were
7 never notified, and we found out about it on
8 inspection. And there were no audit trails for how
9 the data was managed after the fact. It was
10 all -- they deleted it, and I get that. You're
11 scared; holy smokes, you're just ruining us. We've
12 been going through this; we had to do a whole
13 another study. I mean, I get all that. But you
14 already have a problem with data integrity from a
15 first cycle of review, you come up with a problem.

16 As soon as you say, nobody has access to
17 this, the next thing should be, contact FDA. Work
18 with us. What we will do is help you confirm that
19 this lapse doesn't have an impact. But without an
20 audit trail on how this was managed, we couldn't
21 confirm anything. Attestations were taken from the
22 people involved, but none of them were still with

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1 the company at the time of the NDA inspections, so
2 we couldn't talk to them. It's not on the market
3 yet.
4 I could sort of summarize this as saying
5 make sure that data integrity is intact, everything
6 involved in that. But obviously, in the running of
7 the clinical studies large multicenter,
8 multinational studies, things are going to happen.
9 But I think the key for us is to plan how to, to
10 the best way possible, try and put practices into
11 place to limit problems. There is no excuse for
12 sloppiness; that's a planning thing.
13 If you plan on training proper
14 approaches -- and clearly, there's no excuse for
15 intentional integrity lapses, although as
16 applicants and sponsors, I know it's not always
17 possible to know in advance if investigators may
18 run rogue. But when things happen, the next thing
19 that I can say is give us an opportunity to help
20 you create the support you need to limit the
21 damage.
22 So we're going to find out about it sooner

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1 or later. Maybe there are examples that we never
2 uncovered But then an employee gets pissed off and
3 goes to the LA Times or -- these things come out
4 all the time. So I think the other thing I would
5 say beyond attempting to plan to minimize is once
6 something happens, which over time may be
7 inevitable, let's establish a way to try and
8 salvage what you've got.
9 That's what I have, so.
10 (Applause.)
11 DR. HERTZ: Are we doing questions or
12 should I sit down?
13 DR. TURK: Why don't we just take a couple
14 of questions and leave most of the questions
15 for -- we've left 45 minutes to an hour to have a
16 panel discussion.
17 So just a couple of questions for Dr. Hertz
18 at this point.
19 Yes, John?
20 DR. FARRAR: Sharon, great examples, and it
21 never ceases to amaze me that the thing we try and
22 teach our kids -- which is being in trouble is

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1 bad, but lying about it is worse, it also has
2 eliminated a few presidents along the way -- just
3 never gets learned.
4 The side effect, though, of some of
5 this -- and I would be interested in your comment
6 because we're interested in trying to facilitate
7 this process. But the side effect is that when you
8 participate in the trial, you get 40,000 queries
9 about a period on a page that shouldn't be there
10 and other things.
11 There is another side to this, which is
12 there can be an over-control, or an attempt to
13 over-control. And I'm wondering if you have
14 thoughts about how to implement enough control, but
15 not so much as to be onerous. No trial is ever
16 perfect obviously, and I take to heart what you
17 say, which is, if you have problems you need to
18 report them. But I wonder what your thoughts are
19 on trying to sort of balance that issue.
20 DR. HERTZ: Well, you guys are at an
21 advantage because when I was in practice, I really
22 only had a couple of very small clinical trial

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1 experiences as an investigator. So I didn't
2 experience that sort of thing, and I don't know the
3 extent of it.
4 John, is the intensity of that coming from
5 the sponsor, is it coming from FDA inspections?
6 DR. FARRAR: No, it's from sponsors.
7 DR. HERTZ: Well, I think that there is a
8 worry then, so I think that perhaps in an attempt
9 to maintain data integrity, it might be a little
10 bit misfocused. Maybe the effort needs to be more
11 on some of the other issues, planning, training,
12 and a little bit less on that sort of thing.
13 We have a number of -- we have one guidance
14 on monitoring as a way of maintaining integrity,
15 and then there's the ICH document. Those were
16 included in the background. I believe there's a
17 draft guidance being considered also on this topic.
18 But I guess I would -- well, one of part of
19 that may also be the greater use of electronic
20 forms may limit some of that technical stuff, and
21 we're seeing more and more of that. But I would
22 just say that that clearly seems like resources

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1 misdirected. But I'd rather have them brow-beat
2 you over knowing the instruments, understanding
3 criteria. I like some of the things that we're
4 seeing in terms of blinding about criteria so that
5 people can even unintentionally sway. Yeah. I
6 don't know what else.
7 DR. TURK: Rob?
8 ROB: So Sharon, I think your invitation
9 for help is an honorable one, but I was wondering,
10 do you have any examples where -- I'd be interested
11 in our industry colleagues' comments on this. When
12 things go wrong in a trial or within a company, the
13 first impulse is to call the FDA.
14 (Laughter.)
15 ROB: I mean, do you --
16 DR. HERTZ: You'd be surprised.
17 ROB: Do you have any examples where a
18 company has come to you with an issue relative to
19 fraud?
20 DR. HERTZ: Yeah. We have been notified.
21 We've been told when there's been -- when their
22 monitors have found improper behavior at a site,

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1 intentional or unintentional, and what their plan
2 was in terms of eliminating the site, we discussed
3 whether the data can be used for efficacy,
4 frequently not. But we've come to an agreement on
5 whether it's even suitable for safety because it
6 kind of needs to be reported in some manner; what
7 their plans are to make up the numbers.
8 So we have. I mean, if you catch it while
9 something is going and you have to eliminate a
10 site, that's something that's potentially fixable.
11 This case with the data breach, they probably could
12 have survived that if we had an opportunity to say,
13 okay, you've cut access, now here is -- we're going
14 to have OSI come in and take a look, and work with
15 you on creating the kind of audit trails so we can
16 confirm that these 11 people who potentially had
17 access are now completely off the project and how
18 you're going to -- I think that could have worked.
19 But I got to tell you, having had a first
20 cycle full of data integrity issues and having a
21 second cycle where we find out through inspection
22 that there was a major potential breach, had us all

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1 reeling. We couldn't believe it.
2 DR. UPMALIS: This is David. There is
3 another aspect of this I think everybody should be
4 aware of as well, is if a site is bad and has done
5 something bad to you, the chances are that that
6 site is involved in other clinical trials as well.
7 And you're not doing your colleagues in the
8 industry any favors by keeping bad sites out there
9 continuing to do clinical trials when they should
10 be closed.
11 DR. HERTZ: Yeah, and us knowing about it
12 up front, we can do an inspection, we can seek
13 debarment from studies if necessary, have them put
14 on the debarment list. I mean, that does happen.
15 DR. TURK: All right. So let's hold the
16 rest of the questions, of which I'm sure of there
17 are many for the panel discussion.
18 Our next speaker before the panel discussion
19 is Dr. Nathaniel Katz. He's on the faculty at
20 Tufts University School of Medicine. He is CEO of
21 Analgesic Solutions. And he's been a second
22 steadfast stalwart supporter of IMMPACT in action,

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1 going back to the very beginning. And he will be
2 talking about clinical trial quality, what is it
3 and what approaches can optimize it.
4 Presentation -- Nathaniel Katz
5 DR. KATZ: Thanks, Bob and Dennis. Thanks
6 so much for inviting me back again. IMMPACT has
7 been one of my more rewarding professional
8 experiences since the very beginning and I guess it
9 was 2001. Was that the first meeting?
10 Thank you, Sharon, for waking everybody up
11 with those chilling examples of quality problems.
12 And now that everyone is awake, what I'm going to
13 try to do is take it to the next step and present
14 what I hope to be a broader context of what
15 clinical trial quality actually is and how we can
16 go about systematically trying to achieve it.
17 So first, I'm going to offer you a
18 proposition based on my own experiences and
19 observations, which is that quality, which should
20 be about the ability of the clinical trial to
21 accomplish its intended scientific purpose, the way
22 it has evolved historically over the last number of

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1 decades is that there's become what seems to me to
 2 be a dichotomy between what I would call regulatory
 3 quality, which is, are you following all the rules
 4 that you're supposed to be following, GCP, ICH,
 5 what have you.
 6 That's what I would call regulatory quality
 7 and there's a whole set of checkboxes that
 8 inspectors use to ensure that all those rules are
 9 being followed.
 10 Then there's a different thing, which is
 11 what I would call scientific quality, which is more
 12 about, does the clinical trial, as it was designed,
 13 conducted, analyzed, and reported, have the ability
 14 to actually answer its scientific question?
 15 Now, the peculiarity about this dichotomy is
 16 that one would think, or at least I would think,
 17 that the purpose of the rules, of the regulatory
 18 quality, would in fact be to achieve scientific
 19 qualities. So I think, in theory, these should
 20 really be the same, but I'll attempt to illustrate
 21 for you that I think there's been a divergence,
 22 they've kind of gone down different paths. And I

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1 think one of our goals ought to be to try to
 2 reconcile these two.
 3 So what I'm going to do today is try to
 4 present what I think is a concept of scientific
 5 quality, and I'll attempt to inform that concept by
 6 bringing in insights from a number of different
 7 areas, one of them being fundamental principles of
 8 experimentation.
 9 We'll try to clarify some definitions. I'll
 10 present some results of what I see to be a growing
 11 science of clinical trial design and conduct, which
 12 many of us here at IMMPACT and ACTION have been
 13 involved with.
 14 I'll also give you a little bit of a teaser
 15 on all the work that's been done over the last
 16 century or so in manufacturing quality and control,
 17 because I think that we in the world of clinical
 18 trial quality control have a lot to learn from
 19 insights from manufacturing.
 20 So let's dive right in to the real world
 21 now. And this is an extract from a recent quality
 22 audit that was performed by very experienced

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1 quality auditors, quality audits for 30 or more
 2 years.
 3 We're in a position now that we run studies
 4 and we also act as a site for studies that we are
 5 audited a lot. We also do a lot of audits of other
 6 organizations, and so I've got access to a lot of
 7 these audits. We audit vendors. There are a
 8 million audits being done.
 9 So this was an audit of a clinical trial.
 10 And I won't say anything more about who was audited
 11 and who did the auditing. And these are only the
 12 findings from this audit that were considered to be
 13 critical. In other words, they were considered to
 14 have a major potential impact on the integrity of
 15 the clinical trial.
 16 What I want to do is pick out a few of these
 17 examples, and I want us all to ask ourselves the
 18 question of, is it important, and what is the
 19 relationship between these findings and the ability
 20 of the clinical trial to accomplish its scientific
 21 objective?
 22 So here is critical finding number 1. There

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1 was an inadequate security system in the facility.
 2 There wasn't a sign-in log in this particular
 3 clinical research facility. So was that important?
 4 It's important. You have to have some kind of
 5 security system. People could walk in and out with
 6 drugs, with papers. So having a security system is
 7 important. I don't think there's any doubt that
 8 that's an important rule.
 9 Is it closely connected to the ability of
 10 the clinical trial to achieve its scientific aim?
 11 I don't think so. Maybe is it indirectly related
 12 if they're bad on security? Maybe they're bad on
 13 other things. Sure. All that is possible. But is
 14 it closely related to the ability of that clinical
 15 trial to achieve its scientific goal? It's not.
 16 Critical finding number 2, the SOPs in this
 17 particular organization were two days out of date.
 18 The SOP-on-SOPs had a two-year expiration, and that
 19 two-year expiration happened to come two days
 20 before the quality inspector showed up. And so
 21 what this site should have done is monitored that.
 22 There should have been a flurry of signatures so

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1 that these SOPs were actually "in effect" at the
 2 time and they weren't.
 3 So is that a problem? That's a problem.
 4 Your SOPs need to be up to date. SOPs are an
 5 important thing. Is it closely connected to the
 6 ability of that clinical trial to achieve its
 7 scientific aim? I don't think so. I don't think
 8 you think so.
 9 We can go on and on. There were handwritten
 10 notes found on some SOPs. That violates some rules
 11 somewhere. There was one version of the informed
 12 consent form missing from the trial master file
 13 that was someplace else. They had to go find it.
 14 So these things are all important, and they
 15 are reflections of quality. But I would call all
 16 these things regulatory quality, and I would
 17 suggest to you that it's the same for all these
 18 findings. They don't really have a close
 19 relationship with the ability of the study to
 20 accomplish its scientific aims.
 21 I assure you that there's an army of people
 22 like this out there. There's a whole industry of

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1 quality control inspectors, and this is what
 2 they're doing right now at many different clinical
 3 research sites and CROs all around the world. And
 4 this is the sort of stuff that they produce, and
 5 this is important. This is good. This is not a
 6 criticism.
 7 The only point I'm making is that this is
 8 inadequate and has really very little relationship
 9 to the goal of trying to determine whether a
 10 clinical trial can accomplish its scientific aim,
 11 which is what I call scientific quality.
 12 So you can't help but be reminded when you
 13 think about this of that old parable of the drunk
 14 looking for his keys under the street lamp
 15 where -- and I tried looking for the oldest
 16 appearance of this parable. And the first one that
 17 I could find that was popular was from the Mutt and
 18 Jeff comic strip in June 1942.
 19 Here, you see the drunk saying, "I'm looking
 20 for my quarter that I dropped." And the policeman
 21 says, "Did you drop it here?" The drunk says, "No.
 22 I dropped it two blocks down the street." "Then

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1 why are you looking over here?" "Because the
 2 light's better over here." So we've all heard this
 3 story.
 4 Actually, I don't have the last panel, which
 5 is the policeman and the drunk are now both looking
 6 together under the street lamp for the lost
 7 quarter.
 8 (Laughter.)
 9 DR. KATZ: And maybe you could say that this
 10 is the quality inspector collaborating with the
 11 clinical research site to look in the wrong place
 12 for signs of clinical trial quality.
 13 So I think, like with all things, once they
 14 become rules, when we approach quality these days,
 15 we're measuring what's easier to measure, but not
 16 necessarily what's relevant or what we're trying to
 17 get at.
 18 So you've probably noticed by now that I've
 19 used the word "quality" a number of times, and I
 20 have kind of very subtly tried to introduce some
 21 definitions of what the word quality is. But I
 22 think it's time now in the presentation to attempt

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1 to presentation a definition of quality.
 2 I would say that a meeting about quality,
 3 which is what this is, that doesn't attempt to
 4 define quality is kind of a waste of everybody's
 5 time. So let's at least try to introduce a
 6 definition of quality, even though we may not all
 7 agree to it.
 8 The definition of quality that I found most
 9 appealing comes from this presentation from Leslie
 10 Ball, who used to be the head of the Office of
 11 Scientific Investigation, the existence of which
 12 was already mentioned by Sharon a few minutes ago.
 13 And she gave a presentation to the Clinical Trial
 14 Transformation Initiative in October 2010. And you
 15 can find this presentation on the internet, and I
 16 strongly recommend it. It's a very lucid
 17 presentation on this topic.
 18 The definition of quality that she proposed
 19 is the ability of a clinical trial now to
 20 effectively and efficiently answer the intended
 21 question about the benefits and the risks of the
 22 medical product, et cetera, et cetera.

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1 Now, I'll just point out as an aside that
 2 she does incorporate the concept of efficiency into
 3 her definition of quality. And I actually think
 4 that's very important as well. But for the purpose
 5 of the rest of my presentation, I'm not going to
 6 talk about efficiency at all as a marker of
 7 quality. But the ability of the study to answer
 8 its intended question, that's quality.
 9 So then you might ask yourself, "Well, what
 10 is the intended question of a clinical trial that
 11 is the substance of the concept of quality?" And
 12 of course, you can ask a million different
 13 questions in a clinical trial. And there are all
 14 different kinds of questions that are asked. But
 15 for all intents and purposes, I'll take actually
 16 the same approach that Karen just took, which is to
 17 just focus on the measurement of efficacy.
 18 The intended question of a clinical trial
 19 is, what is the magnitude of effect of the
 20 treatment compared to control or compared to
 21 placebo? This is the output of the study that
 22 we're trying to produce in a quality way.

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1 So this is a measurement task. A clinical
 2 trial is a machine that creates a measure -- that's
 3 the output -- of a clinical trial. And there's a
 4 whole world of metrology out there, and there are
 5 multiple societies that have gotten together to try
 6 to better understand in a standardized way the
 7 whole concept of measurement.
 8 They use a term called a measurement system.
 9 And what I would say using that parlance is that a
 10 clinical trial can be considered a measurement
 11 system. And the purpose of that measurement system
 12 is to measure the magnitude of efficacy of a
 13 treatment.
 14 So bringing forward these concepts, what I'm
 15 going to offer you now is a slightly revised
 16 definition of quality, which is, quality means
 17 minimizing sources of error that compromise the
 18 accuracy of measurement of treatment effect.
 19 That's my working definition of quality,
 20 because that's the product, that's the output of a
 21 clinical trial. Anything that interferes with
 22 accuracy of measurement of treatment effect in this

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1 whole conglomeration that we call a clinical trial
 2 with all these different moving parts, those
 3 sources of error, are the enemy of quality.
 4 Now, to move away from concepts for a
 5 second, what I'm going to do is give you an actual
 6 example of an attempt to design quality into a
 7 clinical trial paradigm. And I'm going to give you
 8 the example of bunionectomy because it's familiar,
 9 I think, to everybody in this room. And the
 10 perspective that I'll give you on the evolution of
 11 the bunionectomy model comes from Paul Desjardins.
 12 I don't know if you can see that. Many of you know
 13 him. He was one of the developers of the
 14 bunionectomy model, along with a number of others.
 15 So what Paul will tell you is -- and this is
 16 not actually written anywhere that I'm aware
 17 of -- that the first five or six clinical trials of
 18 bunionectomy failed to discriminate drug from
 19 placebo. Ibuprofen looked exactly the same as
 20 placebo in those trials.
 21 So when Paul and his colleagues, at Scirex
 22 at the time, tried to figure out why that was

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1 happening -- everybody knows ibuprofen works for
 2 pain, what's going on here, this is some sort of
 3 measurement issue, or to use today's word, some
 4 kind of measurement quality issue -- they find that
 5 the patients were getting different kinds of
 6 surgeries. And when they were being assessed for
 7 their pain, some had a tight dressing, some had
 8 Shewhart charts, more, and some had a loose
 9 dressing, which charts less. Some had their feet
 10 elevated, some had their feet hanging. Some were
 11 going to physical therapy, some were just coming
 12 from physical therapy.
 13 So there were all sorts of factors that
 14 impact the output of this study, and namely the
 15 pain intensity measures that were not being
 16 controlled for. And those were those sources of
 17 experimental error: type of surgery, timing of
 18 assessments, et cetera, et cetera.
 19 Once they standardized all these things,
 20 which in the industry you would think about as
 21 standardizing a process, once these things were
 22 standardized, boom, all of a sudden ibuprofen was

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1 better than placebo, p less than .05.
 2 So did the drug all of a sudden start
 3 working? The drug didn't all of a sudden start
 4 working. The drug was doing the same thing. The
 5 drug was having the same impact on these people's
 6 pain that it was having all along. The problem was
 7 that they were covariates. There were factors that
 8 impact on the output of the clinical trial that
 9 were not being controlled. That's the problem.
 10 Now, I also want to mention, in case it's
 11 not obvious to you, what kind of problem and
 12 quality this is and what kind of problem and
 13 quality this is not. This is not a statistical
 14 issue. There's no amount of statistics that you
 15 can do that's going to fix this problem. This is a
 16 problem of experiment, a fundamental problem of
 17 experimentation, of experimental design.
 18 This is also not a problem of your outcome
 19 measure. You could get the SEALD group. You can
 20 get Laurie Burke, and you can have a whole team of
 21 people together. You can figure out what's the
 22 best outcome measure in the world. That is not

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1 going to change this problem one iota.
 2 This is a problem of failure to control
 3 experimental error, which is something entirely
 4 different, and which we've kind of forgotten about
 5 a lot in the work that we do. So if you're going
 6 to design an experiment that fulfills the
 7 definition of quality that I just articulated
 8 earlier, that it's capable of answering the
 9 scientific question, the first step towards quality
 10 is experimental design. And you can design an
 11 experiment, but if it's not conducted the way that
 12 you designed, well, you haven't really accomplished
 13 anything much, either.
 14 So this gets back to the first -- so to
 15 restate what Paul and his colleagues did, they went
 16 back to Claude Bernard's Principles of Experimental
 17 Medicine from the 1850s, which is the first major
 18 work on experimental medicine, and they recognized
 19 that an experiment consists of two things. There's
 20 an input and there's an output. The input would be
 21 in this case the treatment intervention, the
 22 ibuprofen or the placebo, and the output is the

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1 pain score.
 2 So an experiment consists of an input and an
 3 output. And to design a good experiment, you hold
 4 everything else constant. That's the fundamental
 5 principle of the bioassay. And until we do that,
 6 you can have all the statisticians, you can have
 7 all the measurement experts, you don't have
 8 quality.
 9 So to expand from there, what are the other
 10 sources of measurement error in clinical
 11 experiments? The lack of attention undermines
 12 quality, or to put it a different way, what topics
 13 do we need to cover if we're going to produce
 14 quality in clinical experiments?
 15 This is by no means a complete list. We've
 16 already heard about fraud and data fabrication. I
 17 just told you something about the initial design of
 18 your experiment, which in my view is by far the
 19 most important aspect of this. Of course, bad pain
 20 measures can be a problem. Inaccurate reporting of
 21 pain by subjects is a problem, all different kinds
 22 of study conduct problems, as we've heard,

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1 covariates that confound this relationship, data
 2 storage problems, data analysis problems. You
 3 forgot a semicolon in your SAS code.
 4 These are just a short list of all the
 5 different elements of quality that need to be
 6 attended to.
 7 So if you're going to try to minimize
 8 sources of error, you need to have a way of
 9 systematically determining what those sources of
 10 error are. You could guess what sources of error
 11 might be in clinical trials, and I've just guessed
 12 at a few, and other people have guessed at a few.
 13 Some of those will be right. Some of those may not
 14 be right.
 15 So we need a systematic approach to
 16 assessing the validity or the importance of
 17 different sources of measurement error in order to
 18 focus our attention on what's important and what's
 19 not important, and also to know when it's been
 20 fixed. How do you do that?
 21 There's a variety of different ways that one
 22 can try to determine whether a candidate's source

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1 of measurement error is actually a source of
2 measurement error in your clinical trial. There's
3 a couple of different ways to do this. One way is
4 what I would call the candidate variable approach.
5 And you'll all recognize this because your names
6 are on some of these publications.
7 This is what people in IMMPACT and ACTTION
8 have been doing for the last 15 years, which is to
9 try to take an educated guess as to what might be a
10 factor that could influence the ability of the
11 study to measure its intended outcome, what I'm
12 calling quality for today, but what for 15 years
13 we've been calling assay sensitivity.
14 So you can suggest a candidate variable.
15 Then you can do some kind of a study. You can do
16 it retrospectively. You can do it prospectively.
17 You can be John Farrar, and you can say, "Well, I
18 wonder whether baseline pain variability might
19 somehow reflect error in our measurement system?"
20 And you can go to a study and figure out whether in
21 fact high versus low baseline pain variability
22 actually does impact your ability of your study to

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1 achieve its intended goal.
2 You can do the same thing with subject
3 enrollment rate, as Neal Singla sitting in the back
4 of the room did with colleagues from Pfizer in a
5 published clinical study.
6 You can look at placebo response rates, as
7 Bob Dworkin and others have done, to see if that as
8 a characteristic of your measurement system
9 interferes with its ability to accomplish this
10 intended result.
11 You can look at the ability of subjects to
12 report pain accurately, as Mark Jensen has done and
13 as we have done in a number of different studies.
14 If you do that, you can just one at a time
15 go down the list -- it's almost like the candidate
16 gene approach in studies. You can go down the list
17 and see which factors are relevant and which
18 factors are not. All these factors are, as it
19 turns out.
20 I just pulled in a little graphic just for
21 fun to show you one analysis that we did where we
22 were wondering about whether patients who use

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1 scales accurately are able to discriminate
2 treatments from placebos better than patients who
3 are not able to use scales accurately.
4 The problem, of course, is that if you have
5 data from a clinical trial, how do you know whether
6 one of those 800 patients in the clinical trial is
7 using the scales accurately or not. So we decided
8 to play with the idea that, if you ask the patient
9 their pain in two different ways, you ought to get
10 a similar answer.
11 So in this clinical trial, which is an
12 intervention for osteoarthritis, they were asked
13 their pain using the WOMAC pain subscale, very
14 standard, and also using a patient global
15 assessment and measuring pain intensity. And here
16 were the people who had high pain scores on both.
17 Here were the patients who had low pain scores on
18 both. Those patients seemed okay.
19 Outside these red lines are patients who
20 either had high pain score on the WOMAC, but that
21 same patient at the same time told you their pain
22 was low on the PGA or vice versa. And so it turns

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1 out that if you throw out these patients whose pain
2 scores were discordant, which was almost half of
3 the subjects in this 800-patient clinical trial,
4 you increase your observed effect size of therapy
5 by about 50 percent.
6 This has been shown in multiple of the ways
7 and multiple other analyses. I'm just throwing it
8 out there as an illustration that quality requires
9 that the human subject, who is the measurement
10 instrument in the clinical trial, be calibrated.
11 Otherwise, you're, like, measuring the pH with an
12 uncalibrated pH meter. And you can't possibly hope
13 to achieve your intended goal of your study, at
14 least in any kind of efficient way. You have to
15 overcome it by enormous sample sizes, which is
16 wasteful and, I would say, also probably unethical.
17 Now, with all this talk about quality, you
18 think that we were the first people sitting in this
19 room to think about quality. And in fact, in the
20 world of clinical research, if anything, we are
21 very latecomers to the challenge of trying to
22 define and identify quality and figure out

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1 mathematical approaches to measuring it and
 2 controlling it.
 3 This actually began in the 1920s in the
 4 United States in engineering. And the pioneer of
 5 quality in the world of manufacturing and industry
 6 was this guy here, Walter Shewhart. And anyone who
 7 works in virtually any industry, automotive, paper,
 8 radio, whatever, the name Shewhart is a household
 9 name.
 10 So he worked for Bell Telephone in the
 11 1920s, and he had to figure out how to control the
 12 quality of transmission of signals in underground
 13 cables, which led up to a huge explosion of
 14 interest in this in World War II for obvious
 15 reasons.
 16 This is his classic work on this topic,
 17 statistical methods from the viewpoint of quality
 18 control. And he founded this field of statistical
 19 process control, which the use of statistical
 20 methods to control the functioning of processes in
 21 any kind of a system.
 22 He wasn't an awesome communicator. And his

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1 main disciple was this guy here, Edwards Deming,
 2 who actually was the editor of this book, which is
 3 actually a series of lectures that Shewhart gave.
 4 And Deming really became the proponent, the
 5 worldwide proponent, of these statistical
 6 approaches to quality control. He went to Japan
 7 and spent many years there after World War II. And
 8 he's credited with this whole Japanese approach to
 9 quality, which everybody is very familiar with.
 10 The other interesting twist to this story is
 11 that these were both engineering statisticians.
 12 Deming studied statistics in the U.K., University
 13 College London, with R.A. Fisher and Jerzy Neyman,
 14 two of the founders of the modern field of
 15 biostatistics.
 16 But the peculiarity is that their learning
 17 was one way, because he learned from those founders
 18 of biostatistics and then used that knowledge to
 19 create this field of statistical process control.
 20 But there's virtually zero awareness in the field
 21 of biostatistics about the use of statistical
 22 process control methods in engineering.

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1 So -- and there are biostatisticians in the
 2 room -- very hard to find a biostatistician that
 3 knows anything about statistical process control or
 4 uses it. It's even more ironic, because if you
 5 went to a pharmaceutical company and you went to
 6 the manufacturing plant, they're probably very
 7 familiar with these methods and using them every
 8 day. But if you go to the other building, where
 9 they are analyzing the clinical trial data, nobody
 10 has heard of these methods.
 11 I'm not an expert on these methods, either,
 12 although I've used them in a number of projects for
 13 about a 10-year period of time. And I just want to
 14 introduce you to two fundamental concepts of
 15 statistical process control.
 16 One is the notion of a process. You're
 17 controlling a process. What is a process? A
 18 process in this SPC parlance is a unique
 19 combination of tools, materials, methods, and
 20 people engaged in producing a measurable output, a
 21 measureable output, for example a manufacturing
 22 line for machine parts.

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1 Does that sound familiar? Does that sound
 2 like a clinical trial? It's a clinical trial. And
 3 the output from the clinical trial is the
 4 measurement of the treatment effect.
 5 The main tool that's used in manufacturing
 6 quality control is a control chart. And there's a
 7 million different flavors of control charts for all
 8 different kinds of purposes. You can measure their
 9 performance and decide which one you want to use
 10 for a certain application.
 11 A control chart is a graphical display
 12 illustrating variation typically over time in the
 13 output of a process, cell phone defects, sizes,
 14 orientation of a transistor on a circuit board.
 15 Typically, a control chart will show
 16 boundaries of statistical control limits, where if
 17 something goes beyond a boundary, you can say that
 18 that process is out of control, and therefore
 19 likely to lead to a defective product. This is
 20 every day in the world of engineering.
 21 Here are standard control charts that I
 22 actually pulled off of the Wikipedia biography of

<p style="text-align: right;">Page 89</p> <p>1 Shewhart himself. And this just shows some 2 engineering process; it doesn't really matter. 3 This is an upper control limit. And so this is the 4 natural variation in that process. And when that 5 variation exceeds this upper control limit, then 6 the process can be thought of as being out of 7 control. And then someone has to go investigate 8 what's going on and get the process back in 9 control.</p> <p>10 This is a Shewhart chart, is what it's 11 called. But this is actually from a clinical 12 study, where this is one site in a clinical trial 13 that's being monitored using this Shewhart chart. 14 The top red line here is eDiary compliance of all 15 the patients in that particular research site.</p> <p>16 This gray-ish variable here is mean pain 17 intensity scores of all the patients at that site 18 over time. And here on the bottom is variability 19 of pain intensity, week over week, at that clinical 20 research site. And this is out of 20 or 30 weeks 21 of that clinical trial at that site.</p> <p>22 So if you were an engineer, you would look</p>	<p style="text-align: right;">Page 91</p> <p>1 In clinical trials, we have more of an 2 approach of keeping your eyes closed, and hoping 3 for the best, and then looking, and doing 4 post-mortems after the study was done to figure out 5 what went wrong. And this is basically what I do 6 for a living.</p> <p>7 So this is a couple of principles of 8 manufacturing quality control that I think we could 9 learn from. And we have. And this is almost my 10 last slide, so what I decided to do was hire a 11 software engineer from the automotive industry and 12 have him build a system for doing this in clinical 13 trials, which has now been done.</p> <p>14 This is just a few sketches of what the 15 system does. This is a Web-based data 16 visualization interface. And you start out with a 17 map of the world of all your clinical research 18 sites. And if any of those key performance 19 indicators exceed their upper or lower control 20 limits, the dot for that site will turn red. If it 21 gets into a control zone, the dot will turn yellow. 22 And if things are fine, that dot will stay green.</p>
<p style="text-align: right;">Page 90</p> <p>1 at this and you'd say, "Look, at this particular 2 time point," which happens to be about week 7, "the 3 process went out of control." eDiary compliance 4 now exceeded its lower control limit. Mean pain 5 intensity scores followed a week or two after and 6 exceeded their lower control limit.</p> <p>7 Variability of pain scores spiked at that 8 particular research site and got into the zone 9 where, according to John Farrar's paper, you would 10 begin to worry about measurement error of your 11 clinical trial. Then for whatever reason, things 12 went back into control about five weeks later.</p> <p>13 Now, if this were an assembly line in a 14 manufacturing plant, what would have happened is 15 that there would be alarms, there'd be red lights 16 flashing. There'd be alarms that would go off. 17 The assembly line would be shut down. You'd have a 18 whole team of engineers descending on the 19 manufacturing line to figure out what went wrong 20 with our process, because if we allowed this to 21 continue, we're going to be producing a defective 22 whatever-we're-producing.</p>	<p style="text-align: right;">Page 92</p> <p>1 You can click on that, and then go through 2 to review each individual research site. And you 3 can see what's going on with all the different 4 variables at that site and see, well, geez, that 5 site turned red. What variable was it that made 6 that site turn red? Was it eDiary compliance? Was 7 it protocol violations? Was it adverse event 8 reporting? Was it variability of pain intensity? 9 Was it any of the key performance indicators that 10 we can monitor?</p> <p>11 What went wrong? When did it go wrong? You 12 can also see the key performance indicators here on 13 a study-wide level, the red ones being variables 14 that are out of control and also at a site level. 15 You can also click on a variable and rank all the 16 sites in terms of which sites are most out of 17 control with certain variables.</p> <p>18 You can also click on the site and look at 19 individual subjects. So if eDiary compliance is 20 the problem, which subject is it that is the one 21 that threw that site over the edge? And thereby, 22 you can achieve what Sharon was talking about</p>

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1 earlier, which is not just letting the river flow
 2 by and hoping things work out for the best, but
 3 identifying problems early and doing early course
 4 corrections within the limits of what's kosher in
 5 the clinical trial environment to try to keep
 6 things on track and not let the study go over the
 7 cliff, and only find out about it afterwards.
 8 So I'm only presenting this as an
 9 illustration of how there's a lot known about
 10 quality control and there's a whole mathematical
 11 foundation for quality control that exists in the
 12 world of manufacturing. And all you have to do is
 13 realize that a clinical trial is a manufacturing
 14 process of some type or can be looked at in that
 15 way. And the same mathematical principles that are
 16 used in manufacturing can be applied to clinical
 17 trials, and I think this is where we are going now.
 18 So in summary, what I've tried to leave you
 19 with is a framework of thinking about quality in
 20 clinical trials as the following. It's the
 21 identification and minimization of sources of error
 22 that compromised the accuracy of the output of the

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1 trial, which is the measurement of the treatment
 2 effect.
 3 Quality control rests on a few premises. It
 4 rests on evidence that certain variables, which
 5 hopefully are amenable to surveillance, if you're
 6 going to do something about them, are relevant to
 7 the study output, because some things are relevant
 8 and some things are not.
 9 We do know about some of the variables that
 10 are relevant to the study output already. And I
 11 showed you a list of them earlier, and many of us
 12 are continuing to work on figuring out what those
 13 are.
 14 From a statistical quality control
 15 perspective, we can conceive of a clinical trial as
 16 a process with many components, including a
 17 measurable output, which is a measurement of the
 18 magnitude of treatment efficacy.
 19 I think future work is needed to further
 20 define what are the relevant variables to study
 21 quality and what's the best method for surveillance
 22 and correction. And I think the rest of the

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1 presentations at this talk will be to focus on
 2 specific variables that we all know have a major
 3 impact on study quality: medication adherence, for
 4 example, measurement of pain.
 5 I hope that we can now view those talks that
 6 are coming up in this meeting as specific examples
 7 of variables that affect quality control, but that
 8 need to exist in a more general context and
 9 approach to quality. And that's what I have to
 10 say. I hope you enjoyed it.
 11 (Applause.)
 12 Q&A and Panel Discussion
 13 DR. DWORKIN: Dr. Hertz and Dr. Rowbotham,
 14 join us for the panel discussion.
 15 So thank you both very, very much for
 16 getting the meeting off to what I felt was a great
 17 start. I want to ask the first question as
 18 chairman's prerogative.
 19 It seems to me that, speaking just for
 20 myself, in thinking about this meeting, I wasn't
 21 making a distinction that I think now is relevant
 22 and helpful. And I just want to see if I'm on the

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1 right track. And that is, I think we're talking
 2 about three very different things in this meeting.
 3 One is identifying threats to quality
 4 sources of error -- you talked a lot about this,
 5 Nat, and also Sharon -- so this kind of
 6 identification of threats. Another is how to
 7 prevent them. Can we set up systems in advance, in
 8 designing a clinical trial that will mitigate,
 9 lessen, and prevent all of these sources of error?
 10 Then I guess the third thing, that in my
 11 head had been all glommed together and never
 12 clearly distinguished was, okay, once bad stuff
 13 occurs, of whatever type that we've already
 14 discussed, what do we do about it when you discover
 15 that 1 out of 50 sites had some fraudulent data?
 16 Do you just throw out the data from that site and
 17 then just go on, analyzing the rest?
 18 So it's that trichotomy of identification,
 19 prevention, and dealing with these things after you
 20 haven't prevented them. Is that correct? Is that
 21 a reasonable way of thinking about the topic of
 22 this meeting?

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1 DR. HERTZ: Yeah.
 2 (Laughter.)
 3 DR. DWORKIN: Dennis always accuses me of
 4 being long-winded, and I think this was the example
 5 of that.
 6 DR. KATZ: A slightly longer answer. Yes,
 7 although I would add that there's sort of an
 8 evidentiary piece as well because you have to know
 9 what it is that you're looking for before you
 10 identify it.
 11 DR. HERTZ: Yeah, but I also had sort of a
 12 different sense of categories developing. I have a
 13 very concrete example of what I've done in terms of
 14 threats to integrity means that there's a problem
 15 with the conduct, whatever, measurement, management
 16 of the study. But Nat's approach to
 17 quality -- there's almost a differentiation between
 18 the concept of a threat to the integrity of the
 19 data and how to ensure quality of the data.
 20 There's a little bit of an overlap, but
 21 clearly some divergence in terms of -- and I notice
 22 that, actually, in the background reading, when I

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1 actually got a chance to sort of look at the whole
 2 list of what was put together.
 3 I think the contrast between, for instance,
 4 John's paper on baseline variability versus the
 5 guidance on central monitoring, so it's how do you
 6 improve the quality from the perspective of assay
 7 sensitivity, improving assay sensitivity, which is
 8 something that we've dealt with a number of times
 9 and continues to be a challenge, and then also the
 10 concept of these other threats external to the
 11 nature of the data itself.
 12 DR. DWORKIN: Michael?
 13 DR. ROWBOTHAM: So I think there's a way of
 14 unifying both of the talks, and it really comes
 15 from manufacturing systems, like the Toyota Quality
 16 Improvement System that came also along after World
 17 War II.
 18 Under the old system, products would be
 19 manufactured, go down in an assembly line, and then
 20 there would be a final quality inspection. And if
 21 the product was defective, it'd be thrown out. And
 22 if it was okay, it would be sent on for

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1 distribution and sales.
 2 The problem when you have low-quality
 3 systems is you have a very high defect rate. And
 4 so you spend a lot of time and materials
 5 manufacturing widgets. And at the end, you end up
 6 throwing away half or more of them.
 7 So what Sharon was telling us about was
 8 really the hazard of waiting until the end, after
 9 the study has been conducted, to go back, and look,
 10 and see whether or not the widgets met quality
 11 standards. And what you find is that, as you start
 12 eliminating subjects, eliminating subject sites,
 13 study sites because of defects, at the end, you
 14 really just have a basic clinical trial power
 15 problem.
 16 You started out with a thousand subjects
 17 and, after you eliminate all the bad sites, the
 18 subjects that were duplicates or their data wasn't
 19 collected properly, and you throw all those out,
 20 you end up with a hundred subjects left. So now
 21 your study is severely underpowered to answer any
 22 kind of clinical question, and you have to throw it

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1 out.
 2 So that's the hazard of waiting until the
 3 very end to do your inspection.
 4 The revolution that came in with what Nat
 5 was talking about was the idea of monitoring
 6 quality in every single step so that every worker
 7 on an assembly line has the power to pull the cord,
 8 stop the assembly line until things are fixed, and
 9 then, and only then, does the assembly line start
 10 up again.
 11 So no one ever passes a defective widget on
 12 to the next step in the manufacturing process. And
 13 so you don't really need to do that much at the
 14 very end because you really already found the early
 15 mistakes and corrected those before you get to the
 16 end of the line.
 17 So to do that in clinical trials, I think
 18 it's obvious with what Nat was showing us, is that
 19 they really have central data monitoring, and
 20 continuous data monitoring, so that they can find
 21 these kinds of anomalies.
 22 So I think, as we go through these

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1 discussions the next two days, think about the
 2 hazards of waiting until after the fact versus
 3 assessing all the important elements along the way.
 4 It provides a kind of overall framework for
 5 thinking about these questions.
 6 DR. HERTZ: Because I want to go back to the
 7 question or the comment that it's not the initial
 8 thought, do we have a problem once we contact FDA.
 9 But really, what's the outcome of that? One is,
 10 there's a fix and there's an adequate audit. And
 11 when it gets to a regulatory authority of any
 12 country, it'll be noted, and that'll be fine, or it
 13 won't be okay.
 14 So that's the one problem. But the other
 15 issue is, as you saw in my example, sometimes
 16 there'll be an attempt to fix it or ignore it, and
 17 then it's the wait-and-let-the-agency-find-it
 18 approach, which I got to tell you, colors the whole
 19 application and often leads to a lot of suspicion
 20 and a lot of extra inspection.
 21 So I guess if we can get the systems in
 22 place to identify, to set the system up properly

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1 for the most efficient delivery of goods to
 2 identify early and in real-time problems, either
 3 plan for or develop fixes in real time.
 4 Then the one thing that I would add is to
 5 have that extra link to the regulatory authority
 6 that you're planning to interact with because at
 7 some point in time, that's another factor. But
 8 yeah. I think that it does actually fit together
 9 all quite nicely.
 10 DR. DWORKIN: I can't see that far back,
 11 though. It looks like it might be Lee Simon.
 12 DR. SIMON: Yes. So I'd like to take issue
 13 with Nat and his initial comments regarding the
 14 regulatory quality issue and the scientific quality
 15 issue and suggest, as does the cartoon with Mutt
 16 and Jeff, that in fact you have to think about this
 17 in the context of the -- and everybody in this room
 18 has heard this -- the totality of the evidence.
 19 The reality is that if you have a sloppy
 20 site that has two-days-late SOPs, that might be a
 21 harbinger, the canary in the mine, of something
 22 much more complicated that actually then is a

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1 marker, an insignia of a bad site.
 2 Now, it truly may not have a direct impact
 3 on the quality of the clinical trial itself that
 4 took place at that particular site. On the other
 5 hand, if you'd begin to accrue more and more of
 6 these subtle problems, you begin to think about
 7 this in the context of, that site is a problem, or
 8 that trial is a problem, or something else is going
 9 on. I'm sorry I had you come all the way back to
 10 that.
 11 So I think it's really important to
 12 recognize. And having been on both sides of this
 13 table, I can tell you it's really difficult to
 14 separate out what these issues are, particularly
 15 the ones that are the check-box issues. They're
 16 there because it ensures that somebody is thinking
 17 about those issues, while somebody else is thinking
 18 about the actual metric issues. And putting it all
 19 together, the totality of the evidence might make
 20 you be incredibly uncomfortable about what is going
 21 on with that particular data set.
 22 So I think it's a little unfair to suggest

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1 that they were looking in the quarter two blocks
 2 away from what really may be important. In fact,
 3 all of it's important because it reflects the
 4 quality of the site or the quality of the system.
 5 On the other hand, I think you've pointed
 6 out exactly what we need to do, which is actually
 7 real-time metrics, now that we can, of actually
 8 following this and really improving it.
 9 I can't tell you the number of trials that I
 10 saw while in Washington and vice versa, what I now
 11 see as a clinical consultant. And it's pretty
 12 staggering how we actually get anything done and
 13 get approved, given the inadequacies of the
 14 monitoring systems.
 15 DR. KATZ: Maybe I'll make one comment about
 16 that. I actually agree with that. I recognize,
 17 when I made that slide, that there's a danger that
 18 people are going to interpret it as being
 19 dismissive of the regulatory approaches. And the
 20 opposite. As I mentioned, I think those things are
 21 very important, and they can be harbingers of real
 22 issues at those sites.

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1 My point is more that are they direct or
 2 indirect? Are they close to what we're looking at
 3 or further away? And if you want to know whether
 4 pain is being measured accurately in a study, how
 5 does your SOPs being two days out of data, which
 6 certainly could be a harbinger of a problem,
 7 compare to the patient who doesn't know how to use
 8 the pain scale?
 9 Which one is close and which one is far
 10 away? And my only suggestion is that we refocus on
 11 what's close to what it is that we're trying to
 12 produce and not be satisfied with things that are
 13 important, but are further away.
 14 DR. DWORKIN: Let's go from the front back.
 15 John?
 16 JOHN: This has been a wonderful set of
 17 talks, and I think the conversation so far is very
 18 enlightening. And what it reminds me of is that in
 19 thinking about the study of studies, when we teach
 20 about it, we talk about different kinds of error.
 21 We talk about random error, which is, shit
 22 happens. There is confounding, which in an

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1 observational study are things that we hopefully
 2 can monitor, and understand, and do something
 3 about. And then there's bias, where the
 4 understanding is basically that there is a problem,
 5 that is not fixable with the analysis that we're
 6 going to do.
 7 Now, what's been proposed here today, I
 8 think actually contributes substantially to that.
 9 And to, in a sense, complicate things before we try
 10 and make it simpler, we need to think about the
 11 kinds of error that we're looking at, number one.
 12 So I would argue that as we go through the
 13 next couple of days, we may not be able to identify
 14 all of those, but we at least put some of the
 15 things we talk about into buckets to sort of say,
 16 is this something we can monitor and fix as we go
 17 along? Is this something that ought to be designed
 18 out from the beginning because there's nothing we
 19 can do about it if it actually happens? And then
 20 the last one being, what should we deal with in
 21 terms of the statistical analysis, the sort of
 22 random error that happens?

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1 The second issue that's implied by Nat's
 2 talk is that engineers also come up with a
 3 principle called limits. All right? There's a
 4 limit to which we can analyze and look at any
 5 problem. And when you're designing an airplane
 6 engine, you need to have microscopic limits with
 7 regards to how things change because those parts
 8 are going very fast, and if they move a little bit,
 9 it'll blow up.
 10 If you're dealing with things that are much
 11 less complicated, your limits can be much larger.
 12 And one of the concepts that we ought to consider
 13 as we go through this next couple of days, too, is
 14 what are the limits here. And I would remind you
 15 that one of the primary limits we use, 0.05, was
 16 simply chosen out of the air one day.
 17 So we ought to try and be a little bit more
 18 specific about some of these limits. And I'd be
 19 very interested to hear Nat's comment on how you
 20 decided when something turned red, because that's
 21 not obvious.
 22 DR. KATZ: How do we decide when something

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1 turns red? It's not obvious. There are different
 2 types of signals that you can monitor for, and
 3 there are different approaches to determining what
 4 an appropriate threshold is for flagging them.
 5 So we divide them into three categories.
 6 One is what I would call sentinel signals, or if
 7 one things happens, you want to know about it and
 8 it's not a statistical issue at all, so that might
 9 be an SAE or a major protocol violation.
 10 Then there are things that we would call
 11 threshold limits where you decide arbitrarily that
 12 you think something going beyond a certain rate is
 13 likely to be problematic, so something like that
 14 might be in compliance with diary entries. If
 15 you're getting less than 80 percent of your diary
 16 entries filled out in a week, you decide that you
 17 want to know about that, whether or not it's a
 18 statistically significant deviation from your
 19 historical values, as is the paradigm for the
 20 control charts.
 21 Then the third approach is a statistical
 22 approach where if a change in a variable, compared

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1 to its historical value, is very unlikely to be due
 2 to chance -- let's say it's three standard errors
 3 beyond the mean or whatever -- then it will flag an
 4 alarm.
 5 Now, you don't always know how to interpret
 6 that. And it's very difficult to know what are
 7 false-positive and false-negative signaling rates
 8 are going to be when you used statistical
 9 thresholds like that. But that's kind of all you
 10 got in terms of a way of flagging things where you
 11 don't really have a rationale for drawing a
 12 particular line in the sand just based on what you
 13 know.
 14 DR. DWORKIN: Ian?
 15 DR. GILRON: Thanks, Sharon and Nat, for two
 16 super talks. I got a little concerned now when you
 17 sort of described the study patient as a
 18 measurement tool, which I understand that they are,
 19 but they also have another important role. They
 20 are representatives of all the patients who are
 21 going to receive this treatment if the evidence
 22 supports it.

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1 I'm sorry. I had a little flashback from
 2 our Bethesda meeting about assay sensitivity. And
 3 I just wondered whether we should make a
 4 distinction that when we talk about data quality
 5 and pain, we're dealing likely, almost exclusively
 6 with the primary outcome measure that's going to be
 7 based on self-report.
 8 So if we were doing a treatment trial for
 9 sepsis, and mortality was the outcome, we might be
 10 tempted to sort of exclude patients who aren't
 11 going to die no matter what you do or are going to
 12 die very easily, no matter what you do, and exclude
 13 them from the sepsis treatment trial.
 14 So getting back to the story of people who
 15 rate their pain as 10 or high variability, I
 16 suppose we have to be careful how we define a
 17 low-quality patient. So I mean, if they just can't
 18 understand the paradigm of pain intensity
 19 measurement, that's low quality. But if they're
 20 high variability, how do you designate them as low
 21 quality or they just have high variability?
 22 DR. DWORKIN: So Nat has an editorial in, I

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1 think, this month's issue of Pain, that's relevant
 2 to your questioning. And so go ahead. Nat, you're
 3 prepared, I think, to address this.
 4 DR. KATZ: Well, to make a long story short,
 5 the person is the measurement instrument. We can't
 6 get away from that. And it's just, we need to be
 7 honest about that, the concept of human beings as
 8 measurement instruments. The concept of having to
 9 rely on an individual's ability to look within
 10 themselves and estimate the intensity of these
 11 subjective experiences that they're having in
 12 research is an old idea, you know, back to the
 13 1950s with Stevens, how bright is that light? How
 14 loud is that noise?
 15 There are many different types of research
 16 where the human being is relied upon as being the
 17 measurement instrument. And like with every other
 18 human skill, different people have different
 19 capabilities at doing that well.
 20 So I think I'll spare you all a long lecture
 21 on how one does that, but simply to agree with your
 22 comment that in classifying someone as not being a

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1 good instrument or being a good instrument, we have
 2 to be confident that that's not also biasing the
 3 results of the experiment in some way that would
 4 compromise our ability to generalize its results,
 5 that that is an important check box that you have
 6 to do before you deem someone to be good at
 7 reporting pain or bad at reporting pain. But how
 8 we do that, I think we'll leave that for the coffee
 9 break.
 10 DR. DWORKIN: Neil?
 11 DR. SINGLA: So thanks, Nat, for your talk.
 12 That was great, and both talks were excellent. I'm
 13 trying to reconcile and maybe put into context one
 14 issue regarding a human being versus a machine,
 15 which is that you described in your talk the point
 16 where it's above a quality control and the
 17 engineers go down under the floor and flip a switch
 18 or do something.
 19 But the issue obviously in clinical trials
 20 is that it's not a machine that you can go down and
 21 flip the switch. You're getting data from real
 22 people. And as an investigator, oftentimes on the

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1 other end of that red dot, being the red
2 dot -- meaning that you have a patient who started
3 at an 8 and goes down to a 3 in an acute pain
4 trial, and tells you they have no relief.
5 You're there. You're standing in front of
6 the patient, and they're giving you data that would
7 show up on a graph like that. You know it's
8 discordant data. The question is what do you do?
9 How do you educate sites?
10 I go around and educate sites about this.
11 And they ask me, "Well, what am I supposed to do?
12 I mean, the patient gives me this data. What am I
13 supposed to do?"
14 I think there's been a lot of discussion of
15 what should you do. Should you give the patient
16 another chance to answer? Should you do nothing at
17 all because that skews the quality of the data?
18 Should you reeducate the subject on what the scale
19 means? And we need to think about what is the
20 right thing to do.
21 DR. HERTZ: Well, isn't that part of
22 training patients ahead of time, having them

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1 understand things ahead of time? You don't want to
2 be influencing a subject's response after the
3 treatment has been delivered. You want them to
4 report what they're going to report. But they need
5 to have the appropriate skillset to use the
6 instruments so that if there is something
7 discordant, it potentially means there's something
8 going on.
9 So maybe it's because their pain is low, but
10 they're so constipated that they can't bear to
11 move, so overall their relief is not great. I
12 mean, there may be reasons for it. I mean, it's
13 why we ask more than one question, because we're
14 not always looking for concordant answers. We're
15 also looking at the big picture.
16 So I think the answer is that, if the time
17 is spent preparing subjects, training them so that
18 they do understand what's being asked of them, then
19 the results are the results.
20 So in that case, a red signal going off
21 means you might want to look at it and think about
22 it, but no. I don't think we should be intervening

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1 at that point. It's too late.
2 DR. DWORKIN: So I think this is a key
3 question, Sharon. So let me imagine one of Neil's
4 concerns. Let's say it turns out that patient AB
5 hasn't been consistently filling out their pain
6 diaries. Can the site -- patients now in the
7 double-blind phase, and are not consistent about
8 completing their pain diaries.. Can the site call
9 up that patient on the phone and say, "Hey, you
10 haven't been filling out these pain diaries."
11 DR. HERTZ: Well, that's different than
12 questioning the nature of the response to the
13 diary.
14 DR. DWORKIN: Okay. So there are some
15 interventions that would be okay.
16 DR. HERTZ: Right, right, but that's very
17 different to say you're not following the protocol.
18 You're violating the protocol by not doing this.
19 DR. DWORKIN: So I'm going to pursue a
20 little bit. What if the patient this past week --
21 DR. HERTZ: You're going to get to the point
22 where I can't answer, you know?

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1 DR. DWORKIN: -- on a couple of days
2 reported that their worst pain was less than their
3 average pain? Is it permissible for someone from
4 the site to call up the patient and say to the
5 patient, "Hey, remember when we did the training
6 before you started participation in this trial? We
7 told you that worst means the worst pain you can
8 imagine. An average is kind of your usual, but on
9 Tuesday, Wednesday, and Thursday, you said that
10 worst was less than average." Would that be
11 permissible?
12 DR. HERTZ: I don't know because there,
13 you're almost asking them to change the response.
14 I think what could be permissible is to say, "I'm
15 just going to refresh you on what these scales
16 mean," and not make reference to data. I mean,
17 it's a fine point, but if you say -- as part of
18 your protocol, that if we start getting results as
19 part of our QC-ing in real time that aren't
20 necessarily consistent with an understanding or
21 remembrance of instructions. separate from results,
22 maybe they should be reported for everybody. So I

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1 mean, that's the sort of thing.
2 DR. DWORKIN: It wouldn't change anything,
3 but we might do a little bit of a kind of brush-up.
4 DR. HERTZ: Yes. But I think it's extremely
5 important to plan that. I mean, if you think
6 you're going to have a population and the study is
7 long enough where you may need to refresh them, I
8 think just refreshing people who are giving
9 responses that are potentially problematic is not
10 giving everybody the same experience.
11 So if you think that's a risk, perhaps the
12 approach that would be kosher is to say every two
13 weeks, we're going to reinforce everybody and not
14 just the people who are giving us results we don't
15 think are helpful.
16 MALE SPEAKER: Say, Bob, can I just do a
17 follow-up on this particular?
18 DR. DWORKIN: Yes. Jim Witter has been
19 waiting. I'll come right back to you. Jim Witter
20 has been waiting very patiently to say something
21 about this.
22 DR. WITTER: I have a question. As we all

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1 know, there are many sources, causes of pain. We
2 all also age, all of us. So as we age, we tend to
3 get more comorbidities. So the question I have is
4 the issue of attribution. When we ask patients to
5 attribute the cause of their pain to a specific
6 disease, if they have more than one disease, what
7 are your thoughts on that?
8 DR. DWORKIN: The panel, not me.
9 MALE SPEAKER: They usually get excluded if
10 they have another problem of equal or greater
11 magnitude than the one that you're trying to study.
12 So it has to be very clear that the subject can
13 differentiate the pain problem that you're
14 interested in from any other contributor to pain.
15 DR. DWORKIN: So that would be part of the
16 training.
17 MALE SPEAKER: Well, it's part of the
18 inclusion/exclusion criteria, as well as one of the
19 things you go through in subject orientation and
20 training.
21 DR. DWORKIN: Jim?
22 DR. WITTER: So this is kind of staying down

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1 in the weeds here on this specific issue that you
2 raised, Bob. So with electronic data collection, a
3 particular solution might be, in this case of worst
4 pain/average pain, to the IVRS, may not allow an
5 answer that is an illogical answer.
6 DR. HERTZ: That's not acceptable. Let me
7 just interrupt. You cannot have your data
8 collection impact the selection within a scale
9 range. If your IVRS is set up so that worst pain
10 cannot be less than average pain, you are changing
11 the reporting of an individual, or disallowing it,
12 or creating missing data because the numbers don't
13 work. That should never be the case.
14 It wouldn't be the case on paper. It should
15 never be the case just because it's electronic.
16 That's hugely problematic.
17 DR. DWORKIN: Nat, Mike, would you like to
18 add something?
19 DR. ROWBOTHAM: Well, I can add something
20 that Nat actually showed a nice graph of. And that
21 is, if you ask essentially the same question two
22 different ways, using different scales, but it's

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1 essentially the same question, then you always have
2 this issue of scattered, where a patient rates
3 himself at low pain on one scale and high pain on
4 the other scale, even though both scales asked you
5 the same question.
6 So then you decide, do you eliminate answers
7 outside of a certain boundary or do you use it as a
8 composite measure?
9 I think it's an issue in design, having
10 scales where, when the patient answers, you can get
11 internally inconsistent answers, like average pain
12 being higher than worst pain. That's probably an
13 example of maybe not having the right set of
14 measures in your case report forms.
15 DR. HERTZ: I mean, I recently filled out a
16 completely unrelated non-health survey. It was
17 about a shopping experience.
18 (Laughter.)
19 DR. HERTZ: And they gave me a list of
20 questions with a yes or no. But something they
21 asked me was not part of my experience, so it
22 wasn't yes or no. It was not applicable. So do I

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1 say I was satisfied with it do I say it wasn't
2 satisfied with it when I had no experience with it?
3 That made me irritated, and I cancelled the
4 survey. Now they're not getting my opinion. So
5 they created missing data by poorly wording their
6 questions because I couldn't answer it. And if I'm
7 a patient and you won't let me put in the number
8 that I want to put in, that's frustrating, and now
9 what do I do? Do I make it up?
10 It's not going to be relevant because I say
11 my worst pain was a 3, but I'm only allowed to put
12 5 and up. So do I make it a 5 so I can get
13 something done, because it won't let me go to the
14 next page? What do I do? Or do I just forget
15 about today? Then they're going to call me and
16 tell me I didn't answer my -- I mean, it's creating
17 a whole series of problems. So, yeah.
18 DR. DWORKIN: Does anyone else want to ask a
19 question that can be definitively answered?
20 (Laughter.)
21 DR. DWORKIN: This makes chairing a meeting
22 really easy. We were going up this row. We will

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1 get to the next row soon. Penney?
2 MS. COWAN: I just have a question. And I
3 keep hearing the whole measure of pain, but there's
4 so much more involved in pain itself, the function,
5 quality of life, all of those things. And I mean,
6 I'm not sure what all you measure in clinical -- I
7 mean, we've talked about it. We just did a paper
8 on physical function.
9 Are there other things that can compare that
10 so that you can look at the pain score and make
11 more sense of it?
12 DR. KATZ: Could you repeat the question,
13 Bob?
14 DR. DWORKIN: Well, as I understood, Penney,
15 you were saying that we've focused for the last 15
16 minutes on pain, but in this kind of
17 identification, sources of error, threats to
18 quality, is there any value in thinking about the
19 other domains of the pain experience like physical
20 function and mood? Can that contribute to
21 increasing quality?
22 MS. COWAN: Right. And to clarify the whole

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1 question of the pain score, I mean, it would
2 correlate.
3 DR. HERTZ: Absolutely. I mean, we're
4 talking about how to sort of monitor
5 inconsistencies or problems, but in terms of
6 understanding the data, that's critical. And
7 you're going to now call me a hypocrite because I
8 don't allow what I'm about to say in labeling
9 because it doesn't fit with our policy.
10 But when we look at data, we're trying to
11 sort out what's the effect of this product in this
12 population. And we look at the averages, and
13 they're informative, but then we do spend a fair
14 amount of time looking at different groupings,
15 different individuals. We look at outliers. We do
16 a lot of this to see what is the full picture.
17 If we have something that appears
18 potentially inconsistent, we need to look. So is
19 pain intensity shrinking and physical dysfunction
20 worsening? Is pain improving but satisfaction
21 is -- we do. It gives it context. And I think
22 that was part of one of the earliest meetings on

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1 what are the relevant domains.
2 So I think that's all critically important
3 and may speak to part of what's going on with some
4 of this. This one particular example of basically
5 a patient getting it wrong, it's really not a
6 logical set of answers, is probably more one of
7 understanding or the interface with the
8 measurements. But, yeah. In terms of giving
9 context, I think all these other parameters are
10 very important.
11 MS. COWAN: I guess I wonder, is it a
12 standard -- I mean, should they be standard
13 measures in all clinical trials so that you can
14 have maybe better outcomes, better measures of the
15 pain if it becomes a standard. And I don't know if
16 that's required in all clinical trials. It just
17 makes sense to me that it might be.
18 DR. HERTZ: Well, rather than discuss
19 requirements, which I will not discuss, the
20 scientific concept underlying the six -- was it six
21 or five? I always miss one. Five, then I would
22 have missed two.

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1 The relevant clinical endpoints for study,
2 that we're having a debate here, five or six --
3 (Laughter.)
4 DR. HERTZ: -- those core endpoints that
5 were recommended as a group consensus for pain
6 studies are still relevant. And for the most part,
7 I'll say, just based on my experience, it's rare
8 that we only get a measure. We get lots of
9 secondary measures because they are useful for
10 exactly that purpose, Penney.
11 MS. COWAN: I just wasn't --
12 DR. DWORKIN: So let's see if I got this
13 right. Pain, physical function, emotional
14 function, some patient global measure of
15 improvement satisfaction, adverse events, and
16 disposition in the trial; if they dropped out, why?
17 I've been favoring, from my perspective, the
18 right side of the room. Let's see if there are
19 questions on the left side of the room. We'll come
20 back, Rob.
21 Anyone on the left side, all the way in the
22 back, Dave Hewitt, and then Roy?

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1 DR. HEWITT: Yes. I wanted to ask Nat a
2 little bit about -- because I am fascinated by the
3 application of some of these other methodologies
4 from other fields into our own. And I wonder if
5 you have put much thought to something that's very
6 popular in corporations these days, which is the
7 Six Sigma process, which seems to me you're kind of
8 skirting around a little bit. Mike was kind of
9 talking about it as well.
10 Can you talk a little bit more about whether
11 you've actually thought about applying Six Sigma
12 processes to clinical trials and what would that
13 mean? What would that look like?
14 DR. KATZ: Right. This is it. Six sigma is
15 just a fancy buzzword for statistical process
16 control methods in which things are flagged as
17 being aberrant when they're six standard deviations
18 beyond the mean. It might be six standard errors.
19 I might have gotten that statistic wrong. And so
20 that's become a buzzword, and there's a whole
21 industry built around that. But it's just a
22 particular way of thinking about the use of

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1 statistical process control to monitor processes.
2 Those processes could be your employment
3 practices, what time people show up for work, what
4 SOPs that you follow. It can be applied to
5 anything. That's all that Six Sigma is. And the
6 statistical process control principles developed by
7 Shewhart are the foundation for that.
8 DR. DWORKIN: Roy?
9 DR. FREEMAN: Yes. So I'm struggling a
10 little defining meaningful qualitative aberrations
11 and how you do that. And under that heading, let
12 me ask and pick on Bob Dworkin's example of logical
13 inconsistency.
14 So you find a logical inconsistency in real
15 time. Clearly, to reeducate that individual
16 subject about the logical inconsistency is going to
17 introduce some degree of bias in the study. So one
18 potential scenario that I thought of is that you
19 can prespecify that if there are X number of
20 logical inconsistencies in a specific measure or in
21 your scales, then you can reeducate the entire
22 sample as to what the specifics of the measures

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1 are.
2 But even there, it's going to be hard to
3 homogenize that because your clinical trial is
4 dynamic. You could have 20 percent of your
5 subjects in the trial at that point. But what
6 about the other 80 percent who won't have that
7 reeducation? And it's more actually, I think, a
8 question for Sharon than it is a question for Nat.
9 But Nat, as you were about to respond, why don't
10 you go ahead?
11 DR. KATZ: Now, the analogy that I would
12 give is you're doing a chemistry study and you've
13 got five different pH meters in your study, and
14 people are running samples through. And you find
15 one of your pH meters -- you put distilled water
16 in, which you're supposed to do once a week to make
17 sure it's calibrated, and now it's reading a pH of
18 9 for distilled water, which we know it should be
19 7.
20 So what do you do? What you would do is you
21 would recalibrate that instrument in order to
22 prevent bias because it's your instrument that's

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1 off calibration that's introducing bias, not the
 2 corrective action to bring it back into
 3 calibration.
 4 Now, back to human instruments, which is
 5 what we've been talking about, how do you know when
 6 it's off calibration and how do you know when you
 7 bring it back into calibration? How do you know
 8 when you're introducing bias? How do you know when
 9 you're correcting bias?
 10 I think that's the point that you're
 11 bringing up. And if you're recalibrating that
 12 instrument, well, just the fact that you haven't
 13 done anything with your other instruments, does
 14 that introduce bias or are you actually confident
 15 that you're optimizing the issue of bias because
 16 you can read?
 17 So these are the questions that you're
 18 talking about, and I think these are poseable
 19 questions, and these are answerable questions. And
 20 it would be shameful to address them on a policy
 21 level when they can be addressed at a scientific
 22 level.

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1 So I think, without getting into too much
 2 detail, you can actually measure the extent to
 3 which a patient is calibrated or not calibrated,
 4 and you can actually recalibrate them, and be
 5 confident that you've recalibrated them, and
 6 therefore prevented bias.
 7 Now, I understand that there's a risk of
 8 doing that selectively and introducing problems,
 9 which is something that I think requires more
 10 discussion, but I think that we should focus on
 11 correcting bias and not prevent ourselves from
 12 doing that because we're worried that it's just a
 13 bad idea from a policy perspective.
 14 MALE SPEAKER: Can I just speak to that for
 15 one second? Okay.
 16 Quickly. Yes. I think the thing is it
 17 doesn't have to be that way. I think, in clinical
 18 trials, not only the patient but the investigator
 19 and their team should be reeducating. That should
 20 be a process of clinical trials over and over
 21 again, particularly for the controlled placebo
 22 effect as well as other measures.

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1 So I don't think it necessarily creates
 2 bias. You can introduce it across the line at
 3 certain intervals. I think it's very important
 4 because people sometimes, again, think of these
 5 patients as patients when they're actually study
 6 subjects and partners in this program, and they
 7 need to understand what they're doing. And so do
 8 the investigators, who may not understand that they
 9 are impacting the placebo effect.
 10 MALE SPEAKER: I just have a question --
 11 DR. DWORKIN: I'm sorry. Sharon, why don't
 12 you --
 13 DR. HERTZ: I guess I would go back to a
 14 different question first, is how much of an issue
 15 is this? We're always going to get some scatter
 16 with regard to how people can retain instructions.
 17 It's normal.
 18 If it is identified as a systematic threat
 19 to obtaining quality data that reflect the actual
 20 experience, then a systematic approach to dealing
 21 with it, like Dave just said, would be the way to
 22 do it.

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1 So I guess is it a problem? Is it a
 2 consistent problem? Is it enough of a problem to
 3 affect the quality of the study? And if so, the
 4 concept of quality by design is something that the
 5 chemists are using now in manufacturing. It's that
 6 sort of thing.
 7 If you have an item here that you know is
 8 going to crop up in these studies, then design the
 9 study to address it at the beginning, so regular
 10 reeducation or updating of wherever the problem is
 11 to address. And then there's no bias because it's
 12 a protocol item. It's regardless of what's
 13 occurring. You're not reacting. You're planning
 14 and dealing with improving quality.
 15 DR. DWORKIN: John Markman, then Mark
 16 Jensen, and then Mike McDermott, and then coffee,
 17 and apologies to all of you who had questions.
 18 DR. MARKMAN: So I'd just like to come back
 19 to Nat's point about recalibration and tie it back
 20 to Ian's question, which as an investigator
 21 interacting with subjects every day, I find a real
 22 challenge.

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1 So we've seen a lot of research on baseline
2 pain diaries, including or excluding patients who
3 are perceived to be low quality, based on some of
4 those results of those baseline pain diaries.
5 So the question I have is, should we be
6 recalibrating at that level when we get a bad batch
7 of baseline pain diaries? Should they be
8 recalibrated then and then given a chance to
9 reenter the trial once they've been reeducated?
10 Again, that goes to Ian's point because the
11 real question here is, is pain a disorder -- which
12 affects the instrument and the way you experience
13 things? I mean, that's what allodynia is. That's
14 what these problems generally are.
15 So again, it's hard for me to quite
16 understand. I think this goes back to Ian's point.
17 How much recalibration are you allowed to do of the
18 rating instrument when that might be the underlying
19 disease?
20 DR. HERTZ: But that's the question, isn't
21 it? Sorry, Nat.
22 DR. KATZ: No. Go ahead.

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1 DR. HERTZ: Is it the underlying disease or
2 is it the ability to use the instrument? So four
3 patients who you really believe are having highly
4 variable pain, they certainly should be studied
5 because you want to know the therapy is going to
6 work there.
7 But do you want to mix that in with a group
8 that has less variable pain because, well, you have
9 assay sensitivity to pick up an effect in anyone
10 that way? So maybe the approach there is to take a
11 population with one set of pain characteristics,
12 and study it, and take a population with another if
13 you believe that's the characteristic of the pain.
14 So I guess this is not telling you the
15 important question of how you distinguish someone
16 who has trouble with an instrument versus
17 fluctuating actual experience, but if that can be
18 sorted, then yes. They're all important.
19 DR. KATZ: Can I explain? Sorry, Mark.
20 Maybe you were even about to say this. So
21 variability consists of two components. Right?
22 There's true variance, which is, my pain really is

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1 worse today than it was yesterday or worse now than
2 it was this morning. And there's error variance,
3 which is, my pain is really something, but then
4 there's a certain error component put on top of
5 that based on how good my primary endpoint measure
6 is or how good I am at using that instrument.
7 So there's true variance and error variance.
8 And the goal, I think we would all agree, is that
9 we want to minimize error variance. And the
10 question that everyone has been dancing around or
11 talking about directly is how do we distinguish the
12 two?
13 Briefly, I will just say that there are ways
14 of distinguishing the two. For example -- and I'll
15 repeat the same example we always give -- if you
16 give the patient two different questionnaires that
17 get at basically exactly the same problem, and they
18 are widely discordant, there is evidence that
19 that's an error measure. It's not like your pain
20 can't really be high on one questionnaire and low
21 on another questionnaire; it is what it is.
22 There are a number of other techniques that

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1 one can use to establish whether variance is error
2 or true variance. And there are ways of training
3 people to minimize and doing other things to
4 minimize that error component.
5 DR. JENSEN: So there's been some discussion
6 about training patients who have been identified to
7 have a problem such as variability. Two other
8 fixes. One would be, identify them at baseline,
9 and it would be to exclude them from the trial
10 a priori based on a protocol. And the other is to
11 do these assessments after the trial is over and
12 a priori say, if we identify patients who meet
13 these characteristics, they are going to be
14 excluded from the analyses.
15 So one is excluding patients and the other
16 is excluding them from analyses. I'd be just
17 curious, a quick vote from the panel, which of
18 these would you recommend, none or others, assuming
19 it's decided ahead of time?
20 DR. HERTZ: Well, what's the effect of that
21 latter approach on the value of randomization and
22 the intent-to-treat principle? So I see some

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1 potential problems with it from that perspective.
 2 DR. KATZ: To that point, Mark, I don't have
 3 an answer to your question in terms of which is
 4 best, but we are doing a multicenter study now
 5 where patients are being tested for their ability
 6 to report pain accurately using experimental pain,
 7 where it has nothing to do with their clinical pain
 8 disorder. How well can you distinguish hot from
 9 less hot in terms of its painfulness? And those
 10 patients are getting excluded pre-randomization
 11 from the clinical trial.
 12 So we're not excluding them based on the
 13 natural history of their own pain disorder. We're
 14 just excluding them based on whether they can
 15 actually perform that cognitive task well or not,
 16 again, pre-randomization so as not to violate that
 17 intention-to-treat principle. And whether that's
 18 better or not better than other ways, I don't know,
 19 but we're doing it.
 20 DR. DWORKIN: Last question, a comment from
 21 Mike McDermott?
 22 DR. MCDERMOTT: Yes. Nat, your definition

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1 of quality focused on minimizing sources of error
 2 that affect the accuracy of the treatment effect.
 3 I think you need to add the word "precision" in
 4 there. This is sort of a minor comment, but
 5 there's systematic and there's random error. And I
 6 think a lot of what these quality measures are
 7 going to accomplish is increasing the precision, may
 8 be correcting some bias. And that's a different
 9 issue.
 10 I was intrigued by the control chart
 11 discussion, and it's not just one process. You've
 12 got a process for every patient. But you've also
 13 got two different concepts of time here, and I
 14 didn't see the other concept of time come out so
 15 much as you got the concept of time where you've
 16 got patients being followed from the point of
 17 randomization.
 18 You've got this other concept of calendar
 19 time. And I think the speakers later will be
 20 talking about detecting problems at the center
 21 level, not necessarily as patients are going
 22 forward in time, but as the center is going forward

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1 in time. And I didn't know if you had implemented
 2 any of those things in what you had your
 3 collaborator devise.
 4 DR. KATZ: Yes, both. We have constructed
 5 control charts to look at site time. The sites
 6 started today, and they're moving forward, even
 7 though another site might have started six months
 8 ago. That was the nature of the control chart that
 9 I showed, which is site time. The date the first
 10 site begins, that's time zero, and it goes forward
 11 from there. And we also have control charts that
 12 look at calendar time.
 13 So if for example things are changing
 14 between this year and last year, and how the study
 15 is performing according to those metrics, then that
 16 can raise signals as well. And I think we've all
 17 seen that happen in clinical trials, where you do
 18 an interim analysis or multiple interim analyses,
 19 and things look different based on calendar year.
 20 So we're looking at it both ways.
 21 DR. DWORKIN: All right. We're going to
 22 take a coffee break, which is going to be outside,

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1 until 11:00 and resume then. I thank you all very
 2 much. I thank the speakers for a great start to
 3 the meeting.
 4 (Applause.)
 5 (Whereupon, a recess was taken.)
 6 DR. PATEL: [In progress] -- medication
 7 adherence, and patient or participant misbehavior,
 8 and we have another set of great speakers lined up.
 9 Mark Jensen is going to be speaking about
 10 pain reporting. Many of you know Mark. He is vice
 11 chair and professor of rehabilitation medicine at
 12 the University of Washington. As Dennis said, he
 13 is the editor of the Journal of Pain. He is a
 14 longtime contributor to ACTION and IMMPACT
 15 activities, and he has published on a range of pain
 16 topics, including substantive contributions to pain
 17 intervention, behavioral intervention work, as well
 18 as methodological research on pain assessment and
 19 clinical trial methodologies.
 20 So, Mark, why don't you go ahead?
 21 Presentation – Mark Jensen
 22 DR. JENSEN: Thanks, Kushang.

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1 So take a moment now and think back over the
 2 last 24 hours and consider what has been your
 3 average pain in the past 24 hours. Everyone come
 4 up with a number? Nobody came up with a number?
 5 So it happens pretty quickly, doesn't it?
 6 It's pretty fast.
 7 So the question is, was the number you came
 8 up with useful or valid? And I want to talk about
 9 that. I want to talk about the problem that can be
 10 associated with asking people to rate their pain,
 11 rate their average pain. What are the issues
 12 associated with that that can interfere with the
 13 validity of clinical trials? Talk about the two
 14 strategies that have already been discussed some to
 15 deal with that; patient training to improve their
 16 ability to validly rate their experience of pain,
 17 and monitoring how well patients are doing within
 18 the context of the clinical trial; talk about what
 19 we know about these strategies; and then talk about
 20 where we should go from here in terms of future
 21 research. And given what we know, what should we
 22 be doing now, which I think will be a topic of

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1 tomorrow afternoon's discussion.
 2 So the problem is that people are not
 3 consistent. None of us are consistent with how we
 4 use these scales. We don't always comply with the
 5 procedures that are part of the clinical trial.
 6 And the bottom line is at this point, as a field,
 7 we don't know the impact of these inconsistencies.
 8 How do we know that subjects are not
 9 consistent? Well, you've read the paper from
 10 Amanda Williams that 78 patients were asked to rate
 11 how bad their pain was on a VAS and a zero-to-10
 12 scale, and there were problems, as she pointed out,
 13 with how people did that. The patients who had
 14 multiple pains -- of which most patients, in my
 15 experience, have multiple pains, it's the
 16 majority -- some rated their primary pain only at
 17 times. At other times, some rated only the pain
 18 that was worst at the time of the rating, not
 19 necessarily the primary pain of a study, and some
 20 combined them. Patients are inconsistent with how
 21 they use these scales and out of the context of
 22 training.

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1 A question could be are patients rating
 2 their intensity or how much they are bothered by
 3 the pain. Again, some patients reported that they
 4 think of the two separately. Some say that they
 5 are not able to distinguish between the two, and
 6 that it's just one big hurt.
 7 The other thing that Amanda found was that
 8 there were 14 different factors that influenced the
 9 numbers that patients came up with, and these
 10 factors were inconsistent both between and within
 11 subjects. At some points, patients would rate pain
 12 differently as a function of different factors.
 13 So, for example, when asked, "Do you
 14 consider how much pain impacts your functioning
 15 when you came up with your ratings," some said they
 16 often or always do. A large group said they
 17 sometimes do, and a group said rarely or never.
 18 Tiredness sometimes always or often, but also
 19 significant groups just did this sometimes.
 20 Sometimes people took into account their overall
 21 mood when they were rating their pain.
 22 So the bottom line is that the numbers we

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1 get are influenced by a whole lot of factors other
 2 than just pain intensity, and that those factors
 3 differ across time for the same individuals.
 4 This study was basically replicated by Joan
 5 Broderick and colleagues, in which they asked
 6 patients to rate the severity of their pain in the
 7 last week, and then they interviewed the patients
 8 about the strategies used.
 9 Again, some people used the information from
 10 the entire week, but a large group didn't, even
 11 though they were asked to. Some generated an
 12 average, and a large group didn't. Sometimes
 13 patients considered their flare-ups, sometimes they
 14 didn't. Sometimes they considered times without
 15 pain, and sometimes they didn't. And sometimes the
 16 patients focused on just certain days rather than
 17 the entire week.
 18 Most of the patients considered the impact
 19 of the pain, and that is a whole different domain
 20 other than pain intensity. We know that it is
 21 statistically distinct, and it is influenced by
 22 different factors. So if patients are considering

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1 the impact of the pain, you're measuring a
 2 different thing, even when you're asking people to
 3 rate their pain intensity.
 4 So the issue, of course, is that we now know
 5 from these studies and others that pains
 6 [inaudible - mic fades] are inconsistent. What we
 7 don't know is the impact of this inconsistency.
 8 Another way to say that is that you know
 9 from your own experience that to have pain is to
 10 have certainty, but as scientists, we know to hear
 11 about pain is to have doubt. We can say that we
 12 have considerable doubt about what we're actually
 13 measuring.
 14 So how do we fix this? One strategy, as has
 15 been talked about, is to train patients before we
 16 even do the study how to use these measures. So,
 17 of course, the PROTECCT working group from the
 18 ACTION, which is a part of the department acronym,
 19 which is a subgroup of UNCLE [ph] -- so Bob and
 20 Dennis are the men from UNCLE. I'm dating myself,
 21 I think.
 22 (Laughter.)

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1 DR. JENSEN: -- is to train patients how to
 2 use these measures, a really good idea. How long
 3 has it taken us to come up with this idea?
 4 Decades. And in this particular strategy, you
 5 teach patients what is -- talk about what is their
 6 anchor for mild and worse pain. Teach them what
 7 average pain means, at least according to the
 8 training protocol; have them rate their primary
 9 pain condition only and not the multiple other pain
 10 problems that they might be experiencing.
 11 Teach them to rate this distinct from their
 12 mood, fatigue, and the impact of the pain.
 13 Remember, 98 percent of people without training
 14 take the impact into account. And then say,
 15 "Listen, this study is about you. We're working
 16 together. We are research partners in this, and so
 17 it's very important, as a co-investigator of this
 18 study, that you help us get accurate outcomes."
 19 Another strategy is developed by Nat, a
 20 brochure to teach patients how to rate their pain.
 21 And this one, again, elicit the cooperation as a
 22 research partner, introduce the zero-to-10 scale,

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1 have them identify from their personal experience
 2 what are the pain ratings associated with levels of
 3 3, 6 and 9.
 4 Tell them that zero pain and awake times
 5 only should be included for the average pain
 6 ratings, to take these into account, because we
 7 know that if you don't tell the patients what to
 8 take into account when calculating the average,
 9 some will take in the worst pain, average their
 10 worst pains. Others will just say an average of
 11 when I feel pain, and others will take it into
 12 account. So specifying that. And emphasizing the
 13 importance of accuracy, consistency, and that
 14 change can happen -- you don't have to always give
 15 a level of 8 -- and specificity. And then give
 16 them five examples to practice.
 17 So we have these two training programs in
 18 place ready to go. They are currently being used
 19 even in some studies.
 20 What are the unresolved issues? We still
 21 don't know if they improve things or not. What is
 22 surprising perhaps, given how much problems there

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1 are in understanding what patients mean when they
 2 give us a number, is that we are able to detect
 3 effects at all. The darn things work. The
 4 problem, of course, is that they may not work well
 5 enough. So we don't know if these training
 6 programs have any benefits, but research is
 7 underway. So we're starting to study that, which
 8 is a really good thing.
 9 The other issue is that this inconsistency
 10 might be a trait. It may be, as Nat has alluded
 11 to, that there are patients who just aren't good at
 12 this, and all the training in the world won't help.
 13 So perhaps the thing to do, if it's allowed,
 14 is to identify patients who are good at it as part
 15 of eligibility criteria as a way to make trials
 16 more efficient. We just don't know.
 17 It's also the case that we have these
 18 training programs available. They may not get at
 19 what's important. We don't know that. These two
 20 programs that are currently available, they don't
 21 have 100 percent overlap, and there may be things
 22 that neither can get at. And, of course, training

<p style="text-align: right;">Page 149</p> <p>1 has a cost. It costs patient time, it costs 2 investigator time to do this training, and, again, 3 if they don't have a benefit, then that might be 4 time wasted, or it might be simpler to simply 5 exclude patients from the get-go who are bad at 6 this. And there may be strategies other than 7 training to get at increased reliability, for 8 example, measuring a domain other than average pain 9 something easier to recall.</p> <p>10 So there's a lot that we don't know about 11 these issues in terms of training.</p> <p>12 In terms of monitoring, good idea. Nat 13 introduced some ideas for how to develop systems 14 for monitoring, and it seems like it's a useful way 15 to monitor how things are going to fix problems.</p> <p>16 What do we know about the efficacy of such 17 approaches? Well, I did a scoping review about a 18 month ago, and I did search terms. You search for 19 pain and assessment monitoring and set the limits 20 for clinical trials. The result of my scoping 21 review was no studies. I'm not aware of any 22 studies that have looked at this.</p>	<p style="text-align: right;">Page 151</p> <p>1 really like having a person call a person. That 2 has worked out very well for us, and I've grown to 3 trust it.</p> <p>4 But we haven't done the head-to-head 5 comparisons yet to see how these compare, which 6 produces the best results. We simply don't know.</p> <p>7 We want to make sure that the ratings that 8 patients give us are consistent with the protocol 9 and consistent with what you'd expect if they were 10 providing valid and reliable measures.</p> <p>11 So certainly, we could monitor the extent to 12 which the average is between least and worst. But 13 then the question is when we discover that's a 14 problem, what do we do with it. I think useful 15 discussions already have happened around this 16 issue, and it seemed like there was already moving 17 towards a consensus to say you ought not to just 18 intervene when you see a problem.</p> <p>19 So you don't want your interviewer -- when a 20 patient says "My average pain is lower than my 21 least," you don't want the interviewer to go, 22 "Really? Really? Are you sure about that?" So</p>
<p style="text-align: right;">Page 150</p> <p>1 So what do we now know about the benefits of 2 monitoring on clinical trials I think it can be 3 summarized in these ten or so words. Zilch, 4 butkis, zip, diddlysquat, nix, nada, not, nothing, 5 zero, not a bit, and nil. We don't know. It seems 6 like a good idea, but we just simply don't know.</p> <p>7 If we were to do it, what might it look 8 like? These are things to consider if we develop 9 monitoring programs. So certainly we want to 10 ensure that the ratings, when we're asking for 11 multiple ratings, are provided at the correct 12 times.</p> <p>13 How good are paper-and-pencil diaries for 14 this? What do you think? No good. I think the 15 field has pretty much said let's just simply not 16 use paper-and-pencil diaries, to just stop it, and 17 I think, in general, we have.</p> <p>18 But there are a large variety of other 19 options. You can page patients, use interactive 20 voice, IVR assessments, have a person call the 21 patient to interview, do it at clinical visits. In 22 the clinical trials that I'm responsible for, I</p>	<p style="text-align: right;">Page 152</p> <p>1 maybe some kind of ongoing training. But it would 2 be very useful to monitor this in all clinical 3 trials so that we know as a field how often do we 4 need to do the retraining, because we simply don't 5 know.</p> <p>6 We want to have at least some variability. 7 If every patient always has a pain level of 7 8 before and after treatment, that's a problem 9 probably. But as we've talked about there could be 10 a problem with too much variability in terms of 11 being able to detect a treatment response.</p> <p>12 Then once we detect too much variability, 13 what do we do about it? What are the other things 14 that ought to be monitored? And I think that one 15 of the useful things of this meeting might be to 16 come up with a list of things that ought to be 17 monitored in clinical trials, so that as we do more 18 research, we can see which of those are most 19 important.</p> <p>20 So this other question, I want to plant the 21 seed to start to think about what should be 22 monitored on an ongoing basis in a clinical trial</p>

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1 to ensure quality and to assess quality, because I
 2 think we simply don't know.
 3 Everyone here probably knows about the
 4 studies on the impact of variability on ability to
 5 detect treatment effects. First study, Harris,
 6 with 125 subjects with fibromyalgia, and they
 7 compared placebo with milnacipran. They assessed
 8 current pain intensity 4 times a day for 15 days at
 9 baseline, and they wanted to know how much
 10 variability there was in these pain levels and was
 11 that stable. Are there people who just seem to
 12 have variable pain versus those who seem to have
 13 less variability? Is it a trait or is it a state?
 14 And what was the association between this
 15 variability and ability to detect treatment
 16 response?
 17 They found that variability in assessment is
 18 quite strong. There are people who just report
 19 variable pain. Why is the question. How are they
 20 different than those who report more stable pain?
 21 What are the factors that contribute to more
 22 variability?

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1 Importantly, variability was moderately to
 2 strongly associated with response to placebo.
 3 Those individuals with more variable pain are more
 4 likely to respond to placebo.
 5 The association between variability and
 6 active treatment response is very, very weak. Why?
 7 Very, very interesting question. And given this,
 8 of course, you'd expect that if you include
 9 patients who report highly variable pain in your
 10 trial, you'll be less likely to be able to detect a
 11 treatment effect.
 12 John and colleagues looked at this in a very
 13 large study with -- they included over 2700
 14 patients in 12 clinical trials, postherpetic
 15 neuralgia and diabetic painful neuropathy. And
 16 these were trials that specifically compared
 17 placebo with active treatment, 7 days of pain
 18 intensity ratings at baseline, and the question
 19 was, again, does pain variability predict the
 20 ability to detect a treatment effect as a
 21 sensitivity.
 22 Indeed, as predicted, it was associated with

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1 ability to detect a treatment effect; that the more
 2 variability, a greater response to placebo of an
 3 active treatment, replicating Harris' findings.
 4 Interestingly, the effects were stronger for
 5 postherpetic neuralgia than diabetic painful
 6 neuropathy. So there might be some effect of pain
 7 type that influences this variability.
 8 My working hypothesis is that the
 9 variability may be related to pain problems that
 10 are influenced by multiple factors, not just
 11 nociception; things like hope, things like
 12 self-management, maybe perhaps centralized versus
 13 more peripheral pain. But we don't know the answer
 14 to that question. But it certainly seems to be
 15 associated with pain type.
 16 There were meaningful significant effects,
 17 but perhaps not clinically meaningful for age for
 18 postherpetic neuralgia and diabetic neuropathy in
 19 terms of ability to detect treatment effects. But
 20 this variability in response in pain at baseline
 21 was a critical factor.
 22 So given what we know, which is, I think,

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1 this, versus what we don't know, which I think is
 2 more like this, what do we do? We have very little
 3 to base our information on. I think clearly what
 4 we do is more research. I could wear a tee shirt
 5 that says more research is needed.
 6 Some of the questions I think we need to
 7 address are: what are the patterns of inconsistency
 8 in responding to these measures that are most
 9 closely associated with assay sensitivity? We need
 10 to understand at least what they are, if not why.
 11 And which of these are modifiable? Can we actually
 12 train people to respond to these measures in ways
 13 that increase validity, or is it just certain
 14 people ought to be excluded from trials when the
 15 goal is to detect a treatment effect?
 16 Of course, if you do exclude patients from
 17 trials based on something like variability, does
 18 that mean that you can't make conclusions about the
 19 efficacy of the treatment in that group? Does that
 20 limit your generalizability? So there are costs to
 21 doing that.
 22 My leaning right now is that I think it's

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1 fair to a priori exclude some patients from trials
 2 who just don't know how to use these measures or
 3 have problems with them.
 4 Which training programs are most effective
 5 or are more effective to changing modifiable
 6 factors? What is the effect of this training on
 7 variability? We can do this training, and maybe it
 8 has zero benefit. We simply don't know.
 9 It's hard to imagine how it could make
 10 things worse, but I suppose that's possible, too.
 11 And are some pain domains easier to rate than
 12 others? And perhaps we might have a better ability
 13 to detect treatment effects if we measure other
 14 domains other than average pain intensity. Maybe
 15 training isn't needed. So these are questions.
 16 Again, what I hope is that one of the
 17 outcomes of this meeting is that we'll come up with
 18 a list of the critical research questions the field
 19 needs to answer to help guide those of us who are
 20 doing research to say what are the key questions
 21 that we need to know in order to, 10 years from
 22 now, look back and say we now understand much more

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1 of the most important things.
 2 But as trialists, what do we do in the
 3 meantime based on so little information? I guess
 4 we can only base it on common sense. Should we be
 5 using training in our trials? I suspect so. Of
 6 course, we can't say for sure what those might be;
 7 we can only guess. But it seems like it's a useful
 8 thing to be doing.
 9 Should we monitoring? I think so. But then
 10 the question is what should we be monitoring.
 11 So those are the discussions I think we need
 12 to have. And, as I said, if we should be training
 13 and monitoring, what should they look like? What's
 14 going to be most efficient? We don't want to use
 15 things that cost patients a great deal of time, are
 16 involved, or are very, very expensive. But we want
 17 to do them that are good enough that they are going
 18 to potentially improve our ability to detect
 19 effects.
 20 Is it okay -- I hear loud and clear that
 21 it's probably not okay after you collect the data
 22 to remove patients, because that deviates from the

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1 ITT principle, from your analyses, based on
 2 identifying patients with problems who are unable
 3 to respond appropriately to measures during the
 4 time of the study. But it does seem like it might
 5 be fair to identify patients who are more able to
 6 use these measures more consistently ahead of time
 7 based on baseline measures and potentially use that
 8 as an inclusion/exclusion criteria.
 9 But I think answering that question is an
 10 important issue for this meeting. I'd like to walk
 11 out of this meeting knowing an answer to that
 12 particular question. And that's all I have to say
 13 so far.
 14 (Applause.)
 15 DR. PATEL: Thanks, Mark. We have time for
 16 a couple of questions. Jim?
 17 JIM: Thanks for a great talk, Mark.
 18 The more we talk about this sort of people
 19 who don't get it, I guess one question -- I mean,
 20 we've all been thinking about pain for many years.
 21 And so I guess the question is, what is the problem
 22 with the majority of people who need training to

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1 fill out a zero-to-10 numerical rating scale?
 2 So I can imagine a few things. They failed
 3 grade 8 math and haven't gone on since then, or all
 4 of a sudden, I thought -- and pain and cognition is
 5 really important, and left-brain/right-brain
 6 people. So what would the pain rating be like in a
 7 group of electrical engineers versus people who
 8 paint? And those are the people who would draw you
 9 a picture if you asked them to rate their pain
 10 intensity rather than that.
 11 So I'm wondering whether the yield of
 12 training might be limited just because we kind of
 13 think most people should get it, and maybe the
 14 people that need the training may never get it.
 15 DR. JENSEN: Yes. We simply don't know. I
 16 love to speculate, as any of you who know me know,
 17 so I'm going to do a speculation here.
 18 If you've read Daniel Kahneman's book Fast
 19 Thinking-Slow Thinking, you know that there is a
 20 system for making quick judgments. If somebody
 21 walks in the room, you know you'll like them,
 22 you'll know if they're mad, you'll know if they're

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1 happy, immediately without thinking. Associate of
 2 learning, it's no thinking versus slow thinking
 3 when you process, think average.
 4 I suspect that when you ask somebody to rate
 5 their pain, they use the fast thinking. They just
 6 use a quick judgment without really thinking it
 7 through. And when you go back and ask patients,
 8 "How did you come up with that decision," that's
 9 unfair because you're asking them to engage their
 10 slow thinking to determine how something so
 11 quickly.
 12 If I said, "How do you decide within 2
 13 seconds whether you liked Bob Dworkin?" Now, of
 14 course, you know you like Bob Dworkin within
 15 seconds, but how do you know that? How did you
 16 discern that? People go, "I don't know."
 17 So it may not be fair to ask people how they
 18 came up with the judgment. I think it's a fast-
 19 thinking, immediate judgment. You just know. When
 20 I asked you at the beginning of the talk to rate
 21 your average pain, you came up with a number very
 22 quickly. And I suspect that many of you, many of

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1 us, don't know how we did that.
 2 So it may not be that training helps because
 3 training is a slow-thinking thing. That said,
 4 perhaps teaching people to slow down, think about
 5 the past few days, do some "yeah," we might get a
 6 better number, we just don't know, and that's the
 7 issue, I think.
 8 DR. PATEL: Okay. We have Crystal.
 9 DR. CHEN: Yes. Hi. I have a question,
 10 being in pain for many years. But it's getting to
 11 the point, make me thinking, is it time to develop
 12 some other tools instead of a hundred percent
 13 relying on each individual subject's instant
 14 reacting to that question? Because we all know
 15 that it's quick, within 1 second, you know your
 16 number, you are coming up with. But that has many
 17 factors in there. Did you sleep well last night?
 18 Did you have coffee this morning? A lot of factors
 19 right there influencing that number.
 20 This NRIS has become sort of a gold
 21 standard, however. I'm just challenged, and we are
 22 asking the question, is it time to develop some

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1 other type of tools? I can give an example in my
 2 previous life prior to pain.
 3 I worked in restless leg syndrome, and there
 4 is a gold standard. It's called IRLS, and that is
 5 an interview. We know that RLS, restless leg
 6 syndrome, is pretty much measured by subject
 7 measures. However, they developed a scale, which
 8 is very powerful and very reliable, and the
 9 variability is under control; that is, the
 10 interview between the PI and the subject.
 11 Of course, there is intensive training at
 12 the beginning to train a PI how to do the
 13 interview. We even have videos of a mock interview
 14 and not to lead the witness, per se, and not to
 15 insert any judgment. But if you do the training
 16 well, the study outcome is, I have to say, much
 17 more satisfying in many ways than just neuropathic
 18 pain studies.
 19 That's just my challenge to our community
 20 and my question.
 21 DR. JENSEN: So I think it's always useful
 22 to consider are we doing the best possible, and if

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1 somebody has a viable idea for a new way to measure
 2 it, that should be looked at and explored because
 3 it's always useful to have a better mousetrap.
 4 That said, my current belief is that the
 5 training programs have been developed and maybe,
 6 perhaps tweaked and improved, might be a way to do
 7 that. This might be a way to train patients how to
 8 ask themselves, slow down and think about their
 9 experience, and rate what it is we're really after.
 10 So that may be the new strategy, rather than
 11 say on a zero-to-10 scale, what's your average
 12 pain, say let's talk about what pain is for a
 13 little bit. Let's talk about what average pain is,
 14 and then do that for 20 minutes. And then given
 15 all that, as you think about -- slow down, think
 16 about your experience over the past three days,
 17 what number would you give it? I think that's very
 18 worth exploring in the next few years.
 19 DR. PATEL: There will be more time to have
 20 additional questions. Thank you, Mark.
 21 Our next speaker is Eric Devine. He's a
 22 professor and clinical psychologist at Boston

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1 University, treating addiction disorders, and is
 2 vice chair of the Boston University IRB, and he has
 3 carried out research on participant data
 4 fabrication. And one of his article was included
 5 in the background reading.
 6 Presentation – Eric Devine
 7 DR. DEVINE: So the data I'm going to
 8 present is kind of scary. As a clinical
 9 researcher, I look at this and say, what are we
 10 seeing in the literature if this is happening? And
 11 I don't mean to provoke fear among us, but maybe
 12 create some motivation to think about how can we
 13 design studies so that we don't have this problem
 14 in our studies, so we can eliminate some of the
 15 fraudulent data that happens on an individual
 16 subject level. That's the goal of talking about
 17 this.
 18 Actually, maybe I'll give a couple of
 19 examples of why I ended up doing this research. I
 20 started out in clinical trials in the clinic I work
 21 as a therapist on a cocaine study. It was a NIDA
 22 program, a CREST rapid screening of all these

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1 agents that we had high hopes would help solve the
 2 cocaine epidemic. And as a therapist, I'd sit with
 3 patients, and they'd say, "Oh, so-and-so this in
 4 the trial, they're not here to actually change.
 5 They just want the reimbursement to buy more
 6 cocaine."
 7 As a therapist, I'm sitting there, what can
 8 I do about that? It's hearsay, but it's a problem.
 9 And the answer to that question is find a way to
 10 not enroll people in the trial who aren't really
 11 there for the benefit of the trial.
 12 Another example is an NIAAA-funded,
 13 multisite study. There were pretty good firewalls
 14 to keep individual identifiers out of the central
 15 database. I don't think it was truly de-identified
 16 with all 18 HIPAA identifiers out, but in this
 17 particular trial, there was an ancillary study that
 18 was added on where they collected identifiers. And
 19 lo and behold, one subject with the exact same
 20 identifiers at two different clinical centers, and
 21 their data did not match, not one bit, the primary
 22 outcome measure of drinking. There was no

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1 relationship between the two sets of data.
 2 The last example I'll give before I show my
 3 data was an NIH-funded study to try and use
 4 motivational interviewing to reduce sexual risk
 5 behavior among people with serious mental illness.
 6 In this study we had a screening visit,
 7 which paid \$60, because it was a 4-hour visit, and
 8 we had a subject who had been through it who was
 9 selling access to our study for \$20. She would
 10 say, "This is what you need to qualify, \$20
 11 kickback, and I'll tell you."
 12 So she would send all these people, who
 13 actually never qualified. They were just there to
 14 go through the screening and they would rule out.
 15 But it was a one-time payday for them, and that's
 16 what they were after. And so in some ways, they
 17 were churning us for money the way a stockbroker
 18 would churn someone's portfolio just to make a
 19 quick buck in the day. Really troubling stuff.
 20 So I went on to do this study of
 21 professional subjects, and professional subjects,
 22 as I define it, are people that enroll in clinical

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1 trials for the sole purpose of trying to generate
 2 income. And there is really clear evidence that
 3 these people are out there.
 4 You've got subjects that participate in
 5 multiple trials. They report enrolling in
 6 different trials at the same time and lying about
 7 it. They use deceptive practices where they
 8 conceal information. They enroll in a trial. They
 9 never intend to take the medication, they don't
 10 take the medication. They pop it out into the
 11 trashcan.
 12 We actually had an example of that brought
 13 to our attention in our NIAAA trial. The security
 14 camera in the parking lot observed someone over a
 15 trashcan with a blister card punching out, and they
 16 had just left their appointment. And that was
 17 great because we were able to exclude them from the
 18 study. But we don't often get that kind of eye in
 19 the sky to detect fraud. So we need other measures
 20 to do it.
 21 So there is some research on professional
 22 subjects, but a lot of it is around the ethics of

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1 disproportionate risk and these people not having
 2 generalizable data. Not many people have actually
 3 gone out to say how much is this happening, how
 4 many of these subjects are actually doing this, and
 5 that was the goal of my study.
 6 I recruited 100 subjects through news print
 7 and online advertisements, and I just billed it as
 8 an experienced subject study. So I just wanted
 9 people who had at least two studies in the past
 10 year and three in their lifetime. And I put the
 11 advertisement in the Boston Globe, the Boston
 12 Herald, and Craigslist, and the free paper, the
 13 Boston Metro.
 14 These are all sources in the Boston area
 15 where we have a lot of funding. Everybody is using
 16 it. The Metro has a two-page ad for clinical
 17 studies every day and it's one-stop-shopping for
 18 someone who wants to make money.
 19 This is an example of the ad just so you can
 20 see I wasn't looking for liars, cheats and
 21 scoundrels. I was just looking for someone who has
 22 been in multiple studies.

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1 So what I have, I have a questionnaire;
 2 actually, it's an interview. And I asked people
 3 about their rate of concealing information. So the
 4 kind of things I'm worried about in my clinical
 5 trials in alcohol and cocaine dependence, are they
 6 hiding health problems which could be a risk for
 7 them being in the trial based on the medication or
 8 mental health problems that could -- they might be
 9 hospitalized midway through the trial.
 10 There are a lot of potential risks to the
 11 subject from concealing, but more important, there
 12 is a lot of risk to the integrity of the data
 13 because they may not tolerate the medication. We
 14 have an adverse effect profile that is really not
 15 consistent with the population because we don't
 16 understand the population and we don't understand
 17 the population characteristics.
 18 So I actually asked them about this stuff in
 19 a pretty transparent way, and I have to say this
 20 data, if anything, might underestimate the rate of
 21 fabrication and concealment because these are
 22 people that like to fabricate and conceal, and

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1 they're in the study.
 2 (Laughter.)
 3 DR. DEVINE: So the fact that I even got
 4 this, I think this is the tip of the iceberg.
 5 I also asked them about fabrication, which I
 6 think is a more egregious type of deception in
 7 research. Genuine subjects might conceal things
 8 because they are desperate for help and they want
 9 to get in, and I understand that, I accept that.
 10 It's not good. But fabrication is a different
 11 brand of deception, which is more worrisome, where
 12 people might pretend to have a health problem in
 13 order to enroll in a study or might lie about the
 14 very symptoms of the disease that I'm trying to
 15 study once they're in.
 16 So this is above and beyond someone who is
 17 genuinely trying to get help. So we asked a series
 18 of questions. And just a little bit about the
 19 demographics in the sample, skewed a little towards
 20 the male side. Notice the income here. Most of
 21 the sample was below \$30,000, which in Boston has
 22 got to be the poverty level. I know it's not

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1 nationally, but it's so expensive to live there,
 2 and an average of 12 studies in a year. And the
 3 majority of them have had experience enrolling in
 4 medication trials. All of this was in the paper
 5 that was circulated.
 6 Let's look at what I actually found.
 7 Lifetime concealing. Did you ever conceal
 8 something in order to get into a trial?
 9 Seventy-five percent of these people said, "Yes, I
 10 did conceal." I don't know how often they do it,
 11 and I don't know what type of studies they do it.
 12 That's a whole other level of study, but I do know
 13 that they report doing it.
 14 What are the most common types of things
 15 people conceal? Participation in another study,
 16 43 percent; health problems; other prescribed
 17 medications. This is a big one. We really worry
 18 about this when we think about the adverse effect
 19 profile in a clinical trial, that it might be
 20 misattributed when it's some synergistic effect of
 21 medications or effect of a different medication.
 22 Recreational drug use certainly is something

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1 we worry about in our alcohol trials, mental
 2 health, alcohol use, and legal issues. People
 3 sometimes disappear in our cocaine trials midway
 4 because a case is pending, and they don't want us
 5 to know that, and that's something that affects the
 6 overall integrity of the study.
 7 On the fabrication scale, a little lower
 8 number in terms of the risk to study integrity;
 9 33 percent of the subjects reported that they do
 10 fabricate information in order to gain entry into a
 11 trial. And among those different types,
 12 exaggerating symptoms of a disease, which I can see
 13 as something that genuine subjects might do. They
 14 really want to make sure that they qualify for an
 15 alcohol study, so they exaggerate their level of
 16 drinking. So I get that. It's not good for the
 17 data, because once they're in, then suddenly
 18 they're drinking a lot less. They're telling the
 19 truth, and it looks like there is a medication
 20 effect that really was just a return to maybe
 21 telling the truth.
 22 Pretended to have a health problem,

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1 14 percent. Given research -- the symptoms are the
 2 focus of the study, false information, 12 percent.
 3 And this is a good one, done intentional harm to
 4 yourself in order to qualify for a study. People
 5 do this. People will hurt themselves so they
 6 qualify.
 7 Two examples I can remember from the
 8 interviews. One is someone gaining a substantial
 9 amount of weight to have the right BMI for entry
 10 into a trial, and the other is someone who
 11 discontinued their antihypertensive medication so
 12 that their blood pressure would be out of control
 13 for entry into a trial. So stuff that we really
 14 don't want to see.
 15 Then on the last one, tried to enroll in the
 16 same study twice using different names or changing
 17 identity. People do this.
 18 There were other forms of deception, and I
 19 highlighted in yellow findings that I didn't
 20 publish in the article that was circulated before
 21 the meeting, and I think one of them is
 22 particularly egregious and worrisome. It's halfway

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1 down. Enrolling in a medication study where they
 2 have no intention of ever taking the medication,
 3 11 percent of subjects reported doing that.
 4 When you think about the dosing problems and
 5 optimal dose, this is the worst kind of medication
 6 compliance problem you can think of. Come up with
 7 a reason to stop taking the medication without
 8 losing reimbursement, adverse effects is what they
 9 use. And there again, you've got problems with the
 10 study design and also the safety profile.
 11 There are a bunch of other things that
 12 people do. They share information, they give and
 13 receive it, and they tell us that they're getting
 14 better when they're not getting better.
 15 There are also some open questions I asked
 16 about how do you game the system, basically. And
 17 one of the ways, they do study clinicaltrials.gov.
 18 They go to websites, and there are several
 19 organized professional subject websites where they
 20 can get information.
 21 They will telephone screen in a group and
 22 share information. And my favorite of the

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1 strategies is the organized research kingpin, and
 2 that's actually the word they use to describe it.
 3 In the Boston area, there is someone at the VA
 4 doing this, at the JPVA, and there is someone at
 5 BMC. They are different people. And they sell
 6 access to a study.
 7 So they have all the entrance criteria for
 8 screening in that you need to say. And for a fee,
 9 they'll give you that, and they'll tell you who to
 10 call. And if you don't give the kickback, you
 11 don't get any more information. It's an organized
 12 group of people that do this. And for me, as a
 13 researcher, it is frightening to have that.
 14 So the goal is to figure out how do we
 15 prevent this, and I have worked really hard to keep
 16 professional subjects out of my alcohol trials, in
 17 particular. It's harder with the cocaine studies.
 18 And it has a lot to do with the study design and
 19 how I advertise.
 20 For studies with direct benefit, I never
 21 include reimbursement in the advertisement. That's
 22 like just putting out a sign that says come and

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1 game me because I've got this money you can make
 2 quickly.
 3 When I recruit people, I don't offer much
 4 money for the initial screening visit, if any at
 5 all, because some people will just come in, they
 6 know they're going to exclude from the study, but
 7 they just want to churn for a one-time payout.
 8 They're interested in that prorated payout, where
 9 they spend a few hours and they get \$20, and that's
 10 enough to get by for the day.
 11 Telephone screening, we spend a lot of time
 12 trying to make our screening process as non-leading
 13 as possible, not giving away the criterion along
 14 the way. And even once they come into baseline, if
 15 we can include more objective measures, we do that.
 16 A lot of open questions, a lot of converging
 17 information from different interviewers to try and
 18 see is this person really what they appear to be.
 19 We'll look at the medical record. That's
 20 part of our consent, if they're getting care at
 21 Boston Medical Center. We've had people that deny
 22 any medication. And we open up their chart, and

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1 they're schizophrenic, and they've been taking
 2 antipsychotics for 20 years. But we'll do that
 3 because we really can't afford to have people
 4 enrolling in the trial who have that risk.
 5 Certainly, we can spend time looking at
 6 subject motivation, and professional subjects are
 7 very focused on questions about reimbursement, when
 8 it's going to come, how much it's going to be, what
 9 will happen if they only do part of something, and
 10 maybe less focused on direct benefit of being in
 11 the trial or risk of the medication.
 12 We do look at some inconsistent data.
 13 Someone comes in and is drinking 50 standard drinks
 14 a day and blowing a zero on the BAL, it's like that
 15 would really be hard to do. You just don't
 16 metabolize alcohol that fast.
 17 So we're always alert to these sort of
 18 things, and I can talk more about this during the
 19 discussion panel later. But our goal is to really,
 20 as much as possible, use strategies to keep them
 21 out of the trial all together rather than trying to
 22 deal with it on the other side, where I think the

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1 statisticians are going to look at us and say, "Who
 2 is this professional subject that's introducing all
 3 this? I can't tell." It would be nice if they
 4 could. And that's it.
 5 (Applause.)
 6 DR. PATEL: Thank you, Eric. You don't have
 7 time for questions, unfortunately. So we'll have
 8 Bob Dworkin come up. Thanks a lot.
 9 Bob is the herder-in-chief of the meeting,
 10 so I don't think he needs an introduction. But
 11 he's the founding and executive director of
 12 ACTION, and he's going to be talking about
 13 patients.
 14 Presentation – Robert Dworkin
 15 DR. DWORKIN: Thanks, Kushang.
 16 So my role is clear. You've all gotten
 17 indigestion from Eric's talk, and so for the next
 18 15 minutes, I'm going to try and kind of reduce
 19 your indigestion before lunch because, of course,
 20 those data are really quite alarming.
 21 So I want to just talk about a couple of
 22 strategies that might be effective in combating

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1 some of the misbehavior or misconduct that Eric has
 2 really described. And the primary strategy, and
 3 many of you have heard this before, is to blind
 4 everybody to everything they don't need to know,
 5 the site staff and thereby the [inaudible – mic
 6 fades], and to use blinding to a much greater
 7 extent than we typically think about it, which is
 8 double-blinding the treatment assignment.
 9 So if you take nothing away from the next
 10 15 minutes other than blind everybody to everything
 11 they don't need to know, that would be the most
 12 important takeaway message.
 13 I think many people in the room are familiar
 14 with these data and data like these. This is a
 15 dramatic illustration of what in psychiatry is
 16 called baseline score inflation. Let's see, where
 17 is my pointer? Just in case you've ever seen this,
 18 it's almost as alarming or maybe more so than
 19 Eric's data.
 20 So these are clinician-rated Hamilton
 21 depression scores in a clinical trial of some SSRI,
 22 probably for major depression, where the inclusion

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1 criteria -- I can't see the numbers -- were
 2 something like around 20. You only got into the
 3 clinical trial for major depression if you were
 4 baseline. Before randomization, the Hamilton
 5 score -- the patient was 20 or above. And so these
 6 are clinician-rated measures.
 7 These are the patients' responses for how
 8 depressed they were. You can see there's no
 9 correlation between the clinician's pre-
 10 randomization assessment of depression and what the
 11 patient said their depression was at the screening
 12 visit.
 13 So the kind of deduction from these data is
 14 that the clinician investigators at the sites were
 15 inflating the patients' ratings of depression in
 16 order to randomize them to enroll them in the
 17 clinical trial.
 18 These are Hamilton scores at the end of the
 19 trial, where you can see there's a really nice
 20 correlation between the clinician ratings and the
 21 patient ratings, because, of course, at the end of
 22 the trial, the clinician doing the Hamilton ratings

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1 has no motivation to inflate the scores.
 2 So data like these are disturbingly common
 3 in psychiatry trials and led to David Hewitt, who
 4 is in the back of the room, to propose this back in
 5 2011, propose and implement this in a clinical
 6 trial.
 7 David said in his clinical trial, both
 8 investigators and patient were blind to the
 9 following information: entry criteria for patients
 10 pain intensity, baseline pain intensity, definition
 11 of responder groups, visited, which randomization
 12 occurred, blah, blah, blah, blah, blah, blah.
 13 So this is the first example in the pain
 14 literature that I know of, of blinding everybody to
 15 everything that they don't need to know. And if
 16 you have any questions about how we came up with
 17 this, David is here at the meeting.
 18 We implemented this in a clinical
 19 trial -- Andrew Rice here -- of an angiotensin 2
 20 receptor blocker that was published a few months
 21 ago. And I just wanted to show this slide to kind
 22 of make the point that there really aren't any

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1 problematic aspects to blinding people to all of
 2 these aspects of the study design.
 3 There are a couple of things we can talk
 4 about later in terms of IRBs, in terms of cranky
 5 investigators who wanted to know all the trial
 6 details, but the bottom line is it's easy to blind
 7 sites to information that they have no need to
 8 know. Obviously, we're not blinding things that
 9 have implications for safety, et cetera.
 10 So one potential recommendation is, the
 11 obvious, blind patients and site personnel to
 12 absolutely everything they don't need to know.
 13 Also, of course, as you saw from Eric's
 14 presentation, you want to do the same thing for
 15 clinicaltrials.gov, because there is no reason to
 16 give a site a redacted protocol if all the
 17 information is available on the Web. And so
 18 clinicaltrials.gov has to be blinded, if for no
 19 other reason, to prevent the study kingpins in
 20 Boston from educating pseudo patients how to
 21 participate in Eric's addiction clinical trials.
 22 So blind everybody is one possible recommendation.

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1 Now, this is Jeri Burtchell. She lives in
 2 East Palatka, Florida, and she has relapsing
 3 remitting MS. And a number of years ago, she
 4 participated in a double-dummy trial of IM
 5 interferon beta versus oral fingolimod for
 6 relapsing remitting MS. And she went home after
 7 her first randomization visit and started a blog
 8 about her experiences in the trial, where she
 9 explained to patients, other patients in the trial,
 10 on this blog, how it was she became convinced very
 11 quickly that she was randomized to oral fingolimod
 12 versus IM saline.
 13 By the way, she was correct. She was, in
 14 fact, in the oral fingolimod group, and it had to
 15 do with the fact that when the nurse injected her
 16 thigh, she didn't feel anything. And in the past
 17 she had been treated with Avonex and the injections
 18 always felt a little bit of burning. Plus, she saw
 19 that her blood pressure dropped at one visit, which
 20 is an event associated with fingolimod.
 21 So she had a blog where she was basically
 22 training patients around the country who were

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1 participating in this trial how to unblind
 2 themselves, which is a big problem.
 3 Because of this blog, she was invited to a
 4 bunch of professional meetings over the next
 5 several years, and she became convinced that what
 6 she had been doing was terrible. And she now has
 7 this site. She took her blog down because she
 8 understood over time that what she was doing was
 9 really threatening the integrity, the quality of
 10 the data.
 11 She now has this site called Partners in
 12 Research, where she is doing everything she
 13 can -- and it's a great site -- to kind of educate
 14 the patients that they need to be collaborators,
 15 partners in clinical trials, to encourage them to
 16 participate and to encourage them to do a good job
 17 when they are participating in the trial.
 18 I only found out about all of this recently,
 19 Otherwise, we would have invited her to this
 20 meeting, because it would have been great to have
 21 her here.
 22 So there is patient misbehavior, as Eric

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1 pointed out, and it is known and it has been known
 2 for a while. This is an Institute of Medicine
 3 report from 2010, where -- I hope you can read the
 4 slide -- the IOM report describes the existence of
 5 psychiatry trials of professional patients, as
 6 you've heard, noting the example of a 300-patient
 7 schizophrenia trial where 30 patients were
 8 participating in the same schizophrenia trial in
 9 multiple sites.
 10 This is a schizophrenia trial where
 11 10 percent of the patients in the trial were
 12 participating in the same trial at multiple sites,
 13 presumably for the compensation. And the response
 14 to this recognition of duplicative participation is
 15 there are now -- I don't know what to call
 16 them -- websites, organizations, outfits that
 17 provide registries where sponsors and sites upload
 18 demographic information and the -- this is one of
 19 them, DupCheck, which has been started by Jonathan
 20 Rabinowitz as part of the IMI effort in Europe.
 21 What Rabinowitz does with DupCheck is to
 22 identify duplicate patients not only within trials,

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1 but between different trials, and then notifies the
 2 sponsor that a duplicate patient has been
 3 identified. These slides were sent to me by
 4 Jonathan. So he obviously has a conflict of
 5 interest.
 6 This is interesting. I don't want to spend
 7 too much time on it. When patients are duplicate
 8 enrollers in the same trial, what is it they think?
 9 He's done a little bit of research on it. They
 10 believe they know better than the investigator, and
 11 think it's a silly requirement that you can't
 12 participate in the same trial at multiple sites.
 13 They miscalculate how long ago it was that
 14 they participated in the same trial. They say
 15 they're not a criminal, there is nothing wrong with
 16 what they're doing. They want to get paid for an
 17 additional study.
 18 So this is happening, and as Jonathan says,
 19 DupCheck can be used in one of two different ways
 20 at the time of screening: to exclude these
 21 individuals who are trying to game the system, or
 22 after the data have been collected -- prevention is

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1 better than treatment, but if you haven't excluded
 2 them in advance, to identify them and do something
 3 about it during the data analysis stage.
 4 This is an example of a schizophrenia trial.
 5 I don't really know the details. He presented this
 6 at a schizophrenia meeting, as you can see from the
 7 bottom of the slide, where he identified a not very
 8 large number of duplicate patients in schizophrenia
 9 trial and shows that the significance of the trial
 10 before removing the duplicates was not significant,
 11 was .054. And then after he removed the 10
 12 duplicate patients, the trial became statistically
 13 significant.
 14 Take this for what you will, but, obviously,
 15 removing duplicate patients from a trial is a
 16 reasonable thing to try to do.
 17 Mitchell Efros -- actually, no, this is
 18 Thomas Shiovitz, who runs a clinical site in
 19 Southern California, the Los Angeles area, and he
 20 has set up a network of CNS sites in Southern
 21 California that, in a HIPAA-compliant way, share
 22 patient identifiers.

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1 I hope you can read the title of the slide.
 2 He is using the subject registry to create a
 3 duplicate-free corridor for conducting clinical
 4 trials. So he's hoping that by linking together
 5 these CNS sites in Southern California, they've
 6 created a duplicate-free corridor because they're
 7 sharing information, allowing the duplicate
 8 patients to be identified.
 9 He has also done some research on this
 10 question. And in this abstract, how far are
 11 duplicate patients willing to go, he's showing that
 12 most of them are willing to drive at least 25 to
 13 50 miles to participate in multiple studies
 14 simultaneously. That was one meaning of how far
 15 are they willing to go.
 16 Another meaning is how far are they willing
 17 to go in terms of varying their diagnosis, and the
 18 answer to that is these individuals, no problem
 19 being a schizophrenic on Monday in Los Angeles; and
 20 then Tuesday driving down to San Diego and having
 21 bipolar disorder for a bipolar disorder trial; and
 22 then on Wednesday in Irvine having generalized

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1 anxiety disorder.
 2 So they're willing to go physically far, and
 3 they're willing to go diagnostically far in order
 4 to participate in multiple trials at the same time.
 5 Mitchell Efos has a site that's called
 6 Verified Clinical Trials. This seems to be more in
 7 the U.S. as opposed to DupCheck, being more
 8 European. I don't really know anything about the
 9 relative value of either of these approaches or
 10 Shiovitz's Southern California network, but I think
 11 this is on the horizon because as Shiovitz says,
 12 and this is from an e-mail he sent me, while there
 13 is not 100 percent adoption of a system to prevent
 14 duplicate patients, the main message he wanted me
 15 to convey to you all is that use of some system is
 16 better than not using one at all. And it seems
 17 hard to disagree with that, to me.
 18 If there are ways of potentially duplicating
 19 these -- potentially identifying these fraudulent,
 20 fabricating, duplicate patients, why not consider
 21 using these approaches?
 22 So the second potential recommendation,

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1 implement efforts to identify and eliminate
 2 fraudulent and duplicate patients. And this goes
 3 back to Eric's presentation. Let's do our best to
 4 verify the patient has the disorder, has the
 5 symptoms, either by getting medical records from
 6 their primary care clinician or going to electronic
 7 health records and then consider using these
 8 networks, DupCheck, Verified Clinical Trials,
 9 Shiovitz's network, to identify duplications before
 10 they are randomized.
 11 So the last thing I wanted to say, and to
 12 say I mentioned before, were we blinded everybody
 13 to everything they didn't need to know, we
 14 implemented -- and this is mentioned in the
 15 article. Andrew and I and the other investigators
 16 implemented a baseline pain exclusion algorithm.
 17 We kind of created an algorithm where we
 18 interrogated the baseline pain diaries, and based
 19 on the pattern of responses, excluded patients.
 20 And the implementation of that was kind of
 21 straightforward.
 22 So what is an example of it? This is not

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1 the example we used, but it's an example of the
 2 kinds of things we have been talking about this
 3 morning in Mark's presentation, in Eric's
 4 presentation. And so one can imagine a completely
 5 blinded algorithm that is applied to a patient's
 6 week of diaries during the baseline
 7 prerandomization phase of the trial that is the
 8 basis for excluding some patients from
 9 participation.
 10 So they have to complete at least six out of
 11 seven diaries. The mean of their ratings has to be
 12 between 5 and 9, not too mild, not too extreme.
 13 Some variability exclusion, a la what Harris and
 14 Farrar and other people have published.
 15 This is NATC's point, looking during the
 16 baseline week at agreement with two different ways
 17 of assessing pain. It could be agreement between
 18 average and worse pain or NRS and VAS or, as Nat
 19 mentioned, a pain measure that's more generic and
 20 something disease-specific, like the WOMAC, one or
 21 more days with worse pain, less than average pain.
 22 They didn't pay attention to the training. They

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1 are not thinking through their ratings. So maybe
 2 if they mess up in this way, they should be
 3 excluded.
 4 I went back and forth, and this is all just
 5 for argument's sake. One might give them a day of
 6 being a little sloppy, and you might want to make
 7 this greater than one sloppy day, but maybe not.
 8 Then finally -- we're going to hear much
 9 more about this this afternoon -- some trials have
 10 a placebo run-in and maybe it would be reasonable
 11 to exclude patients who demonstrate poor adherence
 12 to taking the placebo during the placebo run-in,
 13 because if they're not adhering to the placebo in
 14 the placebo run-in, then isn't that a bad sign
 15 about what their adherence is going to be during
 16 the rest of the trial?
 17 Of course, if one were to implement
 18 something like this as an exclusion algorithm prior
 19 to randomization, so this would be prior to
 20 randomization, one would hope it increases assay
 21 sensitivity. One would hope it excludes some
 22 fraudulent patients.

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1 My last slide, it has to be totally blinded.
 2 So I wanted to begin with the importance of
 3 blinding and end with the importance of blinding,
 4 because we want to do everything we can to defeat
 5 the study kingpins that Eric told us about.
 6 So thank you very much. We won't take any
 7 questions now. This is time for the lunch break.
 8 And because we went a little bit over, let's
 9 reconvene here at 1:10, and there will be ample
 10 time for discussion after lunch.
 11 Thank you all very much.
 12 (Applause.)
 13 (Whereupon, a luncheon recess was taken.)
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1 AFTERNOON SESSION
 2 MODERATOR: Let me introduce the next
 3 speaker. Dr. Bernard Vrigens is a biostatistician
 4 by training, and he's currently the chief
 5 scientific officer of MWV Healthcare, which is a
 6 packaging company. And he has a lot of experience
 7 with monitoring and evaluating medication
 8 adherence.
 9 I had the pleasure of having dinner with him
 10 last night, and he told me that he's been back to
 11 the United States five times in the past nine weeks
 12 to give talks similar to the one that we're about
 13 to hear. So he's highly sought after, and we're
 14 looking forward to his talk.
 15 Presentation – Bernard Vrijens
 16 DR. VRIJENS: Good afternoon. Thank you
 17 very much. Thank you for the invitation to give me
 18 the opportunity to talk about medication adherence
 19 here today.
 20 Today we have to deal with a lot of very
 21 effective therapies. But if we don't have
 22 appropriate adherence to medications, we will not

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1 achieve effective disease management. And in most
 2 of the adherence talks, you will see they always
 3 start with the sentence, "Drugs don't work in
 4 patients who do not take them." However, the
 5 sentence assumes that adherence is a dichotomic
 6 process, either you are adherent, either you are
 7 not adherent. And what I will do in the next few
 8 slides is to convince you that it's much more
 9 complex.
 10 First of all, about the taxonomy. A few
 11 years ago, we were called by the EU, Union, to come
 12 with recommendation on adherence for the European
 13 Union, and we were sitting together with seven
 14 universities around the table, and we didn't know
 15 what we were talking about.
 16 Was it adherence? Compliance? Persistence?
 17 Concordance? And all the translation in all the
 18 European languages, we didn't know what it was,
 19 really. So we defined it as a process by which
 20 patients take their medications prescribed, but we
 21 recognize that it is a dynamic process over time
 22 and that there are three key elements.

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1 Once there is a prescription, first the
 2 patient has to initiate the therapy. That's the
 3 first thing, initiating therapy. Once the
 4 prescription is initiated, the patient has to
 5 implement the dosing regimen, meaning taking it
 6 once a day, twice a day, with food, without food,
 7 and when we think about polypharmacy, this
 8 implementation piece can be very complex. And then
 9 the patient has to persist with treatment for a
 10 long period of time, especially in chronic
 11 diseases.

12 So what can go wrong in that process?
 13 Either the patient doesn't initiate, and that's a
 14 dichotomic outcome; it's yes/no. Either the
 15 patient delays, takes an extra dose, omit a dose,
 16 and that's a dosing history; it's a time series.
 17 Either the patient discontinue treatment too early,
 18 and that's a time to event.

19 Statistically speaking, those three elements
 20 are very different in nature, very different in
 21 nature. That's why we need to identify and to
 22 tackle them separately. And that's why, for

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1 example, if I say an adherence of 70 percent is
 2 very confusing because you don't know if the
 3 patient is really taking, implementing, 70 percent
 4 of -- taking 70 percent of the medication or
 5 stopping 30 percent too early. You don't know.

6 Okay. What are the measure that were have
 7 to measure patient adherence? And I have
 8 classified the measures here in four categories.
 9 First of all, on the lower end of this figure, you
 10 have methods that are biased.

11 For example, what we do mostly in clinical
 12 trials, pill counting, is extremely biased. I will
 13 show you some data afterwards. But people tend to
 14 drop the pills before showing up at a visit. And a
 15 retrospective questionnaire, asking the patient if
 16 he took the medication in the last month, typically
 17 is extremely biased as well.

18 On the upper part we have, for example,
 19 therapeutic drug monitoring, which is an extremely
 20 reliable method, but it's very sparse. Why?
 21 Because you have the idea of the adherence at the
 22 time of sampling, nothing before.

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1 Most of my research has been focused really
 2 on electronic monitoring, and the idea is that we
 3 put the chip in the package, so that every time the
 4 patients open the package, it's time-stamped, and
 5 we know when the medication is taken.

6 First slide. This method is really rich and
 7 reliable, and I will show you some data about that.
 8 My first slide here is about what is pre-
 9 electronic? Pre-electronic methods are unreliable.
 10 And one example is here, the first upper figure. I
 11 like to show this one because it's done by a very
 12 famous statistician in London, Stuart Pocock.

13 Rather than giving a hundred tablets to the
 14 patient for a hundred days, he give 160 tablets for
 15 a hundred days. So the patients were expected to
 16 bring back what is indicated here by the arrow, the
 17 blue arrow, and you see a very nice distribution
 18 around the blue arrow, but you see 20 percent of
 19 the patients bringing back an empty bottle.

20 Those typically are patients dropping, and
 21 this 20 percent comes always back; when you compare
 22 pill count with electronic monitoring, you come

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1 back to those 20 percent, and those are not at
 2 random. Those are the worst patients who drop the
 3 pills before showing up at the visit.

4 This is an example also about "white coat
 5 compliance" affecting therapeutic drug monitoring.
 6 This is an extreme case that we encounter. Patient
 7 takes a drug, takes one tablet, comes for the blood
 8 sampling. Takes nothing. Takes two tablets, comes
 9 for the blood sampling. Takes nothing. Takes
 10 three tablets, comes for the blood sampling. Very
 11 good. He looks okay. Well, he never took the
 12 medication, really. And we found bias in
 13 31 percent of the samples clustered in 66 percent
 14 of the subjects.

15 Also, when you do self-report, really, it's
 16 sky-high reporting adherence compared to electronic
 17 monitoring. And multiple studies have shown that
 18 physicians or healthcare providers are very bad in
 19 predicting medication adherence.

20 So that's about bias. But the most
 21 important for me is really to see the dynamic in
 22 adherence, and I will show you some examples.

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1 This is an example of electronic monitoring.
 2 You can see this patient is on a twice-daily-dosing
 3 medication. On the X-axis, you have the follow-up
 4 in the study, on the Y-axis, you have a time of
 5 drug intake. Every blue dot, it's a dose taken.
 6 So you can see this patient takes the
 7 morning dose at 7:00 every day, exactly at the same
 8 time, and he takes the evening dose exactly at 7:00
 9 p.m. He was two minutes late here, and then he is
 10 perfect. And there is exactly 12 hours between the
 11 morning and the evening dose. So this patient
 12 exists.
 13 But as you can imagine, a lot of patients do
 14 deviate from that perfect pattern. Something that
 15 we encounter very often is this type, where you see
 16 weekdays patients take the medication at 7:00 in
 17 the morning, but weekends he sleeps out and takes
 18 the medications about noon, but still a very good
 19 adherer; he never missed a single dose. Those are
 20 patients from phase 2 clinical trials, so they're
 21 real.
 22 This patient, you can see every time there

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1 is a gray bar, it's a missed dose. So the morning
 2 dose is okay at the beginning, the evening dose is
 3 already problematic, and the further in the study
 4 the worse it is, especially at the end. In the
 5 evening, he almost takes nothing any more.
 6 I like to show this patient also. This
 7 patient, as you can see, has problems at the
 8 beginning, so at initiation missed a lot of doses.
 9 Then he does it much better. And then there is a
 10 full stop of treatment. There is a full
 11 discontinuation of treatment about halfway. But
 12 this patient shows up at the last visit and doesn't
 13 tell he stopped medication before. He just goes
 14 for the last assessment, and he didn't take the
 15 medication for a while before.
 16 I could show you thousands of those
 17 patients, but this summarizes the data from about
 18 17,000 patients coming from 95 clinical studies.
 19 So what you see here is the blue curve. The blue
 20 curve gives you the proportion of patients who are
 21 persistent with the treatment, who are still
 22 engaged with the treatment. And we see that after

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1 a year, we have lost about 40 percent of the
 2 patients in clinical trials.
 3 It's also striking to see that the day 1, we
 4 have a drop of 3 percent. So that means that even
 5 in clinical trials where patients are highly
 6 selected, patients are highly motivated, patients
 7 get the medication for free at the investigational
 8 site, 3 percent of them roll back home and never
 9 open the box.
 10 Then we have here the adherence curve, the
 11 red one, that over time, it gives you the
 12 proportion of patients who open the box as
 13 prescribed every consecutive day. So if I take the
 14 hundred, I have 80 percent persistence but only
 15 65 percent of them who do it as prescribed.
 16 So that means that every day, because you
 17 see those two lines are pretty parallel -- that
 18 means that every consecutive day among the patients
 19 who are still engaged with the therapy, about
 20 15 percent of them do not do it as prescribed.
 21 Summary. After a year, we have lost
 22 40 percent of the patients. Every day, 15 percent

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1 do not implement as prescribed.
 2 Persistence is very different across
 3 diseases, and we see the worst persistence in CNS,
 4 mainly in depression studies. That's where we see
 5 the worst persistence. And you have to think about
 6 all the diseases that are associated to depression,
 7 like oncology, for example.
 8 Two examples. One is hypertension. This is
 9 a subset of the database. I thought it's
 10 interesting because the persistence in hypertension
 11 is about 50 percent after one year, but
 12 implementation is slightly better. You only have
 13 8 percent non-implementation. Why? Because this
 14 is a very easy to take medication. It's once a
 15 day. Extremely simple, so you have slightly better
 16 implementation, but after a year you have lost
 17 about half of the patients.
 18 What is interesting from this study is that
 19 we looked at when they take their medication. This
 20 is missed doses against day of the week. So the
 21 patients who take it in the morning are the ones
 22 who miss the less doses.

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1 Then the ones who take it in the evening,
 2 they miss slightly more doses, especially on
 3 Saturday evening. And then the wobblers are the
 4 ones we cannot classify, the ones who take it today
 5 in the morning, tomorrow in the evening. They have
 6 no time patterns. Those are clearly the ones who
 7 miss most of the doses.

8 This figure is interesting also because it
 9 shows the persistence curves stratified by
 10 implementation. You see that the better you do it
 11 on a day-by-day basis, the longest you persist with
 12 treatment.

13 So that we come back later in my
 14 presentation when we are thinking about
 15 interventions, if we can work on building a habit
 16 in the patients to do it better on a day-by-day
 17 basis, we increase the likelihood that the patient
 18 will persist longer.

19 Everybody will tell me, in our research, we
 20 started in hypertension, and then we did diabetes,
 21 and then we did -- and every field always, oh, yes,
 22 that's hypertension. We know that adherence is bad

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1 in hypertension. And then you go to diabetes. Oh,
 2 yes, the diabetes is the same. And then you go
 3 HIV. Oh, yes, HIV is also special. So field after
 4 field, we see major issues in adherence across all
 5 therapeutic areas.

6 I want to take this opportunity to show you
 7 this publication that was out last week -- no, last
 8 month, sorry -- from Alabama University. They've
 9 randomized -- no, they didn't randomize -- they
 10 have followed 500 kids with leukemia. They have
 11 followed 500 kids using those electronic monitors.

12 They realized that the kids who had an
 13 adherence, global adherence, above 95 percent,
 14 which requires very precise implementation of the
 15 dosing regimen, had a 5 percent relapse rate. And
 16 the kids with lower than 95 percent adherence had
 17 almost a three-fourth higher relapse rate. It was
 18 15 percent.

19 So it was a drastic difference between the
 20 adherence kids and the nonadherent kids. And what
 21 was even more striking for me is that about
 22 40 percent of the kids were nonadherent. So we are

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1 here in front of a life-threatening disease where
 2 we have a medication that can save those children,
 3 and 40 percent of them didn't reach a level of
 4 adherence what was enough to avoid relapse.

5 That brings me to the point that we have a
 6 major adherence gap, and I think we don't have a
 7 right vision about it because, typically, when we
 8 are talking about clinical trials -- except today
 9 at this meeting -- but usually when are talking
 10 about clinical trials, especially among
 11 practitioners, they say, oh, on trials, everything
 12 is perfect. So we have an idea that they think we
 13 are measuring treatment efficacy, while in practice
 14 we are measuring treatment effectiveness.

15 But given the data that we have collected,
 16 adherence data that we have collected in clinical
 17 trials, my view is that we are measuring something
 18 in between because we have suboptimal adherence in
 19 clinical trials, but we still do better than in
 20 practice because we select better-off patients and
 21 we do better patient follow-up.

22 But that's a very important point because

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1 that means that we end up with an estimate in
 2 clinical trials that doesn't answer the FDA
 3 question, which is, what's the efficacy of the
 4 treatment, and which doesn't answer the payer's
 5 question, which wants to know what's the
 6 effectiveness of treatment.

7 So that means that at the end, when we
 8 conduct clinical trials, we don't answer questions
 9 appropriately. We don't know the efficacy and we
 10 don't know the effectiveness. We are in between.

11 That often leads in drug development to the
 12 failure of the clinical trials to poor estimation
 13 of efficacy, in my view; also, inappropriate
 14 regimens. I will come to that point, but I think
 15 very often we go to a too high dose. And it's
 16 becoming important, I think.

17 The topic of adherence, I was very pleased
 18 to see in the enrichment guidance, the draft
 19 guidance from the FDA, it's mentioned. And I think
 20 it's very important that in the future we take into
 21 consideration this very important aspect, which is
 22 medication adherence, because when we think about

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1 the sources of variability in drug response, how
2 much attention we require on the manufacturing
3 level, at the prescribing/dispensing, it's a lot.
4 When we see the work in drug development
5 that is done to study pharmacokinetics and
6 pharmacodynamics in the last 20 years, it has been
7 a drastic improvement. When you look at how many
8 studies fail because of pharmacokinetics, it's a
9 drastic reduction because it has been a topic of
10 study in drug development that has taken a lot of
11 attention.
12 But it's amazing that nobody takes account
13 of adherence, which is a major source of
14 variability. Drugs don't work in patients who do
15 not take them. Remember the first sentence.
16 So now I will discuss a little bit that
17 impact from adherence, pharmacokinetics,
18 pharmacodynamics. And when we think about what are
19 the consequences of medication nonadherence, it's
20 clear that drugs don't work in patients who do not
21 initiate them. It's clear that drugs stop working
22 in patients who discontinue them. But they key

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1 point here is also drugs work partially or even
2 create harm in patients who implement it
3 sporadically.
4 Here I would like to introduce the notion of
5 drug forgiveness. That's something that we don't
6 very well know, but we should better study the
7 forgiveness of each treatment.
8 What do I mean by that? Is that when we
9 prescribe a treatment, this is the typical
10 pharmacokinetic profile. So we expect that when we
11 prescribe a treatment, after a few days of drug
12 intake, the patient reaches a steady state and
13 maintains a steady state over time, and we hope
14 that that drug exposure is within the therapeutic
15 index, the therapeutic window. That means it's
16 high enough to have effectiveness ,and it's low
17 enough to avoid toxicities.
18 So now if we simulate here three missed
19 doses, you can see that the treatment will still be
20 efficacious for about 24 hours. So we can say that
21 the forgiveness of this treatment, this hypothetical
22 treatment, is 24 hours.

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1 Forgiveness is bidirectional. If the
2 patient takes an extra dose half day, you can see
3 there will be a peak, but it's also forgiving for
4 that peak as well. And in the future, we need to
5 better understand the forgiveness of the different
6 treatment, which we don't do today.
7 Because in practice, when we prescribe a
8 treatment -- here, for example, once a day -- we
9 think the patient reaches a steady state after a
10 few days and maintains a steady state over time.
11 That's all the picture that we have in mind when we
12 saw this patient is on treatment -- you agree, this
13 is on treatment -- while in reality, the patient
14 missed a dose, take an extra dose to compensate the
15 missed dose the day before, takes a little drug
16 holiday, and there is much more variability in that
17 process that can eventually lead to toxicities or
18 periodic loss of effectiveness. And when we think
19 HCV or HIV, there is also emergence of drug
20 resistance.
21 So there is much more variability that we
22 think in the process, and we need to better

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1 understand what's happening in clinical trials
2 especially.
3 This figure shows us also the ability from
4 electronic monitoring to project pharmacokinetic
5 profile, and that's very interesting. I show you
6 two examples here. In a therapeutic area, when
7 people think there is an adherence issue, the first
8 reflex is to say, "Let's measure concentrations."
9 That's happening, for example, at the moment with
10 the NOACs, the new anticoagulants. There is an
11 adherence issue, and the first reaction is, let's
12 measure concentrations.
13 I show you here two patients for which we
14 did therapeutic drug monitoring. So that means
15 that at day 21, we did intensive pharmacokinetics.
16 Patients were hospitalized here also. And then we
17 collected one, two, three, four, one, two three,
18 four expected trough samples. So we are asking the
19 patients to come at trough just before the next
20 dose.
21 What do you decide about this patient? This
22 is a trough. This is a trough, this is a trough,

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1 this is a trough. Too high? Too low? Do you
 2 decrease the dose? Increase the dose? You don't
 3 know.
 4 When you look at what's happening really
 5 based on electronic monitoring, you see that he was
 6 caught [sic]. He was not a trough. He was a
 7 trough. He was caught when he missed a dose. So
 8 without the electronic monitoring, it's impossible
 9 to make sense of those data.
 10 Here do you think this patient is
 11 controlled? Probably yes. It looks like he is
 12 pretty good, while in reality he missed quite a lot
 13 of doses, and the variability in that profile was
 14 at high risk for losing effectiveness, but also for
 15 emergence of drug resistance in HIV. So that's why
 16 it's very important to better have this dynamic of
 17 drug exposure and to better understand that to make
 18 sense of all clinical trials.
 19 This is the last example I wanted to show
 20 you. We were involved in a dose-ranging study,
 21 three groups. It was a cardiovascular medication.
 22 It was a twice-a-day dosing regimen. And this is

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1 cumulative dosing.
 2 If you look, it was 90 days in the study, so
 3 the patient who is taking the full dose twice a
 4 day, he would end up at 180 doses taken here. He
 5 will be perfectly aligned with the upper green
 6 line. And every line, every orange line, is here a
 7 patient.
 8 When you look what's happening in the
 9 placebo, there are deviations in adherence. But if
 10 you look at all those horizontal lines, patients
 11 ending horizontal line, were patients discontinuing
 12 treatment. So the major problem we had in the
 13 placebo group was discontinuation of treatment,
 14 nonpersistence.
 15 When we looked at the 7.5 milligram, there
 16 was no discontinuation. All the patients persisted
 17 to the end, but there was a very strong trend to
 18 dose much lower than the full dose. So that means
 19 that in the 7.5 milligram group, the patients
 20 implement it in a way that they auto-adjusted the
 21 dose, but they persisted with treatment up to the
 22 end; while in the placebo group, they stopped.

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1 They stopped. A lot of patients stopped.
 2 How can you make a decision about which is
 3 the appropriate dose if you don't know those
 4 adherence pattern? Because the highest dose is
 5 auto-adjusting to a lower dose. It's very
 6 difficult to pick the right dose if you don't know
 7 how the patients were really exposed.
 8 So in my view, we do today a lot of
 9 adherence on informed clinical development, and
 10 it's very difficult to find what's the right dose
 11 to balance efficacy and safety because when we are
 12 in phase 1, we have good idea of formulations, we
 13 have good, excellent idea of PK/PD, but adherence
 14 is a big unknown. And the trend is to go to the
 15 highest safe dose to compensate for diluted
 16 efficacy, but there are unexpected adverse effects.
 17 Those are the two reasons. Finding the
 18 right dose is the number one reason why treatment
 19 fail or are delayed at approval because it's very
 20 difficult to pick the right dose when you don't
 21 know what's the exposure.
 22 That brings me to the slide, saying this

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1 Struthian approach is no longer an option because
 2 Struthian is the Latin name for ostrich, because in
 3 the past, we were dealing with treatments which has
 4 a very broad therapeutic window. If we think about
 5 statins, hypertension, the therapeutic window was
 6 very broad. And we could pick the high dose to
 7 build a lot of forgiveness in those treatments so
 8 that implementation was less important.
 9 But when we look at the pipeline of the
 10 pharmaceutical industry today, we are talking more
 11 and more about treatments that have a very narrow
 12 therapeutic index. I'm thinking about oncology
 13 treatment. I'm thinking about the new
 14 anticoagulants. I'm thinking about MS treatments.
 15 The therapeutic windows are much more narrow today
 16 in those niche markets. And in that situation,
 17 it's key to identify what's the best dosing
 18 regimen, what's the best dose, and we cannot ignore
 19 mitigation adherence any more.
 20 It's no more acceptable, it's no more
 21 ethical, to jack up the dose to a level to cover a
 22 population where half of the patients are not

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1 taking the medications prescribed. And then you
 2 end up with 40 percent of the patients on oncology
 3 treatment with serious adverse effects. This is no
 4 more acceptable.
 5 So we need to manage adherence in the
 6 future. And in the past, when the patient was not
 7 taking his medication, it was always said, it's his
 8 problem. We prescribed the best medication for
 9 this patient; it's his problem.
 10 But the cost associated to nonadherence
 11 becomes so important, so gigantic, that we need to
 12 take adherence into consideration. And it's an
 13 entire system. It's the patient, it's the family,
 14 it's the provider, the community, and the
 15 healthcare system.
 16 But the point is that we are not improving
 17 adherence to improve adherence. We are improving
 18 adherence, and the objective is to achieve the best
 19 use by patients of appropriately prescribed
 20 medicine in order to maximize the potential for
 21 benefits and to minimize the risk for harm.
 22 So we don't want to achieve 100 percent

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1 adherence in everybody. The objective is really to
 2 maximize benefits and minimize harm. We have to
 3 keep that in mind.
 4 What we realized in doing a lot of clinical
 5 trials with electronic monitoring is that when the
 6 investigators started to see those data, they said
 7 to us, I need to have those data because I will
 8 manage my patients differently.
 9 This is the first study we did in Belgium in
 10 about 400 patients, and what we did, we provided to
 11 the pharmacist -- we collected data for three
 12 months, dosing history data for three months, among
 13 those 400 patients, and we provided this dose data
 14 to a pharmacist, who could discuss the data with
 15 the patient.
 16 You can see in this individual example that
 17 the behavior before the discussion and after
 18 discussion drastically changed. This is also
 19 reflected in the study globally; we had a
 20 15 percent improvement in adherence.
 21 The idea is here, really, this one. I show
 22 you four patients, and all four patients took

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1 exactly 75 percent of their prescribed doses during
 2 a three-month period. Look at the first patient.
 3 He has a problem in the evening. The second
 4 patient has a problem in the morning and in the
 5 evening. The third patient, when he missed doses,
 6 those are consecutive missed doses, which are the
 7 drug holidays. And the last patient, he implements
 8 perfectly but stops too early.
 9 So those four patients have taken exactly
 10 the same number of tablets. You can imagine that
 11 the clinical consequences of those four will be
 12 totally different. But now also if you want to
 13 build an intervention, imagine that that patient
 14 show up at the investigator's site, at that visit.
 15 You can directly focus your discussion and
 16 say, what's happening in the evening? Can we fix
 17 your habit in the evening? Could we fix and
 18 improve your medication intake in the evening?
 19 While this patient, he clearly has a barrier. He
 20 stopped for a given reason, and you can immediately
 21 discuss that reason with the patient.
 22 So having those data, as the previous

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1 speaker mentioned the control process, I think if
 2 you have those measures, you can really intervene
 3 and build an intervention. Currently, there are
 4 about 20 studies that have done that, and the
 5 average improvement in adherence by feeding back
 6 those data in clinical trials is about 20 percent.
 7 So what I say here is that the measurement
 8 is one aspect. Education to increase knowledge is
 9 key. Motivations to increase self-efficacy is very
 10 important. But by themselves, is not enough. We
 11 need a good measurement of adherence to increase
 12 patients' awareness.
 13 You have to realize that most patients, when
 14 you show them the data, they just say, "Wow. Is
 15 this me? I never realize I miss so many doses."
 16 Because most patients, if you ask them, they say,
 17 oh, it happens. I miss here and there a dose. But
 18 when you monitor them, you realize it's 20 percent,
 19 and increasing the awareness is very important to
 20 understand medication adherence.
 21 So what are the measures that we can use to
 22 summarize them? I think that direct methods like

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1 pharmacokinetics, pharmacodynamics, while a lot of
 2 people think that's the way to go further to
 3 measure adherence, the problem is that the sampling
 4 is way too sparse to measure implementation, and
 5 it's subject to white-coat adherence. People just
 6 take a dose before showing up at their scheduled
 7 visit, and it bias the estimation of persistence.
 8 Self-report is affected by desirability
 9 bias, but also a lot by recall bias. You cannot
 10 ask a patient to remember the dose he forgot last
 11 month, you know? That doesn't work, by definition.
 12 Pill counting has been shown to be censored
 13 by the patients and only gives an aggregate summary
 14 of adherence.
 15 In the medical practice, I think it's
 16 starting to take up, but the use of electronic
 17 prescription databases and electronic refill
 18 databases gives us a very good estimate of the
 19 patients who don't initiate and the patients who
 20 stop taking medication. And it's underused today,
 21 but it will be more and more used, I'm sure, in the
 22 future so that we have good estimates, we can pick

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1 the patients who don't start, and we can pick the
 2 patients who stop.
 3 But for treatments that require a precise
 4 implementation, electronic monitoring will be used.
 5 And for me in clinical trials, electronic
 6 monitoring gives you really a good idea of
 7 adherence and of drug exposure in the trials. And
 8 it's such a big source of variability.
 9 When I see people doing pharmacokinetic/
 10 pharmacodynamic models and searching for weight
 11 effect, sex effect, those are minor, tiny effects.
 12 And then when you do adherence-adjusted analysis,
 13 55 percent of the residual volumes is explained
 14 because it has a major effect, not taking the
 15 medication. And it's not an absorption problem.
 16 It's not an absorption problem; it's the fact that
 17 they don't take it.
 18 So about electronic monitoring, there are
 19 several methods, and most of my research -- in
 20 fact, almost [sic] of my research -- has been based
 21 on detecting package entry. So the idea is that
 22 the chip is put in the package, and we detect when

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1 the package is opened.
 2 So the first question I will get after the
 3 talk is, yes, but it doesn't prove it's ingested.
 4 And that's true. However, we did pharmacokinetic
 5 studies, a lot of pharmacokinetic studies, and we
 6 have a very strong relationship. We have less than
 7 2 percent discrepancies between observed
 8 pharmacokinetics and predicted pharmacokinetics
 9 from the monitoring, electronic monitoring.
 10 So in my view, it's a very reliable system
 11 because you have to cheat every day if you want to
 12 cheat the system, you know? You have to use it
 13 every day.
 14 Recently, and it has been on the news in
 15 most of the countries, even in Europe, the system
 16 with the SmartPill. The idea is to put a pill in
 17 the chip so that every time you swallow the pill,
 18 and the chip for sure, you have to wear a patch,
 19 and the patch will detect the signal and send a
 20 signal.
 21 So it's in theory a very nice system. But
 22 in reality, it's very intrusive, patients'

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1 acceptance is not very high, it's technically
 2 complex, there may be some safety issues, and the
 3 reliability is not that high. I just saw a paper
 4 and say, oh, it's 5 percent discrepancy between
 5 ingesting the pill and detecting the pill, and they
 6 are also affected with people taking PPIs, for
 7 example, because they need the acid in the stomach.
 8 So the idea is nice, but my view is it's
 9 really get a lot of efforts -- difficulties,
 10 safety, technical aspects, burden to the patients
 11 to wear a patch, too little information additional
 12 to package entry.
 13 Then technically, electronic diaries, or
 14 here also a new approach, which is taking a picture
 15 at the moment that you swallow the tablet and send
 16 that picture every day to the center to show that
 17 you have taken the medication, in my view, those
 18 systems have the problem that it adds a lot of
 19 burden to the patient.
 20 The major issue is that we are trying to
 21 solve a problem, that is, patients don't do
 22 something. They don't take their medication. It's

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1 not in their habit. And what we are asking is,
2 and, by the way, now you will take a picture. We
3 are just adding burden and burden to the patients.
4 So for me it doesn't work very well.
5 The two last systems have to be combined
6 with SMS reminder, and it's burden and burden. The
7 patients quit it very early, while package entry,
8 in my view, it's a measure of pill in the hand. So
9 when the pill is in the hand, it's a very good
10 proxy that it will be swallowed. And the most
11 deviations that you will observe is not opening the
12 package, and when the package is not opened, it's
13 not taken.
14 So we mentioned bibliometry. And just about
15 the use of electronic monitoring, there are today
16 700 peer-reviewed publications, which have been
17 cited this month 50,000 times, and the h-index is
18 112. So it's a very well-established, very well-
19 documented method of measuring medication
20 adherence, and I think it's really ripe to be used
21 systemically in clinical trials.
22 There are major opportunities for adherence-

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1 informed clinical trials. It's about time savings
2 because we have better-informed benefit/risk
3 development decisions, shorter time to set the
4 optimal dosing regimen; that's very important.
5 It's cost-saving because it's greater
6 efficacy when the medication is taken, but also
7 much lower variability due to variability in drug
8 adherence, which increases the power and reduces
9 the sample size. Fewer post-approval dose
10 reduction. And at the end, the therapies will be
11 improved because we have much more informative
12 safety and more effective dosing regimens.
13 For example, if I take the NOACs today on
14 the market, we have four NOACs on the market, they
15 compete on adherence, and they have no adherence
16 data. In my view, this is no more acceptable to be
17 on the marketing side with competing nonadherence
18 only because some are once a day, some are twice a
19 day. There are issues there, and they have no
20 data. And this is no more acceptable, in my view.
21 Thank you.
22 (Applause.)

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1 MODERATOR: We have speakers from --
2 and -- there's one more talk. Is there? Sorry.
3 Sorry, there's one more talk.
4 Sorry about that.
5 Presentation – Sarrit Kovacs
6 DR. KOVACS: Good afternoon. I'm Sarrit
7 Kovacs, and I work as a clinical outcome
8 assessments reviewer in the Center for Drug
9 Evaluation and Research at the FDA. And I'll be
10 providing the regulatory perspective on electronic
11 data capture.
12 Disclaimer. So I'll be presenting my own
13 views, which do not necessarily represent an
14 official FDA position.
15 I'll be covering a few topics related to
16 electronic data capture, EDC, including the types
17 of clinical outcome assessments, or COAs, and modes
18 of administration of COAs. I'll also speak about
19 the regulations governing EDC, including FDA's
20 guidance for industry, regulatory standards, and
21 other published guidelines.
22 There are four types of COAs. One type is

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1 patient-reported outcome, or PRO measures, which is
2 a direct report of symptoms felt or functioning
3 experienced by the patient, for example, pain,
4 nausea, or physical ability. PRO measures can be
5 completed at home or in the clinic. There are also
6 clinician-reported outcome measures, where clinical
7 judgment or interpretation is needed.
8 There's interpretation of patient's
9 observable signs, behaviors, or physical
10 manifestations, such as evaluating a patient's
11 motor functioning ability or assessing a skin rash.
12 These measures are typically performed in the
13 clinic.
14 An observer-reported outcome measure is a
15 report by a parent, caregiver, or another
16 nonclinical observer regarding observable behaviors
17 displayed by a patient, for example, crying,
18 vomiting, clutching the stomach. This type of
19 measure can be completed in the home or in the
20 clinic.
21 Finally, a performance outcome measure is
22 based on a task or tasks performed by a patient

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1 according to instructions that are administered by
 2 a healthcare professional, for example, assessments
 3 of gait speed, memory recall, cognitive ability,
 4 and this type of measure is typically performed in
 5 the clinic.

6 Electronic data capture principles and
 7 considerations that I'm presenting today focus on
 8 COA data collection intended for primary or
 9 secondary endpoints in clinical trials. However,
 10 what I present may also apply to other types of
 11 data collection.

12 There are two main modes of administration
 13 of COAs, paper and electronic. Within the
 14 electronic mode of administration, there are a
 15 number of subtypes: IVRS, Web- or browser-based,
 16 and handheld computer devices such as a tablet,
 17 iPad, or personal device such as a smartphone.

18 There are many advantages of electronic over
 19 paper formats. I have listed some of the
 20 advantages. One advantage is that with electronic
 21 modes, there is no need to manually enter the data
 22 into an electronic database for data analysis,

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1 which might introduce human error. Similarly,
 2 direct transmission into an electronic database may
 3 reduce risk to the integrity of those data.

4 Electronic modes allow alarms to be set at
 5 regular intervals or incoming phone calls when
 6 using IVRS to minimize the risk of missing data and
 7 to increase the potential for greater patient
 8 compliance. Electronic modes also allow for time
 9 and date stamps to ensure patient compliance in
 10 that the data was indeed filled out when it was
 11 supposed to be completed.

12 This helps to avoid the chance that a
 13 patient may fill out all of their paper and pen
 14 daily diary entries spanning two weeks' worth of
 15 data in one sitting in the parking lot immediately
 16 before handing them in to the investigator.

17 Another example of an advantage of
 18 electronic modes over paper is that patients
 19 completing electronic diaries can record when they
 20 take their pain or rescue medication and transmit
 21 those data electronically in real time. This way
 22 sites can see which patients are not compliant, and

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1 would know to contact those patients to make sure
 2 that they're complying with taking their
 3 medications.

4 Electronic COAs, just like paper COAs, need
 5 documentation of development and validation for FDA
 6 review of evidence to support labeling claims. The
 7 FDA's PRO guidance describes good measurement
 8 principles for developing PROs. Some of these
 9 principles may be applicable to other types of COAs
 10 as well.

11 It is important to note that the PRO
 12 guidance provides an optimal approach to PRO
 13 development. However, flexibility and judgment are
 14 both necessary in order to meet the practical
 15 demands of drug development such as tight
 16 development timelines. In addition, the FDA
 17 encourages drug sponsors to engage in early and
 18 continued communication with the agency during
 19 instrument development and evaluation.

20 With regard to electronic COAs, additional
 21 documentation may be important for FDA to review
 22 such as design features, like skip patterns and

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1 forced response. For example, it may be
 2 recommended that sponsors include a "not
 3 applicable" choice to avoid inaccurate data when
 4 patients are forced to enter a response for every
 5 question, like was mentioned earlier by Sharon
 6 Hertz.

7 Additionally, it would be helpful if
 8 sponsors describe their plans for addressing
 9 missing data and analyses. Even when sponsors
 10 implement a forced response, patients can turn off
 11 their device, which may result in missing data.

12 Sponsors should include for agency review
 13 any device usability testing and results, as well
 14 as patient, investigator, and site training
 15 materials, and documentation related to migrating
 16 or reformatting an existing paper instrument to
 17 electronic format.

18 There are some device-specific regulatory
 19 issues that FDA reviews, such as comparability of
 20 the data obtained via different collection formats.
 21 For example, some studies include the option to
 22 either bring your own device, where patients use

<p style="text-align: right;">Page 233</p> <p>1 their own personal devices such as smartphones or 2 tablets, or the option to use a site-provided 3 device. 4 There are some differences in these formats 5 that may be important to consider, such as when 6 patients use their own device, it's assumed that 7 they have it on them at all times, which may aid in 8 patient compliance. This may not be the case with 9 a site-provided device. 10 In addition, investigators must ensure that 11 the device should be available to the entire 12 enrolled population. If studies include only the 13 BYOD option, this would likely exclude potential 14 patients from enrolling or participating in the 15 study. 16 Investigators must make sure that 17 replacement devices are available in case of device 18 failures or lost devices to minimize the risk of 19 missing data. And investigators must also include 20 data entry date and time stamp documentation for 21 agency review. 22 There are also some data-related regulatory</p>	<p style="text-align: right;">Page 235</p> <p>1 Exclusive control over the source data by 2 the sponsor must be avoided. The clinical trial 3 protocol or another document should specify how the 4 electronic COA source data will be maintained and 5 how the investigator will meet the regulatory 6 requirements. 7 Direct electronic COA data transmission from 8 the electronic data collection device to the 9 sponsor, clinical investigator, or third party must 10 include an electronic audit trail that documents 11 all changes to the data after it leaves the 12 electronic data collection device. 13 There is FDA guidance for industry available 14 pertaining to electronic data capture. First, 15 FDA's PRO guidance describes specific concerns when 16 using electronic instruments, details the sponsor 17 and investigator responsibilities, and provides 18 warnings regarding practices that sponsors should 19 avoid. 20 The FDA's guidance for industry on 21 computerized systems used in clinical 22 investigations provides to sponsors, CROs, data</p>
<p style="text-align: right;">Page 234</p> <p>1 issues that are reviewed by the FDA. Sponsors and 2 investigators must ensure that the FDA regulatory 3 requirements are met for recordkeeping, 4 maintenance, and access. 5 The sponsor responsibilities are independent 6 of the method used to record data, in other words, 7 paper or electronic. Sponsors should plan to 8 establish appropriate system and security controls 9 as well as cyber-security and system maintenance 10 plans that address how to ensure data integrity 11 during network attacks and system updates, software 12 updates. 13 It is important that sponsors establish a 14 database backup as well as take steps to avoid 15 premature unplanned access to unblinded data. Many 16 of these regulatory issues were mentioned earlier 17 by the previous presenters this morning. 18 The investigator is responsible for 19 maintaining direct control over the source data, 20 providing access to the records that serve as the 21 electronic source documentation for the purpose of 22 an FDA inspection or verification of source data.</p>	<p style="text-align: right;">Page 236</p> <p>1 management centers, clinical investigators, and 2 IRBs recommendations regarding the use of 3 computerized systems in clinical investigations. 4 And this applies to records in electronic form that 5 are used to create, modify, maintain, archive, 6 retrieve, or transmit clinical data required to be 7 maintained or submitted to the FDA. 8 The FDA'S guidance for industry on 9 electronic source data in clinical investigations 10 includes recommendations to sponsors, CROs, 11 clinical investigators, and others, ensuring the 12 reliability, quality, integrity, and traceability 13 of data from electronic source to electronic 14 regulatory submission. And these two latter 15 guidance documents are intended to supplement one 16 another. 17 FDA's Code of Federal Regulations Part 11 18 is related to electronic records and electronic 19 signatures. And this includes the criteria under 20 which the FDA considers electronic records and 21 signatures to be trustworthy and reliable and 22 generally equivalent to paper records.</p>

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1 This regulation requires FDA-regulated
2 sponsors to implement controls, system validations,
3 audit trails, authority checks, electronic
4 signatures, and device and system checks.
5 The FDA's Code of Federal Regulations
6 Part 312 relates to investigational new drug or IND
7 applications, and Part 812 relates to
8 investigational device exemptions. These
9 regulations apply equally to both paper and
10 electronic records. They include the general and
11 specific responsibilities for sponsors
12 and investigators with regard to recordkeeping,
13 maintenance, monitoring, and allowing FDA access to
14 records for investigation.
15 Electronic COA data must also be compliant
16 with International Conference on Harmonizations
17 guideline for good clinical practice.
18 Specifically, sponsors must ensure and document
19 that the electronic data processing system conforms
20 to the sponsor's established requirements for
21 completeness, accuracy, reliability, and
22 validation, and that is consistent with intended

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1 performance.
2 They must maintain the standard operating
3 procedures, or SOPs, and ensure that the system
4 permits data changes so that they are documented
5 and maintain an audit or edit trail. Sponsors must
6 maintain a security system as well as list of
7 authorized individuals who may make the data
8 changes and adequate backup of the data, and
9 safeguard the blinding of those data during data
10 entry and processing.
11 This slide and the next include the relevant
12 references and links that I mentioned during the
13 presentation. Thank you.
14 (Applause.)
15 MODERATOR: Thank you, Sarrit. I'm sorry
16 for missing you.
17 DR. KOVACS: Thanks. Oh, no.
18 Q&A and Panel Discussion
19 MODERATOR: I was looking on an old agenda.
20 Are there any questions for Sarrit? If not,
21 we'll go ahead and go to the moderated session.
22 I just want to thank each of the speakers

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1 for preparing some great talks. They covered a
2 diversity of issues. We started with pain
3 reporting, so just wanted to start out there and
4 just ask a really quick question.
5 The problem of having patients who report
6 their average pain being higher than their worst
7 pain or lower than their least amount of pain goes
8 to issues in numeracy. And we talked about this
9 briefly, Mark, about whether or not it might be
10 useful to have a numeracy screening instrument.
11 I was just curious about, well, one, whether
12 or not you might want to articulate how you feel
13 about that. But then, two, has there been much
14 work done with VAS where the VAS corresponds for
15 VPI? Does the average more often exceed the worst
16 score on the VAS versus the numeric rating scales,
17 or are there differences there? Or is anyone
18 familiar with that?
19 DR. JENSEN: I'm not aware of any research
20 that has compared the VAS versus the NRS with
21 respect to that particular problem.
22 MODERATOR: Issue, yes.

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1 DR. JENSEN: In respect to the first issue,
2 you know, the rates of people actually rating their
3 worst pain as lower or higher than their least or
4 worst pain or average pain are not that high. They
5 do exist, but they aren't that high.
6 It seems to me that if you want to screen
7 for that problem, it would be easier just to screen
8 for that problem rather than assess how good
9 somebody is at math before putting this patient on
10 trial. That's my own sense.
11 MODERATOR: Right. John, please?
12 JOHN: With regards to all of the issues
13 that were discussed, in particular the issue of
14 measurement and enrolling patients who may be
15 professional patients or others, I just wanted to
16 be sure to ask and to make sure that the speakers
17 agree that what we're talking about here is a
18 potentially nondifferential problem, meaning that
19 ideally, if the study is properly blinded, then
20 patients would be randomized to be in either the
21 placebo or the treatment group with equal
22 probability, raising all kinds of issues about

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1 noise and reducing the ability to detect real
2 change.
3 So I don't downplay the problem. But I just
4 want to be sure that we're on the right page here,
5 because I think with each of the issues that we're
6 considering over these two days, we need to think
7 about how it might affect the results.
8 I think the important part of this one is
9 that if the study still shows a positive effect,
10 that the issue of professional patients doesn't
11 negate that finding. And I wondered if any of our
12 speakers wanted to comment on that.
13 DR. DEVINE: I'll take the first stab at
14 that. I think professional subjects in the study,
15 at least for my discipline, there's certainly risk
16 to them. But in terms of the risk to the integrity
17 of the study, we're worried that too many
18 professional subjects will limit our ability to
19 actually answer the question.
20 But also, I think that you need to entertain
21 the possibility that people will exaggerate a
22 disease condition in order to get in. So in my

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1 field, they're telling me they're drinking 28
2 drinks a week for men to qualify for my studies,
3 and once they're in, they're more truthful about
4 their drinking.
5 So there is this tendency to start high and
6 then low, showing the possibility -- now, let's
7 assume it's evenly distributed. That could happen.
8 But I don't like that potential trend for them to
9 start high and then low and show the possibility of
10 efficacy.
11 MALE SPEAKER: I would sort of agree with
12 you in terms of if you had a significant effect,
13 the presence of professional patients doesn't take
14 that away. But more important than is the effect
15 significant or not to me is the estimate of the
16 true effect. And it messes that up.
17 So I love the idea of strategies for
18 limiting the people that enroll who are
19 professional, and if they're identified later, it
20 seems to me that a trial ought to have permission
21 to remove those from analyses if they're later
22 identified.

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1 JOHN: I'm not sure I agree with you on that
2 particular issue. But I think the point you're
3 making makes huge amounts of sense. We need to be
4 a little bit careful about how far down that road
5 we want to go.
6 No study is ever going to be perfect. There
7 are going to be some patients that sneak through
8 the process. There's no question about people
9 complaining more about symptoms to get into trials.
10 It's a large part of the regression to the mean
11 process or the natural history of the disease
12 process.
13 But my point was that we should try to
14 eliminate that as much as possible, but not go head
15 over heels with finding only the three perfect
16 patients in the world to enroll in our study, and
17 that part of the reason for that is that it's not
18 going to give us a positive result when a positive
19 result does not exist. It may well lead to a
20 negative result, which I think is an issue with
21 regards to efficacy.
22 DR. DWORKIN: I generally agree with that,

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1 John. But one concern is if you have a percentage,
2 say, of 20, 25 percent of the patients in the trial
3 are either duplicate within the trial or across
4 multiple trials, they're not taking the drug.
5 So that means your safety signal is going to
6 be some underestimate if a quarter of the patients
7 in the trial aren't taking the drug, are
8 nonadherent to medication. So that's an issue with
9 the professional patients because they're smart
10 enough to realize that drugs have risks so they
11 don't take the drug.
12 The other thing. It's not professional
13 patient. Remember *Jeri from East Palatka,
14 Florida, with relapsing-remitting MS. She was
15 blogging with patients in a trial to basically
16 encourage everybody to unblind themselves. And
17 that could lead to a false positive result.
18 In a placebo-controlled trial, if patients
19 are blogging about the side effects of active, and
20 the absence of side effects with placebo, and a
21 percentage of patients in the trial become
22 unblinded because of that, you can get a real false

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1 positive result because of the patient unblinding.
2 So I think we need to keep in mind the
3 professional patients who are duplicating and who
4 are really some kind of misconduct, and then the
5 Jeris from East Palatka who are unblinding
6 themselves.
7 JOHN: The unblinding issue is separate. I
8 completely agree.
9 MODERATOR: We're going to go to the back.
10 I'm sorry, I don't see your name. Could you --
11 DR. RICE: Andrew. It's because I've turned
12 it over. Andrew Rice from London.
13 I'm asking this question, really, because I
14 don't quite understand something coming from
15 Europe, and that's this concept of professional
16 patients. And I was talking to Philip over lunch
17 about it, and we shared some common experiences.
18 I wonder if someone can just, for the sake
19 of the few Europeans here, explain to us a little
20 bit more about them. I'll tell you how our
21 conversation goes.
22 Surprisingly, there are no European statutes

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1 or regulations, and UK ones, for inducements to
2 participating in clinical trials. Each ethics
3 committee can decide its own. But by and large,
4 you're allowed to refund -- and I'm not talking
5 about phase 1 -- reasonable expenses.
6 To us, reasonable expenses usually means a
7 fairly modest public transport reimbursement. Many
8 of our patients -- Philip and I both share
9 this -- actually just refuse that altogether. They
10 don't even claim.
11 Generally, we're not allowed to reimburse
12 people for lost time at work, and I wonder if
13 that's the difference here, because I can't quite
14 understand how people can earn these kind of monies
15 if you have much the same regulations as we do.
16 And it might be that reimbursement for work issue
17 that's the difference.
18 Just a quick rider on that. We were also
19 wondering whether, having listened to the
20 statistical monitoring talks, whether monitoring of
21 the expenses at each centers, and if you start to
22 see blips with large expenses, implying large

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1 distances of travel, you might be able to detect
2 patients playing the game. So we put it that way.
3 But we wonder if there's a big difference in
4 reimbursement that's allowable between Europe and
5 the U.S.
6 MALE SPEAKER: So, Andrew, I don't know if
7 that's it. But there are two ways that patients
8 can be reimbursed for travel. They could actually
9 get reimbursed from like a taxicab or a bus
10 receipt. But what's also often done is they get a
11 certain amount per visit, and that's considered,
12 for the purposes of the ethics committee, modest.
13 But that modest could be somewhere between
14 25 and \$50. And if the visit involves QST, for
15 example, it's going to be closer to \$50 because
16 it's uncomfortable and it's time-consuming. And if
17 you think about the professional patient who's
18 participating in three trials at the same time, 100
19 to \$150 a week is a reasonable amount of money.
20 And our economy isn't as good as the economies in
21 Europe, so it might be that that's part of the
22 difference, too, that \$150 in the United States

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1 goes further than it does in Europe.
2 DR. RICE: The economy in Europe is not as
3 good as you might imagine.
4 (Laughter.)
5 DR. RICE: But that is a clear difference,
6 and it may be something worth pointing out. And
7 actually, comparisons of the behaviors in patients
8 in clinical trials in those two systems might be a
9 worthwhile thing to suggest because, as far as I'm
10 aware, and Philip can tell me I'm wrong, we don't
11 reimburse patients for their time. So if they had
12 QST, they wouldn't get reimbursed. They'd just get
13 their travel.
14 MALE SPEAKER: If you had a two-hour visit
15 where you did the DFNS QST protocol and a bunch of
16 questionnaires, what would a typical patient in
17 London get for that two-and-a-half-hour visit?
18 DR. RICE: Travel expenses. They may get a
19 cup of tea if it's a good day.
20 (Laughter.)
21 MALE SPEAKER: Yes. We give no money at all
22 for that. And our patients, as Andrew said, often,

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1 if we offer them money for their travel, they'll
2 reject it.
3 MODERATOR: Wow.
4 DR. VRIJENS: But is there not also in the
5 U.S. patients who participate in the trials, they
6 get health coverage?
7 MALE SPEAKER: No.
8 DR. VRIJENS: While in Europe, we're all
9 covered, which makes a big difference.
10 DR. CONAGHAN: I think the drug -- that's
11 important for free drug. That is a difference with
12 our health systems. And we do see people trying to
13 get into the one or two studies where there's a new
14 drug that the health system hasn't okayed. So I'd
15 imagine in the U.S., that's quite a big driver.
16 MALE SPEAKER: Just a point of
17 clarification. In the U.S., there's safety
18 oversight in terms of healthcare. But there's not
19 comprehensive medical care provided for other
20 issues outside of the -- that's my understanding,
21 at least. John?
22 JOHN: Patients still get healthcare. But

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1 certainly we advertise studies that say, come in
2 and have a free EKG. Hopefully, that's all getting
3 better. I'm sure you've followed the arguments in
4 the U.S. about healthcare. But anyway, then
5 hopefully that goes away.
6 I think the other issue, though, is maybe
7 just a difference in philosophy. But there
8 certainly are patients who don't have a lot to do
9 with their time and will travel substantial
10 distances to do this.
11 I guess there's a real question as to how
12 important that is in some of our trials. I can
13 understand that in certain kinds of trials, it
14 would be very important. And we worry about this
15 in trials with opioids, for example, where there
16 are a number of patients who try to get into the
17 opioid trial because they want to be on opioids.
18 But I think otherwise not.
19 MODERATOR: Thank you. I think Mike
20 Rowbotham, and then we'll go to Roy, and then we'll
21 go to this side over here.
22 DR. ROWBOTHAM: Yes. My question is for the

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1 panel but also for the previous speaker as well,
2 Dr. Kovacs. I haven't heard anything about using
3 telemedicine or other techniques to try and do two
4 things. One is to have more central study
5 monitoring and verification that this is a real
6 live subject in a way that's HIPAA-compliant or
7 other kinds of biometrics that would allow you to
8 pick up subjects that are in multiple studies at
9 the same time, even across trial sites.
10 So I just wondered if we could get some
11 comment on telemedicine and similar techniques
12 because those are really coming much more into
13 mainstream medicine now.
14 MODERATOR: You want to --
15 PANELIST: In our studies, even that are
16 multisite, we like to have one center that does
17 data collection. We train the interviewers, and we
18 have a live person who calls up and does the
19 interviews, and they're trained and such.
20 So it's not electronic, but it's not paper
21 and pencil. It's actual phone calls. It seems to
22 work really well from my perspective.

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1 DR. DWORKIN: At my medical school there are
2 a bunch of movement disorder specialists, Mike, who
3 are researching, so it's not really live yet, but
4 researching doing, say, the majority of clinical
5 trial visits using telemedicine.
6 Patients like this, of course, because it
7 means they don't have to schlep from Buffalo to
8 Rochester. They can do visit 3 in a kind of Skype,
9 but HIPAA-compliant, link. And so these movement
10 disorder specialists think this is the future
11 because patients like it much better, and it's
12 cost-effective, and a lot of the visits can be done
13 that way rather than requiring the patient to come
14 into clinic.
15 PANELIST: It reduces missing data, too.
16 DR. DWORKIN: That's right.
17 DR. VRIJENS: Also, when you monitor
18 medication adherence using electronic monitoring,
19 over the 20 years, we have detected fraud several
20 times. A center where all the patients take their
21 medication exactly at the same time, that was in
22 the early days. We have had that.

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1 But also, very recently we had a study and
2 we identified a German site, which was not a real
3 clinic. It was a professional site. And very
4 strangely, all the patients in that site were like
5 the Swiss train I showed you, the perfect patient.
6 There were some deviations, but they
7 were -- and then when we looked at the clinical
8 data, because it was hypertension, it was 100
9 percent success rate in that site. But the
10 difference in outcome was 1 millimeter of mercury.
11 It was nothing.
12 Then combining the adherence data with the
13 clinical outcome, we could determine it was a
14 professional site. But it's only possible to
15 detect when all -- it's really recruiting only
16 professional patients in one site.
17 But we saw also, for example, sites
18 where -- it was a Polish site in one study, and
19 they prescribed a drug systemically, once a day, to
20 all their patients. It was a twice-a-day
21 medication. We detected that very early on. All
22 the patients were on once a day. It was a twice-a-

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1 day medication. The site didn't understand the
2 prescription.
3 MODERATOR: Roy was next, and then we're
4 going to go to this side over here.
5 DR. FREEMAN: This is a question to Eric.
6 We can quibble about the effect of fabrication on
7 drug effect and on adverse event profile. But no
8 matter what, obviously your study is one of the
9 most disturbing studies that we've seen in a long
10 time. And you, rightly said, could be even worse.
11 These are duplicitous people. These are
12 fabricators. It's likely to be worse.
13 So let me maybe give another view, and that
14 is we're used to, in clinical trials, patients
15 coming to the trial saying, you know that nice
16 Dr. Dworkin, he's so enthusiastic about this drug.
17 Let me just make him feel good and tell him that
18 it's working.
19 What about the equivalent in your study?
20 That nice Dr. Devine, he really seems to want
21 patients to be evil and fabricate and be
22 duplicitous. Let me give him a nice positive study

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1 so he can get promoted.
2 DR. DEVINE: Perhaps I created a demand
3 characteristic in my study, and elicited fraud.
4 (Laughter.)
5 DR. DEVINE: I suppose I can't rule that out
6 as a possibility. But I have seen plenty of
7 examples of fraud.
8 DR. FREEMAN: And I have, too. And I'll
9 tell you some stories, too. I've seen it in non-
10 drug studies. But I just want to give this
11 perspective.
12 DR. DEVINE: Yes. When I did the study,
13 something I didn't include in my talk, and maybe
14 not even in the paper, is I used a slight bit of
15 deception to lure them into telling me that they
16 are using fraud.
17 The main purpose of the study and the
18 consent was to evaluate rates of reimbursement and
19 the discrepancy between what subjects think they
20 should be reimbursed and what they're actually
21 reimbursed.
22 (Laughter.)

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1 DR. DEVINE: So I started with those
2 questions. And I actually had a publication from
3 that plan that was looking at whether professional
4 subjects are likely to fall into accepting risk
5 that they shouldn't accept, basically undue
6 inducement.
7 So there was a plan for that. But a little
8 bit of a lure to get them thinking that maybe I'm
9 on their side, and some normalizing around
10 concealing behavior, before I asked them about the
11 concealing behavior.
12 DR. FREEMAN: Then duplicitous on both sides
13 of the table.
14 (Laughter.)
15 DR. DEVINE: Well, it was approved by the
16 BUMC IRB, and the panel that it was approved by, I
17 was not sitting on that panel. I recused myself.
18 MODERATOR: Go ahead.
19 DR. UPMALIS: Hi. I just wanted to --
20 MODERATOR: Could you say your name? I'm
21 sorry.
22 DR. UPMALIS: It's David Upmalis from

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1 Janssen. But I think that the fraud is one issue,
2 but I think there's a bigger issue that's a dynamic
3 where you have a chronic illness, professional
4 trial sites that are encouraged to recruit quickly,
5 and oftentimes say, well, we have this huge
6 database of suitable subjects and that sort of
7 thing.
8 I really wonder if there isn't an issue
9 where you get patients who can qualify for study
10 after study, learn how to do that, and they come
11 not out of any ill intent but out of good intent
12 because they do like the coordinator, they like the
13 visit they have, and everything else. And they're
14 all such nice people.
15 It affects compliance. It affects
16 continuation. They are encouraged to continue the
17 study, so that you're getting a distorted picture.
18 And these patients who are chronic, and I've had
19 this experience not in a pain trial but in another
20 trial, have all their medications that were
21 prescribed to them still at home. And if they
22 really want to stay in the study but they don't

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1 like what's happening to them, they can resume
2 taking them, and more often than not, we don't
3 detect that.
4 DR. DEVINE: I don't believe that we should
5 recycle study subjects.
6 DR. UPMALIS: I agree.
7 DR. DEVINE: And actually, my sponsor is on
8 the same page. It's a typical exclusion criteria
9 for our trials. The past seven years of clinical
10 trial enrollment for alcohol problems is an
11 exclusion for participation in the study.
12 DR. UPMALIS: And in some trials I've done
13 recently, I've limited it to two trials, and that's
14 it. But I think that there's something there that
15 needs to be done or considered.
16 DR. RAUCK: Yes. Richard Rauck, a clinician
17 and academician at Wake Forest. I'll play a little
18 devil's advocate. I think this is something we
19 ought to be able to get out of some of our trial
20 data. You guys did a great job with the
21 pregabalin/gabapentin studies. And maybe alcohol
22 is a little different than pain because chronic

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1 pain tends to be stable.
2 Recently, I was trying to think of a series
3 of trials we've done. So there are all these ROOD
4 trials, these rapid-onset opioid trials. They all
5 came along at the same time. Right? And you had
6 to have a cancer diagnosis.
7 So we found, what we thought -- because they
8 were out of our practice, reliable patients. And
9 it goes a little bit to your training because if
10 they do re-enroll later into a very similar trial,
11 those patients now at least understand the trial,
12 how to record data. If they're good patients, I'm
13 not so sure they don't give you better data and at
14 the end of the day can look at a treatment effect
15 versus placebo more honestly, more effectively.
16 So I'm a little concerned. Clearly, if
17 patients are concealing or fabricating data, nobody
18 wants those if they're doing that kind of behavior.
19 But is that synonymous with saying an experienced
20 research patient who goes through multiple trials
21 is less reliable in the data they give? I don't
22 know. We ought to be able to get at that, and we

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1 ought to try and find out.
2 It may be easy to know in the trials we've
3 all done, right, who is a first time in versus
4 somebody who's a repeat come in. And just like you
5 guys did with the gabapentin and pregabalin trials,
6 it would be great to know. Are they more reliable,
7 less reliable, in differentiating a treatment
8 effect or effect versus placebo? I don't know.
9 Maybe somebody has done that. Nat, have you
10 done that?
11 DR. KATZ: Not yet. But I just wanted to
12 add my voice to yours. I totally agree with you
13 that if you go to experienced pain research
14 centers -- at least I know a lot of people who do
15 this -- the same patients can be great, one study
16 after another. They understand what to expect.
17 They understand what's required of them. They have
18 a lot of experience monitoring their pain
19 intensity. And you know from the last study that
20 they showed up the whole time. They stayed
21 through.
22 So we actually have a practice of

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1 encouraging our recruitment people to find people
2 who've been good in previous studies. Obviously,
3 as long as they -- also, we know them. We've got
4 their medical records. And so I actually think
5 that that's a good practice, and I think we're
6 making a mistake by mixing the fraudulent or
7 deceptive patient with the experienced patient,
8 lumping them all together as the professional
9 patients. I categorically disagree with that.

10 DR. DEVINE: I disagree. I don't see the
11 professional subject synonymous with the repeat
12 subject. But there are issues with re-enrolling a
13 subject, at least in my discipline, where
14 there's -- we fight very hard against the
15 nonspecific treatment effects.

16 Assessment has a therapeutic intervention
17 for alcoholism. Relationship-building has a
18 therapeutic effect. And so people coming and
19 getting to know us well and coming back actually
20 introduces some error variance where they're
21 actually benefiting from a psychosocial
22 intervention, which is the relationship we form

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1 with them over years.

2 They've also had exposure to the behavioral
3 platform that we use in conjunction with our
4 medication. Everybody gets it. So there is
5 something different about re-enrolling people that
6 might get that extra bit of treatment.

7 DR. KATZ: I don't doubt that there are
8 certain circumstances in which re-enrolling
9 patients is bad and should be discouraged. But I
10 just don't think we should paint it all with the
11 same brush and say that repeat patients are always
12 by definition harmful to our objectives in clinical
13 trials.

14 PANELIST: So clearly, Rich, we can get the
15 data from your site, whether this patient has been
16 in a clinical trial at your site previously. Do
17 you capture at the beginning of a trial how many
18 trials they've been in, say, at any site in the
19 past two or three years?

20 DR. RAUCK: That's a great question. We
21 don't historically. So you're right. It would be
22 hard, I guess, to go back. It's something we

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1 maybe, moving forward, should look at. I mean, I
2 agree completely with Eric. There is some bias or
3 something in the re-enrolled patient. There's no
4 question that's a subset.

5 The issue to me is, does it give us better
6 data, though, as far as does it separate real
7 effect from placebo? Which is what we want. The
8 industry more than anything just wants to know, is
9 there a real treatment effect? And maybe it's
10 better, maybe it's worse. I don't know.

11 I agree with you that it's an inherent
12 subpopulation. I just think it would be great.
13 Industry would probably love to know whether it
14 helps give you a better definition of real
15 treatment effect, I would think.

16 MODERATOR: We're going to go to Ian and
17 then to the back there, and then back to Ajay. So
18 Ian, go ahead.

19 DR. GILRON: I have two questions for
20 Bernard. Thank you for an exciting talk. And I
21 certainly think it's an important issue. I just
22 wonder if there's any data to suggest that

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1 medication adherence is less of a problem in
2 conditions associated with symptomatic therapy.

3 So someone gets up in the morning and says,
4 I have a higher risk cardiovascular events and I
5 need to take my statin, or I'm having pain and I
6 need to take that. So that's one question.

7 The second question is, and you referred to
8 this but I'm not sure, do we need to be less
9 worried about medication adherence in phase 3
10 trials? And is most of the emphasis of what you
11 were talking about more in earlier phase trials?

12 DR. VRIJENS: Let's start with the second
13 question. I think we need to address adherence
14 throughout the drug life cycle, and at the
15 beginning. So very early on, we need to maximize
16 exposure. And I would say it would be even more
17 biased than today in trials, and force adherence as
18 soon as possible, the full efficacy of treatment.

19 When we move to the next phase, I would say,
20 in phase 3, for example, we need to understand much
21 better what's the implication of nonadherence. And
22 that's where you will start to learn about the

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1 forgiveness of the treatment in real population and
2 so on. But it's very important to measure that and
3 to see how forgiving is the treatment.
4 Then when you go commercial, then you know
5 exactly what are the strengths and the weaknesses
6 of your treatment. And then you can apply the
7 appropriate methods for commercial. But it has to
8 be taken throughout the whole life cycle. That's
9 my view.
10 Now, for treatment with the feedback, we
11 have done some pain studies. We have done some
12 migraine prevention studies. Where there is very
13 strong feedback also is PPI studies for gastric
14 reflux. What we see is that there is a very strong
15 selective nonadherence. That means patients feel
16 better. They stopped. They quit for a while.
17 Then they feel worse. They take. And you see all
18 types of behavior there, especially in one of the
19 PPI studies, which was prescribed on demand.
20 You see all the behavior there. You see the
21 ones who continue taking it perfectly every day,
22 and you see the ones who take it really as a

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1 feedback. You see the ones who skip a day
2 systemically. You see all over the picture.
3 So in my view is the stronger the feedback,
4 the stronger is the selective nonadherence.
5 MODERATOR: Is there a question in the back
6 back here? I saw a hand earlier.
7 DR. JUGE: Yes. I had, I guess, two points
8 and maybe a question on something --
9 MODERATOR: Could you say your name? I'm
10 sorry. I really can't see your plaque.
11 DR. JUGE: Dean.
12 MODERATOR: Dean. Sorry.
13 DR. JUGE: That's okay.
14 MODERATOR: For the transcript, we'd like
15 everyone to --
16 DR. JUGE: Oh, there you go. My name's Dean
17 Juge. Two points, and they go back, one of them,
18 to the variability in the scores and looking at
19 patients that -- if the variability or the ability
20 to collect the data ahead of time and say, well,
21 these patients might be excluded from the study
22 because they're more variable, my suggestion is

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1 that that might be a subpopulation to look at as an
2 outlier group, not necessarily in the data
3 collection for the primary endpoint for drug
4 approval, but consider them your first set of
5 phase 4 data.
6 Because what happens is you get drug
7 approval on those that fit tightly, and then when
8 the drug's on the open market, you have a lot of
9 issues not seen that end up with problems later.
10 And immediately, a lot of times the drugs get
11 recalled when they could have foreseen programs and
12 trained around.
13 There may have been a narrow therapeutic
14 index. It may have been an adverse event, not
15 really noted but something that's manageable. But
16 it's just yanked because the risk of bringing it
17 out is worse than trying to deal with the problem
18 ahead of time.
19 So if there's a way to collect that data
20 set, to me that's always the outlier data set that
21 might be of value later to look at as what may be
22 these issues that may come out of that group. Or

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1 for the standard practitioner out there, my concept
2 here is how do you take this data from research to
3 reality?
4 We do all these studies and research, but we
5 also want the people to use this information and
6 data to treat their patients routinely, and
7 patient-reported outcomes or whatever to be a
8 routine part of treatment later after the study's
9 approved.
10 So that goes to my second point -- that's
11 one group. But the second point is, you made the
12 discussion about training or not and is it worth
13 it. And from my perspective, it's worth it from
14 two avenues.
15 One, the training is of value to show what's
16 required of the patient, but if you study the
17 differences in training, that's a huge value to
18 payers because right now you have groups out there
19 with people that you're dealing with. And if you
20 can show that the training made a big difference in
21 there, the payers might realize that a few extra
22 minutes on a new patient might be worth an extra

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1 cost for the training or develop something that's
2 worth the extra payment because it showed a
3 difference in the trial when we did that with our
4 patients. People need to understand that.
5 So if you have a study group that were going
6 through the process, and then you had a routine
7 training three months later and better development
8 or whatever that showed that I'm constantly
9 bringing this patient back in because they need
10 more information or more whatever from these
11 particular studies, that's something extra that,
12 from a payer perspective in trying to get the
13 patients in and getting them to understand this
14 particular medication or this treatment or this
15 whatever, might require something a little
16 different than you've normally known. The data is
17 there, and they can't just say, well, we're not
18 going to cover that, we're not going to do
19 whatever, and then those patients get dropped. So
20 there's another reason to capture that type of data
21 as well.
22 DR. DWORKIN: Speaking to the first point, I

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1 completely agree that in a phase 4 effectiveness
2 trial, we're going to exclude a much smaller
3 percentage of patients than phase 2 or phase 3, for
4 exactly the reasons you said. I'd completely agree
5 with that.
6 MODERATOR: So Ajay, and then we're going to
7 go to the back corner there. Then we'll come back.
8 DR. WASAN: Thanks. This is Ajay Wasan.
9 Just a comment on adherence, and I want to get some
10 of the panel's thoughts.
11 So using the electronic chip with the
12 package may be a gold standard. But a lot of us
13 use electronic diaries daily in our studies, or
14 once a week we email a Web link to someone to
15 complete surveys. And I think one thing that Rob
16 Edwards and I have found is that adding just one or
17 two adherence questions like every day can become
18 very helpful, such as, how many pills did you take
19 yesterday? Or what time of day did you take your
20 first dose today?
21 What I wonder is, and I want to get your
22 thoughts on it, whether that's some degree of kind

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1 of a low-hanging fruit that we can add to the paper
2 about recommendations for things that maybe could
3 be done to better at least track adherence. It's
4 not necessarily a gold standard, but it's using
5 what we already use now, just a tiny modification.
6 So just your thoughts on that would be good.
7 MODERATOR: Bernard, would you like to --
8 DR. VRIJENS: The use of diaries for me
9 is -- the first thing is paper diaries. They are
10 all filled just before coming at the visit. That's
11 the first thing. Electronic diaries, they don't
12 work in practice, according to our experience,
13 because people tend not to use them.
14 They only worked when we start to have a
15 reminder, you know? You have the diary, and then
16 daily sent a reminder to fill that diary. Then you
17 start to get some answer.
18 The problem there, in my view, is that when
19 we are thinking about medication adherence, it's
20 building a habit in the patients. And when you
21 look at and you ask the patients what triggered the
22 intake, they say, it's breakfast. It's dinner. I

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1 put my medication on my coffee machine, so when I
2 take my first coffee, I see my medication.
3 When you look at the patients I showed you,
4 most of them have about a three-hour average of
5 taking their medication. So it's a three-hour
6 window within which they take their medications.
7 So when you start to send a reminder to
8 those patients to ask, did you take your
9 medication -- because that's how a diary typically
10 work; did you take your medication -- when do you
11 send this text message, send this message, do you
12 send it like an agenda, 10 minutes before, or do
13 you send it 10 minutes after so you leave some time
14 to the patient to do it? Or do you send it three
15 hours after because we see that the average time,
16 the average window, is three hours?
17 But then if you allow, for example, an hour,
18 in most case, he will get that message while he's
19 in the car and the medication's at home. Did you
20 take it? Oh, yes. And so you get a lot of bias in
21 those questions because it's always associated to
22 time, and time is not a good trigger for adherence.

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1 So that's my point about diaries. Or you
 2 have to ask, yesterday what did you do? But you
 3 know most patients don't remember what they did
 4 yesterday.
 5 A lot of patients -- it's amazing, because a lot
 6 of patients, they like to check they have executed
 7 the habit. How many patients, do they say, (gasp)
 8 "Did I take it today? I don't know."
 9 DR. WASAN: I guess just a little -- in pain
 10 in general, I think all of us would say that we've
 11 found the electronic diaries to be very useful and
 12 a very high compliance rate. So I agree, yeah,
 13 there are some issues with adding adherence
 14 questions. But it doesn't necessary have as many
 15 pitfalls as you've describing. But anyways,
 16 interesting.
 17 DR. DWORKIN: But Ajay, if you could afford
 18 it, so if you were a rich drug company or you had a
 19 big NIH grant, why wouldn't you have the electronic
 20 medication packaging? I can't think of a reason
 21 why you wouldn't implement that. I was quite --
 22 DR. WASAN: Right. Exactly. That's why I

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1 said it's kind of a gold standard. And there's
 2 other similar things for --
 3 DR. DWORKIN: So in a situation of not
 4 having the resources to do it, what are
 5 alternatives that aren't going to work as well that
 6 are cheap? But if you can do it, I can't think of
 7 a reason why you wouldn't.
 8 MALE SPEAKER: I can. We've played with it
 9 here in a number of different situations, and the
 10 ones that you listed, which are -- it really grew
 11 up around HIV, when the initial HIV therapies had
 12 to be taken every five hours. Right? Not every
 13 four, not four times a day, but every five hours in
 14 order to reduce the viral load. Luckily, the
 15 treatment for HIV has gotten more consistent over
 16 time, and so it's less of a problem there.
 17 But the issue with regards to pain, Bob, is
 18 that many of our patients are on more than one
 19 medication. And so a lot of our patients will say,
 20 I put them in a little box that I have. Now, you
 21 can rig those boxes to record whether they open
 22 them or not, and there are other ways around it.

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1 But the issue of just taking off the top of
 2 the bottle to take out a pill is not always as easy
 3 as is suggested because in fact, patients will tell
 4 me, I take out the two pills, I put them in my
 5 pocket, and I go to work, and I take one later.
 6 There are different ways of using them.
 7 I'm not saying that the data's not useful.
 8 I completely agree that in the best of all worlds,
 9 it would make sense, perhaps, to do it. But at
 10 least in the studies where we're treating patients
 11 who have very significant symptoms, their issue is
 12 not about remembering the medication as much as it
 13 is about trying to get better and worrying about
 14 whether the medicines are going to work or not.
 15 So if I had a lot of money, I would invest
 16 in some other things, perhaps, before I would
 17 invest in doing this.
 18 MODERATOR: We've had some hands in the far
 19 back.
 20 DR. CONAGHAN: Hi. I'm Philip Conaghan,
 21 Leeds. I guess back to Bernard on this same
 22 topic -- and to Bob and Dennis, thanks for a great,

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1 stimulating range of topics today because this is
 2 fabulous.
 3 Bernard, how much data is there in the MSK
 4 field for MSK pain -- musculoskeletal pain -- using
 5 the electronic bottle capture data? I'm not aware
 6 of any studies, but maybe there are some. Because
 7 what I'd like to know is how much of an effect we
 8 can attribute to that adherence issue because we
 9 have great troubles with high placebo rates in all
 10 our studies. I think some of the chats here have
 11 really highlighted issues like pain variability and
 12 things.
 13 Now, what if we can never change that? But
 14 adherence, we can. Adherence measurement, we can.
 15 So here we've got a measure -- I'd love to see a
 16 trial outcome that was efficacy by adherence as an
 17 endpoint for the trial. That would really mean
 18 something to me about efficacy, not effectiveness,
 19 but efficacy.
 20 But have we got much data yet in --
 21 DR. VRIJENS: Not that I know. We have data
 22 in rheumatoid arthritis, which is a different

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1 field. But no, I don't know that there are studies
2 there.
3 DR. CONAGHAN: Because, Bob, I think this
4 comes to the point you were just saying about
5 putting it in trials. I would definitely put it in
6 my trials now because I think, wow, maybe that's
7 enough to start to separate out groups, allowing
8 that we pay attention to the previous issues about
9 getting rid of people we don't want in the trial.
10 But this is a big -- we have to examine the
11 question, even if it's not the answer.
12 DR. VRIJENS: Also, if you select the
13 patients -- because you mentioned selecting the
14 patients on training and viability. I have seen
15 some depression studies where they were proposing
16 and they were doing. They select the placebo
17 responder in a running period, and then
18 you -- because the placebo responders are the good
19 adherers, and you just kick them out. And then you
20 end up with worse adherers in the study.
21 (Laughter.)
22 DR. VRIJENS: So that's a big issue also in

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1 selecting based on placebo response.
2 MODERATOR: We've got Sharon Hertz and then
3 Andrew Rice.
4 DR. HERTZ: Has there been any analysis of
5 adherence in clinical studies and the relationship
6 with clinical trial, which treatment arm people
7 have been randomized to?
8 DR. VRIJENS: Which what?
9 DR. HERTZ: Treatment assignment. For
10 instance, is there any correlation either between
11 adherence and efficacy or, conversely, a lack of
12 adherence and adverse events?
13 DR. VRIJENS: Yes. One of the first study
14 that looked at this is the LRT, LRP LRT. It was a
15 lipid-lowering study, a very big study. And they
16 showed that the adherence to the placebo and the
17 treatment were different. And that's where the
18 placebo effect started to be discussed as well
19 because they had a relationship between adherence
20 to placebo and response to placebo.
21 So that started to trigger a lot of
22 discussion among statisticians on how to analyze

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1 those data because there was this relationship
2 between adherence to treatment and response, but
3 there was also a relation between placebo.
4 That's because when you are adherent to the
5 placebo, you are adherent to the other medications.
6 I join your point because when you measure one
7 medication, it's a proxy for the adherence to the
8 other. And when you are adherent to the other,
9 that's why the outcome was correlated as well.
10 So my point in the clinical trial on drug
11 development, typically you are interested in one
12 medication. And that's why monitoring that
13 medication is important, in my view. And patients
14 have to accept to use the package, and they have to
15 accept not to use an organizer, to use that on top
16 of it, which is something, if they accept to use a
17 weekly organizer and this -- patients accept a lot
18 of things in trials, so they have to accept this.
19 Now we are also involved in a lot of centers
20 where they want to do this in practice. And in the
21 elderly population, a lot of patients are on
22 poly medications, and I think that the weekly

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1 organizer is a great, great tool to help adherence.
2 However, when there is an issue on
3 adherence, I think putting one of the medications
4 in a special box and monitoring that for a month or
5 two months, building a habit on that one, focusing
6 on that one, will help. And it has an effect on
7 the other because I don't see in medical practice
8 all patients -- even for a drug that has a very
9 view therapeutic index, I don't see all patients
10 forever on electronic monitoring. That will never
11 happen.
12 However, when you have a very important
13 medication -- I'm taking a NOAC, the new
14 anticoagulants -- having them for one month to be
15 sure he initiates well, a special starting program,
16 that is something that may be useful in the future.
17 But in trials, it's so important to know what's the
18 drug exposure in trials. For me, it's a big help.
19 MODERATOR: Andrew, please.
20 DR. RICE: I wonder if we could just discuss
21 briefly some other methods of monitoring adherence
22 you briefly alluded to that we've had recent

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1 experience of. And again, like John, it comes from
2 the HIV literature, where in the early days there
3 was a lot of evidence of drug sharing in the very,
4 very early trials. So that field is sensitized to
5 the issue.

6 That's the use of unannounced random
7 sampling of patients for plasma levels of the drug
8 outside of the normal PK monitoring. We recently
9 did that for an HIV neuropathy study, and despite
10 all the normal test of adherence that you've
11 referred to, there were a number of patients in the
12 pregabalin group that had no detectable pregabalin
13 in their blood, and even more disturbingly for a
14 widely available drug, some patients in the placebo
15 group who had pregabalin in their blood.

16 It's a very simple precaution, and I'm just
17 very surprised we don't do it more often.

18 DR. VRIJENS: Yes. It works. These blood
19 concentrations work if you do it -- you don't
20 inform the patients when it will happen. It's at
21 random. And there is an excellent study that is
22 recent on the hypertension because they have

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1 developed a test -- it's a urine test -- that can
2 detect about 90 percent of the medications used for
3 hypertension.

4 It's not a measure. It's a dichotomic.
5 It's yes/no, presence or absence of any medications
6 for hypertension. And they did it without
7 informing the patients, and they concluded that
8 half of the resistant hypertensive patients were
9 nonadherent, were not resistant. And they did it
10 through a urine test like that.

11 But it only works if you don't plan it, and
12 if it's acceptable in the population, that a
13 patient walks in and you say, oh, I will measure
14 you.

15 DR. RICE: No. I absolutely agree with you.
16 It has to be done unannounced.

17 DR. VRIJENS: There are some studies they
18 have also done, and they have compared it very
19 successfully with electronic monitoring, is
20 unplanned pill counting. So that's very frequent
21 in California for homeless patients. They just
22 walk in, they catch them, and they count their

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1 pills.

2 They have shown that the bias we see with
3 pill count is not there when you do unplanned pill
4 counting. But again, you have to show up in their
5 home or where they live and catch their pills and
6 count. It's very intrusive.

7 DR. RICE: But blood testing you can do on a
8 visit where you were going to take normal blood for
9 liver function monitoring or whatever, as long as
10 it's not part of a pharmacokinetic part, where they
11 come and take their drug at a certain time.

12 DR. VRIJENS: The problem is when you start
13 to do that, people will know that you do that
14 sometimes. And then it will be on the blood, and
15 then --

16 (Laughter.)

17 DR. VRIJENS: But it works. It has worked
18 in several studies.

19 MODERATOR: We're going to go back to David
20 Hewitt.

21 DR. HEWITT: Yes. My question was,
22 obviously it's good to find these things and then

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1 go back and retrain the patient and retrain the
2 site. But from a statistical analysis point of
3 view, you still are doing an intent-to-treat
4 analysis.

5 Unless you're just going to use it for a
6 sensitivity analysis at the end, it's kind of
7 frustrating to know that at the end, you're using
8 data that's bad, but there's not much you can do
9 about it because you're still stuck with an intent-
10 to-treat. So I was wondering if anybody wanted to
11 speak to that.

12 MALE SPEAKER: We've talked about the
13 usefulness of monitor and adherence, and we've
14 talked about the usefulness of training for pain
15 assessment. I don't think we've mentioned about
16 whether, in trials, we should systemically train
17 for adherence, provide these tips. And then maybe
18 if in two weeks you see an upswing of lack of
19 adherence, then that's the time to kick another
20 refresher. But how many studies now systematically
21 train for adherence?

22 DR. VRIJENS: Yes. My view was changed on

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1 that also because in the past, my first papers on
2 adherence, I have always shown that patients do a
3 wonderful experiment by taking less and more doses.
4 They do a dose-ranging study. Because when you do
5 a dose-ranging study, you change the dose. When
6 they do a dose-ranging study, they keep the same
7 dose but change the interval between dose.
8 So when you capture that information, it's
9 very rich information because you can learn a lot
10 from that experiment. And that was my view of
11 using adherence data.
12 So I would say do the ITT analysis first.
13 The ITT analysis is the base, it's clear. But then
14 in addition, you can learn and you can have an
15 estimate of a PK/PD model. You can have an
16 estimate of full efficacy in addition to the
17 intention-to-treat. That was my view.
18 But today, the FDA drug guidance,
19 "Enrichment in Clinical Trials," they specifically
20 mention that adherence could be used first for
21 screening nonadherent patients in the run-in and
22 kick them out. And secondly, the dose data should

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1 be used to maximize exposure and get full efficacy
2 in the clinical trials as soon as possible.
3 So that's the view, and I think it makes a
4 lot of sense because adherence-adjusted analysis
5 could always be biased because it's a post-
6 randomization variable. There could be bias there.
7 MODERATOR: Nat and then Jim Witter.
8 DR. KATZ: I had a quick question for Eric.
9 I wonder if in the study that you did on the
10 fraudulent patients, whether you ran across any
11 stories of investigator collusion and those types
12 of activities? Because obviously, it's not only
13 the patient that has the financial incentive to get
14 in the trial; it's also the investigator.
15 DR. DEVINE: Yes. That's an interesting
16 question, which I did not investigate. But I would
17 imagine there probably are investigators that look
18 the other way. They know the subject has a
19 disease, and they look the other way. So I might
20 think about that for the next survey.
21 MODERATOR: Jim Witter?
22 DR. WITTER: Mark, one potential way to

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1 improve the sensitivity of the MPRS scale might be
2 to go back to some things that Grace Lee worked
3 with many years ago, where verbal anchors are added
4 to the scale. This could be very simple, so zero
5 to 3 could be marked with mild, 4 to 6 could be
6 marked with moderate, and so forth.
7 So this would be, I think, a simple
8 addition. And in my own experience one-to-one with
9 patients, they are amenable to these kinds of
10 suggestions, and they may use the scale in ways
11 that don't confirm with the majority.
12 So they might say, well, my pain level is a
13 3, and at the same time they're saying their pain
14 is really severe. But if you point out that it
15 would be more useful if they used the broader range
16 of the scale, they're okay with that. So this
17 might be part of a training addition, and clarify
18 the scale also to subjects.
19 DR. JENSEN: I don't know if that's included
20 in your training, where you say, in general, people
21 view this as -- that would be an interesting
22 question. I don't know whether it would have an

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1 effect. But it could potentially improve
2 sensitivity.
3 MODERATOR: Maybe, Nat, have you looked at
4 this at all?
5 DR. KATZ: That's kind of a sad story.
6 Actually, in our first version of our training
7 program, we did have verbal anchors next to all the
8 numbers. Mark, you may remember this.
9 It created a bit of a brawl; if you can
10 imagine psychometricians brawling with each other,
11 that's sort of what happened, where there was an
12 armed camp that thought that it was a horrendous
13 mistake we had made to include verbal anchors along
14 the same side as a numerical rating scale.
15 So with neither data on each side, we just
16 took it out to keep the peace. But I still think
17 that it's an interesting idea, to see if we could
18 train patients to do better.
19 MALE SPEAKER: It's amazing that that's an
20 interesting idea at this point in the life cycle of
21 pain science.
22 MALE SPEAKER: The U.S. military has

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1 implemented a pain scale that they are now testing,
 2 which has color, words, and numbers all on the same
 3 scale.
 4 MALE SPEAKER: And faces, John.
 5 MALE SPEAKER: I'm sorry, and faces. I'm
 6 sorry, I forgot to mention that.
 7 MALE SPEAKER: Everything except the kitchen
 8 sink.
 9 MALE SPEAKER: Yes. It'll be interesting to
 10 see how -- a lot of us commented about that
 11 particular scale, but they didn't think about it.
 12 They went ahead with it anyway. So they're going
 13 to be collecting a data. It will be interesting to
 14 see what happens with it.
 15 MALE SPEAKER: So if empirically one added
 16 labels to a numerical pain rating scale, would that
 17 just be heresy to do that without the backup of
 18 validity data?
 19 MODERATOR: I'd like to let Sharon Hertz
 20 comment next.
 21 DR. HERTZ: I think you just answered the
 22 question. I think we'd like to know what that does

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1 to the performance characteristics, so you'd
 2 probably need to do some study before you wanted to
 3 rely on that.
 4 I think everyone would want to know, not
 5 just from a regulatory perspective. But it will be
 6 interesting to know what that kind of -- does it
 7 really change it to categorical scale, or is it
 8 still a numerical rating scale? What does it mean?
 9 Because we know that 1 to 10 is not an even
 10 distribution, necessarily, of intensity. What does
 11 that do to it and how does that change the
 12 response?
 13 So it would be important, I think, to have
 14 an idea of what you're doing. Just looking for
 15 concordant responses may not really be helpful if
 16 you don't actually know what you end up measuring.
 17 MODERATOR: Jim Witter, would you like
 18 to --
 19 DR. WITTER: Just another question again.
 20 I'm going to pick up on Philip's comment earlier.
 21 We in rheumatology have, over the years now, been
 22 blessed, I guess, with biologics, which are given,

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1 by necessity, by injection.
 2 So what is the adherence, do we know, of
 3 injectables versus topicals versus per os
 4 medications, which is what I assume we've been
 5 talking about mostly here.
 6 DR. VRIJENS: Yes. That's a big discussion
 7 because we have some areas, like oncology, moving
 8 from injectables to oral. We have the opposite in
 9 MS, for example, moving from injectable to oral,
 10 but also in RA, the new ones are oral. There are
 11 problems of adherence on both sides. So it's not
 12 because you go oral or it's not because you go
 13 injectable that you solve the adherence issue.
 14 One of the first studies in leukemia, it was
 15 very clear, when you read the qualitative comments
 16 of the patients, it was like, if it was an
 17 important drug, they would inject me. So because
 18 it was oral, it was less important. So people
 19 perceived it very differently.
 20 Then you have the oral issue of people don't
 21 want the needles, the fear of the needles. But
 22 typically, that disappears very fast. In medical

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1 practice also -- especially in Europe; I don't know
 2 in the States -- but all the injectables, MS, RA,
 3 there is a nurse to initiate the treatment for at
 4 least one year. They are very intensive the first
 5 weeks, and then they will follow the patient till
 6 one year.
 7 The orals, they come in and they get a
 8 prescription, and it's oral. It's done. So that
 9 initiation by a nurse is a major, major difference
 10 in treatment initiation.
 11 So we have monitored injectables, and we are
 12 starting a study last week in RA just with the
 13 injectables where we capture the time they throw
 14 away the needles. And we start to see some data in
 15 MS, but also in RA, that are really suboptimal in
 16 treatment.
 17 Then those biologics, first of all, they are
 18 on top of other treatment, very often, and they're
 19 not by themselves. So it is also the adherence to
 20 the others. And the dosing regimens are pretty
 21 difficult, every other week; every other day in MS,
 22 every other day, every other week in RA. Those are

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1 really difficult to build a habit, and even every
2 month.
3 The advantage with every month, you can send
4 a reminder to the patient because it's only 12
5 reminders in a year, and it's not such a burden.
6 But every month, it's a very difficult dosing
7 regimen. It has been proven in osteoporosis where
8 bisphosphonates, which have to be taken outside of
9 food, they were very difficult to take every day.
10 So every week, it's easy to build a habit
11 every week. Every Monday I do it. But when it
12 starts to be every month, the results were not good
13 at all because the first of the month is never the
14 same day. It's very complex.
15 So we have to think about those. It's not
16 because we go biologics or we go oral that we solve
17 the issue. There are many, many issues, and we
18 need to think about those.
19 MODERATOR: All right. Well, it's our
20 coffee break now. We could keep going if people
21 want to keep going, or people could come up and ask
22 our panelists during the break. But thank you all.

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1 (Applause.)
2 (Whereupon, a brief recess was taken.)
3 MODERATOR: [In progress] -- on site
4 selection and some of the details of central
5 statistical monitoring. The discussion session
6 will be held first thing tomorrow morning. So the
7 plan is to end, I think, at about 5:00 today.
8 Our first speaker is going to be Rick
9 Malamut, who's the vice president of global
10 clinical development and head of the pain
11 therapeutic area at Teva Pharmaceuticals. He's
12 going to be speaking about site selection,
13 training, and surveillance.
14 Rick?
15 Presentation – Richard Malamut
16 DR. MALAMUT: Hi. So again, thanks to Bob
17 and Dennis for allowing me to come here. This
18 slide is not depictive of what some of my employees
19 think of me at the end of a day, but it is an
20 example.
21 So I think this is probably well timed
22 because as I've been listening through most of the

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1 day, not all, we spent a lot of time focusing on
2 the study subject, the study patient, picking on
3 them a little bit. And now I think we're going to
4 switch gears a bit. And we want to talk more about
5 the investigator, more about the sites, more about
6 the monitors and what we could do better for that.
7 The other thing about this is I started to
8 look for all the -- what I assure will be multiple
9 research papers going into outcomes on whether it
10 matters as to which site you pick and training.
11 And we already heard from Mark about all of the
12 studies he showed showing outcomes in monitoring.
13 And I won't show all of them.
14 So a lot of this will come from internal,
15 what we do at Teva, what may be standard across
16 industry, so I'm very curious from my colleagues as
17 to whether they follow these same guidelines, and
18 then a lot about some of potential research
19 questions: What should we do? Does training
20 matter? Does surveillance actually matter and how
21 can we actually prove that?
22 So I think this is familiar to all of you.

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1 A lot of this comes from the '96 ICH guidance,
2 which is currently being revised or updated. And a
3 lot of this has to do with safety and the rights of
4 the patient and the person in the study. So it is
5 about creating a high-quality research study that
6 gives an appropriate result, but throughout it all,
7 we ought to be mindful about the person involved in
8 the study.
9 So I think a lot of this, many of you, if
10 not most of you, are aware of as to what goes on
11 internally when we put together a study, and so
12 this is a slide that doesn't show everything that
13 goes on. But I thought I would just show this, and
14 then I would just highlight the two or three or
15 four items that would relate to this topic.
16 As I started to look, I realized, wow, it's
17 going to be at least half and maybe most of this.
18 So the goal was to try to condense this down into
19 30 minutes. So I'll go through all of this quick,
20 assuming that you-all know a lot about this, and
21 then really to focus on some of the questions.
22 So first of all, site selection, so again,

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1 usually led by the operations group within the
 2 sponsor and is based on input from multiple
 3 functions, including commercial, though mainly, as
 4 you'll see in the third bullet point, based on the
 5 eventual plan as to where you might want to go
 6 assuming success. But certainly, the clinical
 7 group, the medical group who's out there
 8 interacting with the physicians who knows the
 9 individual countries.

10 Regulatory pathways that must be followed.
 11 Clinical drug supply matters between different
 12 countries and different regions.

13 The second bullet point can be applied to
 14 the site selection as well as country selection,
 15 but certainly, we want to know how well the country
 16 has done in prior studies of the same disease
 17 indication. What's the data look like? Has it
 18 been high quality?

19 We heard earlier from Sharon about a country
 20 that had some sites that maybe didn't deliver
 21 high-quality data, and that would go into our
 22 decision-making.

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1 How well have they done with the study
 2 requirements? We are interested in recruiting.
 3 Did the country seem to have enough of the disease
 4 indication with the right qualifications to bring
 5 into the study, and what is the disease indication
 6 prevalence? We wouldn't go to a country that
 7 doesn't recognize or doesn't have a high
 8 preponderance of the disease we're studying.

9 As I said, to get marketing authorization,
 10 which is the long-term goal, we may need to put a
 11 site or select a country. An example might be
 12 Russia, where you have to include a site in Russia
 13 in order to later get marketing in that country.

14 Then, of course, what's in the protocol? It
 15 may be differ based on the protocol. We talked
 16 about disease prevalence. Certain countries and
 17 regions are less accepting of including a placebo
 18 arm. What is the comparator when we're putting in
 19 an active comparator? In some countries, the
 20 comparator we choose may not be available.

21 What's the standard of care? What are study
 22 procedures? So all of this goes into selecting the

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1 country.

2 Now, when you get to the site, a lot of this
 3 is repeat, though with perhaps some additional
 4 nuance. So again, same ideas on the prior slide.
 5 We know that when you're investing in stocks, past
 6 performance is not a predictor of future success.

7 So in site selection, we don't follow that,
 8 and in fact, we actually rely heavily on how well
 9 sites have done in past studies when we're looking
 10 to choose them for the next study. And number one
 11 up there is quality. We are looking to make sure
 12 that the quality of the data that's been provided
 13 is actually high-quality data.

14 We would like the investigator to have some
 15 expertise in the disease area, particularly if it's
 16 a somewhat rare disease area where it needs a
 17 special level of expertise.

18 Unfortunately, logistics play a role. And
 19 if we find a very high-quality site with disease
 20 expertise and a large number of potential study
 21 patients, but we know the IRB at that site meets
 22 only every two months, and when we tried to

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1 contract with the site or that institution in the
 2 past, it's taken six months, regrettably, it gets
 3 very challenging to include that site as much as we
 4 may want to for the other reasons. So that does
 5 come into play.

6 Again, how well they followed study
 7 requirements. Did they not follow the protocol?
 8 What were the protocol violations? And then last
 9 is how well have they done in recruiting. And it's
 10 not just recruiting patients, it's recruiting
 11 high-quality patients, but yes, the numbers do
 12 matter in past studies.

13 If we have a less common or maybe more
 14 complex disease process, we often do, all the other
 15 factors aside, need to go to specialized sites that
 16 have those somewhat rarer patients. I guess
 17 arthromyalgia could be an example, where very few
 18 of these patients out there in the world and only a
 19 few sites may have access to them.

20 Or it may be that the protocol requires some
 21 sort of special skill. You need to be able to do
 22 nerve conductions or QST or some of the other

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1 things. Even recognizing what allodynia is and
2 testing for allodynia. We all know. But some
3 sites, is it better to try to train them and teach
4 them or hopefully they actually know what it is
5 ahead of time. I'd rather they know ahead of time.
6 So once we've made a preliminary list of
7 sites, the sites themselves, look at the protocol,
8 under confidentiality. They let us know their
9 interest. Do they have the capacity? Are they
10 involved in other studies? Do they think they can
11 meet the recruitment goals? Do they have the
12 bandwidth? Are they involved in four other
13 studies, and they can't devote time to ours?
14 Once there's been a mutual agreement that we
15 think they could participate, and they would like
16 to, then there's a preselection site visit. So
17 this is the [inaudible – mic fades] site selection,
18 it's also the first step in training, and it's also
19 the first step in surveillance, where our monitors
20 and study personnel first get to go to the site,
21 meet the site personnel, look at the facilities,
22 and begin to assess whether they can actually do

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1 the study in the way that we want them to do it.
2 The last bullet point, if they've been
3 previously inspected by FDA, we want to know how it
4 went. What were the issues? Were they resolved?
5 Were they resolvable? More ominous, we'll
6 actually -- and we do this with every site. We
7 compare a site that we think could, should be in
8 our study with the FDA produced registries of sites
9 that have been de-barred or have had some of these
10 other restrictions placed on them. Warning
11 letters, maybe not. We may investigate what that
12 was about, but otherwise, we won't include sites
13 that are on these lists.
14 So first break. And again, throughout this,
15 since there isn't a lot of data to present to you,
16 my conclusion overall was that we need data, and we
17 need to know does this matter. Does selecting the
18 proper site lead to a higher quality study with
19 more reliable results, however that's mentioned.
20 So these are just some of my own questions.
21 I don't have answers. I'm hoping some of you do.
22 Opinions are welcome, and we'll get to some of this

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1 during the discussion tomorrow.
2 But what about the selection of an academic
3 site versus a research site? The myth is that the
4 academic site has the high-quality patients with
5 the disease expertise but doesn't recruit so fast
6 and takes a long time to get started. That's the
7 myth.
8 The research site, the myth is, recruit
9 incredibly fast. We'll bring in lots of patients,
10 but they don't have the disease expertise, and a
11 lot of those patients aren't the right patients.
12 So those are myths, probably like all
13 generalizations, maybe not fully true, but what do
14 we think? Does it matter in looking at the results
15 of a study your proportion of academic sites versus
16 research sites?
17 Next, what about those fast recruiting
18 countries that we've heard about? There's a lure
19 there. We know that we can go to certain regions,
20 certain countries, and we'll recruit very quickly.
21 Is the study quality truly not as acceptable as it
22 might be in other areas?

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1 I talked about clinical study experience.
2 So if we want study experience, how do we identify
3 the next generation of high-quality sites and
4 investigators if they haven't done studies? Is
5 there something we can do? Is there some kind of
6 training program? Is there some sort of
7 identification process for a site or somewhere in
8 the world where they might be interested but they
9 haven't done it? And we can sort of nurture future
10 high-quality sites.
11 What about speed and quantity? As an
12 industry, we want to recruit quickly. We have our
13 timelines. We have our metrics. So is that a
14 negative factor in study data if you recruit
15 quickly, or if a site has large number of study
16 subjects, is that a good thing or a bad thing?
17 There are some papers looking at the high enrollers
18 with investigator enthusiasm leading to an increase
19 in placebo rate.
20 So there isn't a lot out there. Do we know
21 that a fast recruiting site necessarily has lower
22 quality data?

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1 Training. So we do a lot of training, and
 2 everyone is familiar with training the sites at
 3 investigators meeting. What maybe not everyone
 4 knows is we spend a lot of time training vendors,
 5 and we'll get to a little about that with
 6 surveillance. And we also train our internal
 7 people.
 8 There's an assumption that, oh, the sponsor
 9 knows everything that's going on with the study,
 10 and, in fact, that's not the case. Let me give you
 11 that insight.
 12 So investigator meetings and other training
 13 meetings are to train everybody involved with the
 14 study. I think everyone here is familiar with an
 15 investigator meeting and what goes on there.
 16 I want to look at the fourth bullet point
 17 where now there's a trend towards virtual
 18 investigator meetings with the idea that it will
 19 save money. I will tell you it may not save money.
 20 I'm looking out there and wondering if my brethren
 21 sponsors have seen the same thing. It's not so
 22 cheap to run a WebEx. And I wonder whether in

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1 trying to make things simpler, we're actually
 2 losing some of the advantages of a face-to-face
 3 investigator meeting. You may guess my bias.
 4 Does it matter that you're meeting the
 5 investigators face to face? If an investigator is
 6 meeting the sponsor and the CRO, are they more
 7 likely to try to do things the right way? Are they
 8 paying attention? Are they even at the computer
 9 screen during the virtual investigator meeting? We
 10 don't always know. We think so. We put tricky
 11 test questions in to make sure that they're there,
 12 but are they actually doing it? Is it the
 13 coordinator?
 14 Then by not having a face-to-face meeting,
 15 you need additional training afterwards to go
 16 through the vendor training. So it's a lot of
 17 indirect training. I wonder whether we had it
 18 right the first time, but want to know opinions.
 19 Then after the investigator meeting, that's
 20 not the end. There's periodic training afterwards.
 21 There may be a need for an interim investigator
 22 meeting, and certainly, multiple teleconferences

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1 and WebExes between the medical monitor and the
 2 sites to discuss study issues.
 3 I think everyone knows about the role of the
 4 principal investigator. Again, it's protecting the
 5 rights, safety, and welfare of subjects and
 6 certainly having control of the drugs and biologic
 7 products.
 8 Look at that fourth bullet point.
 9 "Personally conducts or supervises the
 10 investigation." Well, that's the assumption. We
 11 know for those who have done studies, we have
 12 generally very well trained coordinators that we're
 13 joined at the hip with when we're running studies.
 14 So how much is being done by the coordinator? How
 15 much is the investigator involved, and does it
 16 matter if you've got an excellent coordinator?
 17 What about the sub-investigators? We may
 18 vet the investigator as high quality,
 19 knowledgeable, but the person at the site may not
 20 be the investigator doing all of the procedures.
 21 They're listed, but do we have the same access for
 22 training and assessment? And then, of course, the

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1 investigator is responsible for all that happens.
 2 So hopefully, that's an enticement.
 3 The site initiation visit comes generally
 4 after the investigator meeting and is another way
 5 to train the sites, and again, another way to begin
 6 some early surveillance because it's making sure
 7 that the site staff, including investigator,
 8 coordinator, and sub-investigator, truly understand
 9 the protocol. They understand the process of
 10 informed consent and so on.
 11 Does the site have everything they need? Do
 12 they have dedicated locked drug rooms? Do they
 13 have a dedicated place to perform the study, or
 14 will it be done in the hallway because the exam
 15 rooms could be busy on a given day? And then to
 16 resolve the appropriate needs. The idea is not to
 17 be punitive, I'll say this again, but to actually
 18 help train and facilitate because if we've gone to
 19 this point where we believe the site can do a good
 20 job and they're appropriate, we want to try to help
 21 them to provide the data we need.
 22 So informed consent, I won't go through most

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1 of this. I think everyone here is familiar with
2 the concept of informed consent, but I want to look
3 at that bottom box in which maybe as a way of
4 improving data quality, this has been discussed
5 before about trying to standardized the informed
6 consent process.

7 We've heard talks from -- Nat and Neil
8 Singla have both addressed this issue as to the
9 value of trying to standardized informed consent to
10 eliminate the overly enthusiastic investigator or
11 to try to standardize for the potential study
12 subject so that they're not coming into the study
13 with expectations, negative or positive, that could
14 impact the study. So that's something that I know
15 is already being done and hopefully looking forward
16 to further results of this.

17 So some questions about training. Again, I
18 addressed some of these. What is the relative
19 involvement of principal investigators and
20 coordinators, and does it matter? And in fact,
21 could it be better that a highly trained, invested
22 nurse coordinator who's doing a lot of the

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1 involvement with the study subject, or do we really
2 want the PIs or the sub-Is in the room or
3 interacting more, taking more of the scales and so
4 on?

5 We've already talked is there any difference
6 in study conduct between a face-to-face versus a
7 virtual investigator meeting. We bring people to
8 investigator meetings, and we make this assumption
9 that because we brought them somewhere and we gave
10 them a full day of presentations on the protocol
11 and study procedures that they've got it, and
12 they're now ready to go out and do the study.

13 Or is that they have the investigator
14 meeting, two months later, the first patient walks
15 in, and everyone starts scrambling to find the
16 protocol they were given to remind themselves,
17 well, what are we supposed to do and did I have to
18 do this now or is that later?

19 So is that enough? Do we need some kind of
20 more formal certification? We don't have that
21 really now.

22 What about overall certification? We know

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1 there's courses. We know you can be trained to do
2 clinical studies. We don't require it. Should we?
3 Should a site or an investigator or a coordinator
4 be mandated to take some kind of certification?
5 I'm betting that won't be a popular question, but I
6 throw it out there.

7 Should we standardize the informed consent
8 process? We're hearing again, as I mentioned, Nat
9 and Neil might say yes, but we should talk more
10 about that.

11 Study surveillance. We've already talked a
12 bit about there's surveillance through the entire
13 study, and there's some even surveillance
14 activities that I haven't mentioned in here that
15 come before the study even starts, and I'll show
16 them here.

17 So we talked about the site initiation
18 visit, the site activation where the site is
19 visited and again, a surveillance before starting.
20 And then while the study is ongoing, we have inter-
21 monitoring visits where we send study monitors to
22 the site, and we'll talk about that. And then the

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1 site audits, both internal from the sponsor but
2 also in preparing for an external audit. And then
3 the closeout visit, another means of study
4 surveillance.

5 So inter-monitoring visits are mandated.
6 They are necessary, but sponsors have quite a bit
7 of flexibility. And I know in your pre-read, there
8 were different types of central monitoring not
9 mandated at all sites at all times, based on
10 certain triggers. We wonder whether is that enough
11 or should we standardize the monitoring, looking at
12 the data. It is the monitor who is the primary
13 point of contact between the site and the sponsor.
14 They're our eyes. They're our ears.

15 We know we have inter-monitoring visits, but
16 frequency is really based upon the individual site.
17 What is the patient visit schedule at a given
18 study? How is the site doing? A high enrolling
19 site will probably -- not probably, will generate
20 more monitoring visits. And again, helping the
21 sites to prepare for internal quality assurance,
22 internal audits, and then more formal inspection

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1 audits.

2 So again, the monitoring visit purpose is to

3 make sure that the reported trial data is accurate;

4 that it's complete; that where they were supposed

5 to enter data, it's been entered; and it's

6 verifiable from the source. We're going to come

7 back to that in another way.

8 We want to make sure that the conduct of the

9 trial is being performed following to proper

10 requirements, not only based on following the

11 protocol but also following GCP principles and

12 regulatory requirements.

13 Are the drugs being stored properly? Are

14 they accountable? Are they missing pills? When

15 you walk in, are there pills all over the floor?

16 Not a good sign if you walk in and you see that.

17 Are the safety events being reported? Are

18 the monitors going in and hearing about a safety

19 event that happened a month before and just didn't

20 get around to being reported? That would be a bad

21 thing.

22 Are the protocol violations actually being

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1 identified and reported? Again, monitors have gone

2 to sites in some of our studies, and just like

3 Sharon was expressing unhappiness that the FDA

4 finds these things, sponsors are unhappy when we go

5 in and we find things that haven't been reported to

6 us.

7 Then again, it's not punitive. The idea

8 here is not to say, oh, you're horrible, shame on

9 you, you're out, you'll never work in this -- no.

10 The idea is to try to train them or retrain them,

11 make sure they're doing it properly, make sure they

12 understand what they were supposed to do. Very

13 often, they didn't quite understand. And then

14 assisting the sites in resolving queries that come

15 during the conduct of a study.

16 So the source documents, this will be one of

17 my pet peeves is that -- so the source documents

18 are the patient's medical file, the patient's

19 medical records. And presumably, every study

20 subject, every study patient has a medical file

21 somewhere. Presumably, even healthy volunteers

22 have a medical file somewhere. And so it has the

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1 history, the lab results, the medications and so

2 on. The trick is getting to see it.

3 Again, if it's a site that where the study

4 subjects, study patient is coming from the site,

5 that's relatively easy because presumably, that PI

6 has that chart in their office, or in their

7 partner's office, or one floor down from the

8 referring specialist.

9 But for some sites where a number of the

10 study patients aren't coming from the site, they're

11 coming from referrals, from advertising, at the

12 research sites, maybe most, if not all, of the

13 patients are coming from that route. So then we

14 need to try to make sure that a patient who comes

15 in and says, "Well, I had postherpetic neuralgia

16 five years ago" really had postherpetic neuralgia

17 five years ago. And how do you confirm that?

18 So there's a belief, my belief but also at

19 Teva that, in fact, we need to -- in everybody, is

20 that possible in everybody? But in every study

21 subject, actually do a source document

22 verification, look at that patient's medical files.

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1 Do they have a medical problem that they didn't

2 tell us about? Are they on a med that would be

3 contraindicated for the study? Do they really have

4 the diagnosis we thought they had or maybe what

5 they thought they had?

6 It doesn't have to fall into the fraudulent

7 patient realm. It could be that the patient really

8 didn't know what they had. They knew they had some

9 kind of foot pain, and they had some kind of

10 neuropathy. Maybe they didn't know what their

11 neuropathy was or what the pain was from.

12 So we want to make sure and look at, as best

13 we can, every single study patient's source

14 document. And so our medical monitors do that. I

15 don't know how standard this is. I'm curious to

16 hear.

17 Vendors, we talked about oversight of the

18 sites, but we also need to oversee the vendors.

19 And many sponsors are more and more using external

20 vendors to run studies, to be monitoring central

21 laboratories, central EKGs laboratories, medical

22 monitors. Sometimes the majority of the study is

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1 outsourced to a vendor, so the sponsor does need to
2 have some oversight of what's going on.
3 As we outsource globally, we need greater
4 scrutiny, not less. So just because you've
5 outsourced it to a CRO, no matter how good they are
6 and I'll say most CROs are really quite good, you
7 still need to look. And sponsors still need to
8 have a look and make sure that things are going
9 well. And there have been some instances where the
10 CRO didn't do everything they were supposed to do,
11 and sponsors are responsible.
12 So again, Teva has an actual vendor
13 management plan in which every study that uses
14 external vendors, there's a vendor management plan
15 organized between the sponsor and the vendor in
16 which everyone knows what the roles are, everyone
17 understands how the vendor's activities will be
18 assessed.
19 These are just some of the things we may
20 look at.
21 So data is important, and we've talked about
22 collecting the data. There was an old statement I

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1 used to hear that if it's not recorded somewhere,
2 it never happened. In a clinical study if it's not
3 written down or entered into an eDiary, it didn't
4 happen. So we have to make sure that the trial
5 master file is complete and includes all the
6 necessary documents.
7 Again, some of it has to do with site
8 compliance and site qualifications. Some of it has
9 to do with study conduct. Do they have their SOPs?
10 Is the sponsor personnel CVs in the master -- along
11 with is the data recorded and all the other things
12 that we've talked about.
13 One other means of surveillance is a
14 database lock. So again, it's one last look from
15 the time of last patient out of the study, there's
16 generally around a six-week period, sometimes a
17 little less, sometimes a little more, where the
18 monitors go back again, sponsor data management
19 people go back in again, look one more time at the
20 data, look one more time to make sure that
21 everything is entered where it should be, that
22 there's no discrepancies before we lock the

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1 database.
2 It's only when all that has been resolved,
3 when all queries to the sites have been resolved,
4 all AEs have been reported, that we will lock the
5 database, and then we actually can begin the
6 analysis. It's a frustrating time for a sponsor
7 and for me because you know it's done. You know
8 the data is out there, and I can't see it.
9 I'm going through that right now where we
10 finished a study actually six weeks ago, and we
11 just locked the database yesterday so it's okay.
12 So I will be looking at my email to see if I can
13 see results.
14 Well, there's medical surveillance, and
15 again, medical monitoring is a key bit of
16 surveillance that goes on during a study. Number
17 one and foremost is maintaining safety of the
18 participants in the study, but then also trying to
19 ensure that high-quality safety and efficacy data
20 is collected. And it's not just from the medical
21 monitor or the sponsor; it's the entire team. It's
22 the monitors that go out to the site. It's the

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1 operations folks, the statisticians and so on.
2 So I think everyone knows the medical
3 monitor, generally these days outsourced to the
4 CRO, is the boots on the ground. They're the ones
5 interacting directly with the sites, receiving the
6 queries about inclusion/exclusion criteria at 3:00
7 in the morning, having the direct contact, talking
8 to them on the phone, discussing an abnormal
9 laboratory value and what that means, generally can
10 this patient come into the study or can this
11 patient stay in the study, those types of things.
12 But again, there's a monitor for the
13 monitor, and that's the study physician, generally
14 internal, working for the sponsor, not always, and
15 addresses the issues that the monitor needs to
16 escalate where there wasn't general agreement
17 between the medical monitor and the site, oversight
18 of the medical monitor. And then some key features
19 actually beginning to look at some of the trends,
20 not waiting for the end of the study but beginning
21 to look at some of the blinded data, particularly
22 the safety.

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1 Just like there's a vendor management plan,
 2 there's a medical monitoring plan created jointly
 3 by the clinical study physician from the sponsor
 4 and the medical monitor from the CRO. They're
 5 partners in this study and looks at some of the
 6 issues that we've talked about so that everyone
 7 knows before the study starts who's going to be
 8 responsible for what.

9 Then, as I've mentioned, there's safety
 10 medical monitoring. We actually have the
 11 ability -- and Nat showed one program. Teva has a
 12 program. I think a lot of sponsors have different
 13 monitoring programs -- where at a given time in an
 14 individual study, we can track blinded safety data
 15 looking at what the lab results are.

16 Is there an alarming trend for elevated
 17 liver function tests? Is there something that
 18 we're particularly looking for? Do we know that
 19 there's a risk of elevated liver transaminases and
 20 we want to track that particularly? Or adverse
 21 events of interest, we know there might be a risk
 22 of dermal reactions, so we want to see. And then

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1 looking at population trend, looking across the
 2 entire study mainly for safety of patients in the
 3 study, and we don't want to continue a study where
 4 there's an alarming increase in an adverse event.

5 The data on the right is blurred for a
 6 reason. You're not supposed to read it. It's just
 7 an example of some of the things we see.

8 Periodic reports, the study physician is
 9 looking at some of this blinded data and answering
 10 some of those questions. Are there new adverse
 11 events we didn't predict? Are there things we
 12 didn't expect that we should be aware of? What
 13 about the AEs of interest? What about the study
 14 conduct? Are protocol violations occurring more at
 15 a particular site? Is there some kind of
 16 suspicious medical history? And getting back to
 17 some of the things we talked about earlier in terms
 18 of patient conduct but also site conduct.

19 I think everyone's familiar with IRBs and
 20 ethics committees, but a kind of surveillance that
 21 happens before the study starts and then continues
 22 during the study. We may go to the IRB or the

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1 ethics committee with some alarming blinded data
 2 we're concerned about, or we may for some studies
 3 have a data monitoring committee, an independent
 4 committee that can look at the data and tell us
 5 without us being aware, without breaking the blind,
 6 you guys have a problem with some of this. Again,
 7 all out to protect patient safety.

8 So then just a few surveillance questions.
 9 Should source document verification be a mandatory
 10 requirement? I may have hinted at what I think,
 11 but again, curious to hear.

12 How do we ensure the proficiency of the
 13 monitors? Who's monitoring the site monitors? How
 14 do we know that they're doing what they should? I
 15 don't. We send them out there, but I'm going to
 16 assume that some are better than others. How do we
 17 know?

18 We know that DMCs are out there to evaluate
 19 safety. Do we have any kind of independent board
 20 or group of people that can monitor study conduct?
 21 I mentioned to you that we may do some of that on
 22 our own looking at protocol violations, but do we

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1 need an independent group to do that? I don't
 2 know.

3 So I think with that, I will stop and used
 4 up enough time so there's no time for questions
 5 today. Thank you.

6 (Applause.)

7 MODERATOR: We have time for about five
 8 questions. No.

9 (Laughter.)

10 MODERATOR: So I'm delighted to introduce
 11 our next speaker who has come a long way to talk to
 12 us about central statistical monitoring. One of
 13 the papers you have in your packet was written by
 14 her and her colleagues. So Amy Kirkwood is a
 15 biostatistician and senior research associate at
 16 Cancer Research U.K. and University College London
 17 Cancer Trial Centre.

18 So as I said, she's going to speak to us
 19 about some of the details of the things they do for
 20 central statistical monitoring.

21 Presentation – Amy Kirkwood

22 MS. KIRKWOOD: Thank you.

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1 So I'm Amy Kirkwood. I'm a statistician at
2 CRUK and UCL Cancer Trials Centre. So central
3 statistical monitoring is something I started to
4 look at a few years ago when there didn't seem to
5 be that much interest in it. It seemed to be a
6 topic that had been discussed for about a decade or
7 longer, but no one had really done anything with
8 it. So we thought, is this something we could do
9 for our trials?
10 I'm going to discuss today what we've
11 developed within our trial center, how we applied
12 it to our trials and what we found, what we're
13 going to be doing with it in the future, then some
14 more information on what other people are doing
15 with these sorts of ideas.
16 It's become a much more popular topic in
17 probably the last sort of three to four years. It
18 seems a lot more people publishing papers on it and
19 applying it to real trial data. But there's still
20 things that we haven't answered, and I'll go
21 through some details on questions we still need to
22 answer about central statistical monitoring.

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1 So a little bit of detail before I go on
2 about our trial center. So we run academic
3 clinical trials. None of them are licensing
4 studies. So some of our trial data may be used for
5 licensing applications, but none of them were
6 directly licensing studies. So that means none of
7 our trials have the kind of monitoring that was
8 described in the previous talk.
9 Patients don't receive any financial
10 compensation for entering any of our trials, and
11 the sites don't benefit directly, either.
12 This is something that we discussed earlier,
13 but again, all of our trials are run through the
14 NHS. So there's also no benefit for the patients
15 for going into the trials in order to get free
16 medical treatment. They would be getting the
17 standard of care whether they entered the trial or
18 not.
19 Until last year, all of our trials collected
20 data using paper CRFs, and we've only just started
21 to move into ECRF. So that might change the way we
22 monitor data in the future.

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1 Our databases have minimal in-built
2 validation checks. This is partly due to the fact
3 that we're an academic unit and it takes a lot of
4 resources to program these in, but also because it
5 slows down the programs we use.
6 We use a risk-based approach to monitoring
7 as recommended by the MHRA, which is the body that
8 governs INP trials in the U.K. So this means our
9 early phase, high risk studies. So things that use
10 unlicensed drugs or advanced therapies, will get
11 quite a lot of monitoring, whereas our later phase
12 trials, particularly ones that use licensed drugs,
13 may have very little or no onsite monitoring.
14 When we do these onsite monitoring visits,
15 we look at various things, so drug accountability,
16 lab monitoring consent, and some cases, we will do
17 source data verification.
18 So the aim of central statistical monitoring
19 is really to cut down on source data verification.
20 So this is kind of going to replace the last talk
21 about the views on source data verification.
22 So we thought of the reasons to look at

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1 source data. So they were data errors, which we're
2 talking about just unintentional transcription
3 errors, typos, et cetera. Procedural errors, so
4 these are things we classified as unintentional
5 errors made by the site where they really just
6 hadn't understood the trial protocol. And finally,
7 fraud, so this would be intentionally making up
8 patients or making up patients' data.
9 SDV is a very common activity, and there was
10 a paper in 2011, which may answer some of Richard's
11 questions from the previous talk. They surveyed
12 lots of different types of organizations that
13 performed trials, and they asked them about onsite
14 monitoring.
15 So 77 percent of their respondents always
16 performed onsite monitoring, and at onsite
17 monitoring visits, SDV was always performed by
18 74 percent. And not so surprising, I guess, it was
19 more common in pharmaceutical organizations than it
20 was in academic institutions like ours.
21 There are a few studies that then show that
22 SDV might actually not be that useful. The Bakobaki

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1 paper looked at errors they found during monitoring
2 visits, and they decided that 28 percent could have
3 been found during the data analysis, so this would
4 be the standard sorts of things that you'd look for
5 when you're analyzing the data. And they would
6 have picked up those errors at that point. And
7 67 percent could have been found through other
8 centralized processes, so without actually going to
9 visit the site.

10 Another paper by Sheetz in 2014 said that in
11 over 1,000 trials they looked at, only 3.7 percent
12 of ECRF data was actually corrected, and only
13 1.1 percent was through SDV.

14 This was something else that was shown by
15 Tudor-Smith in 2012, which found that the majority
16 of the SDV findings were random transcription
17 errors and had very little impact on the main
18 conclusions, and actually missed four ineligible
19 patients. And this is something else that Grimes
20 talked about in their 2005 GCP guidelines, that if
21 your source data matches the data that's being sent
22 in, it won't get picked as discrepant even though

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1 it might be incorrect in some other way.

2 So we thought what if we could do
3 statistical methods centrally to try and reduce
4 some of this source data verification? So the
5 idea, it would save time on site visits or even cut
6 down the number of site visits. And if you still
7 go to site, you could spend that time doing things
8 like staff training and other things that you can't
9 do remotely.

10 When I started to look at this a few years
11 ago, there'd obviously been an interest in
12 suggestions that this is something that we should
13 be doing, but people hadn't really applied it to
14 the sort of trials we were running. And no one
15 really developed any software to do it.

16 This is a selection of the references that
17 were around at the time I started this project.
18 The first three sort of covered lots of different
19 possible methods to look for fraud and data errors.
20 A lot of these we used when we developed our
21 programs.

22 The second, although they applied it to real

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1 data, it wasn't necessarily particularly applicable
2 to our trials. Some of the were questionnaire
3 data, some were in animal models. And they didn't
4 necessarily use sort of all of the techniques in
5 the previous papers. They just picked and chose
6 one or two.

7 The aim of our project was to develop a set
8 of programs that could be run in R that would
9 perform most of the sort of common checks that had
10 been suggested. So these are things that wouldn't
11 easily be done by the clinical trial database while
12 the data was being entered, and we wanted to create
13 output that was hopefully straightforward enough to
14 be understood by a non-statistician.

15 So all the checks we selected, we split into
16 two categories: things that were at the trial
17 subject level or at the site level. The checks at
18 the subject level are looking for possible data
19 errors within individual patient's data. A lot of
20 these things are things you would do when you do
21 your data analysis at the end of the trial anyway,
22 so checking the order the dates fell in, were

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1 patients randomized before they were treated, were
2 they treated after they died, sort of obvious
3 things, but we wanted to set up an automated system
4 for this.

5 We also looked at whether the dates fell on
6 weekends or national holidays. And obviously
7 things like dates of death or dates of adverse
8 events could fall at any point, but in our center,
9 there's no way a patient would be randomized on a
10 weekend or a national holiday because we're closed.

11 The same for a lot of radiotherapy treatment
12 and chemotherapy in the U.K., a lot of it won't
13 take place on weekends and national holidays. So
14 this could be an indication that the date is wrong.

15 The next little test we looked at were
16 methods for detecting outliers. Again, standard
17 things that you might do while you're analyzing the
18 data, but we wanted to find some way that we could
19 do all of these things quickly and easily as the
20 trial was going on. So hopefully data errors could
21 be corrected as we go along rather than waiting
22 till the end of the trial.

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1 All of these checks aimed to find recording
2 and data entry errors, but the data checks may also
3 detect fraud if people are being sloppy with how
4 they made up their data. And procedural errors
5 might be picked up either because we'll find things
6 like patients being treated before they were
7 randomized, or if it's a lot of outliers, that
8 might indicate inclusion or exclusion criteria that
9 have not been followed.

10 We could also sort these in our output by
11 site. So if we've got sites that are continually
12 sending in data with errors, then that might be a
13 reason to go and talk to them or give them further
14 training.

15 When we come to checks at the center level,
16 here, we're aiming to flag centers which are
17 discrepant from the rest by looking for unusual
18 data patterns. So these are mostly aimed at
19 detecting fraud and other procedural errors. I'm
20 going to go through examples of these in the next
21 few slides.

22 So one of the things we looked at was digit

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1 preference, the idea being that humans really are
2 poor random number generators, and that if you're
3 making up data it may not follow the same sort of
4 distribution as real data would.

5 What we did is we compared the leading
6 digit, the distribution of the leading digit in
7 each site with all of the other sites put together.
8 And this would flag any site where there seemed to
9 be a difference in the number of ones, the number
10 of twos, number of threes compared with each site
11 and the rest of the sites put together.

12 We also looked at rounding. So we could
13 either look at the tailing digit and use a similar
14 method to the method I just described, and there,
15 you'd be looking for an increased number of zeros
16 or 0.5s, or we'd probably run a graphical method,
17 which would show where integer values had been
18 recorded.

19 So in this case, if you've got a non-integer
20 value, the curve takes a step up, and if you've got
21 an integer value, it forms a horizontal line. So
22 something like site 63 with the two little

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1 horizontal steps, you wouldn't worry about it. But
2 if this was an important variable which had to be
3 recorded to a certain level of accuracy, if you got
4 something like site 68 where they're continually
5 recording integer values, it might be a reason to
6 talk to them.

7 Another thing we looked at was inliers. So
8 inliers are basically exactly what they sound like.
9 They're the opposite of outliers. So an outlier is
10 a point that lies far away from the rest of the
11 data, whereas an inlier is a point that lies close
12 to the center of the data.

13 So here, you take a selection of continuous
14 variables a one in CRF, and you calculate the
15 distance between the mean and the point on each
16 patient and you sum that across all the variables.
17 If you plot this on a log scale, what you're
18 looking for are points that fall at the bottom of
19 these plots. As you can see in the first plot,
20 we've got one that's circled in red.

21 We found when we faked data ourselves to be
22 close to the mean that could be detected, but we

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1 had to be -- we felt you had to look at both the
2 plots and the points, which had been selected by
3 the program, as if you added more than one of these
4 patients, they often wouldn't be picked up.

5 So the idea here is you're falsifying data,
6 you want your data to look as believable as
7 possible, and you want it to look like the other
8 patients. So you're going to make it as similar to
9 the other patients as possible, and this might be a
10 method to do it.

11 The next thing we looked at was checks of
12 the correlations structure. Even if people were
13 good at falsifying individual data points, they may
14 not get the interactions between those variables
15 correct. Here in the graphs, you can see all of
16 the continuous variables on one CRF, and it plots
17 the correlation between the pairs of variables.

18 So if there's a perfect positive correlation
19 of 1, it's represented by a black square, which is
20 why you get a black diagonal down the middle. If
21 it's a perfect negative correlation of minus 1, it
22 would be represented by a white square. And

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1 everything else is like a shade of gray in between.
 2 So what we're looking for here are sites
 3 that don't appear to have the same correlation
 4 structure as the rest of the sites.
 5 The two examples in the middle are sites
 6 that we created. The first one on the left-hand
 7 side, we created by generating patients that had
 8 values to each variable that lay close to the
 9 means. So what this showed is you ended up with a
 10 kind of overall light gray structure. Although it
 11 doesn't look that different to the site above and
 12 below, you'll notice there's some strong
 13 correlations that are missing.
 14 In the second example, we generated a fake
 15 site by just putting random values from all of the
 16 patients, and what you get there is a site that
 17 looks strikingly different, that you've got strong
 18 correlations that don't exist in the other sites.
 19 These are tested to p-values using
 20 simulations which compared the correlation
 21 structure to the overall correlation structure for
 22 all of the other sites put together.

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1 As with the inliers test, we felt there's
 2 another thing we needed to look at both plots and
 3 p-values. Something that looks quite strikingly
 4 different, like the site on the right, wouldn't
 5 have nearly as small a p-value as the site on the
 6 left just due to small numbers of patients.
 7 Another suggested method was to look at the
 8 variance within repeated measurements data. So
 9 there's a suggestion that if people falsify data,
 10 they don't get enough variance when they're looking
 11 at repeated measurements data.
 12 One of the earlier references I had was from
 13 an animal trial where they had detected fraud by
 14 looking at the variance in the measurements
 15 collected. All this does is plot all of the
 16 patients' values for a particular continuous
 17 measurement in a line across, and it highlights
 18 patients with very large variances in shades of red
 19 or very small variances in shades of blue. So a
 20 very large variance might indicate that you've got
 21 data errors or outliers, whereas very small
 22 variance might indicate fraud.

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1 What we can see in this top plot in site 25,
 2 a three-patient chain in blue. So this was
 3 actually data that we had given to an independent
 4 statistician and asked him to falsify some patients
 5 for us. So these were three falsified patients
 6 that he had created, obviously not that well, and
 7 we'd obviously not given him any warnings about the
 8 kind of tests we were doing.
 9 One of the most important sort of monitoring
 10 activities in clinical trials is to look at rates
 11 of adverse events. So we wanted to find some sort
 12 of way to monitor this. This is really to detect
 13 any sites that might be underreporting adverse
 14 events.
 15 Here, we created a severe adverse event rate
 16 for each site as the number of patients who had an
 17 SAE reported, divided by the total number of
 18 patients in that site and a measure of the time in
 19 the trial. So we plotted this rate against the
 20 total number of patients, and what we'd be
 21 interested really are the centers which fall in the
 22 bottom right-hand corner. They have quite a large

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1 number of patients but still a low rate. The
 2 lowest 10 percent of rates are picked out
 3 automatically and shown as black squares there.
 4 The other thing is this output is also the
 5 number of SAEs the site has in total. So this
 6 might be an indication that, okay, they've only had
 7 X percent of patients having an SAE, but they have
 8 reported a lot of SAEs for those patients, so they
 9 may be on top of their reporting. We also felt you
 10 need to look at how this rate compared to the
 11 overall rate.
 12 We also thought this could be adapted to
 13 look at incidence reports where you'd be interested
 14 in sites with high rates of incidence and low
 15 numbers of patients.
 16 This is something that we found pretty
 17 useless, but it creates quite a nice picture. This
 18 was an idea that a lot of the other authors
 19 suggested was some sort of graphical representation
 20 of the means of different continuous variables, so
 21 you could see if some sites stood out compared to
 22 the others. And this is a technique called

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1 Chernoff face plots, the idea being that humans
2 recognize differences in faces better than they do
3 other graphical techniques.
4 Every feature on the face is controlled by a
5 different variable, so the height of the head, the
6 width of the head, the height of the eyes, the
7 width of the eyes, et cetera. We found it to be,
8 though, as I said, kind of useless.
9 What variable controlled which feature had a
10 big impact. So, for example, site 11 here that
11 stands out quite a lot, that was the height of the
12 face being controlled by a variable that had one
13 massive outlier in that site. And as you can see,
14 if we deleted the outlier, it went back to looking
15 much more like the other sites.
16 You can see -- or you might not be able to
17 see because it's quite small, but site 48 has
18 really huge eyes, but it doesn't stand out because
19 it's indicating there was quite a big difference in
20 whatever variable created that. But you just don't
21 really notice it. So this is something that we're
22 still thinking about the best way to approach.

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1 Another suggestion was star plots, which again, we
2 found pretty much uninterpretable.
3 So what did we find in our trials? So we
4 looked at three trials, a phase 3 lung cancer trial
5 where we'd already cleaned the data and had it
6 published, and another phase 3 lung cancer trial,
7 which was in follow-up but the data hadn't been
8 completely cleaned or analyzed.
9 So in the first trial, we found some data
10 errors which hadn't been detected. So we couldn't
11 go back to site, but we could go back to our paper
12 CRFs and we could see that some things were clearly
13 wrong.
14 Some outliers, which were possible errors,
15 though none were used in the main analysis. Some
16 patients who were treated before randomization,
17 though, after discussions with the trial staff, it
18 turned out that this had been known. And because
19 of the nature of the trial, patients who had only
20 just started treatment, as it was standard care
21 plus another drug, were allowed into the trial in
22 this case.

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1 One site had a very low rate of SAEs, which
2 we probably would have wanted to look into, but
3 obviously at this stage, we couldn't. We did have
4 some failures in some of the center level checks,
5 so these are the checks for fraud.
6 For example, the digit preference was
7 flagged by one center, but we looked at this center
8 in another CRF, and we didn't see the same pattern.
9 So we didn't have any concerns that there was
10 actually any fraud in this trial.
11 We found very similar results for trial 2,
12 though, unsurprisingly, we detected a lot more data
13 errors and a lot more potential outliers.
14 The third trial we tested this on was a
15 phase 3 trial of biliary tract cancer. This was
16 another trial that had been cleaned and analyzed,
17 but we used this trial to generate our own fake
18 data to see what could and couldn't be detected.
19 So unsurprisingly, when we generated data
20 that fit the assumption of the programs, we were
21 able to detect it in most cases, though the amount
22 of fake data obviously determined how easy it was

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1 to detect. The independent statistician who added
2 data to this trial, some of his data was also at
3 the sites, but his data were also picked up by
4 several programs.
5 So how is this going to be put into practice
6 in our CTU? So we will choose a test to apply
7 based on the size of the trial and how far along
8 the trial is. So this is one problem with these
9 sorts of methods is that you can
10 only -- particularly the methods for detecting
11 fraud, you can only apply when you have a certain
12 number of patients in your site.
13 So if you've got small early phase trials,
14 they're not going to be very helpful, or if you've
15 got trials that haven't yet recruited that many
16 patients at each site, they may also not be that
17 helpful.
18 So data's going to be checked at appropriate
19 regular intervals. We've done some SAE monitoring
20 using these programs so far, and we went for every
21 six months. But I think it would probably depend
22 on the rate of recruitment into your trial. These

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1 would be set up by the trial statistician, and then
2 they should be able to be run pretty much
3 automatically.
4 Data errors will be discussed with the trial
5 manager or the trial coordinator to see what we
6 should be taking back to site and which we
7 shouldn't. If there's anything more worrying, so
8 this is anything that suggests procedural errors or
9 fraud, these will be discussed with the appropriate
10 trial staff and also our regulatory department.
11 So the SAE monitoring I mentioned, this had
12 been applied to another lung cancer trial in our
13 center. And after two checks on the SAE
14 rate -- there was one site on the third check which
15 had had pretty low rate all the way along. And we
16 thought, okay, so we'll go with the gentle approach
17 and send them just a nice email that sort of said,
18 you do know that you're meant to be reporting all
19 of the SAEs. There's none that you're not
20 reporting, are you? And they came back, oh, no,
21 no, of course not.
22 By the fourth time we looked at this, they

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1 had gone from eight -- they'd got one extra patient
2 and gone from eight, I think, patients with SAE to
3 21 patients with an SAE. So we don't know whether
4 that was our little nudge or not, but it will be
5 interesting to monitor the changes you get when you
6 do contact sites and see if it does alter their
7 behavior.
8 So as I said, this is something that's
9 become a lot more popular in the last few years.
10 So since we finished working on our paper, these
11 are a selection of references that have been
12 published.
13 It seems to sort of split people into two
14 groups. There are papers that tend to use sort of
15 all of the data or systems that use all of the
16 data, and then those that take specific key
17 variables and monitor them, and I'm going to go
18 through two examples.
19 One company that has spent a lot of time and
20 research in the last few years is this company
21 called Cluepoints. So this is a company started by
22 Marc Buyse who wrote one of the original papers on

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1 how to detect fraud and data errors in clinical
2 trials. So they offer their services running CSM
3 to CROs, academic staff, and pharma companies.
4 So they apply similar methods to the ones
5 I've described, and they also look at things like
6 rates of missing data. All of their tests produce
7 a p-value. I went to a talk taught by one of the
8 authors of this paper a couple of weeks ago, and
9 they said for a phase 3 trial, they could have
10 100,000 to a million p-values generated by their
11 programs.
12 They get this huge matrix of p-values, and
13 they use a principal component analysis on it to
14 try and pick out centers that stand out. So that's
15 what these two plots show. So this circled site,
16 site X, was a site where they knew there had been
17 fraud. And what they were looking for is sites
18 that fell far away from the origin because that
19 suggested they're different from the rest. And as
20 you can see, site X does fall far from the origin.
21 But they also have circled centers D6 and F6
22 in one of the plots and D1 and E6 on the second

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1 one. And they do mention in their paper, if this
2 is an ongoing study, you'd want to go and talk to
3 these sites as well. But there didn't seem to be
4 any data about whether there was any irregularities
5 at these sites or not.
6 The second type of use for CSM is more sort
7 of targeted with just specific key variables. So
8 Oxford has done some work with things they call key
9 risk indicators. This paper developed models using
10 data where they knew there had been fraudulent
11 data. So this was a trial for the POISE trial.
12 They knew there'd been nine sites with falsified
13 data.
14 So they used again very similar methods to
15 the ones I've described to build risk scores. So
16 these were three variables in each model that would
17 be able to predict whether the site had falsified
18 data or not.
19 They found these risk scores could
20 discriminate between their fraudulent and their
21 validated centers very well. So they had a very
22 good area under the curve for those. And then they

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1 tested these scores on another trial in the same
 2 disease area but very similar design of trial where
 3 they had had a lot of onsite monitoring. They were
 4 sure there had been no fraud.
 5 So the false positive rates in this second
 6 trial were very low, so that means it was very few
 7 sites being picked as possibly having fraud where
 8 they shouldn't be. But they didn't have another
 9 trial with fraudulent data to apply these to, so
 10 they don't know how well it would be able to pick
 11 up fraudulent data in another trial.
 12 So it seemed like an interesting method, but
 13 only one might work in this disease area where
 14 these particular data points were reported.
 15 So what are the advantages over SDV for
 16 central statistical monitoring? So all data could
 17 be checked regularly, quickly, and we think
 18 cheaply. We'd hope the data errors would be
 19 detected early, which would reduce the number of
 20 queries needed at the end of the trial.
 21 Procedural errors are more likely to be
 22 detected at the end of the trial when they can

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1 still be corrected. So I suppose those last two,
 2 there are more advantages over not doing this
 3 rather than advantages over SDV. And every patient
 4 would have some form of data monitoring, whereas at
 5 the moment, at least in our center, only a small
 6 proportion have onsite monitoring. We'd hope this
 7 might be able to pick up anomalies, which existed
 8 in the source data as well
 9 So the disadvantages, as I mentioned, some
 10 of these methods aren't reliable when there's only
 11 a few patients in each site, which isn't
 12 surprising, but this could also be an issue
 13 particularly early on.
 14 The programs find data errors can be used on
 15 all the sites and again, early on, but programs to
 16 detect fraud will only be able to be used once
 17 you've got reasonable number of patients in each
 18 site. And some of the methods are definitely
 19 somewhat subjective.
 20 So what other research is needed in this?
 21 One thing is how much does it cost. We think it
 22 might be cheaper because it might save money on

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1 site visits, but no one's actually looked into the
 2 cost of implementing these and interpreting the
 3 results. This is the time of the statistician or
 4 someone else who's running these. And in a center
 5 like ours which doesn't do a lot of onsite
 6 monitoring, might you actually end up with more for
 7 cause monitoring visits which will cost more money.
 8 But the most important thing is how can be it
 9 validated. How can we assure that sites which
 10 aren't flagged didn't have any falsified data?
 11 One study which is trying to do this is a
 12 trial which is being run in the U.K. called the
 13 TEMPER trial. What this is doing is it's going for
 14 the few key variables idea. It's selected specific
 15 triggers to look for in a site, and if any site
 16 triggers these, it will have a monitoring visit.
 17 It then matches this site based on the number of
 18 patients it's recruited and the time it's been open
 19 to another similar site in the trial, which wasn't
 20 flagged, and it will also go and visit that.
 21 What it's aiming to do is to show a
 22 30 percent difference in the numbers of critical or

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1 major findings between the trials that were flagged
 2 and the trials that weren't. This would be a
 3 possible way to test some of these methods. And I
 4 don't think anyone's planned a similar study using
 5 the kind of methods that we're using or the methods
 6 suggested by Cluepoints, which look at a lot more
 7 of the data, but that might be something useful to
 8 do.
 9 Another possibility is to run a trial which
 10 looks at central system monitoring and full onsite
 11 monitoring to see what is picked up by each. The
 12 problem with doing that is that if sites know they
 13 have full onsite monitoring, they may behave
 14 differently than if they didn't. And you may not
 15 be able to -- if things are changed as you go along
 16 during the trial, because of findings in either
 17 method, you won't know whether they would have been
 18 picked up by the other method or not. So this is
 19 something that definitely needs more work, and it
 20 needs more consideration of how we can test this.
 21 Finally, there are further details in the
 22 paper that I wrote on this subject, which was

1 handed out in the background reading.
2 (Applause.)
3 MODERATOR: I've just been informed by the
4 person who was number 11, I think, on the Chernoff
5 face plot, Bob --
6 (Laughter.)
7 MODERATOR: -- that we're going to push
8 Paul's talk to 8:00 tomorrow morning. Did you tell
9 Paul that by the way?
10 MALE SPEAKER: Yes.
11 MODERATOR: Okay.
12 MALE SPEAKER: Paul was very actively
13 involved in the decision.
14 MODERATOR: Okay. So I guess we'll end now.
15 We have dinner here at 7:00.
16 FEMALE SPEAKER: We do not (inaudible)
17 dinner in --
18 MODERATOR: We do not.
19 (Housekeeping.)
20 Adjournment
21 MODERATOR: Okay. So thank you.
22 (Whereupon, the meeting was adjourned.)

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