

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

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*June 5, 2015*

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

<p>L*4343*L* Page 1</p> <p>1 INITIATIVE ON METHODS, MEASUREMENT, AND                  2 PAIN ASSESSMENT IN CLINICAL TRIALS                  3                  4 IMMPACT XVIII                  5                  6                  7 Ensuring Data Quality in                  8 Clinical Trials of Pain Treatments                  9 Considerations for Study and Conduct                  10                  11                  12                  13 Friday, June 5, 2015                  14                  15                  16                  17 Willard Hotel                  18 Washington, DC                  19                  20                  21                  22</p>	<p>Page 3</p> <p>1 P R O C E E D I N G S                  2 MALE SPEAKER: Good morning to everyone.                  3 Just a couple reminders to you before we start                  4 formally, the housekeeping things to keep in mind.                  5 Please remember to speak into the microphone when                  6 you want to be asking a question for those in the                  7 audience. Make sure your cell phones are, in fact,                  8 silenced.                  9 Checkout time from your room, just so you                  10 know it, is 12:00 o'clock. If you haven't checked                  11 out, you can do it at the coffee break or at                  12 lunchtime. We will try and end the meeting within                  13 a reasonable time.                  14 Remember what your mission is for the rest                  15 of this session, rest of today, which is at the end                  16 of the day before we let you out the door, we are                  17 going to begin talking about hopefully putting some                  18 information together that Bob is going to summarize                  19 for you, and then start working towards having this                  20 recommendation paper, considerations for improving                  21 data quality based on the conversations that we've                  22 had here.</p>
<p>Page 2</p> <p>1 C O N T E N T S                  2 AGENDA ITEM PAGE                  3 Data Quality Issues in the Design and                  4 Analysis of Clinical Trials, and FDA                  5 Perspective 5                  6 Paul Schuette, PhD 24                  7 Q&amp;A and Panel Discussion 99                  8 Discussant I: An Academic Perspective on                  9 Clinical Trial Quality 139                  10 John Markman, MD 174                  11 Discussant II: Industry and CRO                  12 Perspectives on Clinical Trial Quality 261                  13 David Hewitt, MD 323                  14 Q&amp;A and Panel Discussion                  15 Consensus Discussion: Recommended                  16 Considerations for Ensuring Study Data                  17 Quality in Clinical Trials of                  18 Pain Treatments                  19 Adjournment                  20                  21                  22</p>	<p>Page 4</p> <p>1 MALE SPEAKER: And we submit it to the                  2 journal.                  3 MALE SPEAKER: To be submitted to a                  4 reputable journal unspecified at this particular                  5 moment.                  6 (Laughter.)                  7 MALE SPEAKER: Although she's not in the                  8 room, I want to also remind you about taxis because                  9 it's Friday afternoon and they want to make sure                  10 there's enough taxis, to check at the -- if you                  11 haven't already done so, what time you're going to                  12 be needing a taxi so that, in fact, can be taken                  13 care of by -- and Valorie is doing that.                  14 She's not in here, and I want to just thank                  15 Valorie Thompson and Andrea Speckin, who were the                  16 two people who coordinated this meeting, did all                  17 the correspondence with you, got you the                  18 information, took care of all the logistics                  19 I think from our experience, they've been                  20 extremely helpful, very effective in doing that.                  21 Hopefully, you've all had a reasonable experience                  22 in getting here.</p>

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1 (Applause.)  
 2 MALE SPEAKER: If you have any questions or  
 3 comments regarding your trip back or checking out  
 4 or what have you, definitely check with them.  
 5 They'll be able to help you.  
 6 So let me turn it over to Mike, who's going  
 7 to finish off the session that we had begun, and we  
 8 were slightly off target.  
 9 I want to thank Paul for being willing to be  
 10 flexible on the timing.  
 11 DR. McDERMOTT: Okay. It's my pleasure to  
 12 introduce Paul Schuette, who is a mathematical  
 13 statistician and the scientific computing  
 14 coordinator at the FDA Center for Drug Evaluation  
 15 and Research. He's going to give the FDA  
 16 perspective on, as you can see, contents data,  
 17 quality issues in the design and analysis of  
 18 trials.  
 19 Presentation – Paul Schuette  
 20 DR. SCHUETTE: The standard disclaimer, if  
 21 you don't like what I say, blame me, not the people  
 22 I work for. A little bit of an outline. We'll

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1 talk about data quality, and analysis quality to  
 2 some extent, reviewer experiences, some monitoring  
 3 and some conclusions.  
 4 So data quality. I think it's pretty much a  
 5 given, it's been accepted, that we cannot inspect  
 6 our way to quality. According to Deming,  
 7 "Eliminate the need for inspection on a mass basis  
 8 by building quality into the product in the first  
 9 place." So Deming is perhaps the quality guru from  
 10 the '50s, '60s, '70s and '80s.  
 11 This is one of his 14 points. This is  
 12 actually reflected in one of our guidance  
 13 documents. "Monitoring or oversight alone cannot  
 14 ensure quality. Rather, quality is an overarching  
 15 objective that must be built into the clinical  
 16 trial enterprise. FDA recommends a quality risk  
 17 management approach to clinical trials."  
 18 Let me tell you where that came from because  
 19 that's an important document, which is "Oversight  
 20 of Clinical Investigations: A Risk-Based Approach  
 21 to Monitoring."  
 22 I would say that FDA has embraced the

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1 quality by design paradigm. It was mentioned by  
 2 Nat that this occurs typically in the manufacturing  
 3 side of the house, and there's actually an FDA  
 4 guidance that spells that out. I would also argue  
 5 that what we're attempting to do with the good XP  
 6 guidances, the GXP acronyms that we have all over  
 7 the place, are partially an attempt to correspond  
 8 to this as well.  
 9 GCP most people know, good clinical  
 10 practice. GMP is good manufacturing practice. How  
 11 about GPVP? Good pharmacovigilance practice. And  
 12 does anyone want to take a stab at GLP?  
 13 MALE SPEAKER: [Inaudible].  
 14 DR. SCHUETTE: Yeah. Government tends to  
 15 specialize in TLAs, three-letter acronyms.  
 16 (Laughter.)  
 17 DR. SCHUETTE: So there will be a test.  
 18 CDISC. Let's see. CDISC stands for Clinical Data  
 19 Interchange Standards Consortium. So FDA, some of  
 20 our other regulatory agencies, and representatives  
 21 from both academe and sponsors have worked to try  
 22 to develop data standards.

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1 The data standards are not perfect. They  
 2 don't answer every potential issue, but they're at  
 3 least a step in the right direction. And I think  
 4 we can say, okay, you're missing this data. It's a  
 5 lot more obvious when we all have to report the  
 6 data the same way. So those are out there.  
 7 CDISC has published a therapeutic area  
 8 standard for -- I'll say it's version 1. I'm not  
 9 saying it's perfect again, but it's at least an  
 10 attempt in the right direction. And I would also  
 11 argue that the very fact that we have a  
 12 prespecified statistical analysis plan is in some  
 13 sense related to data quality and analysis quality.  
 14 Statistical quality concerns. Missing data.  
 15 This is perhaps one of the big ones nowadays.  
 16 There's a National Academy of Sciences report that  
 17 is certainly something to look at. There is an EMA  
 18 report. There is an FDA guidance in development, I  
 19 am told, and all dealing with that.  
 20 The basic approach that I think we're saying  
 21 to missing data is don't. Avoid missing data, and  
 22 part of that is looking at how things are designed.

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1 Do the study design and study conduct minimize  
 2 missing data? How do the protocol and the  
 3 statistical analysis plan propose dealing with  
 4 analysis of missing data? So we would like to have  
 5 that more specified as we go along.

6 By the way, last observation carried forward  
 7 is not considered a good way to handle missing  
 8 data. So there's more there.

9 Another thing that has come out, and this is  
 10 a little bit older now, are the patient-reported  
 11 outcomes guidance. One of the things that we do  
 12 see as an issue, and it's sometimes a problem, is  
 13 specifying the choice of instrument. There should  
 14 be some background as to why a particular  
 15 instrument has been chosen. And along with that,  
 16 there needs to be sort of a complete document  
 17 trail, audit trail that is available, that  
 18 specifies the version number, scoring algorithm,  
 19 and so forth.

20 Sometimes it can be very difficult to  
 21 replicate results or know what's going on. And  
 22 unfortunately, the choice of instrument even if you

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1 say it's there, there is some concern as to whether  
 2 or not the version is changing over the course of a  
 3 clinical trial.

4 So I've used a term from the modeling and  
 5 simulation world, at the very last bullet is, for  
 6 lack of a better term, verification, validation,  
 7 and uncertainty quantification. Basically, this is  
 8 called content validation and other things in the  
 9 guidance, but the overall idea is does the  
 10 instrument -- does it do what it says it's supposed  
 11 to do, and are the results reliable? And there's  
 12 been some allusion to some of those types of  
 13 issues.

14 So data quality and the FDA submission  
 15 process, let's go through some of this. So suppose  
 16 a sponsor finishes their study. This is kind of  
 17 what actually happens on our end. They submit an  
 18 application to the electronic documents staff. It  
 19 goes into our systems, and then we start looking at  
 20 it.

21 The review teams must determine whether or  
 22 not the submission is actually what we call

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1 fileable. This comes fairly early on. But  
 2 unfortunately, this is a fairly rudimentary  
 3 process. It's basically are the appropriate  
 4 domains populated, is there a demographics domain,  
 5 is there this other domain?

6 It doesn't say anything about how great the  
 7 data is once it's in there. It just says is it  
 8 there. So that's why I call it rudimentary checks.  
 9 We're trying to put in place incrementally some  
 10 better methods.

11 Within the CDER -- I'm located in the Office  
 12 of Translational Sciences. A companion  
 13 organization within the Office of Translational  
 14 Sciences is the Office of Computational Sciences.  
 15 And they actually have worked with CDISC to provide  
 16 something they're calling a jump start service.  
 17 And this actually provides some rudimentary checks  
 18 of SDTM data.

19 So as I use these acronyms, I assume people  
 20 kind of know what I'm talking about here, but this  
 21 is basically, the "raw data" that come out of the  
 22 CDISC model. And what this does is it checks for

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1 things like is the adverse event start date before  
 2 the adverse event end date, those types of things,  
 3 very basic types of checks that are necessary but  
 4 can be missing.

5 We have Office of Scientific Investigation  
 6 inspections, OSI. But this is usually a very small  
 7 proportion of sites. We're talking about 1 to  
 8 2 percent in many cases, so not a huge amount. And  
 9 data quality issues can emerge throughout the  
 10 review process. So we'll follow this with some  
 11 anecdotes.

12 This should look vaguely familiar because I  
 13 think this is the exact same instance that Sharon  
 14 alluded to yesterday as her first example.  
 15 Reviewer reported an incident in which several  
 16 members of the same family were all enrolled in a  
 17 pain medication trial on a Friday evening. My  
 18 understanding is the dog did it.

19 This raised some red flags. There were  
 20 found to be some other questionable practices at  
 21 this site. Turns out this was also the largest  
 22 site in the trial. OSI is concerned with the

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1 validity of data from the site. The entire trial  
2 was excluded, and if the sponsor wants to pursue  
3 this, they have to submit new studies. So this is  
4 a fairly serious problem for the actual sponsor.  
5 Another experience, misclassification.  
6 Rescue medications were misclassified as  
7 concomitant medications, affecting some domains,  
8 and really changed the efficacy evaluation of the  
9 product because we're looking at a combination  
10 product, in essence, rather than the actual product  
11 itself.  
12 So just because someone says that they're  
13 employing standards doesn't mean that they are  
14 actually doing so correctly, and we need to have  
15 the standards employed in the right manner in order  
16 to be effective.  
17 PRO. One of my division directors says that  
18 we should always have a cartoon in a presentation.  
19 But there is a serious aspect there. I would say  
20 that the circumstances in who is administering the  
21 test can matter, and the context is also important.  
22 I've realized I've gone into government

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1 speak. PRO is patient-reported outcomes, of  
2 course. One of the challenges is, of course,  
3 instrument validation. Perfect validation, of  
4 course, doesn't really exist, but we want some  
5 literature and background as to why a particular  
6 instrument was used, is it fit for a purpose. And  
7 some of that is also spelled out in the PRO  
8 guidance.  
9 One of the problems that has sometimes been  
10 seen is the use of pediatric and adult scales  
11 without making a distinction. They're both on a  
12 zero to 10 scale, gamish them together, and we're  
13 good to go, right? No. We need to look at  
14 pediatric being very different from an adult PRO  
15 potentially, or if they're going to say they're the  
16 same, there needs to be some justification.  
17 Observer-reported outcomes. It may not be  
18 the case that a patient can actually report their  
19 pain. How do we handle this and how should that be  
20 incorporated with the other information is  
21 something to consider.  
22 This was alluded to in some of the other

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1 speakers yesterday, variability of individual  
2 outcomes. Some of this is perhaps related to  
3 subject training. From our perspective, we don't  
4 know if it's a subject training, an instrument  
5 reliability issue. It's all sort of conflated. We  
6 just know that we don't think things are changing,  
7 and the responses are changing quite a bit. So we  
8 saw some challenges being addressed along those  
9 lines.  
10 Missing values. One of the standard  
11 problems, of course, in all this area is what  
12 happens if we have a missing value. Some of that  
13 could be related to the choice of the instrument.  
14 Sharon was saying, for example, that if we don't  
15 have the option to respond in the right way, what  
16 do most of us do, is we just stop the survey at  
17 that point. So there may be multiple reasons why  
18 there's missing values, and we think that needs to  
19 be explored further.  
20 Rescue medication. We're looking at  
21 analyzing the efficacy and safety of medications,  
22 and, if you will, it's necessary to prevent more

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1 missing data, but it can also be a complicating  
2 factor. So the use of rescue medications for  
3 breakthrough pain in both acute and chronic pain  
4 trial poses a challenge for efficacy analyses.  
5 There is a draft guidance that has come out.  
6 It's listed in the references, but it just came out  
7 last year. And they do allude to some of these  
8 types of issues, that it is a little bit more  
9 complicated when we're actually looking at this  
10 type of analysis.  
11 The other thing that we've already seen a  
12 problem with are opioids misclassified as  
13 concomitant meds rather than rescue medications.  
14 And one of the problems is that when we're looking  
15 at these rescue medications and looking at  
16 different rates and different trials, and we're  
17 looking at an overall submission, how do we deal  
18 with integrating these results across all the  
19 trials in a submission is one of the issues that  
20 our reviewers are mentioning.  
21 Some other issues, incorrectly coded AEs.  
22 That's actually something that we've seen some

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1 problems with. In some sense, that's also a  
 2 quality control issue.  
 3       Correctly ascertaining the recorded reason  
 4 for withdrawal. For most of us who do work with  
 5 reviews, this is one of our pet peeves. Lost to  
 6 follow-up is not a good reason. We need to have  
 7 better follow-up as to why someone withdrew from a  
 8 trial. Did they move away? Did they die? Did  
 9 they experience an adverse event? Was it for lack  
 10 of efficacy?  
 11       Those type of things need to be included as  
 12 part of the protocol and actually more effort to  
 13 ascertain what's going on for those purposes.  
 14 Follow-up with phone calls, reaching out more.  
 15       Lab values. This is also a quality control  
 16 issue. In some cases, we were calling this  
 17 investigator error. In some cases, we don't know  
 18 if it's incompetence, ineptitude, not the proper  
 19 training with the instrumentation. But it does  
 20 create some problems and issues. And again,  
 21 missing values, something to harp on is the missing  
 22 value issue, but pain is one of the areas that

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1 there's a higher proportion than some of the  
 2 others. And one thing that one of our reviewers  
 3 mentioned was the need for better tools to discover  
 4 misconduct in errors.  
 5       This gets us to monitoring, and we have two  
 6 basic types, the onsite monitoring, source data  
 7 validation -- was something that Amy was talking  
 8 about yesterday -- and centralized monitoring where  
 9 we're doing a remote evaluation.  
 10       We do have a FDA guidance on the topic, and  
 11 there is a recognition that onsite monitoring is  
 12 time consuming, expensive, and not always  
 13 necessary. And we can even add another point is  
 14 that it doesn't always catch the problem.  
 15       So centralized monitoring. Let me quote  
 16 straight from the guidance. "FDA encourages  
 17 greater use of centralized monitoring practices  
 18 where appropriate than has been the case  
 19 historically with corresponding less emphasis on  
 20 onsite monitoring." And this might even get into  
 21 some of the issues that Nat was pointing out  
 22 yesterday with we see some things being flagged

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1 that may not be necessarily quite as relevant for  
 2 the scientific question under concern.  
 3       Centralized monitoring can be an important  
 4 component of a risk-based monitoring plan, so we're  
 5 focusing on sort of this risk-based idea. The  
 6 guidance has some details, but let me outline, the  
 7 key steps are to identify the critical data and  
 8 processes; do a risk assessment of those, keeping  
 9 in mind who will be actually entering the data and  
 10 those processes; considering risk factors; and  
 11 also, developing a plan.  
 12       Even with the best centralized monitoring,  
 13 remote evaluation, we still think there will be  
 14 need for onsite monitoring, at least in some cases.  
 15 So it's sort of an entire approach, but we think  
 16 onsite monitoring can be reduced in some cases and  
 17 targeted more specifically.  
 18       Statistics and central monitoring. This  
 19 will look vaguely familiar from Amy's talk.  
 20 Distribution of data is one of the things we're  
 21 looking at. Too much variation, too little  
 22 variation, outlier, inlier detection.

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1       The general trend that we want to look for  
 2 in some sense are results that are too good to be  
 3 true, or conversely, they're way, way off scale  
 4 from everyone else. One of the issues people who  
 5 fudge data seem to not know how to look at a  
 6 calendar.  
 7       (Laughter.)  
 8       DR. SCHUETTE: Maybe that's part of the  
 9 numeracy training that we were alluding to.  
 10       But we want to examine the differences  
 11 between and within sites, and we're also looking at  
 12 some ideas from data anomaly detection. The word  
 13 "fraud" has certain legal connotations, so we'll  
 14 refer to things like misconduct or data anomaly.  
 15 And we also need to make the results coherent to  
 16 non-statisticians or data scientists. So those are  
 17 some of the issues that are involved.  
 18       Here are some of the initiatives that we're  
 19 starting, and we're not there yet. We're working  
 20 with companies to bring commercial software into  
 21 FDA for evaluation, research, and development,  
 22 particularly for data anomaly detection.

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1 Amy alluded to the fact that some of these  
 2 programs require hundreds if not thousands of  
 3 individual tests. Many of these are actually going  
 4 to be simulated. This is a very high -- for lack  
 5 of a better term, high performance computing  
 6 environment is needed to actually carry this out  
 7 for the requisite level that we would like. So  
 8 we're looking at using our FDA high performance  
 9 computing environment to actually be able to carry  
 10 out some of that.

11 We're also looking to improve the  
 12 statistical methods to determine some ways we can  
 13 filter out some of the false positives and false  
 14 negatives.

15 We're also looking at improving our existing  
 16 office of scientific investigation site selection  
 17 tool. We just brought in -- I'm actually the  
 18 person that's working on that. We just brought in  
 19 a graduate student who will be working with us this  
 20 summer to do a little bit of data mining in terms  
 21 of looking at the data.

22 There is a potential for our Janus clinical

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1 trials repository. So one of the long-term goals  
 2 is basically we're trying to develop, essentially  
 3 what it boils down to, a long-term data warehouse  
 4 for at least the SDTM data. And depending on  
 5 funding -- that's kind of gone on a herky-jerky  
 6 type of fashion. If you're familiar with sometimes  
 7 riding the Metro, kind of how it lurches and stops  
 8 and moves forward, that's kind of how Janus has  
 9 actually proceeded. Sequester did a number on our  
 10 ability to put that in place.

11 So we're still trying to get all that  
 12 involved, and one of the ideas that's been mooted  
 13 about is to actually include some of these data  
 14 checks as part of putting the trial data into the  
 15 repository. So there's potential. We can't say  
 16 we're there yet. So this is more aspirational than  
 17 operational.

18 Do have some conclusions. I think we're  
 19 making progress, but there is definitely room for  
 20 improvement. On a lot of things, we're at  
 21 version 1. And as you know, for any software  
 22 release, version 1 is not necessarily where you

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1 really want it to be.

2 One of the items that we've talked about  
 3 perhaps overall, and I've labeled this, is can we  
 4 better articulate what we mean by good clinical  
 5 trial practices, good data practices?

6 What I mean by that is that if we look at  
 7 sort of the areas by themselves, clinical practice,  
 8 manufacturing, other aspects, they're all sort of  
 9 individual discrete domains. But the clinical  
 10 trial itself starts with a plan, a design, coming  
 11 up with endpoints, how are we going to measure it,  
 12 recruitment, setting up the sites. That entire  
 13 process is something that I think we can improve.

14 I will say onsite and centralized monitoring  
 15 are complementary and not mutually exclusive  
 16 approaches. We're looking at a blended approach  
 17 for future. And we do need to develop and  
 18 implement some better tools for what we're calling  
 19 data anomaly detection.

20 Let me phrase it this way. Here are the  
 21 four guidances I referenced. Basically, if you  
 22 enter these titles into Google, they'll pop up.

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1 This is the National Academy of Sciences' report.  
 2 And I'd like to thank my colleagues in the DB II,  
 3 analgesics review team, Freda Cooner, Feng Lee,  
 4 Kate Meaker, James Travis, Yan Zhou, and also to my  
 5 colleague Scott Como for his input on PRO issues.  
 6 And I finished on time.

7 (Applause.)

8 Q&A and Panel Discussion

9 DR. McDERMOTT: I'd like to invite the  
 10 speakers and panelists to please come up. So we  
 11 had three terrific presentations, and I think to  
 12 start things, I'll just maybe summarize quickly  
 13 some of the questions that either came up directly  
 14 in the presentations or in my own mind.

15 In terms of central statistical monitoring,  
 16 a number of issues related to -- I guess one could  
 17 put it as cost effectiveness of traditional  
 18 monitoring versus central statistical monitoring.  
 19 I think that can use some investigation.

20 The issues of what does one check in an  
 21 individual study, when, how often do we have to  
 22 check things, who does the checking, what are the

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1 triggers. There are certain actions that might be  
 2 taken, but what should precipitate these actions  
 3 and how strange do these anomalies have to be  
 4 before we take action? What actions should be  
 5 taken in any particular case?  
 6 Paul raised some issues at the very end  
 7 about potential standards for clinical trial  
 8 practice, which I thought was sort of interesting.  
 9 And Rick in his presentation raised a lot of  
 10 questions actually about site monitoring, things  
 11 about selecting -- dealing with other countries,  
 12 for example, that one has to worry about the  
 13 feasibility of recruitment versus quality issues,  
 14 of course; having investigator meetings face to  
 15 face versus having webinars, the sort of training  
 16 issues that are associated with that; delegation of  
 17 responsibilities from investigators to  
 18 coordinators, who's overseeing, is there adequate  
 19 supervision of the people to whom a lot of the  
 20 trial tasks are being delegated; issues concerning  
 21 informed consent training; and a bunch of other  
 22 things that were raised.

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1 So I want to open it up to first the floor  
 2 for any questions.  
 3 John, you're always first.  
 4 JOHN: I guess that's what I get for sitting  
 5 up front. There have been some great talks, and I  
 6 think the move towards trying to make things more  
 7 efficient with central monitoring and not worrying.  
 8 And being willing to say that site monitoring  
 9 actually might not always serve the right purpose I  
 10 think is a real step forward because, obviously,  
 11 it's a lot of effort involved and so on.  
 12 The thing that I haven't heard as much is  
 13 that in trying to implement all of these, there are  
 14 a couple of considerations that I think we ought to  
 15 take into account. And that is, is there a way to  
 16 do it more efficiently and more effectively? And  
 17 when we come to a fork in the road, could we  
 18 perhaps, if they're equal in terms of the benefits  
 19 to monitoring, could we choose the one that's more  
 20 efficient or is likely to work more effectively?  
 21 I wondered -- to the panelists in general,  
 22 but specifically with regards to Paul's

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1 talk -- whether there might be some guidances or  
 2 evidence that could be put forward, or studies that  
 3 could be conducted to say, all right, you need to  
 4 comply with these, but the best way to do that is  
 5 use a pocket data entry system and to make sure the  
 6 data gets entered and checked, et cetera,  
 7 et cetera.  
 8 I'm wondering whether there's a way to carry  
 9 it that next step, something that Nat's been  
 10 working on, which is to try and make all of this  
 11 work in a better way, both from the perspective of  
 12 keeping track of it obviously, but also from the  
 13 perspective of actually getting it done.  
 14 DR. McDERMOTT: Paul, do you want to?  
 15 DR. SCHUETTE: I am not aware of anything  
 16 that says where the dividing lines are for onsite  
 17 versus these others. I think it's still fairly  
 18 early days to actually determine which method is  
 19 best. And I think over time, we'll see that  
 20 methods evolve as to how we approach the best way  
 21 of collecting the data and inputting it.  
 22 We saw, for example, that bring your own

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1 device type of things to clinical trials has  
 2 upsides and downsides. Provision of various  
 3 things, devices to the subjects has its own issues.  
 4 So as far as I know, we don't have any real  
 5 guidance for that, and I think that's probably an  
 6 area where the folks in the field can really help  
 7 out. And if they can -- I'll lapse into FDA-speak.  
 8 If they can work collaboratively together to  
 9 develop best trial practices, that would certainly  
 10 be something I think the agency would tend to  
 11 support.  
 12 DR. WASAN: It's Ajay Wasan. So quick  
 13 question. A lot of us who do investigator-  
 14 initiated trials use REDcap, and REDcap on many  
 15 levels kind of addressed a lot of the concerns that  
 16 all of you have raised. And it's being used even  
 17 more for bigger trials the NIH or PCORI are  
 18 funding.  
 19 So I just want to get what's your sense to  
 20 what extent, when REDcap is used well, that it  
 21 actually is a pretty good data platform for  
 22 capturing a lot of high quality type of data, as



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1 you-all outlined.  
2 DR. SCHUETTE: We do not endorse any  
3 commercial product.  
4 DR. WASAN: That's not a commercial product.  
5 This is funded by Vanderbilt. It's an NIH effort.  
6 I just want to get a sense of in general --  
7 DR. SCHUETTE: We do not -- let me phrase it  
8 this way. We do not support any commercial or  
9 specific product by itself. If it's fit for use  
10 and for other things, we do not stand in the way,  
11 but we don't necessarily, for example, support SAS.  
12 We don't necessarily say you have to use R. So we  
13 try to stay away from particular platforms'  
14 endorsements.  
15 DR. WASAN: And I'm sorry to be difficult.  
16 Let me just rephrase. I just want to get a general  
17 sense of -- the process that REDcap uses, that's  
18 all throughout NIH. In general, what's the sense  
19 of good and bad of that platform? That's all.  
20 DR. SCHUETTE: That's again, one of those  
21 areas where, unfortunately -- and I'm not trying to  
22 be smart-alecky or anything else, but I can't

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1 comment.  
2 DR. WASAN: Okay. Thanks.  
3 DR. McDERMOTT: Have others here used REDcap  
4 on the panel?  
5 So the one thing -- I haven't used it  
6 either, but some of my colleagues have. But one  
7 thing about REDcap or any other platform, I guess,  
8 is there are things you can build into the system  
9 to prevent certain kinds of errors, of course, like  
10 range checks and so forth.  
11 But I think a lot of what -- and in  
12 particular Amy talked about yesterday was the very  
13 many logic checks, for example, or other kinds of  
14 checks that wouldn't be automatically produced by  
15 something like REDcap. And so a lot of people have  
16 moved toward electronic data capture with REDcap  
17 and other systems, but there's, I think, a fair  
18 amount of effort that needs to go into programming.  
19 And I don't know how specific that needs to be for  
20 each trial, how portable some of these methods are.  
21 I suspect that to a large extent, they are. But  
22 it's really a different level, I think, than what

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1 we're typically used to.  
2 One thing that sort of strikes me as  
3 interesting is that in a lot of ways, these ideas  
4 aren't new. I mean, Nat talked about quality  
5 control way back when for industry. But a lot of  
6 the -- I think the first publication of this that  
7 was really noticed by people was in the late 1990s,  
8 and then it was about 10 years of not a whole lot.  
9 And all of a sudden, there were a lot of papers  
10 coming out now about this.  
11 I suspect this has to do with cutting costs  
12 and so forth and trying to move away from  
13 traditional monitoring, but I'm sort of curious as  
14 to why the sudden interest and why there was this  
15 sort of long dead period. I don't know if anyone  
16 here has a comment about that.  
17 If not, go ahead.  
18 MALE SPEAKER: Yes, I have a separate  
19 question. It's kind of just a practical question.  
20 I'm a clinician and have been doing clinical trials  
21 forever. I don't know if the FDA -- one of the  
22 things we get all the time in the new electronic

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1 medical age is how to let monitors have access or  
2 not to EMRs.  
3 So I have a clinical practice, and I have a  
4 research practice. We keep a firewall, obviously,  
5 between the two companies for HIPAA reasons. But  
6 the monitors increasingly beat us up when they come  
7 and they want to have access to our EMRs. So we  
8 take what we think are pertinent records from the  
9 practice and send those over to the research folks,  
10 print those out.  
11 But obviously, it would be an enormous  
12 effort on our part if we let a monitor sit in front  
13 of the EMR, not to even get into whether I think  
14 it's ethical or not for them to have complete  
15 access to a patient's file, and then access to  
16 every other file in that Epic system and so forth.  
17 So I don't know. Has the FDA dealt with  
18 that at all, or do you guys have any position on  
19 monitoring coming in? I mean, we want them to have  
20 access and quality data. That really has been a  
21 practical problem, has been an issue for us.  
22 DR. SCHUETTE: I'm not directly involved

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1 with that level of approach since I'm in the Office  
2 of Biostatistics as opposed to Office of  
3 Compliance. But generally speaking, I would  
4 encourage you to reach out to your contacts in the  
5 Office of Compliance and actually say here are our  
6 concerns and to actually say, okay, how can we  
7 address these needs.  
8 In some case, one can do extraction from a  
9 database and then make that available. That's just  
10 one possible approach, but the short answer is I  
11 don't know. But I would certainly encourage you to  
12 reach out to your appropriate contacts.  
13 MALE SPEAKER: Great. Thanks. That is what  
14 we do. We do extraction out, and then let them  
15 have access to that, but that never seems to  
16 satisfy them. I don't know.  
17 (Laughter.)  
18 DR. SCHUETTE: Well, no, but that's good.  
19 I'm glad they're not satisfied because -- I mean, I  
20 was trying to raise the question as to whether we  
21 should try to collect more, not less, from the  
22 source documents to be distinguished from source

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1 data. But I agree, compliance, HIPAA, privacy, we  
2 get it.  
3 DR. McDERMOTT: Bob?  
4 DR. DWORKIN: Yes. Rick, I had a question  
5 about what you were describing as Teva's new  
6 policy. If I understood you correctly, you were  
7 saying that you would go to a site and you want to  
8 see source documents on the patients, and it  
9 sounded like you really mean medical records, for  
10 example, from their primary care clinician.  
11 Now, I've been at meetings with other  
12 sponsors and CROs, where what we hear is that when  
13 patients are identified through, for example,  
14 advertising on TV, that it's kind of impossibly  
15 difficult to get the physicians or nurse  
16 practitioners, what have you, in the community to  
17 fax medical records, and that if that's required by  
18 the protocol, the CRO, whatever, aren't going to be  
19 able to get any patients through advertising.  
20 So when I was listening to you talk, there  
21 was a real disconnect between what I've heard about  
22 the impossibility of getting medical records and

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1 what you said is the Teva policy, is you want to  
2 see the medical records.  
3 DR. MALAMUT: No, I mean, I didn't say it  
4 was always successful because you're right. The  
5 study subjects who come through advertising, it is  
6 a challenge. But I think it's more of an increase  
7 in effort on the part of us to get those records,  
8 find out from the patient who their primary care  
9 physician is, get them to sign a release and get  
10 the records.  
11 DR. DWORKIN: So to me, it seems almost  
12 essential if you're recruiting a patient for a low  
13 back pain study and you get the patient through  
14 advertising, and you then succeed in getting the  
15 patient's medical records, and it seems that  
16 they've never mentioned to their clinician in the  
17 past three years having back pain, that seems like  
18 a red flag.  
19 DR. MALAMUT: Well, not only is a red flag,  
20 it's an exclusion. So again, I would argue that  
21 those patients are precisely the patients we need  
22 to get the records on. And I agree with you. We

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1 strive for 100 percent. Do we achieve 100 percent?  
2 Of course not. But I think if we don't try for  
3 100 percent, we won't even get close. And for the  
4 reasons we've talked about, you won't have the  
5 right patient in your study.  
6 DR. McDERMOTT: Okay. In the back?  
7 MALE SPEAKER: I just want to follow up on  
8 this because it's really an interesting subject.  
9 If you're a clinician in private practice or  
10 academia and a patient is transferred to you, their  
11 medical records come with them, almost always,  
12 invariably. And if they don't come with them,  
13 there's a problem, and somebody's going to have to  
14 fix it.  
15 I mean, you just don't take on a  
16 patient -- if you have a pain patient that I've  
17 inherited -- I don't do that anymore, but when I  
18 was at Emory, you always get the medical record.  
19 So I think this idea of not being able to get the  
20 medical record is a little bit suspect. It sounds  
21 to the non-clinician like, wow, that's a big deal,  
22 but it happened in the late '90s.

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1 But one point I do want to make is this, is  
2 that in terms of the amount of data we're  
3 collecting, it's huge. And when everything is  
4 important, to my mind, nothing is important. And  
5 so I do think you need to have focus in this world,  
6 and I think one of the things that remote  
7 monitoring and some of the things you're  
8 recommending to try to get actually kind of  
9 addresses that issue.

10 But one of the things that comes up a lot is  
11 100 percent SDV. I might have missed that talk.  
12 But that's part of what I'm very curious about what  
13 everybody's opinion is on that, where you go to the  
14 site. The primary endpoint is what it is.  
15 Obviously, you need to -- for the data that you're  
16 really focusing on in terms of your submission,  
17 obviously, that's important. There are a lot of  
18 ancillary endpoints people collect, and measures  
19 they collect, how well that needs to be done.  
20 Obviously, safety needs to be done well.

21 But I wonder if people can talk about the  
22 SDV issue because I find like a lot of people are

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1 really focused on getting everything.

2 MS. KIRKWOOD: I agree. I think for our  
3 center, we don't do 100 percent SDV. We're an  
4 academic center. We can't afford to do that.

5 I agree that not all data is as important as  
6 some of the data and that -- I mean, we are sort of  
7 looking at lots of data in the kind of methods that  
8 I described, but it was more to look at patterns  
9 rather than actually to try and correct everything,  
10 and that it's much more important to make sure that  
11 your primary outcome measures are all there and all  
12 correct than it is all of these blood measurements  
13 that you take at every cycle of chemotherapy that  
14 no one's ever going to use, and especially if we,  
15 on top of that, also collected safety data about  
16 those sorts of things.

17 I think some studies that have been done,  
18 there doesn't seem to be any proof that 100 percent  
19 SDV is necessary and adds anything.

20 DR. SCHUETTE: And I would actually go with  
21 the guidance on the topic for risk-based. So  
22 that's basically -- it sounds like it's pretty much

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1 an outline for the type of difference that you  
2 might be looking for.

3 DR. SINGLA: So just to get back on this  
4 source -- I mean medical records issue, as an  
5 investigator who has done this for a long time and  
6 recruits a lot of patients through advertising and  
7 different types of patients, I just wanted to  
8 provide some insight, which is that first of all,  
9 it is very difficult to get medical records from  
10 recruited patients. It's not like clinic patients  
11 because clinic patients are inside the healthcare  
12 system, and as such, there's an expectation that  
13 they will come with records.

14 So it is hard. It's also hard because the  
15 screening period is typically like 28 days. You  
16 got to get the patient randomized, and by the time  
17 you get their medical records, you're right at the  
18 end of that, and then you can't rescreen them. So  
19 those are the difficulties.

20 It is possible, however, like you said,  
21 Rick. We've had studies where it was mandated, and  
22 then we found a way to do it sometimes. But then

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1 we lost patients as well. It was a lot of effort,  
2 and then it's a question of is it worth it?

3 So I think it requires a decision on the  
4 sponsor's part to decide a priori, what is the  
5 disease being studied and do we need medical  
6 records.

7 For example, low back pain, yes, you  
8 probably do, and patients who are on opioids, it's  
9 a serious issue. Surgical third molar extraction,  
10 19-year-old patient probably doesn't have any  
11 medical records. You're going to bang your head  
12 against the wall trying to find the medical records  
13 from the time they were like 11 and went to see  
14 their pediatrician. And you know that they have  
15 third molars. You can see them on X-ray, and you  
16 basically know they're healthy. Do you really need  
17 them in that situation? Probably not. It's a  
18 six-hour study. They're going to have the  
19 indicated surgery.

20 So I think that when the sponsor  
21 says -- like, puts a half approach towards the  
22 situation and says, well, we'd like them, then it

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1 just causes a lot of confusion. Nobody does it.  
2 And by the time the trial is 50 percent over, you  
3 just stop trying because the sponsor has given up  
4 as well.  
5 So that's just a practicality of what I've  
6 seen happen over the years. So I think that you  
7 have to consider the disease and then make a choice  
8 as a sponsor. Yes, you must have them, and then  
9 increase the screening period if you're going to  
10 force that.  
11 DR. MALAMUT: So it's a pragmatic approach  
12 is what you're suggesting --  
13 DR. SINGLA: Yeah.  
14 DR. MALAMUT: -- not a mandated thou shalt  
15 provide source records, but a little more  
16 pragmatic. You're right. Bunionectomy study with  
17 younger people or maybe not as important. But I'm  
18 really going to argue strongly about certain -- I'm  
19 still leaning towards the idea of this 100 percent  
20 idea even though I know we can be pragmatic. But  
21 we have to study the right patients.  
22 DR. SINGLA: And I'm just saying, for low

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1 back pain, maybe you do want 100 percent.  
2 DR. MALAMUT: Yes, I think so.  
3 DR. SINGLA: They're on opioids. It's a  
4 serious condition, multiple medications. You can't  
5 verify they have the condition whereas in a  
6 bunionectomy, you can verify it, those kind of  
7 things.  
8 DR. DWORKIN: So I would push and say that  
9 clearly, there are exceptions, and I think, Neil,  
10 you did a great job of giving us an example of an  
11 exception.  
12 But if we're talking about chronic pain in  
13 adults, whether it's low back pain or  
14 osteoarthritis or diabetic peripheral neuropathy,  
15 and assuming it is correct that there are study  
16 kingpins not only in Boston but elsewhere who are  
17 going to clinicaltrials.gov and finding out the  
18 inclusion/exclusion criteria of trials, and feeding  
19 patients into those trials, then don't we really  
20 want to see the clinician's record on 100 percent  
21 of these adults with symptomatic chronic pain?  
22 Otherwise, I mean, we're just making it real easy

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1 for the study kingpins.  
2 DR. MALAMUT: You could make the argument  
3 that the patients you can't get records on and  
4 disappear, maybe they weren't the ones you wanted.  
5 I mean, maybe you're losing out on some very good  
6 study patients, but the tradeoff.  
7 DR. McDERMOTT: Michael, did you have a --  
8 DR. ROWBOTHAM: I just wanted to go a little  
9 further with some of the discussion this morning  
10 and then yesterday about data that's too good to be  
11 true. So one of the possibilities also is that you  
12 could have a positive trial and it comes out  
13 negative because of fraud or fabrication on study  
14 sites just trying to increase their numbers.  
15 So could I hear a little bit more from both  
16 the FDA and the industry perspective as to what  
17 kind of data checking is likely to be done  
18 routinely to make sure that the data that was sent  
19 in a file to the FDA actually is legitimate data?  
20 DR. SCHUETTE: Right now, it's more on a  
21 trial-by-trial basis. There really isn't an entire  
22 across the submission look at data quality on each

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1 and every aspect. So what we have right now is  
2 fairly rudimentary checks, sort of things like  
3 calendar dates and some of the other types of  
4 items.  
5 The example that Sharon gave was noteworthy  
6 in the sense that there was actually a comparison  
7 between one site -- one trial and another trial,  
8 trials that were conducted in the U.S. and outside.  
9 And they said an unbelievable response rate over  
10 here and a middling response rate over here. So  
11 that was a case where we could just say, just by  
12 looking at it, this is way too good to be true.  
13 That's actually where we are right now.  
14 What we'd like to do with some of these other  
15 aspects is to look at it in a more coherent  
16 fashion, and that's still a matter of development  
17 from our perspective.  
18 DR. MALAMUT: I think, as I said, we do our  
19 best -- is that the right word? -- to verify  
20 everything that the study sites tell us, what they  
21 write down, what's documented. A lot of the  
22 efforts go towards making sure data is entered.

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1 We're a little limited in being able at the  
2 time of monitoring, at the time after last patient  
3 out, to be able to verify that a pain score is  
4 actually an accurate pain score. So a lot of the  
5 too good to be true may have to come later during  
6 the all too short time to look at the data and then  
7 in analyses later. And of course, we'd like it to  
8 be good, so there's a bias.

9 When we see something that's successful, we  
10 say aha, we were right, but then we do try to be  
11 critical and look for those patterns, and do take  
12 it to individual sites, individual regions, and try  
13 to see not only why a study may not have succeeded  
14 but why did a study succeed, where did the positive  
15 data come from.

16 DR. McDERMOTT: I think --  
17 DR. DEVINE: Eric.  
18 DR. McDERMOTT: Eric, sorry.  
19 DR. DEVINE: I've come to this meeting to  
20 beat a single drum. Everyone knows what I'm going  
21 to say. But we want people to exclude professional  
22 subjects from their study before they get in.

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1 But assuming the potential that not all  
2 sites will make the efforts to get the medical  
3 records or design the study so it isn't really  
4 vulnerable to being gamed by the professional  
5 subject, and maybe there's collusion on the part of  
6 the investigator who really wants to enroll  
7 quickly, do you think that it's possible, from a  
8 monitoring perspective, to pick up on patterns of  
9 data that are indicative not of a fraudulent site  
10 but of a fraudulent subject?

11 Over a lot of observations of what a  
12 particular disease looks like and the way the  
13 subject answers questions in the trial, would you  
14 see a pattern that you could pick up on that  
15 professional subject because their answers are  
16 similar to someone that's malingering with a  
17 learning disorder because they need services, or  
18 someone who is malingering with pain because they  
19 want the drug?

20 MS. KIRKWOOD: To be honest, it's not  
21 something I ever considered until this meeting  
22 because it's not something we have in the disease

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1 area I work in. You don't get professional  
2 subjects in cancer trials. But it's definitely  
3 something that I think would be interesting to look  
4 at.

5 I think it might be hard to do without  
6 examples of it. So what you would really need is a  
7 trial where you've got a data set with patients  
8 that you have identified as professional subjects,  
9 and if you could get that, then it would definitely  
10 be something that would be very interesting to look  
11 at, whether they could be picked out. But it's not  
12 something I've looked at because it's not something  
13 I'd imagined before this meeting really.

14 DR. SCHUETTE: And I will say that we don't  
15 have -- we'd be interested in the exact same thing  
16 with actual examples, and we're working with  
17 commercial developers in some ways to try to do  
18 research and development.

19 I've already mentioned after reading your  
20 paper, Eric, this idea to one person -- one  
21 developer suggested that this was a product niche  
22 that if they were willing to, they could actually

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1 pursue.

2 DR. McDERMOTT: Way in the back.  
3 DR. SIMON: So slight note of caution for  
4 those of us who actually serve on executive  
5 committees or DSMBs or DMCs or any of these things.  
6 In the last 10 years, it's actually been more  
7 common than not that we've seen inappropriate or  
8 inadequate or mismanaged oversight by hired CROs  
9 that require buy-in from the physician or caregiver  
10 supervisory group.

11 People 20 years ago, when I was a trialist,  
12 25 years ago, were hesitant to become proactive  
13 with the CRO or the company doing the study because  
14 they felt that that was their purview. But the  
15 events that I'm referring to are so egregious and  
16 so extraordinary that, in fact, if we do not exert  
17 some responsibility, we cannot allow or expect only  
18 the regulatory group to pick this up because some  
19 of this stuff is extraordinarily buried in the  
20 database and it may not become evident. And yet  
21 theoretically, a DMC chair and his team should be  
22 cognizant of what's going on in the trial.

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1 So the caution that I'm trying to suggest is  
2 that we keep asking questions that are asking the  
3 FDA to have an answer for how these things get  
4 controlled, but it's going to have to require  
5 cooperation between the external groups that are  
6 supposedly overseeing the studies and the internal  
7 groups.  
8 Just for example, most recently I am serving  
9 as a kind of monitor of a trial, and I was asked to  
10 review the SOPs of the CRO regarding the history of  
11 the patient. And the concerns were for a chronic  
12 pain trial that the history was only going to be  
13 taken for the previous year.  
14 Well, the problem was, is that a lot of the  
15 potential history for allergies and other issues  
16 would either have to be extracted from the chart  
17 or, God forbid, the PI on the trial at the site  
18 would actually have to take a history from the  
19 patient that is actually being recruited into his  
20 site, and he's getting paid for this.  
21 So the reality is we have to take some  
22 responsibility for this, too, and be mature enough

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1 to actually do the work that we're being paid to  
2 do. And I'm not actually hearing anybody  
3 acknowledging that particular aspect of this.  
4 Of course, nobody in this room has any  
5 belief to be malfeasant or not to do what he's  
6 supposed to do, but in fact, it's become de rigueur  
7 that the superficial nature of the supervision of  
8 the trials on our side is actually quite bad, so  
9 note of caution.  
10 DR. McDERMOTT: Yes, I think, Rick, you said  
11 something about vendor oversight yesterday.  
12 DR. MALAMUT: Yes. I mean, again, I was  
13 trying to be veiled yesterday because I didn't want  
14 to actually give strong opinions, although somebody  
15 last night told me they could tell everything I  
16 thought. So maybe that's good. Thanks, John.  
17 But I really do want to hear from others  
18 about this. I think I may have made the case  
19 yesterday that exactly what Lee is saying, that we  
20 do need to take responsibility as sponsors, as  
21 CROs, as investigators to take a proper history.  
22 If you're not at that 100 percent level on

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1 the patient record, we just assume that you're  
2 taking the history and finding out the allergies  
3 and the con meds, and of course, the presumed study  
4 patient may have incentives to not tell you the  
5 whole truth, but we have to at least make sure  
6 we're doing that.  
7 The same on the vendors. I tried to make  
8 the point yesterday that we all have to monitor  
9 each other. Otherwise, the data we get will maybe  
10 not reflect the true nature of the compound we're  
11 testing or be misleading. And I fully agree, Lee.  
12 DR. SCHUETTE: If I can jump in, I'll echo  
13 what Richard has indicated and say we completely  
14 agree with Lee, particularly when we're talking  
15 about multi-regional trials and things that are  
16 done outside of this country where, as was pointed  
17 out by Sharon yesterday, we can't always, as  
18 regulatory agencies from the U.S., get access to  
19 the types of data in other countries. And it  
20 becomes particularly important that the CRO or the  
21 sponsor ensure that the data is good, that there is  
22 not misconduct at the site because some cases,

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1 we're blocked from going very much further than  
2 just an overall look and inspection.  
3 DR. McDERMOTT: Okay.  
4 MALE SPEAKER: Just an obvious follow-up  
5 observation, again, the way we did things 15,  
6 20 years ago, just following up on some of Lee's  
7 comments, was much more personal. So there are so  
8 many more layers now in study conduct.  
9 To your point, Rick, getting to the site is  
10 incredibly important. So all these centralized and  
11 statistical monitoring approaches are very  
12 important, but you really do need to get to the  
13 sites.  
14 As we go up the food chain in industry, we  
15 get further and further away from the sites. In  
16 this meeting here today, I've heard us talk about  
17 some of the most important people are the CRAs.  
18 They're the most inexperienced people in the  
19 system, and we overtax them. We expect them to do  
20 monitoring. If we really want to have onsite eyes,  
21 we either have to do a better job with the CRAs or  
22 get out there ourselves.

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1 So in small companies -- and I don't know if  
2 others have even been to sites. I don't know,  
3 Rick, if you've been out to visit a site  
4 recently --  
5 DR. MALAMUT: Not in a few years.  
6 MALE SPEAKER: -- but, yeah, it's really  
7 eye-opening. And there are a lot of intangibles  
8 that you pick up. And obviously, you can put in  
9 statistical and other central monitoring schemes,  
10 but until you get to meet the investigator, the  
11 coordinator -- I mean, there isn't probably even a  
12 coordinator here at the meeting. I'm not sure if  
13 that's true or not.  
14 But they're the quarterbacks for these  
15 studies, and maybe just as we think about this, Bob  
16 and Dennis, going forward, probably we need to get  
17 some feedback from coordinators and monitors about  
18 this guidance if we're going to be creating this  
19 paper that people will be reading.  
20 But again, very impersonal, lots of layers.  
21 I think CROs are probably -- I mean, I've worked  
22 for CROs. I've worked with CROs. It's a problem.

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1 There's just too many layers from an issue or  
2 problem getting to the source. It has to go from  
3 the coordinator to the CRA, up the chain through  
4 the CRO, through the project manager, back to the  
5 sponsor. And as a CMO in a small company, I'm  
6 eight layers removed from an issue, and it gets  
7 filtered. Basically, we have to do a much better  
8 jobs.  
9 Your thoughts, Rick?  
10 DR. MALAMUT: Again, obviously, I agree  
11 because you made the points I made yesterday. But  
12 no, I'm envisioning a diagram with circles of all  
13 the people involved in the study with everyone  
14 connecting to everyone else because we're all  
15 monitoring each other, and we all have  
16 responsibilities, so yes.  
17 DR. McDERMOTT: I guess way in the back and  
18 then --  
19 MALE SPEAKER: All these comments are really  
20 good, and as somebody who as even like a year ago  
21 when I was at Merck was doing site visits, I  
22 totally endorse that. But one of the greatest

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1 technical devices that's been invented recently is  
2 the phone. And picking it up and just calling  
3 people, you'd be surprised how much valuable  
4 information you get just by talking to an  
5 investigator because they have phones, too. It's  
6 pretty cool.  
7 (Laughter.)  
8 MALE SPEAKER: Now, but the point I do want  
9 to make is a serious one, picking up from Lee's  
10 comment, is I was amazed. The way we do things in  
11 the United States, we think the whole world does it  
12 that way. And I've been used to a system where we  
13 have highly trained study coordinators who really  
14 know what they're doing better than, at one point,  
15 I did when I first got into it. These study  
16 coordinators are sometimes amazing.  
17 Then we go to these sites, and we open them  
18 up for the first time. And in Europe what really  
19 surprised me is that study coordinators are not  
20 these really anal retentive nurses who've been,  
21 we're on the floors for years and now we're working  
22 clinical trials. They're young physicians, who are

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1 really both sub-PI and study coordinator.  
2 I've expressed concerns about that on  
3 multiple occasions during multiple site visits in  
4 Europe. People have allayed my fears somewhat, but  
5 it is something that everybody should be aware of.  
6 I think doctors are pretty good, but not all of us  
7 are trained to be that focused on the minutiae,  
8 which I think a really good study coordinator needs  
9 to be.  
10 DR. McDERMOTT: David?  
11 DAVID: Yes, sort of in all this discussion,  
12 I think we're looking a lot at downstream events.  
13 And when you talk about drug or the kingpin, the  
14 study kingpin, that also could be a study  
15 coordinator. And I'm wondering, has anybody ever  
16 looked at sort of the study equivalent of a secret  
17 shopper where you put a sham patient in and sort of  
18 see what happens at that interface? Because I  
19 think that could be very interesting. I've never  
20 done it myself, but I'm very curious if anybody  
21 has.  
22 DR. McDERMOTT: No takers.

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1 (Laughter.)  
 2 DR. MALAMUT: I don't think I want to reply  
 3 to that. Secret shopper. Wow.  
 4 (Laughter.)  
 5 MALE SPEAKER: No, there have been. There  
 6 have been secret research subjects, and they'll  
 7 publish it. And it's a big splash article in a  
 8 local paper about how they pretended to be a  
 9 patient and how easy it was to get into a study and  
 10 get drugs. It happens every once in a while.  
 11 DR. MALAMUT: So what was the outcome?  
 12 MALE SPEAKER: Oh, no, it always makes some  
 13 great expose article. I don't know when the last  
 14 one was published, but I don't think it's been done  
 15 on a systemic basis.  
 16 MALE SPEAKER: Yes. I was thinking more of  
 17 the quality aspect, not the journalistic aspect.  
 18 MALE SPEAKER: I was thinking about  
 19 actually -- Rob and I were talking last night about  
 20 the undercover diner. It goes into to see who's  
 21 stealing from the cash register.  
 22 (Crosstalk.)

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1 MALE SPEAKER: Just to chime in real  
 2 quick -- sorry. Actually, the secret shopper,  
 3 people may know, in most healthcare systems is  
 4 actually used as a validated way of quality checks  
 5 and auditing. So there actually is a nice track  
 6 record in clinical care for using it.  
 7 So it's certainly a reasonable thing to  
 8 maybe consider as a bullet point in the paper. Do  
 9 you consider such a -- because it has been used and  
 10 validated throughout healthcare, and we use it.  
 11 And I'm always interested in getting the secret  
 12 shopper reports on my service. It's fascinating.  
 13 DR. McDERMOTT: Over here, and then Lee  
 14 afterwards.  
 15 MALE SPEAKER: So I apologize again if this  
 16 has been said. I think we talk out of both sides  
 17 of our mouths. Maybe in the clinical trials area,  
 18 this is a major concern, and I understand that and  
 19 I appreciate that we're spending the time talking  
 20 about that.  
 21 In other research enterprises in the same  
 22 wing of our hospital, they keep lists of

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1 professional patients in laboratory analog trials  
 2 that are clean of any drugs, they're free of health  
 3 problems and so forth, to keep them coming back for  
 4 more and more trials.  
 5 I think it's important that we, I guess as a  
 6 group, appreciate that maybe in our same community,  
 7 this is being thought about in quite different ways  
 8 That's one point.  
 9 I guess I heard really yesterday -- it's  
 10 maybe shifting the gears a little bit here. But at  
 11 the point of making decisions about a person's  
 12 meeting inclusion and exclusion criteria for  
 13 participation in a study, which I think is really  
 14 central to the integrity of the study, I heard both  
 15 in presentations and, then importantly for me, in  
 16 sidebar conversations with a number of people over  
 17 the last day and a half a sense of, yeah, there are  
 18 those. But if I really have a bad feeling about a  
 19 person, I don't include them in the study.  
 20 I have a very serious concern about whether  
 21 we really have additional inclusion and exclusion  
 22 criteria that we're talking about here, which is we

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1 include people if they maybe are close to meeting  
 2 the criteria in terms of, for example, age or some  
 3 other criteria. Then we should be clear that  
 4 there's some wiggle room there. I don't agree with  
 5 that, but I imagine that that's the case.  
 6 Exclusion criteria, which is we have all  
 7 these things, if the person meets those criteria,  
 8 but we still don't feel -- we think maybe they're a  
 9 fraudulent or professional patient, we have a hunch  
 10 or gut, we exclude them. I'm very concerned about  
 11 that slippery slope.  
 12 DR. MALAMUT: I won't speak for all my  
 13 fellow sponsors, but in most studies, there is  
 14 somewhere down at the bottom of the exclusion list  
 15 a exclusion for any other reason the investigator  
 16 feels the patient is not appropriate. And there's  
 17 no rule that says just because a patient meets all  
 18 the criteria, they have to be enrolled. I mean, it  
 19 really is discretionary.  
 20 But I think there's a risk, and I think  
 21 everyone in this room either is, or has been, or  
 22 will be an investigator. We make that check. I



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1 think we're doing -- our internal system is  
2 checking to see is this really what they say they  
3 are.  
4 My concern is more with the less expert  
5 enroller, some of the research sites who don't have  
6 that inner -- and they're checking the box.  
7 They're saying, well, they met all these criteria,  
8 therefore, they must qualify. They're not really  
9 thinking beyond that. And I don't mean to  
10 generalize.  
11 MALE SPEAKER: I've encouraged journal  
12 editors to ask that that disclaimer, if you will,  
13 be added to every --  
14 DR. McDERMOTT: Well, sometimes other  
15 pressures enter into this, too. I mean, pressure  
16 to recruit or to be kicked out of the trial as a  
17 site. All sorts of things come into play.  
18 Lee, you've been waiting.  
19 DR. SIMON: It's really interesting. This  
20 raises the problem that we've assumed that the  
21 people that are out there serving as principal  
22 investigators at the individual sites are actually

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1 capable of doing that because they've actually been  
2 able to recruit before or for any other criteria  
3 that are there.  
4 We are all experienced people, and we all  
5 think we know what we're doing. And we've taught  
6 ourselves since there is no academic process of  
7 learning how to become a clinical trialist, it is  
8 catch as catch can. And basically, in the end,  
9 we've abrogated our responsibilities for these  
10 clinical trials unless we create a methodology to  
11 allow people to become clinical trialists and make  
12 it be a actual learned endeavor.  
13 To complain that people use their own  
14 intuitive nature of deciding if somebody will get  
15 into a trial or not, which is absolutely what  
16 happens all the time, and why that last comment  
17 exists in the exclusion criteria, we have an  
18 opportunity here to identify within this manuscript  
19 what we believe should be the right way to do  
20 things.  
21 It even goes down to how we recompense  
22 people for work. We typically create contracts

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1 where they get paid for recruitment, not paid for  
2 completion. And therefore, that leads to  
3 missingness, which is like a nightmare. And  
4 furthermore, it also leads to inadequate patients  
5 being recruited because the pressure, as you just  
6 mentioned, is to recruit so that you can actually  
7 remain within the trial, because otherwise, you'll  
8 be dropped out if you only have two or three people  
9 compared to somebody else that already has 45.  
10 So I think that we in this community who  
11 believe in this process should, in fact, create an  
12 infrastructure to allow people to learn how to do  
13 these things and become certified or at least  
14 knowledgeable.  
15 To think that this all happens at an  
16 investigator meeting that may take eight hours, and  
17 everybody is asleep and on their computer anyway  
18 during the time, is ridiculous. Let's be honest.  
19 This is a complicated process that requires real  
20 knowledge, and we should be teaching it.  
21 DR. McDERMOTT: Laurie?  
22 MS. BURKE: I completely agree from my

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1 limited knowledge post ex-FDA, from what I've seen.  
2 And I think that this isn't just one curriculum to  
3 qualify people to be clinical trialists, but it's  
4 multiple. It starts with -- there's the multiple  
5 disciplines' worth of qualification of degree  
6 programs, or whatever you want to call them, that  
7 need to be thought about. And of course, my thing  
8 is the measurement area. There's really no place  
9 that people can go to get a degree in clinical  
10 trial measurement, and that, I think, is one in and  
11 of itself.  
12 MALE SPEAKER: Just one comment on the  
13 compensation, which I think to piggyback on Lee's  
14 comment, which is really important. Clinical trial  
15 sites don't get paid to screen in general. There  
16 are screening fees. Yes, of course, there is, but  
17 you get paid to randomize subjects. And it's  
18 completely skewed, the amount of money you get when  
19 a subject randomizes.  
20 I think it's because sponsors want  
21 randomized subjects, which makes sense. They also  
22 find it difficult to pay for subjects who are

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1 screened because it's easy to inflate the number of  
2 patients you screen, so it's kind of just a  
3 necessary evil.  
4 But I think this economic lopsidedness about  
5 randomization leads to a pressure to randomize and  
6 to not get -- because you're not getting  
7 compensated essentially for screening. It's almost  
8 like you're paying for screening, and then you get  
9 paid when you randomize subjects. That's how it is  
10 as an investigative site, which is the genesis of a  
11 lot of these problems.  
12 To talk just one more point about what Bob  
13 Dworkin said yesterday regarding blinding clinical  
14 trial sites to when the subjects can be screened  
15 and randomized, I think that's a good idea.  
16 When that does not occur, in other words,  
17 the decision has not been made to blind. When  
18 there's subjective criteria or like a baseline  
19 entry criteria, let's say, for OIC, patients have  
20 to have less than this many bowel movements, or for  
21 a OA study, they have to have a flare of X, Y or Z,  
22 you can see in the data -- someone's talking

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1 about -- we're all talking about central  
2 monitoring -- that different sites have  
3 differential rates of patients that will make it  
4 through that baseline period and sometimes widely  
5 differential. And when it is widely differential,  
6 that's a problem because it's all based on  
7 competition.  
8 So I think when you look at central  
9 statistical monitoring, this is the key aspect  
10 because it's financially driven and it affects the  
11 randomization.  
12 DR. McDERMOTT: Matt?  
13 MALE SPEAKER: I think it's -- I want to  
14 pick up on comments made earlier about contracting.  
15 Now that we're contracting with sites to do  
16 clinical trials, it's kind of shocking how much  
17 contracting influences quality in the sense that  
18 investigators are never, ever, ever contracted for  
19 quality. They're only contracted for procedures,  
20 whether those are visits or EKGs or visits or  
21 histories and physicals or what have you.  
22 Then when you try to go back to the site

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1 later and say, hey, we want you to really think  
2 harder about patient recruitment or think harder  
3 about how you're coaching your patients -- training  
4 your patients -- to measure pain, or get your  
5 queries resolved more quickly or whatever the  
6 quality metric is, you can't get anywhere because  
7 you don't have any financial leverage over those  
8 sites unless you are in a network where you own the  
9 sites.  
10 I wonder whether it's almost worth a  
11 paragraph in this paper or at least some discussion  
12 of how we fall short of trying to influence quality  
13 because we fail to account for it in our  
14 contracting processes.  
15 DR. MALAMUT: It's almost for the next  
16 study. You're right, in the middle of a study,  
17 it's very difficult, without seeing the data, to  
18 know what the quality of the data actually is. But  
19 I think the act should be on the next study, so  
20 that if I look at site X and they've recruited  
21 30 patients, and did a great job recruiting but, in  
22 fact, most of the data had to be thrown out and

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1 other patients -- then that site is not going to be  
2 selected for the next study. Now, maybe that site  
3 doesn't care. But we would hope they do.  
4 MALE SPEAKER: The facts, I think, show that  
5 if that's the current system, it's not working,  
6 because otherwise, we wouldn't be having this  
7 meetings.  
8 I also think that as much -- ask any CRO or  
9 any sponsor, do they monitor -- do they measure the  
10 quality of the site at the end of the study,  
11 they'll all say yes. And then when you ask them to  
12 show you exactly how they do that, no one can ever  
13 come up with anything. They can't find it. That  
14 was the other CRO. Well, what we really know is  
15 whether there were any major audit findings or how  
16 many patients they recruited.  
17 So there's a huge disconnect between what  
18 people claim they evaluate in terms of study  
19 quality and how they utilize that information for  
20 the next study and what's actually being done. So  
21 I think there are opportunities within the  
22 contracting process to pay for quality and create

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1 that financial leverage.  
 2 DR. McDERMOTT: Way in the back and then --  
 3 DR. HEWITT: So what I'd say is I do believe  
 4 in relationships with sites, and there are sites  
 5 that I've used, we've all used probably, in  
 6 clinical trials that go back to the late '90s. So  
 7 we all know a lot of people who do a lot of  
 8 clinical trials and are good sites.  
 9 And I think when you -- just to pick on  
 10 Nat's point, a high-quality site, I think for those  
 11 of us who have really been in the trenches, has to  
 12 do with their queries. If the data is really  
 13 dirty, no study coordinator -- I mean, no CRA is  
 14 going to want to pick a site again that's just  
 15 given them hell for three months as they're trying  
 16 to clean up the queries.  
 17 So although you could use a lot of metrics,  
 18 I'll tell you, the number of queries and getting  
 19 them rectified in a timely fashion is what will  
 20 either get you on to the next study at work at  
 21 inVentive or not because for those of us who follow  
 22 these things, those are important metrics.

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1 DR. McDERMOTT: Roy?  
 2 DR. FREEMAN: So I want to pick up on a  
 3 point made by I think it was Lee behind me and the  
 4 invention of the cell phone guy, which I think was  
 5 David Hewitt, but I'm not sure.  
 6 Bob Dworkin and I found ourselves at an  
 7 investigator meeting a week or so ago, and we had a  
 8 chat -- they called it a fireside chat -- in front  
 9 of a group of study coordinators and investigators,  
 10 and there were no academic investigators. These  
 11 were all pay-to-play type sites.  
 12 The aim of the chat was to discuss concepts  
 13 related to the placebo response, and topics  
 14 included things like how to balance your desire to  
 15 recruit more and more subjects versus selling the  
 16 study drug as the new wonder drug and raising  
 17 expectations, how to balance study retention versus  
 18 being warm and nurturing and fuzzy, and again,  
 19 enhancing placebo response. And I could go on  
 20 about the nature of the discussion, which was kind  
 21 of entertaining.  
 22 But what was eye-opening was at the end of

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1 it, the number of study coordinators that came up  
 2 to me -- I don't know about Bob -- and said, "I've  
 3 never really thought of that before." And it was  
 4 so interesting to hear that.  
 5 So picking up on Lee Simon university for  
 6 clinical trialists, university for study  
 7 coordinators kind of concept, obviously, really  
 8 difficult to operationalize. But what I do think  
 9 is a really good idea, and perhaps this could go  
 10 into the document as well, is at each investigator  
 11 meeting, there should be a clinical trial 101 type  
 12 meeting in which the protocol is not just discussed  
 13 and how to do an EKG, but actually the nature of a  
 14 clinical trial and what we are doing in it. This  
 15 is an experiment in clinical equipoise, and all of  
 16 the things that we kind of take for granted, but  
 17 they actually don't understand, and they really  
 18 don't.  
 19 DR. McDERMOTT: Scott?  
 20 DR. EVANS: So in statistics, we have a  
 21 saying that there are lies, damn lies, and  
 22 neurologists.

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1 (Laughter.)  
 2 DR. EVANS: You guys may have heard a  
 3 different version.  
 4 I'd like to pick up on that point because  
 5 much of the discussion is sort of focused on  
 6 detection of fraud and malfeasance and outliers in  
 7 a sense. But when I think about data quality from  
 8 a broad perspective and where we can make the most  
 9 impact -- and I'm someone who's been teaching  
 10 clinical trials for 10 years, so hopefully, there  
 11 is some academic process to this.  
 12 The first thing that comes to mind from a  
 13 statistical perspective, where I do think we could  
 14 make enormous impact, and it's probably old news,  
 15 but it's a point that Paul made on missing data.  
 16 And the National Academy of Sciences put out a  
 17 report a couple of years ago, and there was a New  
 18 England Journal of Medicine summary of that report  
 19 a couple of years ago as well.  
 20 Basically, the message in that report is  
 21 that missing data is not a data analysis problem.  
 22 It's a design and conduct problem, with the message

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1 at prevention and dealing with this upfront.  
2 Now, I'm a part of a new clinical trials  
3 network, and I've essentially said that efforts to  
4 minimize missing data is a standard section in the  
5 protocol, and we have to figure out ways to prevent  
6 it and deal with it because if you get it at the  
7 end, as you know, prevention is the best medicine.  
8 But fancy statistical methods are not going to  
9 rescue design and conduct flaws. So I think this  
10 whole process is really sort of a prevention issue.  
11 Picking up on the education piece, I think  
12 that that's really an educational message, that if  
13 you can train people to understand fundamentals  
14 about clinical trials, your quality is going to go  
15 up.  
16 Just getting people to realize the important  
17 distinction between needing to go off study because  
18 of toxicity -- or needing to go off treatment  
19 because of toxicity doesn't mean you have to go off  
20 study and that I'm going to lose your data.  
21 So there are a number of things, and there's  
22 a checklist in the New England Journal of Medicine

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1 article or the Academy's report, data management  
2 practices about clear CRFs and not overburdening  
3 patients and doing things that enables them to be  
4 able to stay on study; the intention to treat  
5 principle, getting people to understand the intent  
6 to treat principle, that follow patients regardless  
7 of adherence; and their example language about if a  
8 patient wants to withdraw, whether we could  
9 actually withdraw you from treatment but still  
10 collect your data and follow you, and that has  
11 important implications.  
12 Things in design, clearly thinking carefully  
13 about the population, whether you want to do run-in  
14 periods, which may reduce missing data later on;  
15 flexible treatment regimens, how would you handle  
16 the rescue medication issue? And this actually  
17 gets at the effectiveness versus efficacy piece.  
18 And in academic medicine, I try to get people to  
19 think more about effectiveness.  
20 If a patient goes off treatment because of  
21 an adverse event, a toxicity associated with the  
22 medication, and therefore, maybe they go off study

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1 even, and you don't get their measurements that you  
2 expected to get at the end of the day, and we go to  
3 analyze pain, oh, all of a sudden, we've got a  
4 missing data problem.  
5 Well, it's a missing data problem when  
6 you're trying to evaluate causal pathways and  
7 mechanisms of action and understand biology. It's  
8 not a missing data problem in clinical medicine.  
9 It failed the patient.  
10 So either having to go off therapy or having  
11 to rescue them is actually part of the outcome.  
12 It's not missing in a sense and getting to think  
13 about whether you need to characterize outcomes  
14 that bring in this information.  
15 So I've been pushing in other areas that in  
16 clinical trials these days, our tradition is we  
17 collect data on patients and then analyze the  
18 endpoints. Well, I want to reverse the order.  
19 Collect data on the endpoints and analyze the  
20 patients. That's who we're treating. That's  
21 what's going to apply in practice. And that will  
22 help eliminate some of the missing data issues.

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1 So there are certainly things we can do -- I  
2 did have a couple of comments about the central  
3 monitoring issue, statistical monitoring. We  
4 already do in clinical trials, as Mike mentioned,  
5 range checks and logical checks, and we can  
6 certainly turn up the temperature in that. And it  
7 will take effort and thought.  
8 You need to decide what you're looking for,  
9 and this is not entirely clear what we're looking  
10 for. And that's going to require more thought than  
11 perhaps Amy's had to get in the tall weeds about  
12 it. But I think when you apply it, it's going to  
13 take more thought than sort of this 40,000-foot  
14 approach.  
15 Then when you say, well, what is an outlier?  
16 And how do we decide what's true and false? This  
17 is really a diagnostic problem. You're trying to  
18 figure out whether I can diagnose fraud or outlier  
19 or something that's a problem. And so this is a  
20 balance of sensitivity and specificity in a sense.  
21 We can detect more outliers, but you're also  
22 going to detect more false positives, and there's

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1 going to be a consequence to that. And frankly, I  
2 don't even know what the gold standard is. We  
3 don't even have a gold standard. It's an imperfect  
4 gold standard in many cases. So there are some  
5 real challenges here in thinking that through.  
6 Then I think deciding how you handle a  
7 particular issue, if you've identified  
8 it -- there's been talked about intent to treat and  
9 whether you exclude them or whether you  
10 don't -- we're really going to need to  
11 think -- we're going to need a more detailed  
12 evaluation on the nature of the issue and the  
13 consequences of different actions.  
14 If you're on a case where you're running a  
15 blinded trial and the blinding actually works, then  
16 if there's malfeasance going on or people are just  
17 enrolling patients that are just nonsense data,  
18 well, that's going to hurt assay sensitivity. But  
19 if the blinding is really -- and so it's going to  
20 hurt the ability to detect differences and so  
21 forth. But it's not necessarily differential  
22 between arms. Although if you're doing a

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1 noninferiority trial, it actually would bias toward  
2 non-inferiority, and you get a different problem.  
3 So I think the blinding issue is a real  
4 important one, and I often encourage people to  
5 evaluate the success of the blind. We often say  
6 we're running blinded trials, but whether the  
7 blinding worked is a whole different issue. And  
8 people often just refrain or refuse to evaluate if  
9 it worked or not through questionnaires, and I  
10 think that may help us understand what the  
11 potential consequences of this are.  
12 So I'll end there. Thanks. Very quiet  
13 after that.  
14 DR. McDERMOTT: You just quieted the room.  
15 DR. EVANS: So you guys have been thinking  
16 your lives about how to reduce pain, and  
17 statisticians think about how to inflict it.  
18 (Laughter.)  
19 DR. DWORKIN: This is only partly related to  
20 your comments, Scott, and follows up on what Lee  
21 was saying. I don't know whether this exists in  
22 other therapeutic areas because it's certainly

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1 clear it doesn't exist for pain.  
2 In other therapeutic areas, are there kind  
3 of training certificate programs for study  
4 coordinators and principal investigators? And it  
5 goes back to what Roy said, that maybe the  
6 beginning of an investigators meeting should be  
7 some kind of general introduction to analgesic  
8 clinical trials 101.  
9 But doing it in that kind of decentralized,  
10 leading up to the sponsor ad hoc way is clearly not  
11 as good as if some organization, for example,  
12 ACTION, put together a two- or three-day boot camp  
13 for junior investigators, senior investigators,  
14 study coordinators, and it was kind of introduction  
15 to analgesic clinical trials 101 with people like  
16 Mike and Scott and everybody on the panel, and many  
17 of us in the room, instructing the people who come  
18 to the meeting. And they all walk home with a  
19 little certificate. It could be set up as CME,  
20 that they spent three days learning all these  
21 challenging issues about clinical trials.  
22 So this just occurred actually completely

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1 independently to both Dennis and me while we were  
2 sitting here. Does that exist? Does anyone know  
3 whether anything like that exists anywhere else?  
4 DR. McDERMOTT: You just caused eight hands  
5 to go up.  
6 DAVID: There is an accredited organization  
7 called the American Association for Pharmaceutical  
8 Scientists, I believe. They've been around for a  
9 number of years, and they do grant some sort of a  
10 certification process. However, it's costly, it's  
11 time consuming, and a bit onerous.  
12 So I think the solution that you propose, to  
13 have some sort of a training during an investigator  
14 meeting that is iterative, that can be accessed on  
15 a corporate or a CRO website, I think is part of  
16 the solution.  
17 DR. DWORKIN: David, I know there are  
18 existing programs, but the ones I'm familiar with  
19 are all generic. I'm talking about something  
20 that's pain specific. I don't know whether it's  
21 just chronic pain or chronic and acute pain.  
22 So is there something like for

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1 cardiovascular clinical trialists or people who do  
2 type 2 diabetes trials? Does anyone know of  
3 anything that's -- any kind of training program for  
4 clinical trialists, both investigators and  
5 coordinators, that's therapeutic area specific?  
6 DR. EVANS: So recently, because of problems  
7 associated with performing rheumatoid arthritis  
8 clinical trials, which require you to actually do  
9 hands-on outcomes -- and it turns out that the most  
10 experienced rheumatologists can't do a physical  
11 exam appropriately, therefore, this has been  
12 studied -- people like at Keystone and others in  
13 Canada actually put together training programs for  
14 investigators at investigators meetings, where they  
15 go in and get tested whether they can actually feel  
16 tender and swollen joints. I mean, it's like wait  
17 a minute, this is what I do for a living, and yet,  
18 in fact, passing such a test is ridiculous.  
19 Furthermore, there's another training system  
20 for injectable drugs, intra-articular drugs. As it  
21 turns out, even the most experienced orthopedist  
22 and rheumatologist miss 33 to 40 percent of the

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1 time getting the needle in the joint. My God, even  
2 the knee, which is like the size of Manhattan.  
3 (Laughter.)  
4 DR. EVANS: So they actually have created  
5 very specified training programs for this, and then  
6 they also have reminder programs during the time of  
7 the trial to bring people back up to date. And you  
8 cannot become a PI at a site for some of these  
9 trials unless, in fact, you pass this.  
10 DR. FARRAR: Just a quick comment on that.  
11 Misha Backonja about seven years created a tape for  
12 study on exam to identify neuropathic pain, for  
13 instance. So there are very specific instances  
14 like Lee is defining. And you're right. There are  
15 other training programs for coordinators.  
16 At Penn, we had a four-week training  
17 program, but it's not specific on a particular  
18 area. And I think that there could be real benefit  
19 to doing that.  
20 DR. McDERMOTT: Mike?  
21 DR. ROWBOTHAM: To Lee's comment, maybe an  
22 aside, that's why they went into research.

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1 (Laughter.)  
2 (Crosstalk.)  
3 DR. ROWBOTHAM: Their offices are so full of  
4 patients, they don't have time to deal with doing  
5 research.  
6 But I just wanted to make one point.  
7 Sometimes the investigators meetings will have a  
8 lot of materials. I've done this like on how to  
9 examine postherpetic neuralgia patients and do  
10 sensory mapping and injections and stuff.  
11 We create those, but one issue that comes  
12 up, especially at the organization that I'm in  
13 where we do a lot of cancer trials, is that you can  
14 have sub-investigators enroll patients as long as  
15 they've been trained by the PI on how to do  
16 everything.  
17 So then you've moved one step away from what  
18 actually was covered at the investigators meeting,  
19 and we have to spend a lot of time making sure that  
20 when a PI trains a sub-I that we're confident as a  
21 research organization that the sub-I really does  
22 know what they're doing on the protocol. And that

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1 may not actually happen at all research  
2 organizations.  
3 DR. MALAMUT: I think I had briefly hinted  
4 at that yesterday, that whoever shows up at the  
5 investigator meeting, often at the site, they may  
6 not have gotten the benefit of the training we're  
7 proposing. So if we're going to put some kind of  
8 training at the IM, we're going to then have to  
9 insist that everyone who's involved in the study  
10 will show up and get that training, which isn't  
11 always possible.  
12 In regard to training, we've done it a few  
13 times in studies where we've wanted to stratify or  
14 assess the presence of allodynia or mechanical  
15 hypersensitivity. So we put together training  
16 tapes with -- I guess Brett Stacey did our most  
17 recent one.  
18 So I think amongst everyone, there might be  
19 individual training videos and pieces specific to  
20 different studies, and maybe they just need all  
21 that to come together.  
22 DR. McDERMOTT: Our coordinating center will

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1 do webinar training or they will have -- it's been  
 2 like that when you have new personnel coming  
 3 onboard. I don't know if that's standard across  
 4 everyone, but that's what we typically do.  
 5 In the back?  
 6 MALE SPEAKER: There are some aspects of  
 7 this that kind of exist within -- as people have  
 8 said, that exist now like GCP training, everybody  
 9 has to. All investigators hate the fact that they  
 10 have to do their GCP training every time they do a  
 11 clinical trial with a sponsor. That's a big issue.  
 12 But certainly with site initiation visit,  
 13 there's a lot of training that should be going on  
 14 as well as stuff that goes on at the investigator  
 15 meeting. And certainly for site initiation visits,  
 16 they should be able to get pretty good training,  
 17 and there's training online.  
 18 But with all of that said, I think the point  
 19 Bob is making is a good one, is that we're really  
 20 going beyond something. And I think if you can get  
 21 like a certification so that people really get it  
 22 and understand it, I think that's a huge, huge

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1 thing because medical schools aren't going to do  
 2 it. Medical schools have been -- we've been trying  
 3 to teach medical schools to teach about chronic  
 4 pain for 20 years. They're still not going to do  
 5 it. So I endorse the idea.  
 6 MALE SPEAKER: I guess I have a quick  
 7 question. How is this being handled for  
 8 international folks where we're dealing with  
 9 multi-regional trials and folks who are not always  
 10 proficient or even fluent in the language in which  
 11 the primary training materials have been created?  
 12 MALE SPEAKER: Well, that actually is an  
 13 issue that people have to address. Frequently,  
 14 these materials are translated. Certainly, all the  
 15 patient materials are translated into other  
 16 languages. But it is a good point that you need  
 17 to -- and then is the translation right is a big  
 18 thing as well. There are all these dedicated  
 19 translation services that go back, translation  
 20 forward to make sure that they've got it right.  
 21 And then your CRAs speak the language, too. But it  
 22 is an important issue.

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1 DR. McDERMOTT: Lee, did you have a comment?  
 2 DR. SIMON: I just wanted to comment that  
 3 one has to wonder whether national professional  
 4 societies, be it in the U.S. or in Europe, have an  
 5 obligation to do that. If they're going to help  
 6 their membership professionalized themselves, one  
 7 of the ways to professionalize is to become a  
 8 professional trialist. And what the problem has  
 9 been is it's not considered an academically  
 10 scholarly activity to do clinical trial work here  
 11 in the United States.  
 12 So there is no real pressure on somebody who  
 13 does it in an academic site to publish. I mean, if  
 14 you're one of 400 investigators, you're not going  
 15 to be one of the people who are going to be the  
 16 author on the paper. You might get acknowledged,  
 17 but then that's not recognized. And in certain  
 18 institutions, even if you're a first author because  
 19 it's a clinical trial, it's meaningless for  
 20 academic promotion.  
 21 Until that changes, unfortunately, we're  
 22 going to have to rely upon either national

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1 professional societies to do this, the sponsors to  
 2 do this, or groups like this. And I think we can't  
 3 rely because it hasn't worked so far. So something  
 4 has to be changed, and perhaps this group can do  
 5 that.  
 6 DR. McDERMOTT: John?  
 7 JOHN: Just one quick comment that I made to  
 8 Bob that I think is probably worth saying out loud  
 9 is that there's clearly a big effort now on what's  
 10 called team science. It means lots of things in  
 11 lots of situations. but in this particular case,  
 12 one of the issues that we know about investigator  
 13 meetings is that everybody gets together at the  
 14 beginning, and then the coordinators go off and do  
 15 their thing and the investigators go and do their  
 16 thing. And that's never made sense to me because  
 17 we really want the coordinators and the  
 18 investigators to, like, hear the same thing so that  
 19 they can hold each other accountable.  
 20 So I would argue that the best of all  
 21 worlds -- obviously, you can't always do  
 22 that -- you would want actually to train the team

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1 to work together to provide the services necessary.  
2 DR. McDERMOTT: Nat?  
3 DR. KATZ: I have sort of a change of the  
4 subject, which is more back to the issue of central  
5 surveillance of clinical trials. I think we need  
6 to say something about what corrective actions in  
7 response to surveillance findings are and are not  
8 appropriate. If we're going to be monitoring for  
9 quality interpreted one way or another, then the  
10 next question is, well, if you find something, what  
11 are you going to do about it? Otherwise, there's  
12 no purpose to surveillance unless it's connected to  
13 some type of corrective action.  
14 The risk-based monitoring guidance has a lot  
15 of information about possible corrective actions,  
16 but it's a very suggestive and non-specific and  
17 certainly not focused in our therapeutic area. And  
18 I wonder if folks on our panel maybe could comment  
19 on what types of corrective action are and are not  
20 appropriate because as we're designing these  
21 systems, we need to know.  
22 DR. SCHUETTE: I think the -- well, there's

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1 two types of things. At the FDA, we get the data  
2 at the end. So corrective action is basically  
3 exclusionary from our perspective, although that  
4 can help. We're thinking of using some of these  
5 tools to help determine where we can send our  
6 office of scientific investigation inspectors.  
7 Before it happens, though, during the  
8 course, if it's done at the sponsor level,  
9 certainly, there's an opportunity to go in and make  
10 an intervention either by going through and  
11 training, confirming what's going on and making  
12 sure that the site investigator is following  
13 protocol, that their staff is following protocol,  
14 that there's a potential for corrective action  
15 there.  
16 I think if it's done sort of in combination  
17 with sort of a DMC approach, that there's certainly  
18 a possibility for, shall we say, rescuing some of  
19 the sites.  
20 MALE SPEAKER: I think this is an important  
21 question. I mentioned before that in some ways you  
22 want to understand the nature of it and

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1 whether -- the success of the blind, I think was  
2 one important issue. But also the people doing  
3 analyses are the ones making decisions about  
4 whether there's an exclusion from the database or  
5 not. In some ways, I want those people blinded. I  
6 don't want that to be potentially based on  
7 treatment assignment, either.  
8 I think there are consequences, of course,  
9 with exclusions. There was a mention in one of the  
10 talks earlier about, well, of course, you're going  
11 to lose power because it's going to have fewer  
12 patients. So there's one issue.  
13 But it's probably not the biggest issue.  
14 The biggest issue is whether, one, if you analyze,  
15 say, what's left after you exclude, how  
16 generalizable is it or have you hurt  
17 generalizability because now you're selecting. Is  
18 it differential between treatment and is what I  
19 have left now a distorted view of what I started  
20 with?  
21 So if the malfeasance is actually a result  
22 of poor results, I see poor results so I make them

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1 more positive. Well, clearly, if I exclude those,  
2 I'm excluding what was poor results, and if I  
3 include them, then I've got trouble.  
4 So in some ways, you've got a real tough  
5 statistical problem because the data that you're  
6 either excluding or including is biased either way,  
7 and you've got real informative censoring problem  
8 going on. So that's where I think that much of the  
9 effort from a statistical standpoint, you've got a  
10 real hard problem.  
11 Therefore, I think that as with the message  
12 with the missing data problem, that efforts are  
13 about prevention and avoidance.  
14 DR. McDERMOTT: I get the sense that your  
15 question was about an earlier stage of correction,  
16 though.  
17 DR. KATZ: Yes, let me maybe follow up with  
18 a more specific version of my question. What  
19 patient level corrections of problems that are  
20 observed in the patient performance in the clinical  
21 trial would and would not be acceptable?  
22 So for example, yesterday we heard that if a



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1 patient is providing nonsensical data, we can't  
2 correct that on a patient level, and we need to  
3 accept that. I think that was the message we got  
4 from Sharon yesterday. The approach would be to  
5 sort of provide as much general training as  
6 possible across the board, and then cross our  
7 fingers and hope for the best without any type of  
8 for cause response in terms of retraining the  
9 patient on how to use the instruments more  
10 effectively. That was the message I got yesterday.  
11 So I think that's one example of what I'm  
12 trying to ask in a more general way, which is  
13 what -- and we can talk about patient level  
14 corrective action or site level corrective action,  
15 which I think was the comment, Paul, that you made  
16 earlier, that site level -- what I heard from you,  
17 Paul, is that site level corrections in general  
18 sort of anything goes, right, except for unblinding  
19 and sort of obvious violations of the rules of  
20 clinical trial conduct.  
21 I'm getting at least the beginning of an  
22 impression from you that, from your perspective,

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1 virtually anything could go at a site level. If  
2 there are exceptions to that, it would be great to  
3 know about.  
4 How about on a patient level? Let's say,  
5 for example, the patient's not being compliant with  
6 their electronic diary. Well, is it okay to call  
7 the patient and say can you be more compliant with  
8 your electronic diary?  
9 So it seems like there probably are some  
10 things that you would consider forbidden on a  
11 patient level as a for-cause response and some  
12 things that would be considered acceptable. I'd  
13 like to know what those are, and then the same  
14 thing on a site level.  
15 DR. SCHUETTE: I'm not necessarily the  
16 person to ask for some of those. I think  
17 everything has to be consistent with the protocol.  
18 Now, I think that's something that's  
19 actually discussed further, and maybe there can be  
20 other meetings where what can be done could be  
21 discussed. But I don't have a great answer.  
22 The types of things that I see where things

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1 are going out of sync can be an issue, and I think  
2 Amy referred to one site where they basically said,  
3 "Hmm. Your adverse event reporting rate seems to  
4 be a little off," and just that intervention seemed  
5 to be sufficient.  
6 So in some cases, maybe just actually being  
7 a reminder or actually part of a site inspection  
8 from the sponsor saying, "Show me how you're doing  
9 this" could be sufficient. So I think that's the  
10 level that I'm talking about. But that's actually  
11 something that would have to go through an entire  
12 process that's separate and distinct.  
13 So I don't have a great answer for each and  
14 every aspect here.  
15 DR. DWORKIN: This is on the agenda for this  
16 afternoon, this exact issue of what can be done,  
17 midstream course corrections versus what can be  
18 done legitimately after database lock and evidence  
19 of something funky is discovered. So this is  
20 pretty high on the agenda for this afternoon, Nat.  
21 DR. McDERMOTT: I think that we're going to  
22 have -- I know there are other questions, but I've

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1 been told it's time for a coffee break. So 10:30,  
2 we'll reconvene. Thank you.  
3 (Applause.)  
4 (Whereupon, a recess was taken.)  
5 DR. McDERMOTT: It's terrific that everybody  
6 is so stimulated for the discussions, but please  
7 take your seats and quiet down because we want to  
8 move on to the next session.  
9 I want to congratulate you all. By  
10 attending this meeting, you are all now qualified  
11 at phase 1 to be a clinical investigator. However,  
12 to be a fully -- non-provisional -- qualified  
13 IMMPACT trialist, it is essential that you have to  
14 respond to the manuscript, which will eventually be  
15 drafted. And responding is not sufficient because  
16 the certifying committee, consisting of Dr. Dworkin  
17 and Dr. Turk, will evaluate the quality of your  
18 responses and comments to the manuscript. So  
19 simply saying "good job" will not do it. We need  
20 to have your input.  
21 So thank you all very much. And thank all  
22 of the speakers, both yesterday and today, for

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1 really creating what I think, in hearing from the  
 2 people around the room, from listening in at  
 3 people's discussions, has been extremely  
 4 interesting, stimulating, exciting.  
 5 So thank all the speakers for accomplishing  
 6 that so far. We're really moving forward now.  
 7 This session will take us up to lunch and then  
 8 after lunch we'll really have an opportunity to  
 9 spend more time discussing some of the kinds of  
 10 issues that we've been talking about.  
 11 In the last panel discussion, we were really  
 12 starting to segue nicely into what we want to do  
 13 now, which is -- yesterday and early this morning,  
 14 there was a perspective of quality in clinical  
 15 trials that was really coming from somewhat of the  
 16 ideal what we'd like to see, what we really need to  
 17 do, what we need to accomplish. But there is  
 18 another side to that balance, which is the people  
 19 who are actually in the clinical trials trenches  
 20 doing the work.  
 21 We started going into those things, and what  
 22 we thought we would do when we organized this is to

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1 allow people who are sort of at the other side of  
 2 this, who are actually in the trenches trying to do  
 3 the work, to try and carry out the best possible  
 4 clinical trial that they can given the realities.  
 5 I think the old adage that we need to be  
 6 cautious about having the perfect be the enemy of  
 7 the good is that we have to face some reality to  
 8 what we can feasibly and appropriately do, given  
 9 that we are knowledgeable about some of the  
 10 problems that could occur, but yet we still have to  
 11 find ways to get these trials done.  
 12 So what we're going to do in this session is  
 13 take the perspective from somewhat in the trenches,  
 14 from the clinical perspective, from the CROs, from  
 15 the companies. We heard a bit about company  
 16 perspective from Rick Malamut, so we'll follow-up  
 17 on that.  
 18 Before I introduce our next speaker, I want  
 19 to say it's John Markman. And I want to say,  
 20 belatedly, happy birthday, John, yesterday. I  
 21 understand you are finally now eligible to have  
 22 alcohol consumption in some states.

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1 (Laughter.)  
 2 DR. McDERMOTT: Our next speaker is going to  
 3 be John Markman, who is a -- unfortunately, he was  
 4 told -- neurologist, and the bad news we heard from  
 5 Scott Evans about what neurologists are. So John  
 6 Markman is a neurologist, and he is director of one  
 7 of the pain programs at the University of  
 8 Rochester. He has been involved with a large  
 9 number of clinical trials, particularly related to  
 10 back pain.  
 11 John is going to, I think, give us some  
 12 perspective of what it's like actually being there  
 13 as the clinician and being the investigator in  
 14 these types of trials and maybe having some  
 15 reflections on what he has heard to this point and  
 16 how it influences the concerns he may see about  
 17 being able to accomplish some of these things.  
 18 So, John, you're up.  
 19 Presentation -- John Markman  
 20 DR. MARKMAN: The big 3-0.  
 21 (Laughter.)  
 22 DR. MARKMAN: I just want to, first of all,

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1 thank Bob and Dennis. I think I come to these  
 2 meetings -- and I know this was said  
 3 yesterday -- and this is one of the most  
 4 professionally rewarding moments of the year for  
 5 me. I think I come out of this room thinking that  
 6 there are a cadre of incredibly talented people  
 7 around the world who actually can move the field  
 8 forward and have sort of the knowledge and the  
 9 reach and the wherewithal and the energy to do it.  
 10 And so, I always leave these meetings energized.  
 11 So it's a privilege to be here, and it's  
 12 certainly a privilege to speak here. I'd also like  
 13 to thank Valerie and Andrea for shepherding us to  
 14 this moment.  
 15 I'm going to try and provide what I will  
 16 call an academic perspective. This is in italics.  
 17 These are some of my relationships in terms of  
 18 research, as well as consulting. I serve on DSMBs.  
 19 I have served as a special government employee.  
 20 But most importantly, for this talk, I've  
 21 buttonholed most of the people in this room to get  
 22 their opinions on my talk before I gave it, which

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1 is a real insurance policy against hostile  
 2 comments.  
 3 (Laughter.)  
 4 DR. MARKMAN: So phone calls, long runs,  
 5 cocktails, just about everyone here. So I think  
 6 I'm in good shape.  
 7 So I want to come back to where Nat started  
 8 when he talked about quality as the ability of the  
 9 system to detect, in our case, an analgesic signal.  
 10 And he introduced these two twin notions, one of  
 11 scientific quality that had to do I think with the  
 12 question being asked about analgesic signal. And  
 13 then he sort of parsed this into a second concept  
 14 or construct, which was regulatory quality, which  
 15 was a little bit more about fidelity to the rules  
 16 of the trial and the execution piece.  
 17 As a sort of preamble to my talk, I think  
 18 all of us need to think about, to the extent that  
 19 we subscribe to these two constructs, what is their  
 20 relationship? Is it hierarchical? Is the  
 21 scientific somehow superior or more important or  
 22 privileged relative to the regulatory? Are they

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1 are on par? Are they on an equal footing? And  
 2 does it matter the question you are asking? And  
 3 the way they are balanced might depend whether  
 4 you're doing a phase 3 confirmatory trial or  
 5 whether you're doing a phase 2 exploratory study to  
 6 develop differential response to a certain  
 7 neuropathic pain phenotype. And maybe how you  
 8 weight these things will be different.  
 9 The way I was thinking about more  
 10 colloquially, if you have a hierarchical  
 11 relationship, and you put the scientific on top, I  
 12 think you sort of run the risk of saying that  
 13 foolish consistency is the hobgoblin of little  
 14 minds, and you sort of take the Emersonian view  
 15 that somehow the details are not quite that  
 16 important; whereas if you say they are on par, in  
 17 my mind, what you're suggesting is sort of God is  
 18 in the details, in the sense that when Flaubert  
 19 said that, he was saying that with a really  
 20 important creation or a significant scientific  
 21 work, it's equally inspiring or equally powerful as  
 22 you get down to the most minute details.

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1 When you look at the whole creation versus  
 2 when you look at the particular sentence, in his  
 3 case, it's equally well constructed. So I think  
 4 we're going to try and kind of balance between  
 5 those concepts.  
 6 The second set of concepts I think we're  
 7 going to work through are also, again, as I alluded  
 8 to, this notion about whether scientific and  
 9 regulatory quality, whether these consideration  
 10 weigh equally across different types of scientific  
 11 questions.  
 12 In an explanatory trial, a trial with an  
 13 explanatory goal, versus a trial that has a  
 14 pragmatic goal, versus one that has an exploratory  
 15 goal, and how these different types of questions  
 16 that we ask in clinical trials -- I'm going to give  
 17 you an illustration of that in a moment -- how do  
 18 those different types of trials help us think about  
 19 how we would emphasize quality more or less in a  
 20 particular case.  
 21 So I'm going to start with this trial, which  
 22 last fall, a lot of people were talking about and I

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1 found particularly interesting. And this is a  
 2 small trial done at a relatively small shop  
 3 compared to a lot of the trials that we've been  
 4 talking about today.  
 5 This is a study looking at the effect of  
 6 oxcarbazepine on peripheral neuropathic pain, and  
 7 it asked the question whether a response to  
 8 oxcarbazepine was differential with different  
 9 phenotypes of peripheral nerve injury pain  
 10 syndromes. And the take-home message of the study  
 11 was peripheral neuropathic pain stratified by  
 12 phenotype. And I know there are different views in  
 13 the room on NNTs, but this is one way of  
 14 illustrating there was a difference by phenotype.  
 15 Basically, the notion of this trial was the  
 16 idea that the irritable nociceptor phenotype, which  
 17 is related to sensitization of the unmyelinated  
 18 cutaneous nociceptors, and where there was small  
 19 fiber function preserved -- again, that has a  
 20 particular -- and I won't go too deeply into the  
 21 weeds here, but this obviously has a very  
 22 particular clinical signature with regard to exam

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1 findings -- that would respond differentially to  
2 oxcarbazepine than a picture, which was the sort of  
3 non-irritable nociceptor phenotype, the  
4 deafferented small fiber picture with profound pain  
5 and temperature impairment, and oftentimes  
6 associated with allodynia.

7 Again, the hypothesis was that the compound  
8 would respond differentially to oxcarbazepine with  
9 these two different phenotypes. And what they  
10 found was very interesting. And I'm not going to  
11 go into all the details, but they found that there  
12 was a significant treatment by phenotype  
13 interaction for the irritable nociceptor group  
14 relative to the other group.

15 But it was a very aggressive dosing  
16 schedule. I think it went to 2400 milligrams, and  
17 there was a very large amount of dropout in this  
18 study. And as they say, the high dropout due to  
19 adverse side effects, which led to low power  
20 ultimately led them to do an analysis, which is  
21 very hard to follow in the manuscript, at least for  
22 me, and I've read it several times.

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1 They said that they used last observation  
2 carried forward, and basically they went from 281  
3 subjects screened to -- what they would hope to  
4 have would be 97 randomized, and end up with only  
5 39 subjects. There is no irritable nociceptor  
6 phenotype placebo interaction at all when you look  
7 at the data they provide.

8 As you learn further when you read the  
9 manuscript, 81 percent of the patients correctly  
10 guessed their treatment allocation in period one  
11 and 84 percent in period two.

12 So I think the question that this raises for  
13 me is I thought this was a very important study. I  
14 think I learned a lot, and I think it's a study  
15 that needs to be replicated and sort of revisited  
16 because it raises some important questions. So for  
17 me, there is a fair amount of scientific quality in  
18 this study.

19 I think from the point of view of regulatory  
20 quality, obviously, we just heard about LOCF  
21 analysis, we've talked about a study being  
22 underpowered. So clearly this does not have a

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1 sense of regulatory quality in the sense that we're  
2 asking of these large phase 3 confirmatory trials,  
3 where a drug is going to go into millions, if not  
4 tens of millions, of patients.

5 But there is an enormous amount of  
6 scientific quality in this trial, and I think it's  
7 going to be studied further and further. How do we  
8 think about how we approach quality evaluation in a  
9 study like this differently than in a phase 2  
10 trial?

11 This is another trial, one that we recently  
12 published, which has a slightly different set of  
13 issues, but also was underpowered. And it wasn't  
14 underpowered because of drug tolerability. It was  
15 underpowered because one of the study drugs was  
16 pulled from the market, so basically we terminated  
17 the study early.

18 But this was a novel design, again. Our  
19 novel design is a single-dose design for a problem  
20 called neurogenic claudication, which is the evoked  
21 pain in the low back and legs that patients have  
22 when they are standing and walking. We used a

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1 paradigm where we put patients on the treadmill,  
2 and we'd only enroll them if we can induce moderate  
3 pain from a baseline of mild pain.

4 Basically, this is a phase 2 clinical trial  
5 platform that we're trying to validate. This is  
6 very exploratory. It's a single-dose design,  
7 trying to test a lot of compounds against this  
8 very, very common clinical pattern. And it was  
9 active placebo controlled.

10 We ended up terminating this study early.  
11 And the problem with that is that in terminating  
12 earlier, basically it became underreported to  
13 detect a 2-minute difference in the onset of  
14 moderate pain intensity.

15 But the fact that it was not sort of at the  
16 level of the threshold that we were looking for  
17 when we originally designed it didn't mean that we  
18 didn't learn anything. It basically learned that  
19 with a larger confidence interval, what we could  
20 really say was that the results suggested, in this  
21 case, oxymorphone and propoxyphene-acetaminophen  
22 combinations could not improve or did not have any

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1 evidence that it demonstrated basically providing  
 2 any more than 5 minutes of low pain walking.  
 3       So we wanted it to be 2 minutes. It turned  
 4 out it was 5 minutes. Now, whether that's  
 5 clinically relevant or not and whether we should be  
 6 allowed to change our prespecified endpoint is an  
 7 important question to ask. But I do think for us,  
 8 there is some scientific good quality to this.  
 9 There is obviously not regulatory quality. So,  
 10 again, how would we think about this differently,  
 11 this flexibility?  
 12       So I'm going to talk now about -- with that  
 13 preamble, I'm going to talk about the spectrum of  
 14 academic clinical sites because I'm giving the  
 15 academic talk, and then I'm going to talk about  
 16 data quality, and then I'll talk about some future  
 17 considerations.  
 18       So an academic medical center -- this is the  
 19 academic talk. But we all know that what it means  
 20 to be an academic medical center is something which  
 21 is in an incredible amount of flux. There are 119  
 22 or so of them in the United States, and they're

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1 very diverse. They're very different. And they  
 2 are rapidly becoming these regional networks where  
 3 we have a set of laws how, which is turning them  
 4 into either duopolies or triopolies in major  
 5 cities.  
 6       That has important implications for patient  
 7 fraud, of course, because that means that basically  
 8 every one of us is going to be in one of these  
 9 large systems' medical records very soon, if you're  
 10 not already, and it's going to be -- and I know  
 11 Dr. Rauck was raising this issue about let a  
 12 monitor sit in front of your Epic console or your  
 13 Cerner system.  
 14       But there are basically three large medical  
 15 records out there. It's a very consolidated  
 16 industry. The hospital industry is getting more  
 17 and more consolidated. Physicians are employees,  
 18 and basically there aren't going to be that many  
 19 medical systems out there, and we're all going to  
 20 be in these systems.  
 21       So I think some of the fraud issues are  
 22 going to be harder and harder to achieve in this

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1 changing environment. That's one thought.  
 2       Another thought is that these are the  
 3 largest employers and the economic engines in the  
 4 region when you read their annual reports. I think  
 5 that this has a little bit reprioritized the  
 6 commercial interests in the output of a clinical  
 7 trial, and that has implications when you're trying  
 8 to do a small trial and there is maybe some  
 9 potential intellectual property. It makes  
 10 contracting harder. It makes it harder to be a  
 11 small site because the level of scrutiny even any  
 12 trial you do gets at the level of contracting. It  
 13 just creates a whole other level of review, in my  
 14 experience, and in terms of attention, and it makes  
 15 a little harder to work in that environment.  
 16       There is also an increasing division of  
 17 labor in these large systems where there aren't  
 18 really that many clinician researcher investigators  
 19 anymore. You're being asked to sort of  
 20 differentiate from -- you're not going to be a  
 21 triple set anymore. That really is going to go  
 22 away.

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1       I think at certain institutions, like the  
 2 University of Washington, where there is \$1 billion  
 3 almost of annual funding and sponsored funding and  
 4 a few others, that may not be the case. But in the  
 5 vast majority of those 119 medical centers, I do  
 6 think that the imperatives of serving their local  
 7 region and living up to the Affordable Care Act  
 8 will not really allow for a system that has people  
 9 who want to live this hybrid life where they  
 10 practice 40 percent of the time and do research  
 11 60 percent of some variation there. At least at  
 12 our institution, I think there's a lot of pressure  
 13 to sort of differentiate further.  
 14       Then lastly, I think that as we've talked  
 15 about a lot, there are less training opportunities  
 16 in these environments, and one of the reasons there  
 17 are less training opportunities is because we're  
 18 moving sort of to a winner-take-all funding of the  
 19 infrastructure of these places.  
 20       If your institution has a CTSA or a CTSI,  
 21 you have a huge largess from the government, which  
 22 supports this infrastructure not only for training

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1 future investigators, but also supporting a lot of  
 2 pilot work where people get skills.  
 3 But the reality is that the grants that are  
 4 sort of in the next tier down are far, far smaller,  
 5 and the ability to support a robust clinical  
 6 research infrastructure for a lot of those 120  
 7 academic medical centers is going to go away,  
 8 because they're not going to be in the 25 or 30  
 9 places that get those big grants.  
 10 So I think that there is going to be an  
 11 erosion in who is an academic medical center and  
 12 what that means over the next 15 years, because  
 13 unless there is a real change in the funding  
 14 environment, I think what an academic medical  
 15 center is will look very different. So that's just  
 16 a simple preamble.  
 17 So what is it like in an academic medical  
 18 center when you're running a research enterprise?  
 19 Well, I think all of us probably have relatively  
 20 similar structures at some level. There is an IRB,  
 21 and there's a lot of, obviously, review that goes  
 22 along with that, with the consent and a lot of

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1 ancillary reviews about risk and other things  
 2 potentially.  
 3 Then there is the projects administration  
 4 component, which has a lot to do with financial  
 5 reporting and budget allocation and CMS  
 6 reconciliation of care and those sorts of details.  
 7 And a lot of the sort of quality checking there is  
 8 just making sure that those two parts of the  
 9 organization are talking and the data you submit to  
 10 one is reconciled with the other.  
 11 Then there is the academic department level,  
 12 scientific merit, which his very different from  
 13 department to department. I work in a department  
 14 with 11 faculty, with one clinical investigator  
 15 basically, and there are departments with 200  
 16 faculty with 60 investigators or 60 people who are  
 17 doing some clinical projects. And the review  
 18 process for scientific merit is very different  
 19 across those different kinds of academic  
 20 departments.  
 21 Then at the site center, there is a lot of  
 22 training for folks who do sponsored studies,

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1 because they go to study site trainings, and we  
 2 send them off to organizational trainings through  
 3 the ACR and others.  
 4 But the reality is there is not as much sort  
 5 of moment-to-moment supervision of sites in an  
 6 academic center for those that are doing sort of  
 7 non-industry trials. There are some, but it  
 8 certainly pales in comparison to the kind of  
 9 moment-to-moment supervision you would have if you  
 10 were, say, doing clinical work.  
 11 If you tried to take a patient with an OR  
 12 and don't sign the day of surgery update, nobody  
 13 will hang the bag of antibiotic. That's happening  
 14 in real time. That's not some monitor call at the  
 15 end of the day, that's not some query that you're  
 16 answering. That's a query that's right now every  
 17 second of every day.  
 18 So even though there are some checks, and  
 19 the IRB will come and they'll audit your site and  
 20 make sure you're being compliant, that's happening  
 21 in a real time lag. It's not happening in real  
 22 time, whereas in clinical practice at these

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1 institutions. It's literally happening on a  
 2 minute-to-minute basis.  
 3 So again, what goes on in an academic  
 4 medical center is I think very diverse. I'm the  
 5 little dot, the little yellow dot down there are  
 6 the bottom. I called this week to find out how  
 7 many investigator-initiated and clinical  
 8 research-sponsor studies there are at our  
 9 institution. There are almost 300. We have  
 10 \$400 million of sponsored funding, and only  
 11 5 percent of that, really, \$20 million, is from  
 12 dedicated drug trials.  
 13 Now, there are different ways to account for  
 14 that money, but it's a relatively small amount of  
 15 the total research pie when you think about the  
 16 organization and what their priorities are.  
 17 There's a broad range of investigators and  
 18 sites. There are sites like mine, which are a  
 19 single investigator doing a combination of  
 20 sponsored research studies, as well as  
 21 investigator-initiated trials, and then there's a  
 22 group, of which Dr. Dworkin and Dr. McDermott are

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1 professors, where there is an entire clinical trial  
 2 infrastructure, and they're leading multicenter,  
 3 international, investigator-initiated trials in  
 4 Parkinson's disease and Huntington's study group,  
 5 which are of a whole different order of magnitude.  
 6 They have their own in-house attorney and a core  
 7 team of biostatisticians and a materials  
 8 department.

9 You can imagine managing quality in these  
 10 two different types of environments, just  
 11 completely different efforts. The amount of  
 12 quality control you need and what you can ask is  
 13 sort of like being a public company versus being a  
 14 tailor shop or a dry cleaners on your corner. You  
 15 just can't ask whether it's in compliance for both  
 16 of those structures.

17 So I'm just going to give you a snapshot of  
 18 where my perspective comes from over the last five  
 19 years. I've been a primary investigator in  
 20 probably about 20 trials. These are mostly in  
 21 neuropathic pain and OA. They have been in small  
 22 molecules, they have been in oral drugs, IV drugs,

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1 biologics, device studies, and neuromodulation  
 2 tools, abuse-deterrent opioid formulations, opioid-  
 3 induced constipation studies, long-term open label  
 4 studies, and obviously every possible design you  
 5 can imagine in that area.

6 Then we have a lot of single-site  
 7 investigator trials. I showed you a little snippet  
 8 of one, a crossover trial for low back pain. And  
 9 like many small investigators, I tend to do a lot  
 10 of crossover trials. And again, those are largely  
 11 in low back pain, but we also do trials with pain  
 12 syndrome phenotyping.

13 We do them in outcome studies for our  
 14 department and larger pain in the community, and we  
 15 also do a lot of things related to service delivery  
 16 in pain, for example, in urine tox screens, where  
 17 for us the quality issue is really about the  
 18 laboratory more than it is about other issues in  
 19 that case.

20 But the main reason I do these sponsor  
 21 trials, at least initially, was to gain the skill  
 22 set and train my team to do our own trials, because

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1 that was really how we learned best practices,  
 2 because one-half percent of the funding from the  
 3 NIH is for clinical trials, some small, paltry  
 4 amount.

5 So where was I going to get the skill set to  
 6 do these trials? The only way to really earn  
 7 what's done in industry and the best practices  
 8 would be for me to do those trials and learn by  
 9 going to investigator meetings, and sitting down  
 10 with monitors, and looking at the protocols myself  
 11 and trying to figure out what to do.

12 I know Lee has addressed this and others,  
 13 but this is really the core issue. It was an  
 14 on-the-job process where I learned one trial at a  
 15 time.

16 Again, I think that the question here when  
 17 we think about quality, and this is what I tried to  
 18 raise in the beginning, is the attempts that we're  
 19 going to take to minimize sources of error at the  
 20 level of identification, at the level of  
 21 prevention, at the level of management, again, may  
 22 not be exactly even across these two types of

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1 enterprises.

2 You know that today is my birthday, and you  
 3 know that I'm a Gemini. And we have the sense that  
 4 there are sort of two Johns in the world, there is  
 5 placebo John and there is assay-sensitivity John.  
 6 Right? And I live these two lives, and my office  
 7 and my clinical research space are the same space.

8 Neil Singla and I were talking about the  
 9 challenges of what that might have impact on  
 10 quality for and how that might affect assay  
 11 sensitivity when you have patients come into that  
 12 same environment. And these are the kinds of  
 13 quality issues which a lot of academic sites  
 14 contend with. There are a lot of sites that have  
 15 their own clinical practice.

16 But I want to come now to the factory floor,  
 17 if you will, because I see myself doing clinical  
 18 trials more in the manner of someone who has a  
 19 little independent bookstore and every morning goes  
 20 out and hoses off the sidewalks, and people come in  
 21 and look at the new books; or running a micro  
 22 brewery, not some big Budweiser or Heineken

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1 brewery.

2 The nuts and bolts of our organization when

3 we're doing clinical trials are the coordinators.

4 They are running the trials. They are doing every

5 one of those assessments, and their office is only

6 eight feet from mine, and I'm talking to them all

7 day long about all these decisions. But I think

8 Rob pointed out this and it was very poignant to

9 me, they are the guts of this.

10 So I wanted to ask them some direct

11 questions, and I did this in the couple weeks

12 before I came so we could hear from them.

13 By the way, you don't get to be a

14 coordinator in my group unless you have gone to

15 Catholic high school, unless you went to West

16 Point. You have to be a very rule-oriented person.

17 You cannot be someone who studied the hermeneutics

18 of French modernism --

19 (Laughter.)

20 DR. MARKMAN: -- because that's not what I'm

21 looking for. I'm looking for someone who follows

22 rules, and they just are completely rule-bound.

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1 I found two incredible women who are

2 incredibly rule-bound, and you need that. And I

3 think that David made a great point about why you

4 would be concerned that your physician might be

5 your clinical trial coordinator? I think it's a

6 total concern because clinicians are taught to use

7 their own judgment, and that's not what you should

8 be doing in a lot of these trials, as we learned

9 yesterday even about training. You don't want

10 people on the ground using their own judgment every

11 moment. You want people following the rules every

12 moment.

13 So I asked Maria, "What's the most important

14 training experience you've had recently?" And here

15 is what she said.

16 (Whereupon, a video recording was played.)

17 DR. MARKMAN: I got chills when I saw this

18 video. I was looking at this, and I was like, oh,

19 my god, we had this issue yesterday. Are you

20 allowed to retrain people on the scale or can you

21 only do it the first time? I was like, oh, my god,

22 I'm going to show this video and people are going

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1 to be like -- but I think this has been something

2 which has been very powerful, I think.

3 We talked a lot about patient engagement and

4 making our patients our partners in research. It's

5 incredibly important to make your coordinators your

6 partners in research, and you can see how important

7 it is to them to feel like they're getting more

8 consistent reports and they're helping patients do

9 that.

10 I think that rather than having them

11 convince the patient that they're on the wonder

12 drug or trying to guess what they're on, what

13 they're actually do with the patients is coach them

14 into being better subjects.

15 That's a fairly neutral thing, actually. I

16 think about it, and I think that's actually a

17 fairly positive thing. And you can see how

18 important it is to them in their work because they

19 are concerned about arbitrariness and randomness,

20 and you saw Maria, the first woman who spoke,

21 perfectly say -- I asked her does this make a

22 difference. She says, "How do I know?" And that's

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1 the right answer, right?

2 She doesn't know if this makes a difference,

3 and she's not doing it to make a difference on the

4 outcome of a trial. She's not doing this to

5 increase the analgesic signal of the trial. She's

6 doing this to have a less sort of arbitrary

7 interaction with these people, and that's her goal.

8 And that's a more meaningful interaction with them.

9 So I think it's important to talk about

10 what's your motivation for doing clinical trials

11 within an academic medical center -- Neil Singla

12 and I were talking about this yesterday -- as

13 opposed to an independent research group that

14 basically their business is doing clinical trials,

15 whereas in my case, how do we choose which trial to

16 do. I think that's important.

17 I know Rick gave a great talk yesterday

18 talking about how companies and CROs -- we're going

19 to hear from David -- choose sites. But here is

20 how sites choose trials.

21 What drives my choices are what I'm

22 interested in. I'm here today, and I'm interested



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1 in trying to develop better pain treatments for the  
 2 problems that I see every day in practice for which  
 3 I have to stare at people and don't have good  
 4 answers, or I have drugs which are intolerable,  
 5 unsafe, or don't help them very much.  
 6 So I tend to be in trials that are related  
 7 to the indications of the target populations where  
 8 I see the unmet need every day in my practice, and  
 9 I feel it. And I also tend to be interested in  
 10 being in trials where, as I said, my team is going  
 11 to learn best practices and learn from being in  
 12 those trials.  
 13 We're going to learn how to do an IV trial  
 14 or follow the potential immunologic complications  
 15 of being on a biologic. And I want my team to  
 16 learn how to do that, and collect those samples,  
 17 and send them down, and send them out, and store  
 18 them in all those records, and do those follow-up  
 19 exams.  
 20 We participate in a certain herpetic pain  
 21 trial because I want them to learn how to use a  
 22 tuning fork. But that's a lot of how I choose to

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1 sort of decide what we're going to do.  
 2 Now, they have a different agenda. They  
 3 have an entire Excel scoring sheet that they got at  
 4 their own industry conference, which is probably  
 5 like this, just in a bigger ballroom. And it comes  
 6 with a spreadsheet, which looks at different  
 7 components of clinical trial complexity,  
 8 inclusion/exclusion criteria, study design,  
 9 screening steps, the study procedures themselves,  
 10 the duration of the study. And you can see those  
 11 bullet points down there. I just redacted that  
 12 from their spreadsheet.  
 13 So they're looking at operational  
 14 complexity. They're looking at -- and we both are,  
 15 looking at the feasibility, can we get these  
 16 patients? Can we keep these patients.  
 17 Then we're obviously also looking at the  
 18 financial impact, and we've talked a little bit  
 19 about financial incentives for folks in the system,  
 20 obviously. My financial incentive for the system  
 21 is to break even. I want to keep it going. This  
 22 makes my clinical life richer.

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1 I think that I'm part of a larger project,  
 2 which is important and helpful to people. And  
 3 again, this is not sort of my core sort of  
 4 compensation. This is no compensation, basically.  
 5 This is just something that I think is important to  
 6 do and offer something to my work every day on the  
 7 larger purpose.  
 8 I think that's a different motivation to do  
 9 this kind of research than at other centers, and I  
 10 do think that may or may not matter. I don't know  
 11 how impacts quality, but I think it matters at some  
 12 level.  
 13 So we talk a little bit more about  
 14 recruitment, because I think recruitment  
 15 issues -- as we've touched on it a lot of ways.  
 16 And I thought Dr. Kerns' comment about what we're  
 17 really assessing for when we're screening patients  
 18 for a trial is sort of how engaged they might be  
 19 and things like that.  
 20 There's a whole covert set of screenings  
 21 before the inclusion/exclusion criteria, I think,  
 22 when a site is looking at patients, which are not

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1 as explicit perhaps as we think they are. And I  
 2 thought that was a great, insightful comment.  
 3 This is from the WIRB application when  
 4 you're trying to fill this out, but this is the  
 5 only thing I could find about incentives for  
 6 enrolling patients. Will the PI or the research  
 7 team receive recruitment bonuses, yes or no?  
 8 That's it in all of our work. And basically this  
 9 is how WIRB defines a recruitment bonus or  
 10 incentive.  
 11 But otherwise, the university doesn't really  
 12 specifically ask me too much about it. There are  
 13 some lines in our IRB, but it's not a direct  
 14 question like this. But this is really all we have  
 15 at our institution.  
 16 So the other issue around recruitment is how  
 17 do we recruit? And I am a convert. I got into a  
 18 sidebar conversation several years ago with Jim  
 19 Campbell, who was here earlier, about recruiting  
 20 for one of his trials. And he said -- I'm like,  
 21 "What's the secret? How do you do it?" And he  
 22 said to me, "Drive Time radio." I was like we're

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1 going to do Drive Time radio because that works.  
 2 I did a trial here -- this is just some  
 3 graphs on -- we do an analysis on how we recruit  
 4 patients to our trial to figure out how we're  
 5 spending our time and our resources and what we're  
 6 asking for.  
 7 This is from 60 weeks of recruitment of our  
 8 first study with 260 screens, and we looked at the  
 9 yield on patients who we looked to recruit from the  
 10 office versus the folks we got from Drive Time. Of  
 11 course, I'm interested in who is listening to Jimmy  
 12 Buffett and who is listening to Rush Limbaugh and  
 13 whether that's going to separate differently for  
 14 placebo versus other listening preferences.  
 15 (Laughter.)  
 16 These are the deeper questions which I'm  
 17 interested in. But we spent a lot of time looking  
 18 at these patients. And again, we don't know if  
 19 these are better or worse patients.  
 20 I have spoken with some of you about this  
 21 before. There is some experience, I think, in the  
 22 psychiatry literature about how patients who are

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1 recruited by advertising might perform differently  
 2 as a clinical subject than folks who are not.  
 3 We have found this to be an incredible  
 4 evaluator of recruit patients. I think as Neil  
 5 made the point earlier, screening patients is  
 6 extremely laborious, and screening patients from a  
 7 Drive Time radio ad is much more laborious because  
 8 we don't have their source records. They're not in  
 9 our electronic medical record. They're out there  
 10 in the world driving around the freeways of New  
 11 York. So we have to go collate and get all that  
 12 information, and we have to rely on them to verify  
 13 what we do in a phone screen. So it is enormously  
 14 labor intensive, but it's very high yield for us.  
 15 When I say high yield, I mean we've got like 10  
 16 patients out of 200-plus screened.  
 17 Here is a little graph just about the  
 18 different reasons why patients don't want to  
 19 participate in our trials and how that shapes up  
 20 whether they come from radio or they come from our  
 21 office.  
 22 So we do this analysis on every mode of

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1 recruitment, whether it's Twitter or anything else,  
 2 and we think about what are the reasons that  
 3 patients turn us down, and how is it different,  
 4 whether it's concomitant medications or comorbid  
 5 pain conditions, and how is that different for the  
 6 radio group versus our in-office group.  
 7 There is a lot of artifact there, and it's  
 8 only 260 patients, and it's a small sample, so I'm  
 9 not presenting this as hardcore statistical data.  
 10 I'm just telling you this is kind of how we  
 11 approach it as a shop to think about.  
 12 So I think academic sites in the future are  
 13 going to have potentially some advantages, maybe.  
 14 Again, I think that one of the questions that we  
 15 face, though -- and I heard the rap yesterday in  
 16 Rick's talk a little bit about I think our site  
 17 has, in the past, had some low recruitment in some  
 18 studies and a few others, we've been the highest  
 19 recruiting site.  
 20 But the question is what is the low  
 21 recruitment and how does that relate to quality?  
 22 And I definitely think, in my own personal biases,

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1 there is definitely a relationship, especially with  
 2 these large phase 3 trials.  
 3 When I'm doing a 50-person crossover trial,  
 4 obviously, we're going to do the recruiting. We're  
 5 going to see all those patients. We're going to  
 6 know our own protocol. But I think that the first  
 7 person we enroll in a protocol on the 10th, we're  
 8 just handling that differently. We know the  
 9 receipt, we know the drill, we're doing it again  
 10 and again.  
 11 Everyone is kind of -- we have the flow  
 12 diagram up on the wall. Everybody can just point  
 13 to exactly where the patient is, patient number 9.  
 14 It's not the same way with patient number 1. And  
 15 that uncertainty affects every interaction. So I  
 16 definitely think that being too low recruiting is  
 17 an issue with quality, and I think that -- again,  
 18 one of the reasons I got interested in the Drive  
 19 Time radio is because I thought it was a way to  
 20 improve our quality, because as we get more  
 21 patients into the trial, we'll be better at doing  
 22 that trial, and that matters to me.

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1 So I do think it's important for a lot of  
 2 these private sites that can recruit a lot of  
 3 patients. Obviously, there are dangers about the  
 4 incentives, and I understand that, but I also think  
 5 there is an upside to volume. And I don't know  
 6 what the magic number is, and I don't know where  
 7 you cross the threshold for quality, but I do think  
 8 it's a compelling issue, in my opinion.  
 9 Again, we try to do -- one of the other ways  
 10 we try and address the recruitment issue is we do  
 11 multiple drug trials in the same population with  
 12 similar indications and the same drug class. And  
 13 again, that develops our expertise in dealing with  
 14 that drug class.  
 15 We've done the COWS now in six different  
 16 trials. We're good at doing the COWS, right? We  
 17 can do it on an iPad. We've got all these little  
 18 tools that everyone develops, but we can do the  
 19 COWS, and we're good at it. And my clinical  
 20 coordinators are good at it, and I know when they  
 21 do it, it's done right.  
 22 For me, that gives me the confidence that

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1 we're doing a better job, because we've done six o  
 2 these trials, and we use the same instruments.  
 3 Again, these things are very helpful because they  
 4 are not specialists in managing opioids. I'm that  
 5 guy. So the more comfortable they get, though, the  
 6 better they are at handling every question and  
 7 query. So that's why I do a lot of overlap in what  
 8 I cover.  
 9 So let me just talk to you a little bit  
 10 about documentation. Let me come back to Valerie.  
 11 I approached Valerie from the cardiac surgeon. She  
 12 has been a cardiac CCU nurse. She worked and did  
 13 cardiac surgery, different types of protocols with  
 14 valves and heart replacement for many years. And  
 15 then later in her career, she came to us. She is  
 16 an incredible coordinator.  
 17 I think that one of the challenges -- one of  
 18 the challenges of clinical medicine, but also  
 19 designing clinical trials, is how much you're going  
 20 to put upon people who are actually doing then  
 21 trial.  
 22 When I work in the neuro ICU and a patient

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1 comes in, and they have an altered mental status,  
 2 they might have had an intracranial hemorrhage, I'm  
 3 concerned about that patient overnight. And I can  
 4 tell the nursing staff to do q 10 minute neuro  
 5 checks, q 10 minutes. Every 10 minutes they're  
 6 going to wake the patient up and shine a light in  
 7 their eyes, and disturb that patient's sleep to see  
 8 if their pupil is bigger or lower.  
 9 That patient is going to have a terrible  
 10 clinical outcome because they're not going to sleep  
 11 because they're going be woken up every 10 minutes  
 12 to look at their pupil.  
 13 Now, I'm anxious about that patient. I want  
 14 to make sure that patient gets a lot of  
 15 surveillance. But that's not going to help that  
 16 patient, and it's probably not going to change the  
 17 outcome.  
 18 I think that that's what Valerie is getting  
 19 at in this thing, and she's doing it in her own  
 20 way.  
 21 (Whereupon, a video recording was played.)  
 22 DR. MARKMAN: So she will stay there until

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1 9:00 at night until every query is answered. She  
 2 is not going to go home until they are buttoned up,  
 3 and I know that, and it's every day. But when you  
 4 ask her to report in when the blood pressure is 139  
 5 one day and 141 the next, and she's got to deal  
 6 with that, and she's got 50 of those to deal with,  
 7 you can see that frustration and what that does to  
 8 her work.  
 9 So again, I think Ajay mentioned  
 10 earlier -- and I know this came up with Rick's  
 11 comment, as well -- about the sort of data  
 12 infrastructure that academic medical centers are  
 13 developing and whether that's going to have  
 14 important implications not only for source  
 15 documents and looking at people's medical  
 16 histories, but also important implications for  
 17 fraud.  
 18 This is just a diagram of Epic, which is the  
 19 dominant large health care system, electronic  
 20 medical record in the country; i2B2, which is able  
 21 to scrape that. So I can go look for -- for about  
 22 400,000 people, I can go look and see who is on

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1 300 milligrams of gabapentin and who has a  
 2 neuropathic pain diagnosis right now with the click  
 3 of a button. Now, there are some IRB issues around  
 4 that and recruiting through that if I'm not  
 5 touching that patient clinically, but we have the  
 6 capability to do that now, and that's only to get  
 7 more and more robust.

8 So I think that's going to have enormous  
 9 implications not only for source document  
 10 verification, but also for identifying fraud and  
 11 also for recruitment ultimately. And obviously,  
 12 the goal is that we'll have an implication for  
 13 doing pragmatic clinical trials in the clinical  
 14 record, as well, down the road.

15 So better recruitment and optimize source  
 16 document verification may be something on the  
 17 horizon in a consolidated health care system where  
 18 your academic medical centers change.

19 So just to come back to the opening point,  
 20 again, are the quality considerations for  
 21 investigator-initiated clinical trials somehow  
 22 different or related to the clinical question or

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1 the design of the trial or the number of subjects?  
 2 We know there will be no central statistical  
 3 monitoring for a trial with 20 patients in a  
 4 crossover trial. That's not a feasible  
 5 recommendation.

6 So the question is what are the types of  
 7 things which could be equally prioritized in an  
 8 investigator-initiated trial, and what are the  
 9 things which should be less important?

10 In one sidebar we had yesterday, obviously,  
 11 the quality issues as they relate to the primary  
 12 endpoint or adverse event reporting I think are  
 13 going to have to be of the highest priority and on  
 14 an equal footing everywhere, in all trials. But  
 15 again, quality issues related to the signatures on  
 16 the CVs an whether those are up-to-date, those  
 17 administrative issues, may not be the core issue  
 18 that's going to improve the ability to detect the  
 19 analgesic signal or test your hypothesis in an  
 20 investigator-initiated trial.

21 So I'm going to stop there. I want to thank  
 22 you all for your invitation and your attention.

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1 Appreciate it.  
 2 (Applause.)

3 DR. McDERMOTT: Thanks, John. I think that  
 4 demonstrated that some neurologists are able  
 5 actually to be listened to, incredible, and not  
 6 liars. At least I'm going to assume so. However,  
 7 we can do a reliability check because we have  
 8 another neurologist who is going to come along, but  
 9 now give us the perspective from -- in contrast to  
 10 the academic medical center, the perspective from  
 11 CROs, but also from industry about how they think  
 12 about these things and what they have to do  
 13 day-to-day in their actual operations.

14 So it is my pleasure to introduce Dr. David  
 15 Hewitt, who is a card-carrying neurologist.

16 Presentation – David Hewitt

17 DR. HEWITT: Well, thank you for inviting me  
 18 here today. This is something that is really  
 19 important to me. In fact, I was at Merck, and some  
 20 events that happened at Merck, actually probably  
 21 related to the quality of doing one particular  
 22 trial, led me to the interest of going into a CRO,

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1 at least for a while to try to understand some of  
 2 the things that happened.

3 So in terms of my disclosures, I am  
 4 currently working with inVentive, which is a  
 5 contract research organization/commercial contract  
 6 organization combined. As inVentive, we are  
 7 involved in multiple large and small  
 8 biopharmaceutical company studies and involved in a  
 9 lot of commercial work, as well. Before that, I  
 10 worked for Merck, and before that, Johnson &  
 11 Johnson. So most of you know me.

12 I wanted to talk about a few things. I have  
 13 a different perspective a little bit. Part of it  
 14 comes from being in big pharma. I've only been in  
 15 the CRO industry for about a year. So I still  
 16 carry a lot of my Merck view of the world. I  
 17 haven't lost that yet, and maybe a little bit of my  
 18 J&J view of the world, but definitely Merck  
 19 oriented.

20 I want to talk a little bit about quality by  
 21 design, the need for -- that it's more than just a  
 22 good protocol, and all the quality that I'm

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1 interested in, which is really not just the  
 2 quality, I should say, of the clinical trial and  
 3 the integrity of the data, it's really the quality  
 4 of the product that you're going to bring to market  
 5 that people are going to take, and it's going to  
 6 potentially impact their lives.  
 7 That's important because I do think that the  
 8 higher the quality is, before it even hits a  
 9 patient and before it gets into a phase 3 study,  
 10 the higher the quality that phase 3 study will be,  
 11 as well. That would be my argument.  
 12 I'll talk a little bit about investigator  
 13 sites and trial execution, but I think a lot of the  
 14 points have been made already, so I won't belabor  
 15 them.  
 16 I do want to talk a little bit about the  
 17 differences -- and I do think this affects  
 18 quality -- between big biopharmaceutical companies  
 19 and small. One is that in big pharmaceutical  
 20 companies -- and some of you can correct me if this  
 21 has not been your experience, because I know we  
 22 have got a lot of big pharma here -- is that there

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1 is a significant time to think, rethink, reconsider  
 2 decisions, and then change things again. And I  
 3 think that that churn that exists within big  
 4 pharma, which I'm sure we're all familiar with, can  
 5 really impact quality.  
 6 Big pharma, there is our complex decisions  
 7 process with significant input from a hierarchical  
 8 reporting structure, and I think there are pluses  
 9 and minuses to that. It does ensure that the  
 10 protocol at the end should not need to be amended  
 11 too many times because it's been looked at a lot.  
 12 Small pharmaceutical companies, there are a  
 13 number of stakeholders, and they can be very  
 14 influential. Ultimately, there is a different  
 15 intent with small pharma companies. I think it  
 16 makes it different, particularly the small, almost  
 17 virtual companies.  
 18 I do also want to make the point that I  
 19 think money is important. Money impacts quality.  
 20 There is no question in my mind that it does. We  
 21 bid with a lot of companies right now, and they  
 22 don't want to spend like a little extra money for

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1 like major things, like rater training. They say,  
 2 "Well, we'll just pas by the rater training. You  
 3 know, well just give us the Reader's Digest version  
 4 of that."  
 5 The other thing is that small companies burn  
 6 through cash verify quickly, and they can actually  
 7 lose money as they're waiting for the first patient  
 8 to be entered, which I think is a really stressful  
 9 experience for them.  
 10 Also, their goal is often to be sold or to  
 11 go public and really to make money in a relatively  
 12 short period of time, which I think can influence  
 13 them.  
 14 Big pharma has cash, but there are limits.  
 15 They're not going to invest in everything. And the  
 16 important part of cash, I think it was kind of  
 17 mentioned previously, is that sites might enter  
 18 patients into clinical trials based on how much a  
 19 clinical trial actually pays, so they may  
 20 preferentially go and enroll patients into the  
 21 study that's paying more than the one that's paying  
 22 less.

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1 Also I should say, that they are more likely  
 2 to enroll patients in the study that's less  
 3 complex. And we all, as bright people, like  
 4 complexity.  
 5 A little bit more about contract research  
 6 organizations. Obviously, there are issues with  
 7 contract research organizations. Some of you work  
 8 with them closely, you have positive experiences,  
 9 negative experiences. My view, in general, is  
 10 whether you do a study internally or externally,  
 11 you're going to be complaining because it's not  
 12 enrolling fast enough or there is some issue. I  
 13 don't think it's germane to whether it's a CRO or a  
 14 big company.  
 15 But for CRO, there is a focus on study  
 16 execution, quality and speed, and the idea is that  
 17 if you do one thing over and over again, whether  
 18 you're at the medical monitor level or you're at  
 19 the CRA level, that you're going to bet better at  
 20 it.  
 21 You also have a project team, and the CROs  
 22 benefit from the experience of having run multiple

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1 trials in the same area. On the other hand, the  
2 pharmaceutical company, the biopharm company, this  
3 may be the first time doing a study in Parkinson's  
4 disease or neuropathic pain. Maybe they haven't  
5 done a neuropathic pain study in five years, so  
6 there's a reason that a CRO may be of some value.  
7 And for small companies, there is really no other  
8 choice. They need to use a CRO.  
9 Now, one of things I have as underlined, in  
10 italics, and shaded is the CRAs. And I think the  
11 point that John made before about the study  
12 coordinators is also made about the CRAs. The CRAs  
13 are where the rubber meets the road for clinical  
14 trials. That's the ability for the sponsor to have  
15 eyes on the ground. You know, the eyes thing?  
16 That's it.  
17 So you really do need to have great CRAs.  
18 And I think if we can -- I could spend a lot of  
19 time talking about CRAs and study coordinators  
20 because I think they're hugely important, and they  
21 need to be experienced.  
22 I think somebody said, "Oh, they're

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1 inexperienced and they're underpaid." Well, that's  
2 true, except at companies where you don't hire  
3 people who are inexperienced and underpaid.  
4 I left the meeting yesterday, in part, to  
5 talk to a sponsor and say, yeah, the reason these  
6 people cost a little bit more is because they're  
7 experienced, and they've done this multiple times,  
8 and we get into conversations like that. And they  
9 really are the ones who are the control of ensuring  
10 the quality of the data, and I really can't stress  
11 it enough.  
12 If you're a CRO, you know sites, you know  
13 them well. I mentioned this earlier to Nat's  
14 comment. You get to know how they respond to your  
15 queries. We also had a CRO no contracts.  
16 Contracts would be a killer, as many of you know.  
17 So if you know the sites, you know the contract  
18 issues, that could be hugely important. We have  
19 regulatory experience.  
20 Then there is this ability to have what I  
21 think is the most exciting part of being in a CRO,  
22 for me, is I get to see all these clinical trials

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1 from all of these sponsors, from big and small.  
2 And I get to say to them, well, you know what?  
3 Maybe you should be using Bob Dworkin's algorithm  
4 for baseline pain.  
5 I will throw that out there, and some people  
6 like to say, we're going to actually revise our  
7 protocol because we think that's important. And I  
8 actually had a big company do exactly that, revise  
9 their protocol just based on adding that in. But  
10 we do other things, as well.  
11 But I think there is a huge actual joy. If  
12 you're into clinical trial and clinical trial  
13 methodology, being able to see this is great. And  
14 of course, being within and covering such a large  
15 group of people, I get to see everything from  
16 Duchenne muscular dystrophy, to Alzheimer's,  
17 Parkinson's disease, and, of course, pain.  
18 The other thing that's kind of interesting,  
19 as well, which I like where I'm at, is that we do  
20 have this contract commercial organization. So in  
21 every protocol that we look at and that we get, we  
22 actually look at the market and the need and the

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1 value of it.  
2 What's interesting there is it really will  
3 change the measures that you may want to put in by  
4 understanding who you are marketing this -- who  
5 this is actually intended for. And I say market,  
6 and that's kind of business speak. But it's really  
7 is it going to really meet the needs of the  
8 patients who might potentially be getting this  
9 drug.  
10 But I do think that quality clinical trials  
11 begins really early on in development. When you're  
12 a big pharmaceutical company, you have a portfolio  
13 of products. And if you buy another company, like  
14 Schering-Plough, you even have more portfolio  
15 products, and you have to decide what are you going  
16 to move forward and what are you not going to move  
17 forward.  
18 In the absence of information, really good  
19 information, it's really, really difficult.  
20 Consequently, as many of you know, there are great  
21 drugs that are withering away in the vaults at big  
22 pharma that may never get developed, were

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1 interesting historically. But the goal is to  
2 really make these drugs safe and effective, and  
3 that's all about quality.  
4 Now, there used to be this idea we want to  
5 take multiple shots on goal, and that I think was a  
6 risk to quality when you're trying to push  
7 everything forward. Now, I think in most  
8 pharmaceutical companies, there is a de-risking  
9 exercise that really does ensure the quality of the  
10 molecule or the compound.  
11 We spend a lot of time demonstrating things  
12 like target engagement, proof of pharmacology,  
13 safety, really, in order to select the optimum  
14 dose. Again, I think this all really does fit into  
15 efficacy.  
16 In terms of the quality of the clinical  
17 trial, I think there's a tension that we need to be  
18 honest about between stopping clinical trial  
19 development early and recognizing that a lot of  
20 clinical trials, a lot of drugs that are out there,  
21 have only survived because they have had one person  
22 who was really willing to take all the shots, go

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1 the distance, and really be an advocate for the  
2 molecule. And those drugs, like topamine, really  
3 became very important drugs. There are other  
4 drugs. We all have examples of them.  
5 So that's a challenge as you're trying to  
6 focus in on quality. And I think there is a focus  
7 on the clinical development plan and life cycle  
8 management, where we're kind of focused right now  
9 on I think the registration study, but really there  
10 are a lot of other studies that go on, and there's  
11 a lot that really gets built in here.  
12 Again, in this process, there is significant  
13 time to put in to de-risking; again, a significant  
14 time put into what are the customers' needs, how  
15 can this molecule be used and how should be  
16 investigated appropriately.  
17 There are a lot of health economic  
18 considerations. One of the things we really  
19 haven't hit on today is that these drugs that we're  
20 developing cost a lot of money, and you really have  
21 to defend the cost of these drugs.  
22 I was just at ASCO at the cancer meeting,

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1 and one of the issues that came up is they've got  
2 these great drugs, checkpoint inhibitors, that cost  
3 hundreds of -- like \$100,000, \$200,000 a year. And  
4 there are some implications about financial  
5 toxicity, as well as the toxicity associated with  
6 the drug. And that's something that comes  
7 from -- actually, from all of Sloan Kettering.  
8 It's a big issue for them now.  
9 I think to ensure quality, it's important to  
10 talk to KOL. I think a lot of times people ask me  
11 for KOLs. Luckily, I know a lot of you in here.  
12 Some of you may want me to stop referring people to  
13 you, but I'm often referring people who work with  
14 IMMPACT, as well as others.  
15 I think it's also important -- and I stress  
16 this point a lot, is I think we need to put  
17 in -- to really ensure quality, we need to talk to  
18 patients more. We need to get their perspective on  
19 what they want.  
20 The FDA is really important, there is no  
21 question about it, but it's the patient, and  
22 they're really -- at the end -- let me just say

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1 this. The FDA, when we're talking about quality,  
2 that's what Congress created to ensure that our  
3 products that hit the market for patients are of a  
4 high quality. And I think that needs to be put  
5 into the paper, as well, because that's important.  
6 Historically, it wasn't necessarily that way 200  
7 years ago.  
8 But I do think patients have a lot to offer.  
9 They have a lot to offer in terms of what are they  
10 willing to put up with in terms of pain and side  
11 effects, what does success look like. You can take  
12 a lot of the lessons from cancer and put them into  
13 pain patients, and sometimes just having a good  
14 response is a pretty good thing and how many  
15 patients have a good response.  
16 In terms of clinical trial designs,  
17 obviously, I won't go into a lot of choice on this.  
18 But there is a decision on co-primaries versus one  
19 primary, what the secondary endpoints are.  
20 Sometimes the studies I think get very  
21 complex as we're trying to really put science  
22 forward. There a lot of people who want to do

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1 quantitative sensory testing, which I'm obviously  
 2 an advocate for. I think they're very important.  
 3 But in large phase 3 studies in the United States,  
 4 it's hard to find a lot of centers that are really  
 5 good at quantitative sensory testing, and it  
 6 increases the cost of the study significantly. So  
 7 I do think we need to be careful about, as we add  
 8 these in, there are some risks associated.  
 9 But the big thing for me is the large number  
 10 of outcome measures and the complexity of the study  
 11 decreases quality. There is no question about it.  
 12 If you have a complex study, and you are getting  
 13 the study coordinator and the investigator really  
 14 annoyed, and the patient is annoyed, and if a  
 15 patient has to spend four or six hours at the  
 16 clinic, I think your quality is going to decrease  
 17 and decrease significantly. Patient burden needs  
 18 to be considered an important part of quality, as  
 19 well.  
 20 Now, obviously, sometimes protocol  
 21 complexity is really important. I'm working on a  
 22 very complex protocol, and it's to assess a very

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1 important safety measure. And it has led to huge  
 2 complexity. There is imaging that needs to be  
 3 done. There's lab work that needs to be done.  
 4 It's huge. Obviously, I can't talk about it in  
 5 detail, but it's big.  
 6 There is no question, as I mentioned before,  
 7 that the PI would much prefer to work on less  
 8 complex studies. Part of this comes from my own  
 9 experience at Merck. Merck was actually known for  
 10 creating very complicated protocols. We've prided  
 11 ourselves on that. And then they kind of pushed  
 12 back on that, our bosses, but it was really an  
 13 important issue.  
 14 I'm not going to belabor this point. I  
 15 think this was discussed before. I think to have a  
 16 clinical trial that's really successful, you need  
 17 to blind the patient and the investigator to as  
 18 many things as possible, from what the entry  
 19 criteria are to really when the study drug is  
 20 actually started and when it is discontinued,  
 21 because if they know, there is an expectation. If  
 22 they don't know when the drug is going to get

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1 started and they don't know when it's going to get  
 2 stopped, you are actually collecting data that is  
 3 going to be, I think, potentially more -- less  
 4 biased, I should say.  
 5 I do want to encourage people, I think  
 6 adaptive designs are really important. I think  
 7 they're very informative. I think they're very  
 8 efficient. I did a very nice adaptive design  
 9 study, while the enriched enrollment one that many  
 10 of you know is clearly and adaptive design in some  
 11 ways.  
 12 I did a nice migraine study where we could  
 13 add dose at the bottom end, and it was really kind  
 14 of cool. But it can be very informative to  
 15 clinical trials; not necessarily approved for the  
 16 FDA right now for phase 3 studies, but very useful  
 17 in phase 2.  
 18 Definitely it's important for efficacy and  
 19 safety, and I like to think it minimizes harm. I  
 20 think anything we can do to minimize harm to  
 21 patients is a huge thing.  
 22 The other thing I wanted to mention, I think

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1 we touched on this yesterday, was the importance of  
 2 the placebo, but I also an active placebo. An  
 3 active placebo combined with a placebo can tell you  
 4 whether you've had a failed study or not.  
 5 As some of you know, I did a very large  
 6 study, international, worldwide study with  
 7 thousands of patients, unfortunately, that failed.  
 8 We actually were able to demonstrate rasagiline,  
 9 made by Teva, very good drug, that we know works in  
 10 Parkinson's disease. We were able to demonstrate  
 11 that it was no better than placebo and, in fact, in  
 12 certain countries, placebo was a lot better than  
 13 rasagiline and pramipexole, which was the drug I  
 14 was studying for Parkinson's disease.  
 15 So a failed study really does suggest a  
 16 problem, and it was that failed study that really  
 17 said to me, you know what, as I'm looking at career  
 18 options and possibly becoming -- where I could go  
 19 from where I was at Merck, where should I go? And  
 20 I thought, CRO would be a good place.  
 21 It is kind of like the candy store. When I  
 22 left academia and went into industry, one of the



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1 reasons I went in -- there were two reasons. One  
 2 is because I wanted power, statistical power, that  
 3 is --  
 4 (Laughter.)  
 5 DR. HEWITT: -- and then the other one is  
 6 that's where the drugs are. It's like -- what is  
 7 it? Willy Sutton? Why do you rob banks? Because  
 8 that's where the money is. I went into the  
 9 pharmaceutical industry because that's where the  
 10 drugs are. So it's pretty fun.  
 11 But going into a CRO is also fun because  
 12 that's where the studies are, and you get to see  
 13 all -- I have like 35 people reporting in to me.  
 14 Each one is running -- there's a medical monitor  
 15 involved in at least two or three studies. So the  
 16 number of protocols I see across everything from  
 17 oncology to -- it's really, I think, going to make  
 18 me -- and has made me better at thinking about  
 19 clinical trial issues.  
 20 I wanted to talk about rater training, which  
 21 I think is huge. I think this is one of the  
 22 biggest things. And really, this is where

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1 the -- in this article, there has got to be a lot  
 2 of focus on this, as far as I'm concerned.  
 3 The placebo effect is real. It's very real.  
 4 As I just mentioned, it killed my study in  
 5 Parkinson's disease. There is tremendous  
 6 investigator enthusiasm for the drugs that we are  
 7 investigating. They're novel mechanisms often.  
 8 It's really exciting. It's hard to contain your  
 9 enthusiasm.  
 10 You're looking at somebody who, in general,  
 11 finds it hard to contain his enthusiasm, and my  
 12 patients saw that I was always concerned that I  
 13 might be increasing the placebo effect.  
 14 But there is also something that to me is  
 15 equally important, which so therapeutic  
 16 misconception. And we've kind of talked around  
 17 this issue a bit, but it's a really important  
 18 issue.  
 19 One of the things I was really happy with  
 20 coming to my new job at a CRO is because they had a  
 21 rater training group, and I was going to be able to  
 22 educate them about therapeutic misconception.

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1 Unfortunately, they had already had videos, and  
 2 they were way ahead of me already. But this was  
 3 something that was really exciting to me that I  
 4 didn't even know existed when I joined.  
 5 So in this case, patients confuse  
 6 participation in clinical trial with the primary  
 7 care for their condition, and this is done all the  
 8 time. The study subject is really a partner in  
 9 clinical research and not a patient.  
 10 I know we keep referring to them as  
 11 patients, but I think there are ethical issues  
 12 that -- I'm into ethics -- need to be recognized,  
 13 that the power relationship between a patient and  
 14 doctor is sacrosanct. That is a very special  
 15 relationship. And once a patient goes and makes  
 16 the decision that I want to do you, Dr. Hewitt, a  
 17 favor and become a study subject, that leads to a  
 18 whole other set of ethical considerations.  
 19 I think we need to respect them because  
 20 they're really -- and by doing them and making that  
 21 study subject our partner, they understand their  
 22 role better, and that is part of what rater

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1 training does as well.  
 2 My other concern, of course, is that in some  
 3 countries, that are underinsured, clinical trials  
 4 may be a way for people to get primary medical  
 5 care. And of course, as many of you know, this was  
 6 really an issue and a concern in India.  
 7 Obviously, the KOLs and PIs know a lot about  
 8 how to assess pain in Parkinson's disease and all  
 9 of these things. But on measures where the  
 10 investigator matters, you really need to make sure  
 11 that there is consistency, that everybody does it  
 12 the same way.  
 13 I can tell you some of the world's greatest  
 14 Parkinson's disease experts go into battle about  
 15 how you do UPS Part 3. And it's kind of funny to  
 16 watch when that hasn't been your whole thing, but  
 17 it's very important to get consistency of  
 18 assessments across sites.  
 19 You need dedicated teams with real expertise  
 20 in rater training. You need to ensure the quality  
 21 of the data collected. So they don't only just do  
 22 the rater training, they do a lot of the things we

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1 talked about before, which is they look at  
2 consistency across measures, both qualitative and  
3 quantitatively, and that's a huge issue, too much  
4 for today. And it's already been touched on, but I  
5 can't stress that enough.  
6       Ensure that all sites are thinking the same  
7 way. We want to provide significant materials to  
8 understand the placebo effect. So we have videos.  
9 You guys were talking about what you did live,  
10 which I think is really good. But we have videos  
11 that people can watch over and over and over again.  
12 And we say how often do you have to watch that  
13 placebo video? And we'll say, well, maybe we need  
14 to do it once every month or maybe it's every two  
15 months, but it's one of the things we talk about a  
16 lot.  
17       There is ongoing training of patients.  
18 We've talked about this in the meeting. There is  
19 no problem. Part of being a medical monitor is to  
20 monitor the study. If things are not going well,  
21 you fix them. You still have an intent-to-treat  
22 analysis, you can't change the data, but you can

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1 fix and make the data that comes in following that  
2 intervention much better.  
3       You have to train the PI and their staff.  
4 When the receptionist says, "Mrs. Dworkin, you look  
5 wonderful today and that medication must be really  
6 working for you," you know that you are pushing the  
7 placebo effect. Again, I can't mention this  
8 enough. Patients are our partners more than  
9 patients, and the question is does the patient  
10 exist?  
11       Patients are study subjects with a specific  
12 skill set. I want to get back to this because we  
13 talked about this yesterday. We have  
14 inclusion/exclusion criteria that enrich our  
15 population and make our population different, much  
16 different than the general patient out there, and  
17 we can go into that. But there is no reason -- and  
18 we've already done this.  
19       We select out people based on their pain  
20 intensity with the algorithm, for instance, or with  
21 their ability to -- in a run-in period, their  
22 ability to do an electronic diary. We certainly

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1 can exclude them based on other factors if we don't  
2 think that they're going to be able to do well, and  
3 if they can't be good observers of their own  
4 experience.  
5       So one of the questions that I ask myself a  
6 lot is why do patients participate in clinical  
7 trials. I don't know the answer to that. I myself  
8 participated in a clinical trial when I was in  
9 medical school at the University of Rochester, and  
10 I know why I did it. I did it for money. I had  
11 somebody put a catheter -- put a tube down in my  
12 lungs, and they collected the macrophages from my  
13 lungs for a very interesting study. But I knew why  
14 I was doing it, and it was not really to better  
15 humanity. I wanted 400 bucks.  
16       So what is the benefit for the patient?  
17 There really is none. It's really an altruistic  
18 thing, getting back to concepts of ethics.  
19       Are they really seeking primary care? I  
20 mentioned that before.  
21       Are they refractory pain patients? A major  
22 concern of mine.

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1       Are there comorbidities that will impact the  
2 results that the patients have? We've hit upon  
3 that, as well. We've hit upon professional  
4 patients.  
5       Should subsets of patients be assessed based  
6 on QST or biomarkers, stratification based on these  
7 things?  
8       These are all very interesting kind of  
9 endpoints that one could look at to verify the  
10 patient has what you think they might have, but  
11 also to ensure the quality of the study. John did  
12 a nice example of that with, I think, the irritated  
13 nociceptor as an example.  
14       Now, I want to move on to sites. Sites are  
15 really important. What I always think about is  
16 that we don't do basic research and have lab rats.  
17 We basically have an extended team. And so this is  
18 the way I think about it.  
19       I have a team that is very large, and  
20 sometimes we have 50 sites, and all those  
21 investigators and all those people are part of my  
22 team. And when I go into investigator meetings,

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1 and some of you may have seen me do this, I say,  
2 "You're part of our team." One of the things I  
3 want to make sure is that everybody feels like  
4 there is skin in the game. I always talk about  
5 skin in the game, so everybody is going to do the  
6 best quality work they can do.  
7 So it is important, though, in terms of  
8 sites, to have geographic diversity, but too much  
9 diversity can be a problem. I think a lot of  
10 places, like Eastern Europe, have gotten much  
11 better at doing clinical trials, based on my  
12 experience, over the last 10 years in industry.  
13 But still you need to pick the right sites.  
14 In Latin America, there are still issues,  
15 and we can talk about this. The placebo effect is  
16 clearly regional. If you want an example of that,  
17 I'll send you a poster on my Parkinson's disease  
18 study.  
19 There are different practice patterns when  
20 it comes to what we're treating patients for, and  
21 that can be impactful. There are different startup  
22 times, which can impact study execution, as well.

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1 And then there is -- I think this point of  
2 controlled drugs has been mentioned. We talked  
3 about academic versus quality private research  
4 institutions.  
5 I've changed my view on this. I used to  
6 think that academic institutions were the best, and  
7 I used to think that these -- what did we call  
8 them -- mills, these drug mills were horrible and  
9 that they were really bad.  
10 But then I got to meet some of these guys,  
11 and there are sites and there are networks that are  
12 truly amazing, where they pride themselves on the  
13 quality of their work, and they will get the  
14 neurologist to do a neurology study or an -- well,  
15 you need an anesthesiologist to do a lot of  
16 anesthesia studies. But there really are  
17 Parkinson's disease experts doing Parkinson's  
18 studies. So they're very serious places, and there  
19 are more of these.  
20 Sites are important. A large number of  
21 sites can be certainly useful to enroll studies  
22 faster. Contrary to a lot of the thoughts that

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1 have been doing on in this room, I don't think  
2 there's a problem with studies enrolling too fast.  
3 And one of my folks who are in industry might want  
4 to contradict me on that, but I've never seen a  
5 study enroll too fast because people are so eager  
6 to get patients in and are pushing that hard.  
7 But I do think the longer there is an issue,  
8 it takes sometimes a long time to get sites up and  
9 running, particularly after the investigator  
10 meeting. There are issues with contracts. I  
11 mentioned some of these issues, as well.  
12 But I did want to mention one of the points  
13 that Rob mentioned, which is I do think it is very  
14 important to visit the sites and to know the sites  
15 and talk to the sites. And I like to have a lot of  
16 conversations with sites, particularly when things  
17 aren't going well.  
18 Again, there is huge value in face-to-face  
19 investigator meetings. I think that they know that  
20 you really are -- basically, when you're dealing  
21 with these drugs, it's like giving your baby to a  
22 stranger or to a babysitter, and you shouldn't be

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1 doing that lightheartedly. And I think one of the  
2 issues is that there's this thought that if you go  
3 to a CRO, you give it to the CRO, and you go away.  
4 I don't like that method. I don't like that  
5 interaction. I think you really need to have a  
6 partnership as you do these studies.  
7 I think that part of it, whether you're a  
8 CRO or whether you're the biopharmaceutical  
9 company, face-to-face is better than on the phone.  
10 Relationships are relationships that can really  
11 last a very long time.  
12 One of the things I do want to mention is we  
13 don't have enough sites in minority areas. This is  
14 one of the biggest failings of clinical trials  
15 right now. And I think to Bob's point, if you get  
16 your school up and running, I would like to get  
17 some hospitals that serve -- under the sites that  
18 serve minorities to really take the opportunity to  
19 put them in clinical trials, as well, because they  
20 really need to be.  
21 I do want to mention that speed of  
22 enrollment really does negatively impact quality.

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1 We are always pushing, pushing, pushing, and when  
 2 you do that, there is a concern that investigators  
 3 may start to enroll patients who are not really  
 4 truly qualified for your study.  
 5 We had one example of a study that was  
 6 really positive in the first half, with a low  
 7 placebo effect. In the second half, it was a huge  
 8 placebo effect. It was really problematic. And we  
 9 know that enrollment increases over time, and when  
 10 it speeds up, we should be a little concerned.  
 11 I want to talk a little bit about diaries.  
 12 My time is running out; I should be careful here.  
 13 Paper diaries, I don't think they should be used  
 14 anymore. Electronic diaries are very useful. They  
 15 can assess compliance in the run-in period. You  
 16 can avoid the hood effect that you have with paper  
 17 diaries, where people fill them out on the hood of  
 18 the car while they're waiting to come and see you  
 19 in the clinic.  
 20 There is evidence that supports that diaries  
 21 are not only filled out retrospectively, but in one  
 22 study in Parkinson's disease, they were filled out

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1 prospectively.  
 2 (Laughter.)  
 3 DR. HEWITT: So that was a major new one to  
 4 me, and I think that will be presented in the near  
 5 future.  
 6 There is also the assumption that the more  
 7 accurate the data is, there is an increase in  
 8 quality of the study results. I know some people  
 9 believe that a lot. I'm not sure if it's  
 10 absolutely true, but it probably is.  
 11 Translation is an issue we talked about.  
 12 Let me skip over that.  
 13 Obviously, safety monitoring is a big part  
 14 of what we do, and the CRAs and the medical  
 15 monitors and the MDs are a big part of that. I  
 16 think this was covered pretty well previously in  
 17 terms of alerts of these lab values, I think is  
 18 important.  
 19 Efficacy I think is a huge issue for  
 20 monitoring. It's hard to monitor efficacy in a  
 21 blinded fashion, but there are methodologies that  
 22 one can use to look at consistency of response on

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1 scales to make sure that they are aligned and  
 2 correlated. And then you can look at site  
 3 differences and regional differences, which I think  
 4 can be helpful.  
 5 One of the big issues that we do in industry  
 6 and CROs is really look at the inclusion/exclusion  
 7 criteria because a lot of times they are not  
 8 followed, and that leads to significant protocol,  
 9 major protocol deviations. And those are  
 10 high-quality problems, because then you're not  
 11 really studying the population that you thought you  
 12 were studying.  
 13 I do want to speak to the importance of  
 14 DMCs. I think these independent data monitoring  
 15 committees are huge. And if any of you want to  
 16 participate in one, just let me know. People are  
 17 asking all the time for people to do this. It's  
 18 big. It's a big industry now, I think.  
 19 Of course, they need an independent  
 20 statistician. You can assess efficacy and safety,  
 21 and you can actually stop studies. But for  
 22 efficacy, you can stop studies for futility, which

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1 I think is a very important thing, and I talked  
 2 about that before in terms of interim analyses.  
 3 We've talked about risk-based monitoring. I  
 4 think we've hit a lot of these things already. Let  
 5 me skip over that.  
 6 So the data, I think this has also been hit  
 7 on already, the use of flags in programming data  
 8 checks. I do think one of the things to ensure  
 9 quality is the use of soft locks. That's where you  
 10 really lock the patients' data, and you really  
 11 clean it up, really as you go along instead of  
 12 trying to do it at the end.  
 13 Unless you're a pharmaceutical company, you  
 14 may not know what I'm talking about. For those of  
 15 us in the industry, that's a big issue because you  
 16 spend a lot of time at the end trying to clean up  
 17 data. So I'm a big advocate of soft locks. And to  
 18 check, of course, the program before you finish.  
 19 We talked about this before, ensuring that  
 20 people take the drug, and I was very excited by the  
 21 technology that was just mentioned. I do think  
 22 that the quality of a study overall begins way

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1 before even your selection of a molecule. It's  
2 really the intent of the pharmaceutical company.  
3 It's a decision on what mechanisms you're going to  
4 pursue and what molecules you're going to push  
5 through.  
6 I think, obviously, you need more than a  
7 good protocol, but a good protocol is essential.  
8 We've talked about some clinical trial designs. I  
9 think there are some really interesting clinical  
10 trial designs that we're using right now, but one  
11 of the benefits of my position right now at a CRO  
12 is I get to see clinical trial designs from other  
13 areas, including oncology. And there are things  
14 like umbrella designs and basket designs -- I don't  
15 know, John, maybe we can talk about this at some  
16 point -- which are really kind of interesting to  
17 me, whether we could start to employ adaptations of  
18 those designs to pain studies, as well.  
19 I think trial execution is important. But  
20 the last point is this. It really is a  
21 collaborative partnership that is the quality among  
22 sponsor, the biopharmaceutical company, the CRO, if

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1 there is one, the site, and, most importantly, the  
2 study subject partner, which I'll emphasize again.  
3 I think with that, when you realize that  
4 it's really a partnership and that you have to work  
5 together, observing how to do that well is I think  
6 what really will ensure the quality of studies and  
7 the quality of the output, and hopefully the  
8 quality of drugs that are going to get to the  
9 patients who need them.  
10 Thank you.  
11 (Applause.)  
12 Q&A and Panel Discussion  
13 DR. McDERMOTT: As always happens, we're  
14 sort of tweaking and modifying the schedule. Not  
15 John Farrar. John Farrar, stay there, and Markman  
16 come up here.  
17 We're doing some slight modification. What  
18 we're going to try and do is the panel discussion  
19 we're going to save until after lunch, but rather  
20 take a few minutes to have an opportunity to ask  
21 questions of our two presenters, and then we'll  
22 break for lunch in 15 or 20 minutes.

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1 Just a caution that I should have mentioned  
2 in the housekeeping details. This is being  
3 transcribed. So, David, to say you get fun from  
4 drugs, I'm not sure you want that to be in the  
5 record.  
6 (Laughter.)  
7 DR. McDERMOTT: It could be a concern. For  
8 those who have looked at their program and are  
9 expecting Sharon Hertz to be here, and I'm not her,  
10 in case you were wondering, she, unfortunately, was  
11 ill and wasn't able to come in today. So I've been  
12 filling in for her.  
13 So let me start this off and then I'll let  
14 any questions. One thing that both of you pointed  
15 out, and I think really maybe we need to underscore  
16 even more, is we've talked about patient training  
17 and we've talked about site staff training. But I  
18 also heard both your two coordinators mention this,  
19 and, David, you mentioned this, is the  
20 recalibration.  
21 Doing this once at the beginning of the  
22 study is probably not sufficient. This may be the

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1 kind of thing that should be planned into your  
2 protocol, or could be considered to plan into the  
3 protocol, both the site training and  
4 potentially -- and we can talk about it  
5 later -- about how you want to do this with  
6 patients, should that be planned, that is not to  
7 wait until it's a problem, but to actually plan  
8 that recalibration.  
9 I know we're involved with some procedures  
10 that do require some physical examination, and what  
11 we've learned early on is that training our  
12 physicians to do these evaluations, if you follow  
13 them up two or three months later, they were fine  
14 initially, but they start drifting from that. So  
15 that that becomes important.  
16 So I don't know if you want to add anymore  
17 to that or expand, but I think it's something that  
18 you both mentioned, and I think it's something that  
19 we haven't talked enough about.  
20 DR. MARKMAN: We mentioned sort of the  
21 paradigm of prevent, identify, and manage. And it  
22 would seem to me that doing it up front is the

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1 prevention piece. But in the protocol, if you sort  
2 of had a remediated component, if you identify an  
3 issue that you think raises a question about how  
4 the rating is going, based on some statistical  
5 analysis or other observation, and then a dose of  
6 education to manage it, I think if that were  
7 prespecified, that might be a way of not creating  
8 the issue which we were concerned about yesterday,  
9 where education might be started on an ad hoc  
10 basis, and that might be even be introducing  
11 variability from subject to subject.  
12 So I think maybe making that a little more  
13 standardized with some contingencies built in would  
14 be the way to go.  
15 DR. HEWITT: I think it's huge. Obviously,  
16 we're talking about pain. But if we were talking  
17 about Alzheimer's disease, this wouldn't even be a  
18 question. Rater drift is recognized in a lot of  
19 areas within neurosciences as a really big issue,  
20 and you have to keep training people.  
21 It can even get more complicated. You could  
22 have central raters who look at videos to make sure

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1 people are doing the physical exam correctly, or  
2 you can record people to see if they're really  
3 presenting the instrument correctly.  
4 So how you do it, even how you talk to the  
5 staff about interactions and whether you're sort of  
6 gaming the system to increase the placebo effect,  
7 you can record sessions, you can videotape them,  
8 you can send them in to the central reviewer and  
9 see how that works.  
10 But I do think whatever the -- particularly  
11 for the outcome measure, it's important to get  
12 training and re-training. And I think for a lot of  
13 times, even though we're doing electronic diaries,  
14 we think they're going to be better. I have to  
15 say, if I were a patient and I were doing it, there  
16 are going to be some times if I'm filling this out  
17 every day that I might -- I'll put down a 6. This  
18 is a 6 day. And I might not give it the  
19 consideration that it was really worth doing.  
20 So I think it's very important to stress  
21 that with patients.  
22 DR. McDERMOTT: Let me precaution, I can't

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1 see all that far back. So if, for some reason, you  
2 are sitting in, I'd say, the last two-thirds of the  
3 room, I may not see you by name, but I'll sort of  
4 point at you to call on you.  
5 But in this part of the room, I think I saw  
6 already a hand going up. Yes, Rob?  
7 ROB: John, one thing you mentioned I wanted  
8 to just follow-up on, and it resonates with some of  
9 the work that Nat has done about sites that don't  
10 enroll a lot of patients. And you hinted that the  
11 first patient or two that come into your trial,  
12 you're learning on.  
13 It would be interesting to know if there's  
14 actually an evaluation of that first patient at  
15 each site and whether -- we do all learn with the  
16 first patient. Are there more mistakes made? Is  
17 there more data missing? Is the quality of that  
18 first patient or two worth looking at?  
19 One thing we did when I was with a recent  
20 company is we ran a number of pilot studies, and  
21 you almost wonder do you want to run the first  
22 patient in as a pilot at each site to get the site

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1 greased. They have all been to investigator  
2 meetings. We know they don't pay attention until  
3 they have that first patient, and that's when they  
4 work out the kinks of the study.  
5 But I'd be curious to know if, one, the  
6 analysis has been done. Even sites that enroll  
7 lots of patients, what do those first one or two  
8 patients look like when you separate them out?  
9 Again, I know, Nat, you've done an analysis  
10 that suggested if you're a site and you only enroll  
11 one or two patients, that's not a very good site.  
12 You want the sites that have more patients. But  
13 I'm just curious about your thoughts.  
14 DR. MARKMAN: I'm not aware of any data on  
15 how -- basically, how the detection machine is  
16 affected by that initial patient. But I agree with  
17 you, there is learning on that patient.  
18 I think of the analogy as to surgery,  
19 basically. You don't want someone to do your  
20 Whipple procedure who does two a year. You're  
21 right. You want to go to someone who does a lot a  
22 year. That's how we practice medicine, and that's

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1 how we think there's a relationship in medicine,  
2 and we think there is some level at which quality  
3 improves after exposure.  
4 I don't know what that is, and I don't know  
5 what the effect of that is on analgesic signal  
6 detection. But I do think it's an interesting  
7 question, and I've observed it myself and in our  
8 team.  
9 I think the other countervailing factor,  
10 though, is I do think that the first patient you  
11 enroll, in our experience, tends to be a super  
12 buttoned-up crisp patient. Right? Because you've  
13 been searching for that patient for a while.  
14 Right? It's sort of like dating, and now you've  
15 got Mr. and Mrs. Right. And you could have  
16 screened 200 people to get that person.  
17 In some ways, though, I think that that is a  
18 very crisp patient, and you tend to have less creep  
19 with that first patient. So I don't know, might be  
20 a couple of ways.  
21 DR. McDERMOTT: David, do you want to  
22 comment? I'll get to you, Nat. I just want to see

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1 if David wanted to comment.  
2 DR. HEWITT: No. I think that that's a  
3 really good question. In my experience, I have  
4 looked at the data in a few studies, and I haven't  
5 noted that the first patients are that much  
6 different from patients who come in later. I have  
7 seen studies where it definitely feels like the  
8 quality drops off over time and that people may be  
9 more cautious. Particularly, sometimes the CRA  
10 might be really close at hand, and they may be  
11 being guided by the sponsor very carefully to the  
12 CRA in those first few patients.  
13 With that said, I do think there is a  
14 learning curve and people get better and better  
15 over time, particularly for good sites.  
16 DR. MARKMAN: You're very invested in that  
17 first patient, though. You want that first patient  
18 to make it through. It's sort of like not making  
19 the sale at the local market to the first person  
20 who comes to your stand. It's a bad omen.  
21 DR. KATZ: Just a quick correction in  
22 response to Rob's comment. That was actually Neil

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1 Singla's study with folks from Pfizer, where they  
2 showed that in three studies of pregabalin for  
3 acute pain, sites that only enrolled a small number  
4 of patients did not separate pregabalin from  
5 placebo, whereas sites that enrolled more than a  
6 certain threshold of patients --  
7 MALE SPEAKER: Talk into the mic.  
8 DR. KATZ: Sites that enrolled more than  
9 that certain threshold, patients all of a sudden on  
10 pregabalin did look better than placebo. I don't  
11 know, Neil, if you want to add anymore comments to  
12 that.  
13 DR. SINGLA: No. I don't mind being  
14 confused with you, Nat. That's a compliment. We  
15 look so much alike, too, that's the thing.  
16 (Laughter.)  
17 DR. SINGLA: That's the summary of that  
18 study exactly.  
19 DR. HEWITT: I just want to say one other  
20 thing, though, since this is about quality. I  
21 really believe that after the first two or three  
22 patients get in on a site, the site stops

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1 enrollment. So the CRA has to be out there, and  
2 they have to look at the data to see if it's  
3 quality data or not.  
4 I think this idea, and I have seen this  
5 before, where people let patients enroll at five or  
6 six sites, just go crazy with enrollment, because  
7 there is such speed to get the studies done, is an  
8 example of quality being diminished.  
9 I didn't put that in there, but if I was  
10 going to redo the slide deck, I'd say you need a  
11 visit after the first two or three patients.  
12 DR. McDERMOTT: I can't see.  
13 DR. JUGE: Dean Juge. In these discussions,  
14 you have academic and CRO as kind of two pieces,  
15 but in the last 10 years, I've seen kind of a  
16 hybrid, and let me explain that. It may be an  
17 issue to the companies and their sponsors when  
18 they're getting studies done in that you have a lot  
19 of academic areas or the academic PIs that belong  
20 to an outside CRO entity to get their research  
21 done.  
22 So the patients are coming from an academic

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1 institution, but for whatever reasons -- and the  
 2 biggest reasons I've seen, primarily two, is that  
 3 it takes so long for an institution to get an IRB  
 4 reviewed and approved, or the institution wants to  
 5 collect so much funds from that for the  
 6 institution, and not as much is coming back to your  
 7 department, that it's easier to take outside if the  
 8 rules of that institution allow it. But that could  
 9 be an issue for the research organization.

10 For instance, at the University of Iowa, we  
 11 were doing a study in a company I worked for in the  
 12 past, and we had a sleep apnea study going on. So  
 13 within the pulmonary department, they had to use  
 14 internally, and it took forever to get the IRB,  
 15 that they just didn't meet the timeframe and we had  
 16 to drop them and contract on that end.

17 Yet, with the psych department in a TBI  
 18 study that we were doing with the same product,  
 19 they were using an outside IRB institution and  
 20 conducting it through an outside organization.

21 So the principal investigators are part of  
 22 an outside group, but yet the patients and their

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1 day job is within the institution itself. So it  
 2 was really like they are there an academic,  
 3 however, the studies are done through an outside  
 4 institution.

5 In some of those studies, when you go look  
 6 up their address or their affiliation in the study  
 7 protocols, you'll see that affiliation is not the  
 8 institution, but the affiliation is the  
 9 organization they did the study through, although  
 10 they are an academic institution and the patients  
 11 come from that.

12 So I don't know if there are issues with  
 13 quality or sites or whatever that happens there,  
 14 but those are things that I have dealt with in the  
 15 field, and I was wondering if you could respond to  
 16 that.

17 DR. MARKMAN: I think that's exactly -- I  
 18 think it's a very astute comment. I think that is  
 19 what I tried to get at with this notion of what it  
 20 means to be an academic is changing. And I think  
 21 there's going to be all sorts of hybrid models and  
 22 other versions which evolve, because, again, I

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1 think as the focus of these large academic medical  
 2 centers and their networks change, which they will,  
 3 I think their research priorities are going to be  
 4 recalibrated. I don't think that's going to be at  
 5 all 119 in the same way, but I do think that these  
 6 changes are happening.

7 I think in our own institution, we use WIRB  
 8 for a lot of our sponsor trials, which is pretty  
 9 efficient, and our IRB is now run from someone who  
 10 came from industry. So that's been incredibly  
 11 helpful, or at least the administrative component,  
 12 and that's been a real sort of accelerant.

13 But what has not improved, in my experience,  
 14 in fact, may be just as challenging as eight years  
 15 ago, is contracting. I just find that to be just  
 16 incredibly laborious and frustrating, and it's  
 17 literally months, and there is no reason it needs  
 18 to be.

19 I think that, from my perspective, that's  
 20 the biggest disadvantage to our own institution,  
 21 and I think that, as I mentioned, the larger groups  
 22 at our institution have their own attorney. And so

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1 for them, that person really is accountable to that  
 2 department, but I'm using the attorneys and I'm  
 3 using the individual contracting infrastructure  
 4 that those other 300 investigators are using, and  
 5 I'm just one group. I think that is the biggest  
 6 rate-limiting step in our process.

7 DR. McDERMOTT: Let me just add one thing  
 8 that might be related to this. I think you're  
 9 right and you're right from what we're seeing. At  
 10 the University of Washington, there is a new  
 11 concept that they've been using. Somebody  
 12 mentioned that they were a highly funded research  
 13 facility. And that is the concept of dollars per  
 14 square foot.

15 That is, they look at clinical space, and  
 16 they want to know how much revenue is being  
 17 generated on that clinical space. And the amount  
 18 of revenue that's generated on clinical space on  
 19 these types of trials is substantially lower than  
 20 we developed if, in fact, John was doing a  
 21 procedure on a patient.

22 So I think you're going to see more of that



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1 partnering out, extending out. I think that is the  
 2 wave of the future.  
 3 Mike Rowbotham, I saw your hand up.  
 4 DR. ROWBOTHAM: I just wanted to say  
 5 something about the contracting process. Dave,  
 6 maybe you're in a position now to do something  
 7 about it. But our contracts for Sutter Health are  
 8 all done centrally, one office for all 27  
 9 hospitals, all the physicians. And we work hard to  
 10 try and develop master contract templates with the  
 11 major sponsoring companies. But then when they  
 12 send the study to a CRO, the CROs insist on their  
 13 own contracts, and that just hugely slows things  
 14 down.  
 15 There has been an effort in California that  
 16 I've been a part of for a few years. I'm not sure  
 17 if it's ever really going to get off the ground.  
 18 It's something called PACT, Partnership to  
 19 Accelerate Clinical Trials. And that was bringing  
 20 together 13 major research organizations from the  
 21 state. So it was all five UC biomedical campuses:  
 22 Stanford, USC, Sutter Health, Dignity, all the

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1 biggest healthcare organizations, to have a single  
 2 contract template, a single IRB, and really try and  
 3 streamline things and get all those barriers out of  
 4 the way.  
 5 But it has actually been very hard to get  
 6 industry to actually fund these kinds of  
 7 streamlining efforts on a regional basis and to try  
 8 and reduce the number of thinkers messing around  
 9 with the contracts that make it take so long.  
 10 DR. HEWITT: Yes. Look, I think that one of  
 11 the biggest impediments to -- actually, this is a  
 12 good point. I didn't make a point of it on mine.  
 13 I think that impacts quality, because when there is  
 14 a huge time for site startup, particularly the time  
 15 between the investigator meeting and the site being  
 16 ready to get their patient in, I think that's a  
 17 huge negative. I talked about this when I was at  
 18 Merck, and I talked about it at inVentive, as well.  
 19 I do have some power to make changes like that, so  
 20 I have started to do that.  
 21 I think that one of the issues is it's not  
 22 always as simple as it may appear because most of

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1 the time, if the CRO is going to be the one that  
 2 manages the contracts, that's fine. But I think  
 3 when it gets into trouble is when you have the CRO,  
 4 the site, and the biopharmaceutical company all  
 5 wanting to play with the -- because the sites  
 6 change it. Most of the time, it's the sites that  
 7 want to change things. And then you spend a lot of  
 8 time with the churn.  
 9 So this has been a big issue, and I'm always  
 10 working on this one. This is a continuous issue.  
 11 So it's important.  
 12 DR. McDERMOTT: Roy?  
 13 DR. FREEMAN: A couple of things. I think I  
 14 was little bothered yesterday with Nat's very  
 15 creative fall below the threshold, intervene,  
 16 coach, retrain, system, although I think there are  
 17 ways of getting around that and doing it in a way  
 18 that does not induce bias.  
 19 I liked John's Catholic high school  
 20 graduates way of coaching each time the patient  
 21 came in, provided that that is done globally across  
 22 the trial. And it was fascinating that they picked

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1 on the average daily pain and we train them what it  
 2 is. I'd love to hear how they explain the average  
 3 daily pain.  
 4 MALE SPEAKER: Dr. Dworkin will be happy to  
 5 talk to you at lunch about how you do that.  
 6 DR. FREEMAN: But the point I do want to  
 7 make with that preamble is that training is  
 8 obviously so very important, and I think patients  
 9 need to be retrained, and I think sites need to be  
 10 retrained. And here I'm going to -- the question  
 11 is really directed at David.  
 12 There seems to me to be a reluctance on the  
 13 part of CROs to actually get involved in the  
 14 retraining process. And I know specifically with  
 15 the bedside QST that I've introduced to a number of  
 16 studies and have wanted for reproducibility,  
 17 reliability, all of the obvious reasons, have the  
 18 CROs get involved in training, and somehow there  
 19 has been a block. They haven't wanted to do it.  
 20 Perhaps the pharmaceutical companies felt it's too  
 21 expensive and have made the CRO be the bad guy and  
 22 say, no, we can't do it, but there has been some

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1 reluctance.

2       So I wanted to get a sense of the notion of

3 the CRO not just looking at data and putting yellow

4 stickies in, but actually training the sites on

5 measures and assessment tools. That's the one.

6       Then the other thing is who actually trains

7 the trainers? How well do your guys actually know

8 the protocols? You're sending people out to sites,

9 but do they know the story?

10       DR. HEWITT: What I would say is that,

11 obviously, ours, there aren't that many CROs that

12 have a rater training group embedded within them.

13 As a matter of fact, I think we're the only one.

14 So we put a lot of effort into rater training, and

15 we always recommend it to every single study that

16 we do, because I think it makes a big difference.

17       There are people who have been doing this

18 rater training for a long time. They've had a lot

19 of experience in the instruments, whether they are

20 pain instruments like the BTI, or they're

21 instruments for Parkinson's disease, like the

22 UPDRS. So they have that experience.

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1       We, as a company, really believe in the

2 power of retraining in terms of having quality

3 data. I can't really speak for other CROs in this

4 regard. It is true that if the sponsor doesn't

5 want to have it, it won't get done.

6       In terms of who trains the trainer, it

7 really depends a little bit on what the instrument

8 is. So, for instance, this came up about QST, and

9 we would get somebody who was like an expert in QST

10 to train the trainer, like you, for instance.

11       So we would make sure that whatever it is

12 that you do -- I mean, we'd probably have you do a

13 video, probably have you at the investigator

14 meeting, and we would probably have you and some

15 people like you that you've trained and that you

16 have -- because this is a really big issue. QST

17 can be very different in different hands. You need

18 to make sure everybody is doing it the same. So

19 we've talked about this in studies where they've

20 had QST.

21       In the year I've been there, nobody has done

22 QST, but this is something that I'd recommend, and

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1 then I recommend that we have a way of checking it.

2 So it's a really good point.

3       In terms of -- yes. I answered both

4 questions.

5       DR. McDERMOTT: Laurie?

6       MS. BURKE: Right. I would like to take

7 this discussion one step further, because it is

8 really standard now that every measurement

9 instrument is accompanied by a user manual and a

10 training module for the reporter. That is part of

11 what is required for review at -- well, required.

12       I can talk about required now because I'm

13 not at FDA. Okay. But the user manual and the

14 accompanying training module will have an impact on

15 the measurement properties of any assessment tool.

16 So in order to evaluate the measurement properties

17 of an assessment tool, there has to be those

18 accompanying modules, and they have to be

19 standardized.

20       So it's not a recommendation. This isn't

21 like something that's a good idea. It really is a

22 best practice bordering on if you don't do it, you

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1 really aren't even implementing your assessment

2 tool in a way that is scientifically valid and

3 reliable.

4       So I'm having a really hard time in my

5 current life because I'm working with companies who

6 are developing clinician-reported outcome measures,

7 taking tools and assessing patients. And we create

8 a training module for the clinician, and they think

9 I'm being unreasonable, and they don't want to sit

10 through it. They all know how to do this thing.

11 This is part of what they got trained in medical

12 school, everybody knows how to do it. But we know

13 that they all do it differently, and in a clinical

14 trial, this is going to be a problem.

15       So I think this paper really needs to be

16 much more strong than what we've actually been

17 discussing here, and say that if you don't do it,

18 it's contrary to standard recommendations. The PRO

19 guidance talks about this. The qualification

20 guidance at FDA talks about this. All the best

21 practice papers put out by ISCOR on outcome

22 assessment and clinical trials, all state this. So

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1 it's not just a good idea.  
2 DR. HEWITT: Let me clarify that. I think  
3 the difference we should make is the difference  
4 between being trained on these things the first  
5 time, which is what obviously -- versus the ongoing  
6 continuing training over time. I think that's the  
7 distinction I was trying to make in response to  
8 that question.  
9 MS. BURKE: Well, I think that that should  
10 be in the training manual. Whether you have found  
11 that you need to do this only the first time at  
12 baseline or whether this is something that needs to  
13 be re-administered throughout over time, how long  
14 does it stick in terms of the training.  
15 DR. McDERMOTT: I'm going to take two more  
16 questions, and then we're going to go to lunch.  
17 And then we will come back, so that those questions  
18 that don't get picked up during these next two,  
19 which his going to be Bob and Nat -- and, Ajay, I  
20 saw your hand up, but you were the third. But  
21 definitely when we come back, we'll have an  
22 opportunity.

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1 Probably the best thing about question-and-  
2 answer sessions is when people leave with more  
3 questions, because that means that there's a lot of  
4 interest and enthusiasm. So Bob, and then we'll go  
5 to Nat.  
6 BOB: David, I'm all for training, as you  
7 know. I think, first of all, there are two huge  
8 problems. And this has been alluded to, but I'll  
9 say it explicitly. One is it's not evidence-based.  
10 I take Laurie's point that it's important, but we  
11 don't have any evidence of any kind of improvement  
12 associated with training, that I know.  
13 Secondly, every SRO does it differently.  
14 What you guys do at inVentive is not what they do  
15 at Premier, is not what they do at INC, is not what  
16 they do at Quintiles. So we have this incredible  
17 variability of what exactly we mean by training,  
18 and however it is being done, no one has ever  
19 systematically studied the impact of it.  
20 I don't have an answer to that but I think  
21 it's a huge set of issues.  
22 DR. HEWITT: I think that's an interesting

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1 point, because I've worked with -- when I was at  
2 Merck and J&J, I worked almost exclusively with  
3 CROs, and so I've worked on a lot of studies. I  
4 don't remember there being that much variability in  
5 the pain world, but you may be right. And I think  
6 it's worth looking into further.  
7 In terms of Parkinson's disease, it's pretty  
8 uniform. Whether you work on a Parkinson's disease  
9 study done by -- you all have to have training  
10 videos, and you have to show them what a  
11 Parkinson's disease patient looks like in the  
12 on-state and the off-state.  
13 Part of that training is it goes beyond what  
14 you do in pain. It really goes on to can I  
15 identify a patient who is in the on-state or the  
16 off-state. And you'd need to talk to the patient  
17 about whether their dyskinesias are troublesome or  
18 not troublesome. And so you need to talk to them.  
19 So there is this training. There are two  
20 different types of training. One is the training  
21 that looks at intra-rater reliability or whether  
22 all sites are doing it the same way and when there

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1 is variability there, and do you follow that and  
2 test that. And you do do that. There are people  
3 who spend a lot of time looking at intra-rater  
4 reliability to make sure that there isn't  
5 discordance over time. I think that's one thing.  
6 But the other thing is just to make sure  
7 people know how to do the study in the first place,  
8 they need to be trained. So if you don't train  
9 somebody for a study, they're untrained. It's not  
10 going to go well.  
11 I'm not sure if you need to do -- I mean,  
12 there are some things that are kind of so obvious,  
13 I'm not sure they need to be trained.  
14 BOB: I wasn't clear. I really meant  
15 training about our efficacy assessments, our  
16 zero-to-10 scales, and the other secondary  
17 endpoints in a clinical trial. And I think that  
18 varies all over the map from no training at  
19 all -- the patient is given BPI --  
20 DR. HEWITT: Right. I see what you're  
21 saying.  
22 BOB: -- to what Nat and Neil and we have

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1 begun to do, which is to look at the kinds of  
2 things that the FDA would require.  
3 DR. HEWITT: No. I mean, I think that's a  
4 good point. I think that's a good point.  
5 BOB: And it's huge variability, and it  
6 isn't evidence-based. I think at this stage,  
7 variability is good because one could at least  
8 imagine a study where Nat's training program is  
9 compared to our training program is compared to  
10 Neil's training program, and that would be really  
11 cool, and which of the three training programs have  
12 the best performance.  
13 DR. HEWITT: I see what you're saying, yes.  
14 I agree.  
15 BOB: None of that is being done. Right now  
16 it's all totally ad hoc.  
17 DR. McDERMOTT: Nat. And then we're going  
18 to have lunch. But before we're going to go to  
19 lunch -- and don't run out the door -- I'm going to  
20 ask Valorie if she's got any comments. So Nat,  
21 then Valorie, then lunch.  
22 Nat?

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1 DR. KATZ: I wanted to follow on Laurie  
2 Burke's comment in that I completely agree with her  
3 that anything that you want -- any instrument that  
4 you want the site to utilize to assess a patient,  
5 if it's important to assess that aspect of the  
6 patient's state, it's important to train the people  
7 doing it how to do it.  
8 So I agree with that. But I wanted to point  
9 out that there is a certain trap there that is  
10 worth recognizing that I've run into once or twice,  
11 where I've run into people who say, "Yeah, we want  
12 to do a training" -- it's fine to use a training  
13 program, but if you're going to do that, you have  
14 to revalidate the entire instrument from the very  
15 beginning because the training program might  
16 somehow -- if you were going to put an 8, maybe you  
17 would have put a 7. It changes the performance  
18 characteristics of the instrument sufficiently that  
19 we can't really sign off on the use of that  
20 instrument.  
21 If we wanted to stifle improvement in  
22 quality, that's the best way to do it, I think,

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1 would be to require that instruments have to be  
2 revalidated from the get-go.  
3 So I wonder what other people think about  
4 that and whether that's worth addressing in this  
5 paper.  
6 DR. McDERMOTT: Well, first, back to these  
7 gentlemen. Do either one of you want to comment on  
8 that observation?  
9 DR. HEWITT: I guess one of the comments I'd  
10 make is this. We've had a lot of clinical trials  
11 over the years, and we've had a lot of drugs to get  
12 approved by the FDA. So I think one of the things  
13 that I think this kind of raises, to my mind, is  
14 what we're really trying to do is do it better.  
15 I think the question we always have to ask  
16 ourselves is are there any drugs that have not  
17 gotten approved because there was not adequate  
18 training on an instrument. I think that's a  
19 question we can ask ourselves. Do we know that  
20 that -- have there been drugs that have not been  
21 approved, and then, conversely, are there drugs  
22 that have been approved that shouldn't have been

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1 approved.  
2 BOB: David, I have to interrupt. What do  
3 you think happened with topiramate for DPN? You  
4 were involved in that. Your trial was positive,  
5 three other trials in Europe, as I recall, were  
6 negative.  
7 DR. HEWITT: Worldwide.  
8 BOB: Do you think if those European trial  
9 investigators had been trained, topiramate would  
10 now be available?  
11 DR. HEWITT: I think that's a good point and  
12 I think -- yes, I mean, I guess just prove me  
13 wrong.  
14 BOB: You couldn't have been more central.  
15 (Laughter.)  
16 DR. HEWITT: That is a good point, but -- I  
17 guess that is true that you can -- that that has  
18 happened. But the flipside is --  
19 BOB: Three European trials killed your  
20 drug.  
21 DR. HEWITT: I know, I know. That is true.  
22 That is true. But the thing is that even with

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1 that, I will say this, that all those studies, it  
2 could be -- I mean, to be honest, it could be that  
3 topiramate really isn't that good for neuropathic  
4 pain, and that our study was the outlier, and that  
5 the other three studies were better.  
6 From an evidence-based point of view, I have  
7 to be -- obviously, I wanted my study to be the one  
8 that's positive, but the way the world goes is it's  
9 not necessarily the greatest -- I mean, sorry for  
10 those people who do topiramate. But part of the  
11 problem with that study -- we could go on a lot  
12 about it -- had to do with dropouts due to taste  
13 differences and to the fact of CNS, what they call  
14 Topamax.  
15 So there is no question that the drug -- who  
16 came up with it? There was a great line that  
17 somebody had today about effectiveness, that it may  
18 not be -- it might be an efficacious drug, but it  
19 may not be an effective drug.  
20 In that regard, it probably isn't a bad  
21 thing that Topamax isn't approved. It's getting  
22 used for it, as well, but good point.

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1 DR. McDERMOTT: I don't think we need to get  
2 into the details of the studies here.  
3 Laurie, let me just have the last  
4 word -- you need to respond. Okay.  
5 MS. BURKE: I need to respond to Nat. I  
6 think that there is revalidation and then there's  
7 revalidation. And so there may be some confusion  
8 about this. If you implement a training program  
9 that you think really tightens up your measure,  
10 then, of course, you would want to have additional  
11 test/retest reliability on that measure so that you  
12 have a better idea of how you interpret your  
13 clinical trial results. You would want to have  
14 that. You also would want to do exploratory work  
15 during your clinical trial to correlate with other  
16 related measures and do some construct validity.  
17 I completely would argue with anybody who  
18 says that you have to start from scratch and  
19 revalidate from the get-go and go through your  
20 whole process. But there are some -- it is going  
21 to modify the measurement properties of the  
22 instrument. And, therefore, in order to know what

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1 the new measurement properties are, like  
2 test/retest reliability, you would have to  
3 re-measure them.  
4 DR. McDERMOTT: Let's hold it there. You  
5 want to go back and forth, and that's great, but we  
6 do need to go to lunch.  
7 So, Valorie, any comments that you want to  
8 make to people?  
9 MS. THOMPSON: If you want to order a taxi,  
10 we will have a notice at your desk when you come  
11 back after lunch -- [inaudible - off microphone].  
12 DR. McDERMOTT: Valorie was not in here when  
13 I thanked her and Andrea earlier. So I want to,  
14 again, thank you for all the efforts that you and  
15 Andrea have done to make this meeting useful.  
16 (Applause.)  
17 DR. McDERMOTT: So we're going to be going  
18 to lunch, which is back where we had lunch  
19 yesterday. Come back here at -- let's make it  
20 1:30, to give you a little bit of extra time, and  
21 we'll then have the panel discussion.  
22 (Whereupon, a luncheon recess was taken.)

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1 AFTERNOON SESSION  
2 MODERATOR: Okay, please take your seats so  
3 we can get started again. And for those of you  
4 that are sort of wandering around, come in or you  
5 won't be able to get your certification. It would  
6 be required. Only your level 1 certification.  
7 Remember, you have to go up to -- it's provisional  
8 until you do the paper.  
9 Okay. So we want to pick up with the panel,  
10 but I realize that as I was sort of rushing you to  
11 lunch, because I could see hunger in your eyes,  
12 that I may have short-circuited a bit the  
13 conversation that was going on with Laurie Burke  
14 and with Nat Katz.  
15 So Laurie, I just want to give you the  
16 chance to -- in case there was something you wanted  
17 to finish off that I didn't give you the chance to.  
18 And then if Nat has any comment on that, and then  
19 we'll go back to the panel.  
20 MS. BURKE: Sure. I think I had the  
21 opportunity to say most of what I wanted to say,  
22 but I think that there may have been some question

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1 mark in some people's minds about exactly what I  
2 did say.  
3 The point is that Nat's question was do you  
4 have to revalidate the instrument once you have  
5 changed it in terms of attaching a training program  
6 and a user manual to it. The answer is --  
7 (Laughter.)  
8 MALE SPEAKER: The FDA talks.  
9 MS. BURKE: -- yes, but not in the way you  
10 might think. The answer is you would want to know  
11 what the new measurement properties of that  
12 instrument are. You would want to know, in  
13 particular, what the test/retest reliability of  
14 that measure is, and what the variability, then,  
15 estimates are to help you in the interpretation  
16 with clinical trial results.  
17 If nothing else, at a very minimum, you  
18 should do this testing at baseline in the week  
19 before randomization in your clinical trial. So  
20 therefore, you have an estimate of variability in  
21 your patient population. You'll be able to use  
22 that in the interpretation of your treatment

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1 effect.  
2 At the end of the day it will give everybody  
3 more confidence in the particularly small-ish  
4 differences between treatment groups, and it can be  
5 a real advantage. And also, the other types of  
6 validation like construct validity testing can be  
7 done as exploratory analyses in the phase 3 trial.  
8 Of course, optimally, you would want to do  
9 this in a stand-alone study, but few people want to  
10 fund that, and it's not necessary.  
11 MODERATOR: Nat, do you want to amend at all  
12 your comment?  
13 DR. KATZ: No, we agreed on that, so we're  
14 friends again now.  
15 (Laughter.)  
16 MODERATOR: Okay. Well you know when Laurie  
17 Burke wants to talk, everybody stops.  
18 MALE SPEAKER: We're all going to listen.  
19 MODERATOR: So let's go back to the panel.  
20 Just before lunch, we had had David Hewitt and John  
21 Markman sort of give perspectives again from  
22 academic and from the CRO industry. But I think

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1 what we heard was these are coming closer and  
2 closer together. So what I thought I would do is  
3 start by having Ian Gilron and John Farrar, any  
4 comments they have about either what they heard in  
5 those presentations in particular, also to chance  
6 if they want to drift off other places we might let  
7 them. But try and focus, at least initially, on  
8 what you heard from David and from John.  
9 DR. GILRON: Okay. I was just telling John  
10 earlier I usually give unsolicited opinions, so  
11 I've actually been asked for it, so it's kind of  
12 exciting.  
13 MODERATOR: I'm asking for an unsolicited  
14 opinion.  
15 DR. GILRON: Yes, okay. Well I'm just going  
16 to start just with some general comments talking  
17 about the dichotomy that Nat started talking about  
18 and John discussed further. And I think of it, as  
19 well, from the perspective of, as John described,  
20 someone who does trials more from a proof of  
21 concept, academic perspective.  
22 I think of the onus on the scientific part

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1 of things really to be exploratory and to provide  
2 appropriate guidance towards coming up with new  
3 treatments, whereas the regulatory approach is  
4 really one of public health responsibility and  
5 looking at cost effectiveness, meaning not to  
6 approve treatments that are only marginally  
7 effective and possibly very expensive, but also a  
8 big emphasis on safety.  
9 So I was wondering that -- I don't know if  
10 we have spent enough time talking about quality  
11 with respect to safety assessment in reporting, and  
12 I know ACTION has very involved in sort of waving  
13 the flag of improving safety reporting. So I was  
14 just wondering whether we need to, in the paper,  
15 make more noise about quality with respect to that  
16 part of things.  
17 MODERATOR: John?  
18 JOHN: So, I was taken in the presentation  
19 by John Markman of the comment of the obviously  
20 very talented coordinators that he has, relative to  
21 the conversation or multiple conversations that  
22 she'd had, obviously recently, relative to blood

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1 pressures of 141 over 82, versus 139 over 79.  
 2 It brought to mind something that I think  
 3 was brought up a little bit yesterday, which is  
 4 that we need to be very careful as we move forward,  
 5 to meld a couple of ideas that IMMPACT and ACTTION  
 6 have been working on, which is -- one of them is  
 7 obviously to make trials responsible and conducted  
 8 in a way that makes sense and that provides valid  
 9 results.  
 10 But on the other hand, not to impose on  
 11 those trials a burden of control, regulatory  
 12 control, that doesn't actually benefit the trial  
 13 and adds additional time and effort, frustration,  
 14 to the process.  
 15 I'm reminded that many of our young  
 16 investigators that come to us, when we ask what  
 17 they want to measure, they basically say  
 18 "everything." They want to know how the patient's  
 19 feeling. They want to know a host of different  
 20 things, and we need to remind them that we have  
 21 only so many things that we can ask in any one  
 22 trial. And I think that applies through a number

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1 of different components of what we've talked about  
 2 today.  
 3 All of the things that we've talked about in  
 4 terms of looking for potential signs and markers  
 5 for different kinds of problems -- careful  
 6 monitoring, visiting maybe after the third patient,  
 7 doing central monitoring on ongoing basis -- are  
 8 all important. But we do need to take them with  
 9 just a few grains of salt and ask ourselves the  
 10 harder question, which is, are we going to gain  
 11 benefit from what we're actually doing?  
 12 Is the trial going to be better at its  
 13 ability to differentiate a real effect between a  
 14 treatment, either two treatments or a treatment and  
 15 a placebo, assuming that that treatment actually  
 16 exists?  
 17 So I really feel very strongly that we need  
 18 to be cognizant of the cost benefit value of the  
 19 kinds of things that we might impose to improve  
 20 both the ability to detect efficacy and safety. I  
 21 would just push that as a component of how we go  
 22 about implementing all of the various steps,

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1 realizing that nothing is ever perfect and that we  
 2 are always going to have to make some compromise.  
 3 We just need to decide where those  
 4 compromises are and be efficient and comprehensive  
 5 and careful to try and make the studies answer the  
 6 right question and provide us with the data that we  
 7 need.  
 8 MODERATOR: John, did you want to comment on  
 9 that? I saw you look at me.  
 10 JOHN: Well I just thought -- I think John's  
 11 point about a little bit of flexibility is  
 12 important. I think that's some of what you're  
 13 suggesting.  
 14 The other question I've had, and I've been  
 15 really trying to get my head around is, at some  
 16 level when you're doing one of these smaller  
 17 trials, too, you're thinking about the next trial,  
 18 because your hypothesis comes out of the  
 19 observations of doing the trial you're currently  
 20 doing. And I think that -- and I thought of this  
 21 kind of vis-à-vis the issue of blinding a site to  
 22 all, and blinding every piece to it.

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1 I mean you're really -- how much are you  
 2 really giving up a serendipitous observation, which  
 3 will be the germ of your next hypothesis, by  
 4 disengaging everyone at the site from their little  
 5 local observations?  
 6 It's sort of a little bit of tangential  
 7 point, but it also kind of plays on this notion of  
 8 how much flexibility and, again, the  
 9 differentiation between a public health consequence  
 10 of a trial versus a trial which is exploratory.  
 11 MALE SPEAKER: But I think your point is  
 12 exactly the right one, which is that the question  
 13 is what's the goal of the trial? If the goal of  
 14 the trial is to approve a drug that's going to be  
 15 used in millions of people, then you damn well  
 16 better be sure it's safe.  
 17 If the goal is to know whether that drug  
 18 works at all so that you might use it as a model  
 19 for another drug that you might develop or you do  
 20 formal testing, or if it's a pilot study, then the  
 21 requirements are somewhat less.  
 22 So keeping in mind what the goal of the

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1 trial is, and you presented three different  
 2 potential goals I -- one might argue that there are  
 3 four or five. But if we understand what the  
 4 question is that we're asking, we're much better at  
 5 figuring out how to answer it.  
 6 MODERATOR: An important point that you're  
 7 sort of implying, and I was thinking about this  
 8 when I was sitting there was that we, in some  
 9 sense, have been talking about and thinking about  
 10 these trials as if they are, once you do it, you  
 11 design it, you run it, you're done. But what we  
 12 learn from those trials potentially influences the  
 13 things we can benefit.  
 14 So when Bernard talked about the placebo  
 15 issues and when we've heard issues about fraud from  
 16 Eric Devine, as we learn those things, that feeds  
 17 back to -- so that we improve the science. So take  
 18 the information you're gaining, and in addition to  
 19 whatever you find out for that one study, that  
 20 information then becomes --  
 21 So if we talk about what can you anticipate  
 22 and try to prevent in the next study, you'll use

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1 this as an opportunity to learn something and not  
 2 about the study, study design going forward; and  
 3 not just, okay, we've now done our study, we're  
 4 done with that, and move off to our next study and  
 5 start essentially as if nothing was really  
 6 acquired.  
 7 I don't mean nothing, because obviously the  
 8 outcomes people will be aware of, but to realize  
 9 other things that came up along the way, problems,  
 10 issues, difficulties, things you need to control,  
 11 some of which may be controllable, some of which  
 12 you may have to understand that are not  
 13 controllable.  
 14 But I think we really need to think about  
 15 programmatic research, where we used to talk about  
 16 when we were promoting professors, it wasn't that  
 17 they had one article or one well-known paper, but  
 18 what's their program of research. And maybe we  
 19 should be thinking more broadly about what's the  
 20 program of a research related to clinical trials.  
 21 And maybe that goes back to the discussion we had,  
 22 which I think went into much more detail on.

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1 But if you're educating people about being  
 2 qualified to be clinical trial investigators, what  
 3 are we learning that we could then feedback to  
 4 those people?  
 5 So unless any of you want to comment on each  
 6 other's -- David?  
 7 DR. HEWITT: I just want to make a comment  
 8 about what you said --  
 9 MODERATOR: Sure.  
 10 MALE SPEAKER: -- because I think that's  
 11 really key is -- and I was kind of getting to this  
 12 with the Six Sigma comment I made yesterday, is  
 13 that this is really an iterative process, and it's  
 14 actually iterative during the course of the study  
 15 when you're retraining people.  
 16 But it's also iterative in terms of taking  
 17 the lessons you've learned and making sure that you  
 18 disseminate them. And so it doesn't matter if it's  
 19 a bid defense for me or a clinical trial, I'm  
 20 really kind of a stickler for having a lessons  
 21 learned meeting after whatever's happened, as soon  
 22 as possible. And I think in that way, you can

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1 disseminate that information across an organization  
 2 or a group.  
 3 But a lot of it has to do with how groups  
 4 and organizations work and how they get better at  
 5 what they do. And I think you're right. It's if  
 6 you reinvent the wheel each time for -- you  
 7 shouldn't. You should have methodologies, and you  
 8 should be realizing this is where you're going to  
 9 have the potential to really screw up, so  
 10 don't -- there's no reason to screw up twice.  
 11 MODERATOR: Well, I think this gives you a  
 12 sense of why Bob and I and the rest of us who've  
 13 been involved going back to the early days of  
 14 IMMPACT and to ACTION, was to say not only do we  
 15 want to have meetings and discuss things and get  
 16 things around, but how do we get that information  
 17 out there so that -- and we'll be talking very  
 18 shortly about a manuscript. It's because we want  
 19 to make sure that the information gets there, so  
 20 that whatever wisdom we've picked up along the way  
 21 from the presentations, from the discussions, gets  
 22 disseminated, and then hopefully better trials will



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1 come along and people will learn from this  
2 experience.  
3 So okay, let's open it up for the audience.  
4 Any questions for our panelists? Yes, Rob?  
5 ROB: So maybe this has been emphasized  
6 enough, but certainly one size won't fit all. I  
7 mean, in the drug development process at  
8 Wyeth -- no longer Wyeth, now called Pfizer -- we  
9 had this concept of learn and confirm, and whether  
10 those terms mean anything.  
11 Learn, from my perspective, was explore.  
12 You're early in the stage of drug development. You  
13 want to work with small numbers of sites, very  
14 scientifically based questions. Confirm, not to  
15 label it as a regulatory requirement, but that  
16 really was the burden of a drug development program  
17 to look at all the safety issues and to confirm  
18 what you've learned in earlier trials.  
19 The burden and the responsibilities of each  
20 of those two phases takes on a very different  
21 profile. You might have a Web-based medical  
22 investigator meeting once you've established sites

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1 and you've established the product, but early on  
2 you want to have face-to-face. You want to have  
3 very personal relationships with your investigators  
4 and your study staff.  
5 Again, as we start to think about solutions,  
6 there may be some that run across both a learn and  
7 a confirm phase of drug development or even a  
8 post-approval. We haven't even talked about how  
9 you control trials after they've been approved.  
10 But I think we need to think about -- there  
11 may be common threads, but there may be distinct  
12 differences.  
13 MODERATOR: Anybody want to comment?  
14 Everybody nodding agreement.  
15 MALE SPEAKER: There is one comment I want I  
16 want to pick on, which I think one first made,  
17 which was the difference between academic studies  
18 and pharmaceutical studies and about the drug.  
19 The fact is, all the drugs that are out  
20 there, for the most part, that are done within  
21 academic centers are drugs that have been approved  
22 or -- I think for the most part. I think it's very

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1 hard to get a drug before it's been approved and do  
2 a study on it. You can, but I think it's a big  
3 challenge to do that.  
4 So in a way, once you get through all that  
5 safety data, right, and the efficacy data with the  
6 original approval and the regulatory process,  
7 things ought to -- to John's point, things should  
8 be a little bit easier. There should be  
9 less -- not less rigor, but maybe less neurosis  
10 around the compulsion to cross every T and dot  
11 every I, because the drug's already been approved,  
12 and we know that it's safe, from a safety point of  
13 view.  
14 Now from a quality point of view and  
15 demonstrating that your efficacy really is your  
16 efficacy, that goes back to I think the point  
17 you're making. But I think that's important.  
18 MODERATOR: Let me just add one thing, and  
19 I'll get to you. We keep talking about drug  
20 studies, and I'd be interested in knowing whether  
21 there's anything that we've talked about, if we  
22 took the word drug out and put complementary

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1 medicine or put rehabilitation, other than unique  
2 features that are specific to a particular drug's  
3 side effects or the worry about other medication  
4 they're taking, is there anything different about  
5 what we've been describing for what would go into a  
6 well-done, well-designed, carefully-controlled,  
7 high-quality clinical trial, anything that isn't  
8 necessarily a drug?  
9 MODERATOR: John? You've done some of those  
10 studies, complementary medicine.  
11 JOHN: Right. I think that exactly the same  
12 principles apply. Procedural studies, however, add  
13 an additional complexity. If you have trouble  
14 blinding the patients to a particular procedure, if  
15 you have trouble figuring out how to standardize  
16 the application of acupuncture in your trial, if  
17 you are trying to compare surgical outcomes and  
18 you're using five differentiation surgeons, you  
19 know that you're going to have slightly different  
20 techniques by those various surgeons.  
21 So I think there may be some value, and I'm  
22 not sure we have time today, but some value of at

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1 least thinking whether there are some additional  
2 issues that we might want to consider in those  
3 trials.  
4 When talked about blinding, we all agreed  
5 that blinding in a pharmaceutical trial and making  
6 the pills look the same, maybe even -- I mean there  
7 was talk, back in the day, in the testing of  
8 opioids, of trying to use a benzodiazepine as a  
9 placebo, or putting a little benzodiazepine as a  
10 comparator, because in fact you wanted to make the  
11 patients a little sleepy to hide the side effects.  
12 But in situations where it's really not  
13 ethical to do that, and certainly surgical and many  
14 procedural things fall into that category, I think  
15 there may be some other things to consider and how  
16 to deal with those.  
17 MODERATOR: Blinding the control groups may  
18 be more challenging in a surgical study or a  
19 physical therapy study or an acupuncture study, but  
20 as far as the need to pay attention to the kinds of  
21 things we're talking about --  
22 JOHN: I agree.

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1 MODERATOR: -- those would be -- let's  
2 say -- and the only reason I'm pushing that is  
3 that, to the extent possible, I try to make the  
4 papers that we write be as general and then  
5 refer -- when there are specific callouts to refer  
6 to those. So I would hope that we'll be able to at  
7 least talk about the importance of these in  
8 clinical trials and not in just in drug clinical  
9 trials.  
10 I'm sorry. That's all I have.  
11 MALE SPEAKER: So I would say I disagree.  
12 MODERATOR: Okay.  
13 MALE SPEAKER: I think that a big chunk of  
14 what we do, like biggest part of it is safety.  
15 It's safety, safety, safety. And the safety issues  
16 associated with a clinical trial I think are going  
17 to be different if you're looking at yoga, or  
18 bicycling, or tango. I'm giving you examples of  
19 things from Parkinson's disease world that have  
20 shown to be effective.  
21 I think it's much different. I think it's a  
22 good thing. Now some of the things there are going

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1 to be overlap. Does every tango dancer instructor  
2 need to teach the person how to tango exactly the  
3 same way for the results of the trial to be  
4 important? Are you comparing hip hop versus tango?  
5 Will it make a difference?  
6 But I think the point is, is that I think  
7 that the questions are different and the  
8 methodologies are different. In terms of writer  
9 training and quality and consistency across  
10 centers, yeah. I mean, I think it's -- you know,  
11 you want to try to do that.  
12 Hopefully everybody does -- like in  
13 Rochester, they had a big tai chi effort, didn't  
14 they, way back when? You want to make sure  
15 everybody does tai chi the same way.  
16 What interests me, and I've mentioned this  
17 before -- and in emails as well, which maybe I  
18 shouldn't have -- combining these drug studies with  
19 alternative therapies like yoga or physical therapy  
20 maneuvers, because it does interest me  
21 whether -- because we don't control for that.  
22 One of the things we haven't talked about

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1 for a lot of this is we're not controlling for  
2 activity. And we say don't change your activity  
3 level, but I would say everybody who gets into a  
4 drug study should probably -- particularly if they  
5 have a severe pain, you may want to add some  
6 physical therapy modality and just make that  
7 constant through the study, so everybody's getting  
8 that, so you control for that.  
9 I think it's really problematic when you're  
10 just studying a drug, and then you just leave it up  
11 to whomever, whatever they want to do, in terms of  
12 what -- if I were in a study, all of sudden I'd be  
13 like, "Oh, I want to get healthy," so I should  
14 start doing healthy things. I'm going to change  
15 the way I eat. I'm going to go to sleep at a  
16 better time.  
17 There are all these other things I might do  
18 because I'm now taking care of myself, because I've  
19 just enrolled in a Farrar study, and I really want  
20 to make sure that I do a good job. So I start  
21 doing these things that potentially would help me  
22 get better because I think that's the goal. But

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1 the goal isn't to get better. The goal is to make  
2 a controlled trial and keep things as much as  
3 possible the same.  
4 MODERATOR: But wait a second. Let me push  
5 you a little bit on that. So the issue of blinding  
6 can be more challenging. The issue of alternative  
7 comparative treatments can be more challenging, but  
8 we still think about this.  
9 But the safety issue, did I hear you say  
10 that you don't think safety is a concern for  
11 rehabilitation studies, or for physical therapy, or  
12 for surgery, or for acupuncture?  
13 MALE SPEAKER: I think they're  
14 different -- I think the regulatory issues are much  
15 different. The safety -- the amount of hoops we  
16 jump through in the pharmaceutical industry to  
17 follow the safety of a drug is much more  
18 significant.  
19 You won't get lab values, I don't think, for  
20 most rehabilitative processes. You won't get chest  
21 X-rays or -- you know, there's a lot of really  
22 invasive stuff we do. I don't know why you would

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1 get an ECG on somebody if you're looking for  
2 long-QT syndrome and things like that.  
3 MODERATOR: Is Ann Costello here  
4 still -- can't see her -- who works with devices?  
5 I'd be interested in her perspective of whether  
6 safety is an issue for devices within the --  
7 MALE SPEAKER: Well, they are. I mean  
8 devices are a little different though.  
9 MODERATOR: Okay. But we did some studies  
10 early on for self-disclosure in a rehabilitation  
11 program, and one of our people fell off the  
12 exercycle and twisted his ankle. Is that a safety  
13 issue I should have been concerned about? Was it  
14 reported then?  
15 MALE SPEAKER: No, absolutely. I'm not  
16 saying that there aren't any safety issues, but the  
17 way we approach safety and we assess safety is  
18 different in a drug trial than it would be in one  
19 of these other trials.  
20 MODERATOR: Is the rigor different?  
21 MALE SPEAKER: Yes. I mean, you're doing  
22 much more surveillance of safety issues.

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1 MODERATOR: I disagree, but okay, that's  
2 another discussion.  
3 MALE SPEAKER: Unless you're getting chest  
4 X-rays and CT scans and lab work every month or  
5 something, looking for particular things -- maybe  
6 I'm misunderstanding what you're saying. I might  
7 be being too literal. I don't know.  
8 MODERATOR: Okay. Well, I'm going to close  
9 on this one and take my prerogative and turn it  
10 off.  
11 (Laughter.)  
12 MODERATOR: We're doing a geriatric study,  
13 and we're putting people into some type of exercise  
14 program, am I going to be concerned about the  
15 potential safety issues with whether people should  
16 be doing tai chi? If they have limitations in  
17 their ability to walk, do you have to modify the  
18 tai chi? Do I have to record that? So I obviously  
19 need to pay attention to that.  
20 MALE SPEAKER: Well, I'm not saying you  
21 don't pay attention; I'm just saying that the  
22 safety issues are different. You still need to

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1 follow safety. It's just that they're different.  
2 MALE SPEAKER: So I just have to interrupt  
3 and say that we focused this meeting on quality of  
4 efficacy outcomes, and we obviously haven't had any  
5 presentations, haven't had any discussion about  
6 quality of safety outcomes. And so that's really  
7 off the table.  
8 Though Ian, thank you for an idea for  
9 another IMMPACT meeting, which would be just like  
10 this one, but addressing safety outcomes and trying  
11 to resolve the difference of opinion between David  
12 and Dennis.  
13 MODERATOR: Okay. And I think, Michael  
14 Rowbotham, I think I saw your hand.  
15 DR. ROWBOTHAM: This may seem a little off  
16 topic now, but I think it's a good segue to the  
17 next section. I'm going to give a talk, an  
18 informal talk, at the end of the month, and I've  
19 decided to entitle it about the -- what I learned  
20 here, and it's the four "F" words, which are fraud,  
21 fabrication, failure, and futility.  
22 So as we go through the discussion, I'd

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1 really like to get an idea, from the panel and also  
2 everybody, really how big an issue -- especially  
3 when you start putting them all together, are these  
4 different things we've talked about: people not  
5 taking their meds on time, people lying to get into  
6 studies, study sites fabricating subjects or  
7 fraudulently double enrolling them, and all these  
8 other things.  
9 When we put it all together, does that mean  
10 that many of our trials are doomed to failure or  
11 futility because there's so much data and so many  
12 subjects you just have to exclude as not being  
13 usable for data analysis?  
14 MODERATOR: I'm tempted, but I'm not going  
15 to do this. You're going to give this talk in a  
16 month, we'd be more than happy to have you  
17 practice.  
18 (Laughter.)  
19 MODERATOR: Obviously, you're waiting to get  
20 more data to do it. Does anybody want to comment  
21 on Mike's comment?  
22 MALE SPEAKER: I would, because this is

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1 something I think about a lot. And I was thinking  
2 about this across -- I've done a lot of clinical  
3 trials in industry over the years, and I would say  
4 that on average, I see about one or two sites per  
5 study where there are real concerns. And these are  
6 large studies; they're large phase 3 studies.  
7 So I do think there is an issue there. I  
8 don't think it's an overwhelming issue, but I do  
9 think it's an issue. And what I see at those sites  
10 are not necessarily fraud; sometimes it's  
11 absurdity, like people who keep their medical  
12 records in the basement of their house. You're  
13 supposed to hold on to all of this stuff for like  
14 whatever the rules are until this drug's approved  
15 or two years after or whatever.  
16 The point is, I've seen a lot of -- I've  
17 seen not a lot of -- I've seen that happen. I  
18 haven't seen -- I don't always know when the data's  
19 being fabricated. That's the problem.  
20 There was a study in India where we used  
21 Topamax as one of our drugs for migraine, which it  
22 is approved for migraine, and nobody responded.

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1 Nobody responded at placebo; nobody responded to  
2 Topamax. And it was like a profound thing.  
3 So when nobody responds to a drug that you know  
4 that it works -- and they had like 12, 14 people,  
5 is that fraud? I don't even know. I still can't  
6 figure that out. So I don't think these are easy  
7 questions to answer.  
8 MODERATOR: Lee?  
9 DR. SIMON: So I think that the problem is  
10 pervasive, but it is not ubiquitous. So I would  
11 bet you that every trial, no matter who's running  
12 it, where it's being run, will have some problem.  
13 It probably isn't consistently fraud, but I do have  
14 to just share one unbelievable story with everybody  
15 in the room.  
16 So there was a new formulation of  
17 methotrexate that was being developed by a guy who  
18 spent 22 years in Louisiana at the university doing  
19 this work, extraordinary idea, physical chemical  
20 property difference, and he got his buddy in Peru  
21 to actually do a clinical study.  
22 Adequate and well-controlled by design.

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1 They did this trial in Peru, and they had -- we use  
2 in rheumatoid arthritis something called the ACR20  
3 as the primary outcome. And typically, you get 60,  
4 40, and 20. Sixty percent of the patients will  
5 have a 20 percent ACR20 response with a drug that  
6 works. Ninety-eight percent of the patients had an  
7 ACR20.  
8 The way this trial was designed, the patient  
9 came in, got picked up, they actually included them  
10 in the trial, they got the drug, and they  
11 disappeared for 12 weeks. And then they came back  
12 at the 12-week mark to get analyzed.  
13 Basically, I did due diligence on this  
14 product for a company. Despite what I told them,  
15 the company said, "We're going to buy this." They  
16 bought the product. They actually started to study  
17 it, and it was totally non-bioavailable. You would  
18 take the drug orally, and there was no drug in the  
19 body, and yet they had a 98 percent ACR20 response.  
20 I don't actually happen to believe that it's  
21 fraud. I actually happen to believe they probably  
22 took whatever they took after they left the clinic,

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1 and they were never seen again until the 12-week  
 2 mark, and may have had a response.  
 3 If you do a trial in India, if you do a  
 4 trial in China, if you do a trial in some other  
 5 places, this is the kind of data that you get.  
 6 Every autoimmune disease trial in China, every  
 7 patient in China takes thunder god vine, off the  
 8 shelf from their, you know, naturalist physician,  
 9 despite the fact that they're told not to.  
 10 So I think that every trial has a problem,  
 11 and every system has a problem, but I don't believe  
 12 it's probably fraud. There'll always be something  
 13 you'll find. The more we can improve the quality  
 14 and the more we can improve the PI's behavior  
 15 associated with what's required, the more likely it  
 16 is that it'll get tighter and tighter and tighter.  
 17 MODERATOR: Laurie, did I see your hand up?  
 18 MS. BURKE: Right. I'm responding to what I  
 19 heard on the panel before Lee's comment, and that  
 20 is a reason -- I want to support the idea of  
 21 training and certification and some sort of  
 22 initiative that this group could lead in terms of

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1 good practice in clinical trials and teaching  
 2 clinicians and investigators and whoever wants to  
 3 be participating, because there is a big huge  
 4 movement to train people in another type of  
 5 science, and that's what sometimes is called  
 6 comparative effectiveness research. It's sometimes  
 7 called pharmacoconomics.  
 8 It's the real-world ideas of not really  
 9 looking for a treatment effect, but looking for the  
 10 effect of a conglomerate of issues in different  
 11 types of environments, in the clinical  
 12 environments. And I think that this has really  
 13 taken hold and is being talked about a lot because  
 14 of the billions of dollars of the Cory funding,  
 15 because of HTA and AMCP being convinced that they  
 16 need real-world, non-clinical trial data.  
 17 So in terms of weighing the amount of  
 18 information out there for well done, randomized,  
 19 controlled trials, with the amount of other types  
 20 of information that are now being generated because  
 21 of all this interest and money being poured into  
 22 it, I worry that there's going to become more

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1 disregard -- less regard for what we're trying to  
 2 promote here.  
 3 So the idea of getting it discussed out  
 4 there in the public, producing these materials to  
 5 explain why rigor is important, why these ideas  
 6 that we're talking about are important to think  
 7 about, are critical. So I just wanted to make that  
 8 point before the end of the day.  
 9 MODERATOR: Before I ask the panel to  
 10 respond, Mike Rowbotham, I know you've done a lot  
 11 of thinking about comparative effectiveness  
 12 research or effectiveness research. Do you have  
 13 any response to what Laurie was raising a concern  
 14 about that type of research?  
 15 DR. ROWBOTHAM: I think the hardest part is  
 16 to get it funded, because it's just not -- it's not  
 17 the new-new. It's not going to lead to a  
 18 regulatory approval or anything else. But really,  
 19 it's so important, we should be looking at  
 20 everything that we do in clinical medicine for  
 21 whether or not it's better than something that  
 22 might be less expensive or easier or safer.

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1 So I don't know how much we're going to try  
 2 and put comparative effectiveness research into  
 3 this particular document, but it really gets to the  
 4 kind of things that you do with pragmatic trials,  
 5 where some of the issues that we've talked about  
 6 actually go away because the patients are treated  
 7 within their usual practice setting, and then it's  
 8 embedded within the electronic health record.  
 9 So a couple of the biggest issues we've  
 10 talked about in terms of potential fraud or  
 11 fabrication are people exaggerating to get into a  
 12 trial that just disappears because they're already  
 13 in it, and they may not even know it, because it's  
 14 just really how their care is delivered. And  
 15 that's one way of doing comparative effectiveness  
 16 research, almost a little bit in the background, is  
 17 through pragmatic trials.  
 18 MODERATOR: Thank you. Anybody? John?  
 19 MALE SPEAKER: Laurie, I understand where  
 20 you're coming from, from the perspective of a drug  
 21 approval, but I agree completely with Mike  
 22 Rowbotham that comparative effectiveness trials are

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1 actually very important in terms of understanding  
2 how drugs end up being used in an environment and  
3 understanding the interaction of complex medication  
4 combinations and complex environmental medication  
5 interactions.  
6 But I think the point to be made is that  
7 we're talking about clinical trials, and I think  
8 we're talking predominantly about phase 3 clinical  
9 trials. So we need to keep focused on the question  
10 we're trying to answer.  
11 Clinical effectiveness research is trying to  
12 answer a different question and has a whole  
13 different set of issues. And so if we --  
14 MS. BURKE: And that's exactly my point.  
15 And I'm sorry if I wasn't clear. But yes, there's  
16 a place for both, but they're very different.  
17 MALE SPEAKER: Yes, no question.  
18 MS. BURKE: And I think that we hear people  
19 say they devalue clinical trials because they want  
20 to see the real-world pragmatic stuff. And there's  
21 not enough information about the value of clinical  
22 trials and why, in fact, you have to have a

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1 randomized, controlled trial that's not real world,  
2 that's not pragmatic, in order to be able to detect  
3 a treatment effect.  
4 MALE SPEAKER: Yes. I think there isn't a  
5 person in this room that would disagree with the  
6 concept that we need clinical trials in order to  
7 demonstrate effects. But I guess where I was going  
8 is that I think that the answers to some of the  
9 questions that we're going to try to put forward in  
10 this paper are going to be different, in different  
11 circumstances, in different situations. And how  
12 broad to make this and how restricted to make it,  
13 I'm not sure. But it seemed to me that the purpose  
14 of the meeting was really to focus on sort of large  
15 phase 3 trials where we're really trying to  
16 demonstrate efficacy.  
17 Just to sound like a broken record, I think  
18 we need to include in that the ability to do them  
19 efficiently, effectively, and validly, looking for  
20 issues, but keeping in mind something, which is  
21 that we all know somebody who has something, who  
22 has something that's very rare. And so we've heard

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1 a lot of stories about fraud and about the  
2 professional patient and a bunch of other things,  
3 and I think it behooves us to look at the relative  
4 risk of those problems to the cost of trying to  
5 detect them.  
6 I'm all in favor of a little bit of  
7 monitoring going a very long way. So I'm very much  
8 in favor of doing a lot of the things that we've  
9 just talked about over the last couple of days, but  
10 to be a little bit careful about over-emphasizing  
11 some of the stories that we hear.  
12 MODERATOR: I think we are going to narrow  
13 this down, so it's probably not going to be broad  
14 to cover both of these. It doesn't mean we won't  
15 have a sentence or a small paragraph saying that  
16 some of these principles are relevant and they've  
17 been modified, but that's not the purpose of the  
18 paper.  
19 So I don't think we're going to go -- unless  
20 Bob Dworkin tells me otherwise, I don't think we're  
21 going to focus on comparative effectiveness, but  
22 it's not to say sweep it under the rug and say it

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1 doesn't exist.  
2 MALE SPEAKER: I thought one of the most  
3 provocative comments in the last two days was  
4 Bernard's comment regarding medication adherence  
5 when you said, we think we're doing an efficacy  
6 trial, but we're really doing something between  
7 efficacy and effectiveness. I thought that was  
8 just beautifully framed.  
9 To Laurie's point, I think it might just be  
10 important to say that we think these types  
11 of -- answering the questions in these ways are  
12 different. They give us different answers for  
13 different methodologies to get there. And the  
14 reason to get this right is because we want to be  
15 sure that we're asking the question in this world,  
16 not in the comparative effectiveness world. So I  
17 thought that was what was particularly compelling  
18 about how you framed that.  
19 DR. VRIJENS: I think the answer to that in  
20 the future -- because the problem today, we try to  
21 navigate between the two. We try to be selective,  
22 to show something, to show a difference against

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1 placebo, but we still want to be somewhat  
 2 representative of real world. So we try to  
 3 navigate in between the two, and we don't answer  
 4 either of the questions.  
 5 I think the future is, at the beginning, we  
 6 will need to be even more selective and even better  
 7 train the center, and do everything even better to  
 8 show efficacy as soon as possible with a limited  
 9 number of patients.  
 10 Then we need to go to the more broader  
 11 population, and there will be other -- in the  
 12 effectiveness measurement. And we have to measure  
 13 the sources of viability because we need to  
 14 understand when it doesn't work, why it doesn't  
 15 work.  
 16 MALE SPEAKER: Exactly.  
 17 DR. VRIJENS: But we need I think to answer  
 18 the two questions a bit separately. And I don't  
 19 know if it still fits the phase 1, phase 2, phase 3  
 20 design that we are used to. But I think that's the  
 21 way to go in the future.  
 22 I was at the AU Union, and there was a

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1 president of the [indiscernible]. This is an  
 2 association of GPs of any AUs from the U.S. It was  
 3 striking. He said, "I have not a single patient  
 4 who fits a clinical trial. I don't trust clinical  
 5 trials at all."  
 6 Those messages become very dangerous because  
 7 they don't want trials at all. They don't trust  
 8 them at all anymore. And I think navigating in  
 9 between makes us -- they don't trust us anymore.  
 10 So I think we need to be more selective at the  
 11 beginning and more broad at the end, and answer  
 12 both questions.  
 13 MODERATOR: I think we're reached our first  
 14 consensus. I saw every head nodding in agreement,  
 15 so I put that into the paper.  
 16 MALE SPEAKER: I just want to follow that  
 17 just by saying that working clinically in the  
 18 operating room, we have problem rounds every Friday  
 19 morning, and we talk about the horrendomas that  
 20 happened all week. And it's really all we think  
 21 about. We don't think about there were a couple of  
 22 quiet nights

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1 We talk about fabrication and fraud, and  
 2 that's really scary. And as Lee said, I don't know  
 3 how -- it's not going to stop, but we don't know  
 4 how common of a problem it is.  
 5 So I'm just wondering like, for example,  
 6 whether we should change the title from "Ensuring"  
 7 to "Improving" and make sure that we're not giving  
 8 the impression that there's a crisis here in data  
 9 quality.  
 10 MODERATOR: Bob?  
 11 BOB: Yes. So I want to take issue with  
 12 that. You know I haven't done these kinds of  
 13 studies, but I presented yesterday three very  
 14 different groups that have been looking in a very  
 15 focused way on duplicate patients: that  
 16 Rabinowitz' IMI EU Israeli initiative; Mitchell  
 17 Efros, who's based in Long Island, New York; and  
 18 the guy in Southern California, Shaevitz. And  
 19 they've all come up pretty much the same estimate  
 20 of 8 to 10 percent of the patients in CNS and kind  
 21 of symptomatic trials are duplicates.  
 22 That, to me, is a huge number, because if

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1 you then add to that 10 percent of patients who are  
 2 participating in the same clinical trial in  
 3 Los Angeles and San Diego, all the stuff that Eric  
 4 has found, to me it suggests -- and I know, as has  
 5 been said, it's terrifying -- there could be  
 6 30 percent of the patients in a trial are doing  
 7 something seriously funky.  
 8 So I'm really struck by the Rabinowitz, the  
 9 Efros, and the Shaevitz coming up with the same  
 10 10 percent duplicate. And I want to say one other  
 11 thing. By the way, that 10 percent was exactly the  
 12 figure in the IOM report for that schizophrenia  
 13 trial with 300 patients. And when the FDA  
 14 investigated, 30 of them were duplicate.  
 15 So to me, that's not a kind of minor  
 16 problem. That seems to me like a huge canary.  
 17 MALE SPEAKER: Inasmuch as that's a  
 18 problem -- well, I mean I don't want to minimize  
 19 that. But is it systematically biasing results in  
 20 a particular direction?  
 21 BOB: Well, it's hard to imagine how  
 22 duplicate patients, if they're intact at all,

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1 aren't taking twice as much medication and probably  
2 aren't taking any medication at all, it's hard to  
3 imagine how that'll give you a false positive. But  
4 it's awfully easy to imagine that it's responsible  
5 for false negative results.  
6 In fact, there was the analysis that  
7 Rabinowitz did showing that when he removed  
8 post hoc, 10 duplicate patients from a  
9 schizophrenia trial, the p-value, for what it's  
10 worth, went from 0.08 to 0.03.  
11 MALE SPEAKER: I want to make one quick  
12 point, which is that it wasn't that the study went  
13 from being positive to negative. It went from  
14 being statistically significant to not  
15 statistically significant. I would be willing to  
16 bet that the effect size was altered a little, but  
17 it didn't change direction.  
18 BOB: But if that was a phase 3  
19 schizophrenia trial and the missing data were  
20 handled in the way that the FDA requires, in one  
21 case the trial doesn't get the drug on the market,  
22 and in the other case it does.

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1 MALE SPEAKER: No, no, no. I'm not arguing  
2 that issue. What I'm saying is that we talk about  
3 them as negative trials. And the best way to  
4 present a trial is that the trial shows an effect,  
5 but that it did not reach statistical significance.  
6 Because to talk about it as a negative trial  
7 suggests that it showed no effect, and it doesn't.  
8 It's a pet peeve of mine.  
9 BOB: I'm using it as shorthand for the  
10 FDA's not --  
11 MALE SPEAKER: I understand.  
12 BOB: -- going to consider it, in most  
13 cases, as evidence that counts towards approval.  
14 MALE SPEAKER: The point I'd like to make is  
15 that I think that a little bit of monitoring would  
16 go a long way to avoiding duplicate patients. It  
17 makes a great deal of sense. I would argue,  
18 though, that our target is not zero. Our target is  
19 5 percent or our target is something; that if we  
20 said that this is a huge problem and we need to  
21 focus on getting it to zero, that we're going to  
22 over expend resources on trying to do that.

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1 So I would argue that it's well worth  
2 looking at; that there ought to be some way to do  
3 that within HIPAA regulations that would allow us  
4 to compare. And that a little bit of monitoring  
5 that way would go a very long way to reducing the  
6 number.  
7 It's never going to get to zero, and so we  
8 need to just be cognizant of the fact that we need  
9 to focus on looking at each of these problems,  
10 trying to make them smaller, and being efficient  
11 about them and not being onerous in terms of the  
12 regulations and other things that we impose that  
13 would make clinical trials harder.  
14 MODERATOR: Ajay?  
15 DR. WASAN: One thing to add about this  
16 pragmatic versus efficacy trial issue is that I  
17 know we've all been keeping in mind phase 3  
18 clinical trials with our comments, but I would say  
19 almost every single issue we've talked about  
20 actually applies to large pragmatic trials as well,  
21 and the thinking about them and how you would  
22 design them.

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1 So I really see our comments being kind of  
2 broadly applicable, not necessarily just the  
3 phase 3 trials. Plus, I think the vast majority of  
4 sort of published clinical research in pain  
5 medicine are blended trials that have both aspects  
6 of effectiveness and efficacy in there, if not for  
7 the only reason of adherence, for instance.  
8 So I think that's part of what we want to  
9 come across, too, is saying that these are -- to  
10 get to your sense of trying to be as general as  
11 possible, but mention some specifics, I think that  
12 would be important, too, for what we're coming at.  
13 We're not just giving this narrow lens. So I'd  
14 like to see that go forward as a group with that.  
15 MODERATOR: David?  
16 MALE SPEAKER: Yes, I just want to kind of  
17 pick up on what Bob has said is the general theme  
18 of the conference which is, I do think a lot of  
19 this is really terrifying. I just don't want to  
20 minimize it. I want to make sure some of my  
21 comments aren't out of hand. I mean I've been  
22 dealing a lot with Parkinson's disease lately, and



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1 Alzheimer's, and fraud in those is probably  
 2 different than fraud in pain.  
 3 But I do think -- I am a very big advocate  
 4 of -- and Mitchell Efos has reached out to me many  
 5 times. And in many bid defenses and many  
 6 proposals, I've suggested using that in the past,  
 7 was to try to find duplicate patients.  
 8 I think what Bernard came up with is  
 9 probably the most terrifying thing that I've heard  
 10 yet, and I don't even -- I'm almost stunned and  
 11 speechless by that presentation. And I think that  
 12 it really behooves all of us, particularly those of  
 13 us that are doing a lot of clinical trials that are  
 14 for pivotal studies, where there's really a lot of  
 15 dollars on the table, to think about whether we can  
 16 really go home and be happy knowing what we've  
 17 heard and not be really, really disturbed by what  
 18 Bernard said.  
 19 I think that all of these things together  
 20 makes me wonder -- in certain areas wonder like why  
 21 is there placebo creep? And one of my favorite  
 22 areas is migraine, and there's this placebo creep

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1 in migraine. And I always thought, well, migraine  
 2 is this great area, because of course they're  
 3 always recycling these patients.  
 4 I guess Nat left. But the point, the  
 5 question is it ever right to have a cadre of  
 6 professional patients? What I would say, in  
 7 migraine maybe it makes sense, because they've  
 8 certainly -- they know what it is to take a  
 9 triptan, and these studies go very quickly, and I  
 10 think they're pretty accurate.  
 11 But it could explain why there's this  
 12 placebo drift, and our drugs seem to be less  
 13 effective for migraine, like if you look at a  
 14 Maxwell study from 20 years ago, and now it seems  
 15 to be a little bit less effective.  
 16 Bob, you were going to say something?  
 17 BOB: No. what you said there makes me  
 18 think one thing we've left out for the last two  
 19 days is thinking about this from the perspective of  
 20 the patient in the clinical trial who's actually a  
 21 partner and is doing his or her best to provide  
 22 high-quality, valid data.

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1 If a clinical trial subject like that was at  
 2 this meeting, they would be very upset, because  
 3 they're putting themselves at risk of side effects,  
 4 of getting placebo. And what we've spent two days  
 5 talking about is all these things that are working  
 6 to make the data uninformative.  
 7 So I think we need to somehow get into the  
 8 article not only how terrifying this is to us, as  
 9 the people doing the trials, but how terrifying  
 10 this should be to the patients who are  
 11 participating, who are the straight-shooting  
 12 patients and trying to make a contribution, but  
 13 there are all these forces that are working against  
 14 them.  
 15 MALE SPEAKER: But I mean it's an ethical  
 16 issue, I think.  
 17 MALE SPEAKER: Exactly.  
 18 MALE SPEAKER: They go into clinical trials  
 19 with the idea that they're going to suffer, they're  
 20 going to have inconveniences, maybe have bad side  
 21 effects, but with the idea that they're results are  
 22 going to have meaning and are interpretable. When

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1 we have all of this going on, it impedes that. And  
 2 if we don't address it, there is an ethical  
 3 dimension to it in my mind.  
 4 MODERATOR: There's going to be two more  
 5 questions. I'm only going to take two more because  
 6 we've got a lot of things we want to cover. But it  
 7 seems to me like, number one, I would imagine that  
 8 Penney Cowan got extremely excited when she heard  
 9 the comment from Bob about, "Gee, we really need to  
 10 look at the patient's perspective on this," or the  
 11 person who has the problem and since you might want  
 12 to use it.  
 13 Also the lady in Palatka on her website, I  
 14 don't know if she at all talks about that  
 15 perspective that might be of interest for us, those  
 16 that haven't -- I'm not familiar with it to go look  
 17 at it and see what she has to say.  
 18 There are going to be two last questions.  
 19 One, Eric Devine's had his hand up, and then Mark  
 20 Jensen. Then I'm going to cut it off at this  
 21 point. If you have additional questions, hopefully  
 22 we're still going to have a lengthy discussion and

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1 maybe they'll fit right in there. So Eric, you're  
 2 first in line.  
 3 DR. DEVINE: Oh, thank you. So despite the  
 4 numbers that I saw in my study with a high level of  
 5 deception and fabrication, and the numbers that Bob  
 6 is referencing, I don't have the perception that  
 7 this is a crisis across lots of phases of research,  
 8 because I think it has to do with the vulnerability  
 9 of the study.  
 10 Studies with criterion that are diseases  
 11 that are assessed by subjective assessment versus  
 12 objective, like Amy said earlier, in an oncology  
 13 trial where there's no reimbursement and people  
 14 already have free access to healthcare, the chance  
 15 of people gaming for some sort of study enrollment  
 16 is very low. And while there could duplicate  
 17 entry, because people are desperate for care,  
 18 that's a little bit different than the population  
 19 that I'm noting.  
 20 So when you think about how do you allocate  
 21 resources to combat this problem, you really have  
 22 to look at the vulnerability of the study. Is it

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1 paying money? Is it a condition for which subjects  
 2 can fake their way, and we know that they can. Do  
 3 they have access to it through clinical trials? Is  
 4 it something that's a network where they can go  
 5 from site to site?  
 6 If you have a narcotic pain relief that's  
 7 part of being in the study, that bumps up the  
 8 vulnerability, because the street value is just too  
 9 tempting. So you get reimbursement plus a little  
 10 recreational drug use, and maybe some money on the  
 11 side from selling what you don't use. So  
 12 vulnerability is what we need to --  
 13 MODERATOR: So obviously, some balance.  
 14 Yes, Mark? Last word on this section.  
 15 DR. JENSEN: So I'll just respond a little  
 16 bit to what David said about it, the issue of  
 17 adherence that Bernard mentioned. We've talked  
 18 about training patients for better assessment, and  
 19 I don't know that it was specifically talked about  
 20 whether we should include in the paper training for  
 21 adherence, that we would want to include issues  
 22 about that. We always do that in our psychosocial

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1 events, is we use MI to train for adherence, but I  
 2 don't know how many drug trials do that now.  
 3 MALE SPEAKER: The only thing --  
 4 MODERATOR: Last word.  
 5 MALE SPEAKER: Okay. The issue about  
 6 adherence, I think we need to be a little bit  
 7 circumspect from the perspective that I'm convinced  
 8 that pain trials have different adherence issues  
 9 than an Alzheimer's or a blood pressure trial, or  
 10 things where patients are not symptomatic. And  
 11 it's somewhat telling that they're -- unless  
 12 Bernard knows of a larger population of studies.  
 13 But there are very few studies that look at  
 14 adherence and anything related to pain. Maybe  
 15 those should be done.  
 16 I'm not at all suggesting it shouldn't be  
 17 mentioned in the paper. I'm simply saying that I  
 18 think we should be cognizant of the fact that, at  
 19 least in my patient population, the issue is not  
 20 taking too few rescue drugs, it's taking too many.  
 21 And so the problem of taking their drugs on a  
 22 regular basis is not as much an issue.

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1 One could argue that in drugs where we're  
 2 giving them and they don't see a dramatic effect  
 3 immediately -- pregabalin would be an example -- I  
 4 certainly have patients who come back and say, "I  
 5 took two pills. It didn't help" and I have to  
 6 educate them on taking them regularly. So I would  
 7 agree with teaching in that area.  
 8 MODERATOR: I think you better be careful  
 9 about saying that there's no studies on adherence  
 10 in pain. Just as a crude area, in the opioid area,  
 11 there have been a number of studies that looked at  
 12 urine tests on people to people who are supposedly  
 13 being prescribed opioids, and by far, many more  
 14 underuse the medication than overuse the  
 15 medication.  
 16 So it's not as it, number one, we don't do  
 17 this, and number two, there are plenty of people  
 18 who underutilize. So let's end this session.  
 19 Now the fun begins. This is the part you've  
 20 all been waiting for. The exam. This is the exam.  
 21 This is the did you earn your provisional  
 22 qualification? Dr. Dworkin, do you have the page?

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1 Thank you, gentlemen.  
 2           Consensus Discussion  
 3       DR. DWORKIN: Okay. So you're in the home  
 4 stretch. There is no formal coffee break this  
 5 afternoon, so it won't hurt my feelings if you  
 6 wander out. We have a very hard stop at 4:00,  
 7 because there are taxi arrangements and everything  
 8 else.  
 9       I only have a couple of slides. And really,  
 10 for the next hour and a half, or however much time  
 11 is left before 4:00, or we might finish sooner,  
 12 it's going to be discussion and argument.  
 13       I thought a good place to start was with the  
 14 two definitions of quality that Nat put up  
 15 yesterday morning; the one from the FDA  
 16 presentation and his own. This is more or less  
 17 what we've been talking about. And as you all  
 18 know, these two days really are to provide the raw  
 19 material for an article with recommendations. Or  
 20 if we don't have recommendations, because there's  
 21 not a lot of evidence, there'll be considerations  
 22 or recommended considerations. We've used all of

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1 very knowledgeable about clinical trials.  
 2       This is David Hewitt's clinical trial shop.  
 3 This is obviously on a much larger scale. And if  
 4 you look really hard, you can see Tom Hanks showing  
 5 up for work. Tom Hanks was one of David's early  
 6 study coordinators. But so you all know, this is  
 7 from You've Got Mail.  
 8       But I think this is important for us to  
 9 remember as we go to the next slide, which is  
 10 really the important slide. We would like these  
 11 recommendations to be as relevant to the small  
 12 boutique, clinical trial, academic operations as  
 13 they are to the much larger situations.  
 14       So what we've tried to do on this slide is  
 15 to kind of summarize what a few of us thought were  
 16 the high points of the last two days. And so this  
 17 is really my last slide, except for one more that  
 18 is at least an initial summary, an initial kind of  
 19 scaffolding of the article that will be drafted.  
 20       So it seems that we've really been talking  
 21 been talking about sources of discordance,  
 22 discrepancy, mismatches, between what a clinical

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1 that language in the past.  
 2       Dennis, I thought made an important point  
 3 about this effort, these recommendations, is that  
 4 to the extent possible, we want them to be as  
 5 applicable to a clinical trial of yoga or  
 6 acupuncture or cognitive behavior therapy or  
 7 hypnosis as they are to drugs, and that's always  
 8 been our hope with IMMPACT articles, that the  
 9 recommendations are kind of generally promiscuously  
 10 applicable to clinical trials.  
 11       The other thing -- and that came out this  
 12 morning -- is we'd like the recommendations to be  
 13 as relevant as possible in non-regulatory settings,  
 14 you know, academic settings, foundation clinical  
 15 trials, et cetera, Bill and Melinda Gates studying  
 16 treatments for malaria in Africa.  
 17       To make that point, I wanted to show you a  
 18 photograph I took of -- this is the outside of John  
 19 Markman's pain clinic. That's Meg Ryan who was his  
 20 very first study coordinator, showing up for work  
 21 one day. And you can see this is a very small  
 22 operation, and they're very sophisticated, they're

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1 trial protocol is intended to do, the study the  
 2 investigators intended, the objectives they had  
 3 mind, and the way the study gets executed that can  
 4 adversely affect the quality of efficacy data.  
 5       As I said a moment ago, we really haven't  
 6 focused at all on safety. That's a whole other  
 7 meeting. And so what are these kind of  
 8 discordances, discrepancies, between the intent of  
 9 the protocol and what actually happened when the  
 10 rubber met the road?  
 11       This is really the summary of those sources  
 12 that seems to have come out of the last two days.  
 13 There are patient sources, site sources, so  
 14 characteristics of the patients, whether they have  
 15 the disease that the clinical trial is studying;  
 16 has there been some exaggeration of their symptoms  
 17 so they can get randomized; are they hiding, as  
 18 some did in Eric's study, treatments from the  
 19 investigator?  
 20       There are sources of discordance involving  
 21 outcome reporting. This is, of course, Mark's  
 22 presentation yesterday morning, the intentional

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1 unblinding that I talked a little bit about. Of  
2 course what we were all very, very troubled by, the  
3 lack of medication adherence that Bernard talked  
4 about, and then a set of site characteristics; I'm  
5 not going to go through them in detail.  
6 One of the themes it seems over the last two  
7 days has been what can we do to prevent these  
8 discordances. Quality by design is obviously an  
9 approach to this. You build in, as much as  
10 possible, safeguards into the protocol, but of  
11 course nothing is perfect. And what can we do to  
12 identify these mismatches between the intention of  
13 the protocol and the study execution, as they're  
14 occurring.  
15 Then -- this is something we've danced  
16 around a lot about, and I don't know that we've got  
17 a whole lot of answers here -- once you've  
18 identified something funky, what do you do? What  
19 can you do legitimately, to address it in the  
20 middle of a trial; and if you can't, afterwards in  
21 the analysis?  
22 So when I look at this slide -- and forgive

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1 my inability to work with Excel -- it really should  
2 be a 9 by 4 grid that we would be filling in. So  
3 there are kind of 36 cells on this slide that you  
4 can't see, but hopefully you can imagine, which are  
5 these four ways of addressing discordance across  
6 these nine aspects of patient and site arenas,  
7 domains for discordance. Bob?  
8 BOB: Immediate reaction, I think this is  
9 actually terrific. Two things that come to mind:  
10 one is another dimension, which was in the  
11 definition of quality, may be possible to both  
12 address, I guess, the importance of these factors  
13 in the integrity of the study and the ability to  
14 produce reliable results and protection of human  
15 subjects.  
16 DR. DWORKIN: Yes.  
17 BOB: So bringing both those. And then the  
18 only other thing I would say is I wonder -- I'm  
19 very interested in the medication adherence thing  
20 we had a presentation on. I don't think we really  
21 focused much discussion on that. I think Dennis  
22 just mentioned it. I think there's a lot more that

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1 we didn't talk about, so I'm not sure how that will  
2 be brought to bear here.  
3 DR. DWORKIN: So four cells -- so in a row  
4 obviously -- Bernard had to leave early.  
5 Obviously, we will rely on Bernard to fill in the  
6 four cells here: prevention of medication  
7 mis-adherence.  
8 Identification, he talked a lot about that  
9 yesterday in terms of the electronic approaches to  
10 identifying medication adherence; and then of  
11 course the issue of --  
12 One question I talked about at the break  
13 with someone is if Bernard's electronic system says  
14 the patient stopped taking their medication a week  
15 ago, is it appropriate for a coordinator at the  
16 site to call the patient and say, "Mr. Smith, we  
17 noticed that you stopped taking your medication a  
18 week ago; what's going on?" Or is that that kind  
19 of midcourse correction not appropriate?  
20 I know what I think, but I'm not sure we  
21 could get an answer today.  
22 Then, of course, what Bernard talked a lot

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1 about is after the fact when you've got the  
2 adherence data, you can do a secondary post hoc  
3 analysis to look at the relationship between  
4 whether the patient was taking their medication and  
5 efficacy and et cetera. So that's the 36 cells  
6 that aren't on this slide.  
7 BOB: One other minor -- well, maybe not so  
8 minor -- I think we did focus on  
9 unintentional -- or excuse me -- intentional  
10 unblinding. That really isn't unblinding, and  
11 including unintentional --  
12 DR. DWORKIN: Yes.  
13 BOB: There are things at the level of  
14 prevention, et cetera, related to -- well,  
15 prevention of --  
16 DR. DWORKIN: You know, I agree, Bob. I'm  
17 not sure --  
18 BOB: -- not intentional.  
19 MODERATOR: I'm not sure why I made this  
20 intentional, because as one of the speakers -- I  
21 forget who mentioned -- assessing whether patients  
22 became unblinded from side effects is a very

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1 reasonable thing to do. Consider the word  
 2 "intentional" withdrawn because it's very  
 3 reasonable to ask patients at the end of the trial,  
 4 Which group do you think you were randomized to?  
 5 Just because some of you may not be able to  
 6 see it, at the bottom, I tried to emphasize that  
 7 this all applies to eligibility criteria, efficacy  
 8 outcome data, adherence data, follow-up, and  
 9 subject disposition, but not adverse events.  
 10 David?  
 11 DAVID: One of the things we didn't mention,  
 12 I don't think, was the idea of overdose, and that's  
 13 kind of the opposite, right, of this adherence  
 14 issue. But certainly, it speaks to quality issues.  
 15 And how we give out drugs, whether we use blister  
 16 packs or bottles, we didn't get into that, I don't  
 17 think. I think that becomes very impactful as  
 18 well. In addition to missing doses, is overdose.  
 19 Of course, with that is always the concern,  
 20 particularly for some of our drugs, that there may  
 21 be diversion of these drugs as well if there's a  
 22 concern that there is a positive reinforcing effect

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1 of the drug and sharing it outside of the confines  
 2 of the study.  
 3 DR. DWORKIN: So you see overdose an adverse  
 4 event?  
 5 DAVID: It can be an adverse event.  
 6 MALE SPEAKER: So shouldn't that be off the  
 7 table for this if we're focusing on efficacy  
 8 outcomes?  
 9 MALE SPEAKER: It depends what you're  
 10 attempt on the trial is, what's your -- the  
 11 importance of the trial. There are trials that  
 12 have overdose as a primary outcome.  
 13 DR. DWORKIN: Absolutely. Right.  
 14 DAVID: Well, it's an adherence issue, I  
 15 think, because you're taking too much. Not all  
 16 overdoses are assigned the designation of an  
 17 adverse event. If there's no adverse event  
 18 associated with it, it's not an adverse event.  
 19 It's not adherence.  
 20 DR. DWORKIN: Right. Mark?  
 21 DR. JENSEN: Just another complication,  
 22 assuming that this table will be filled with

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1 recommendations, there's going to be different  
 2 levels of evidence, the strength of evidence before  
 3 those recommendations, so we need to incorporate in  
 4 the table or in the text how strongly we think you  
 5 ought to be doing the thing that we're saying.  
 6 So I think there's a consensus, no paper  
 7 diaries to assess adherence, but there are probably  
 8 other ways to assess adherence that we think are  
 9 pretty good. But in terms of training, for  
 10 example, we don't have the evidence yet. We think  
 11 this would be a good thing to do, but we don't  
 12 have -- so just some way of indicating the level of  
 13 evidence in the table or in the paper.  
 14 DR. DWORKIN: Yeah, we're going to need to  
 15 do that. I actually think that we're probably  
 16 going to end up -- my guess based on previous  
 17 impact articles is that we're going to end up  
 18 calling these "considerations" rather than  
 19 "recommendations" because there is no evidence, so  
 20 we can't really have evidence-based  
 21 recommendations.  
 22 I think even for electronic versus paper, my

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1 sense is we all agree that at this point in time,  
 2 electronic is preferable, but it would be really  
 3 hard-put to cite something showing that you get  
 4 better quality data from an electronic device than  
 5 from a paper diary. I don't know. What would I  
 6 cite?  
 7 MALE SPEAKER: I would cite that the paper  
 8 diaries we know are bad. We know they're bad. The  
 9 electronic diaries, we don't know that they're bad.  
 10 DR. DWORKIN: So what would you cite to show  
 11 that paper diaries are bad?  
 12 MALE SPEAKER: Oh, there's plenty of  
 13 evidence, observations of people doing the hood,  
 14 the lack of consistency in their responding. We  
 15 have papers. I can find them for you that have the  
 16 evidence.  
 17 Clearly, we'll have some qualifiers saying  
 18 these are recommendations. But I think there may  
 19 be some recommendations we feel more strongly about  
 20 than others, and I think we should just make that  
 21 clear. That's my point.  
 22 DR. DWORKIN: You know, I think we should

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1 have strength of recommendation or considerations,  
 2 strength of evidence. And those could be -- we  
 3 could have a strong recommendation with weak  
 4 evidence because it's just common sense. And any  
 5 reasonable, thoughtful person would agree with it,  
 6 even though we can't cite chapter and verse of  
 7 randomized trial.

8 I think that's brilliant, kind of strength  
 9 of evidence, and it's often going to be not very  
 10 much at all. But we can also give the strength of  
 11 our recommendations. Yeah, Mike?

12 MIKE: I just have a question about this  
 13 intentional unblinding aspect. If it's really  
 14 intentional on the part of the site to either have  
 15 access to something that they're not really  
 16 supposed to be looking at, that's really site  
 17 misconduct. But I've always had concerns about  
 18 explicitly asking subjects what treatment they  
 19 think they got assigned to, partly because it helps  
 20 unblind the staff who may not have thought very  
 21 deeply about it, so in the process of querying the  
 22 subject, the subject will say I felt this and I

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1 to be patients and getting on to these kind of  
 2 patient websites, and then inquiring about side  
 3 effects and sort of going by what was maybe in  
 4 clinicaltrials.gov or something else. Then getting  
 5 to know electronically other subjects, and then  
 6 asking them about efficacy, and trying to pick out  
 7 the ones that they thought were really on the  
 8 active drug and getting an early read as to whether  
 9 or not they should buy this stock or dump the  
 10 stock.

11 MALE SPEAKER: That's brilliant.

12 MALE SPEAKER: Oh, yeah. It makes a lot of  
 13 sense.

14 DR. DWORKIN: If you will send us a  
 15 reference -- Mike, I promise to include this in the  
 16 article if you can send me a reference to that.

17 (Laughter.)  
 18 (Crosstalk.)

19 DR. DWORKIN: That is too titillating a  
 20 tidbit to ignore. Ian?

21 DR. GILRON: Thanks to Mitchell Max, how we  
 22 did this when I trained and learned how to do

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1 felt that; and when I put all these things  
 2 together, it convinced me that I was actually  
 3 receiving the experimental drug.

4 I would want to have some caution in this  
 5 about explicitly asking subjects too many things  
 6 about what treatment group they were assigned to  
 7 because, cumulatively, if they're guessing more  
 8 correctly than by chance, it will start to unblind  
 9 the investigators in the studies.

10 DR. DWORKIN: I never thought about that,  
 11 and I don't know that anyone else has in print.  
 12 One way to address it would be to have the  
 13 assessment being done at the end of the trial  
 14 electronically with the study staff being blinded  
 15 to it. The patient says in some kind of electronic  
 16 capture did they think they were randomized to drug  
 17 or placebo and why, and the site staff never see  
 18 those responses.

19 MIKE: Can I just add a quick follow up?  
 20 I'm sorry. There was something in the news some  
 21 years ago where they were reporting on venture  
 22 capital and other equity groups who were pretending

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1 trials with him was to routinely ask people to do  
 2 blinding questionnaires. We routinely, at the same  
 3 time, asked the research staff to see what they  
 4 thought.

5 John Markman showed obviously a very  
 6 dedicated and insightful research staff who pay a  
 7 lot of attention. You can't have it all ways. We  
 8 want good quality and stuff, but they also -- they  
 9 think about what they're doing, right?

10 Our experience has always been that the  
 11 research staff has always been more unblinded than  
 12 the patient. We do it at the end of the study.  
 13 And to be honest, I can't say that we've  
 14 protocolized the order in which it's done.

15 I think Mike's concern is that it's going to  
 16 somehow affect allocation concealment. I'm not  
 17 even sure what the problem would be. If you're  
 18 asking at the end of treatment -- if you think  
 19 somehow that the study subjects' response is  
 20 unblinding the research staff for that particular  
 21 patient, I'm not sure what the implications would  
 22 be there.

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1 If they're thinking about the block  
2 randomization, it might affect their allocation  
3 concealment for its subsequent patients. But I'm  
4 not sure what the liability is for doing unblinding  
5 questionnaires.  
6 MIKE: For example, there were some drugs in  
7 development that caused this distinct change in  
8 taste in the part of the subjects. So really,  
9 elaborate procedures were done to change the way  
10 the pills looked, or other things, to get it into  
11 clinical trials and not have inadvertent  
12 unblinding. And that's fine. You may want to test  
13 the adequacy. But it really is more the  
14 interaction between the subject and the site  
15 personnel.  
16 So if you're doing it after the fact,  
17 completely separately from like an independent  
18 grader, completely separately from these active  
19 clinical staff, that's fine. I already found the  
20 reference -- at least one. There's lots of them  
21 from 2002 Wall Street Journal.  
22 DR. DWORKIN: So Ian, I'm not sure I

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1 understood your question because isn't the risk  
2 that the study staff become unblinded because they  
3 start to -- and the expectations that they then  
4 have somehow unintentionally, nonverbally get  
5 communicated to patients if the staff over the  
6 first few patients learns that half the patients  
7 seem to have dizziness and half don't.  
8 The patients are kind of saying, I think I  
9 was on drug because I was dizzy, but my pain also  
10 got better; that the staff develops an expectation  
11 that patients who report dizziness are going to get  
12 better, and that somehow augments the drug effect  
13 and decreases the placebo effect when there's no  
14 dizziness.  
15 DR. GILRON: I understand that. But I mean,  
16 except for a phase 1 trial, every consent form is  
17 going to have AE information. I mean there's  
18 always a potential that patients are going to be  
19 unblinded and --  
20 DR. DWORKIN: But I assume that the patients  
21 either don't read the consent form or forget it  
22 within 15 minutes of leaving the clinic. Please

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1 don't repeat that outside of this room.  
2 DR. GILRON: It's in the transcript.  
3 DR. DWORKIN: John?  
4 JOHN: In thinking about this table, I think  
5 it's a great table in terms of the implementation.  
6 But we heard a number of presentations that talked  
7 about things and issues related to the design.  
8 Maybe you're going under that. But the other  
9 one --  
10 DR. DWORKIN: [Indiscernible] my last slide.  
11 JOHN: Okay.  
12 DR. DWORKIN: So I sent Nat -- because Nat  
13 had to leave early, I sent him the previous table,  
14 and he said it's leaving something out, which is  
15 kind of my bunionectomy example of designing the  
16 trial to minimize -- and Amy, and Nat, and I tried  
17 to come up with a term, and the best we came up  
18 with was minimize experimental noise in the way the  
19 trial becomes conducted.  
20 We thought about whether the word is  
21 "covariates," so see if this is what you were  
22 mentioning. This is Nat's slide really, not my

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1 slide.  
2 In the bunionectomy example that he  
3 presented yesterday, remember when, I guess it was  
4 Scirex, first started doing that as a phase 2  
5 design, they hadn't really learned -- and Rob, I  
6 think you were there -- the different factors in  
7 the procedure with the patient who was being  
8 assessed while they were lying down or sitting up.  
9 And over time, they standardized all those  
10 experimental procedures. and all of a sudden, assay  
11 sensitivity went up.  
12 So Nat said what's left off the previous  
13 slide is this set of considerations about these  
14 sources of noise in a trial that should be  
15 addressed ideally in the design.  
16 So is this what you were thinking of?  
17 JOHN: Partially. But for example, it's  
18 alluded to even in the second statement there,  
19 which is the factors that affect the primary  
20 endpoint.  
21 An issue that was brought up, I think, very  
22 nicely by Scott Evans in his comments on the panel

<p style="text-align: right;">Page 281</p> <p>1 was the issue of designing the trial to avoid                  2 missing data. I'm not sure how that fits here, but                  3 it's critical.                  4 I like to say that if you want weekly data,                  5 measure it daily; if you want monthly data, measure                  6 it weekly; and if you want quarterly data, measure                  7 it monthly because that way, at least you get                  8 something that you can then average if you're                  9 missing a little bit.                  10 If you design your outcome as a very complex                  11 multi-leveled questionnaire, you're going to get                  12 different kinds of answers. So I think that the                  13 issue there is -- I could see it fitting here, but                  14 I don't see it there. And I'm wondering how you'd                  15 see it there.                  16 DR. DWORKIN: I was going to say, Shouldn't                  17 missing data be number 6 on -- well, either                  18 number 5 --                  19 JOHN: I understand.                  20 DR. DWORKIN: -- number 5 under patient. So                  21 wouldn't we consider having missing data one of                  22 these discordances between the intention of the</p>	<p style="text-align: right;">Page 283</p> <p>1 some of that is sort of built in to this process.                  2 DR. DWORKIN: Yes. Laurie and then Andrew.                  3 MS. BURKE: I think that the bunionectomy                  4 example is part of the assessment; it's part of                  5 what you would do with this training to make the                  6 assessment in the assessment tool. Maybe outcome                  7 reporting is just part of that assessment.                  8 I think it's combined in there. I think it                  9 should be more than reporting. The whole                  10 assessment process would take care of that missing                  11 piece, don't you think?                  12 DR. DWORKIN: I mean, I agree, but I also                  13 think it's sort of assay sensitivity. I think                  14 about like third molar extraction, the type of                  15 extraction, as I understand -- I don't know much                  16 about it -- is associated with the assay                  17 sensitivity of the model.                  18 It's something about outcome assessment and                  19 also the model. So I think we're going to have to                  20 struggle how this set of issues -- can it be                  21 incorporated into the previous slide or is it a                  22 kind of separate set of issues?</p>
<p style="text-align: right;">Page 282</p> <p>1 protocol --                  2 JOHN: Yes.                  3 DR. DWORKIN: The intention of the protocol                  4 was that everybody gives you complete data, but the                  5 execution, of course, some patients drop out; there                  6 are missing data. I think missing data is omitted                  7 here, inadvertently, and it should be number 5                  8 under patient. And we build into the trial                  9 everything we can to prevent missing data, but we                  10 also want to identify it, and then how do we deal                  11 with it?                  12 JOHN: Correct. I don't know if this is                  13 exactly right, but you start off at the bottom,                  14 which I can only partially see, I think with                  15 eligibility. I think it actually backs up to the                  16 issue of project design. and I'm not sure how to                  17 include that exactly.                  18 My point -- I mean, I think you get the                  19 point, which is that I think we need to think about                  20 the design issues that lead to improper data                  21 collection for a variety of reasons. These are                  22 what the patient does and what the site does, but</p>	<p style="text-align: right;">Page 284</p> <p>1 Amy, and Nat, and I did struggle with it for                  2 about a half hour over lunch, and this was the best                  3 we could do, to put it on a separate slide, but we                  4 will be working with this. Trudy?                  5 DR. VANHOVE: I was thinking could you not                  6 put it under site because, really, you would want                  7 the procedure to be similar between sites, the                  8 bunionectomy procedure.                  9 DR. DWORKIN: Standardization of --                  10 DR. VANHOVE: A standardization of the                  11 procedure or whatever it is that you're looking at.                  12 DR. DWORKIN: And that's partly training but                  13 partly protocol. So that's right.                  14 DR. VANHOVE: Partly protocol, exactly, yes.                  15 DR. DWORKIN: Yes, it's partly protocol,                  16 partly training.                  17 DR. VANHOVE: It's not a training issue, but                  18 it is an assessment issue as which size are you                  19 going to enroll.                  20 MALE SPEAKER: It could be a separate                  21 section.                  22 DR. VANHOVE: Selection?</p>



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1 MALE SPEAKER: You have patients and site;  
 2 you could also have protocol, or design, or  
 3 something that would just fit therein, and then you  
 4 could put the missing data and the other pieces  
 5 right into that. It might be a way.  
 6 DR. VANHOVE: But it's a site selection  
 7 issue.  
 8 My other comment would be, could we -- well,  
 9 would it be possible to replace "mid-trial" with  
 10 "during the trial"?  
 11 DR. DWORKIN: Yes, absolutely.  
 12 DR. VANHOVE: Okay.  
 13 DR. DWORKIN: I think we will have a whole  
 14 lot of back and forth with our colleagues at FDA  
 15 about this, what is appropriate, reasonable to do  
 16 during a trial versus -- and I think Sharon was  
 17 very clear about one thing.  
 18 One example of this yesterday, where Sharon  
 19 said quite clearly that saying to a patient, during  
 20 their participation in a trial, "Notice that you  
 21 said your worst pain was less than your average  
 22 pain. You need to think more clearly because that

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1 really isn't logical." Sharon said that's  
 2 unacceptable.  
 3 So that raises the question, I think, in a  
 4 lot of our minds, well, then what is acceptable?  
 5 Is it acceptable to say to the patient you haven't  
 6 taken your medication; you haven't completed any of  
 7 your diaries? Obviously, we're going to have to  
 8 get those issues ironed out after this meeting.  
 9 Andrew?  
 10 DR. RICE: Bob, I wonder if we can put one  
 11 other factor under patient, and it's been the issue  
 12 that I was aware about before I came, but it's been  
 13 really emphasized. That's the issue of the  
 14 healthcare setting or the country in which a  
 15 patient is recruited.  
 16 So this concept of a professional patient is  
 17 totally news to me. We've had a lot of interesting  
 18 discussions about the fact that patients can earn  
 19 money and income from participation in clinical  
 20 trials. That just wouldn't happen in Europe. And  
 21 therefore, the motives of the patients entering the  
 22 trials are different. I suspect that's true of

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1 most of Northwestern Europe.  
 2 There's also a very interesting comment that  
 3 was made over lunch that there's a very close  
 4 relationship, generally in the UK and many other  
 5 European countries, between patients and their  
 6 doctors. And you'll often hear a form of bias  
 7 creeping in where you suspect patients are giving  
 8 more positive answers because they don't want to  
 9 upset the doctor about his nice new drug.  
 10 I suspect the motives may be different also  
 11 in other healthcare settings. I've done trials in  
 12 the developing world, and that to do not financial  
 13 gain but to gain access to healthcare.  
 14 I guess we've got two choices here. We can  
 15 either talk about these professional patient issues  
 16 and say this is just about -- I'm not sure it's  
 17 just the USA or it includes Canada as North  
 18 America. And these issues are pertinent to those  
 19 settings, but there are very different issues with  
 20 regards to other healthcare settings.  
 21 I think it's a really interesting research  
 22 question just to try and document what incentives

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1 might be in different countries.  
 2 DR. DWORKIN: I agree that we need to have  
 3 something in the manuscript that whatever we end up  
 4 putting in this 36-cell table is very likely going  
 5 to vary by region, country.  
 6 It might vary importantly by whether it's  
 7 phase 2 or phase 3, whether it's a single-site  
 8 academic study or a kind of multinational,  
 9 multisite phase 3 protocol. So region would go in  
 10 the category of moderators of these factors and  
 11 what can be done about them.  
 12 DR. RICE: But I do think it's important to  
 13 have a discussion about this professional patient  
 14 and earning from a clinical trial issue because I  
 15 think a lot of people in Europe just don't  
 16 understand that. It's not a concept that they  
 17 grasp very easily.  
 18 MALE SPEAKER: I would agree, Andrew, and I  
 19 think it's not kind of up there because we did  
 20 spend a lot of time. But under patient, you could  
 21 call just "patient misconduct," and that would  
 22 cover the duplicative patient.

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1 I'm a little surprised that you would think  
2 in today's world it'd be so easy to have software  
3 for the CROs or sponsor, but certainly the CROs.  
4 And it should be picked up at screening this  
5 patient has already been in a trial, and that would  
6 be a huge service to those guys, where it doesn't  
7 disrupt the trial or turn a significant trial into  
8 a non-statistically significant trial as you said.  
9 You know what you could do? You could carry  
10 it one step further. Is it inappropriate? If a  
11 patient has done that, that's a willful act.  
12 That's sort of -- me, that's a one and done if it's  
13 a urine analysis. Certain urine analysis in my  
14 clinic, a little THC, I sort of forgive the  
15 patient, ask who their supplier was, and then move  
16 on or whatever.  
17 (Laughter.)  
18 MALE SPEAKER: But a duplicative patient in  
19 the same trial, that is a pretty much of a serious  
20 thing. The CROs could blackball that person from  
21 ever going into any clinical trial again, at least  
22 within that context. John is shaking his head no.

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1 I don't know. But it seems to me like you could  
2 penalize, to some extent, that patient. That's a  
3 pretty -- most of the people, I would think in this  
4 room, would not want to risk, if they could, that  
5 patient participating, subsequently.  
6 DR. DWORKIN: I completely agree. I think  
7 the HIPAA issues and confidentiality issues have  
8 been resolved by Rabinowitz, and Efos, and  
9 Shaevitz . And we thought about inviting all three  
10 of them to this meeting. But since they're all  
11 doing this separately and presumably are competing  
12 with each other, we didn't want this meeting to  
13 turn into a kind of slug fest of who has a better  
14 online system for identifying duplicate patients.  
15 But I agree, that all three of their  
16 approaches seem very straightforward, and it's hard  
17 to imagine a reason why you wouldn't implement it  
18 because these are people you don't want in the  
19 trial. Dave?  
20 DAVE: Yeah, just a couple of things. One  
21 is, with all due respect to England and all the  
22 medicine being better there, which I'm sure that it

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1 is, until you do the study, you don't know whether  
2 there is, in some level, fraud going on there. The  
3 motivations could be completely different. I mean  
4 I think it's a study that was worth doing.  
5 Certainly, it would have different  
6 motivations. I mean, it wouldn't be for money.  
7 But I'm not sure how much of it is all about the  
8 money in the United States either. I think that's  
9 one question. I think that's something to  
10 consider.  
11 DR. DWORKIN: Dave is suggesting that  
12 ACTION fund Eric Devine to go to London and redo  
13 the Boston study there.  
14 (Laughter.)  
15 DR. DWORKIN: And it looks like Eric is all  
16 for this idea.  
17 (Laughter.)  
18 MALE SPEAKER: I just wanted to find out if  
19 this is going to be part of the paper as well, is  
20 that when you address all these areas, one of the  
21 things you may do at the end -- and it will be  
22 interesting to opine on -- is whether you're going

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1 to increase the assay sensitivity of the study.  
2 With that, what is the implications for  
3 moving forward in terms of our historical data and  
4 how we power studies. I mean, it might change  
5 things in a very fundamental way, and maybe we'll  
6 be able to get away with smaller numbers of  
7 patients to be able to do some of these studies.  
8 It's an interesting thought.  
9 DR. DWORKIN: I think that's the hope.  
10 Raymond?  
11 DR. CHEUNG: I notice with Nat's -- the  
12 slide that you showed -- Neil and I both have  
13 bitter experience with failed clinical trials,  
14 specifically in the post-op space where  
15 standardization of the procedure would affect the  
16 baseline pain if you didn't do that.  
17 If you didn't standardize the procedure and  
18 the post-operative analgesic regimen -- and I guess  
19 Nat also pointed out some other factors like how  
20 you actually ask the patients their pain. I think  
21 maybe there could be a category of the condition of  
22 the procedure that could affect the results.

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1 DR. DWORKIN: Yeah. No, I think -- John  
2 suggested this, that there's probably a third block  
3 on this slide that is something about the model,  
4 the design, and that's where we'll put in things  
5 like missing data, standardizing the procedure, the  
6 assessment; partly, that's training as well as  
7 Laurie pointed out. So yes, we will add some third  
8 category here to address Nat's bunionectomy and  
9 related issues.  
10 Neil?  
11 DR. SINGLA: Yes, just one quick point  
12 regarding the site factors; there's five factors  
13 listed. This is just my opinion, but I think that  
14 it's more actionable right now to help sites get  
15 better quality by improving their processes, and  
16 that most investigators out there are not  
17 fraudulent, and that the FDA -- the whole construct  
18 of clinical trials that are being done for industry  
19 right now very much looks for fraud a lot instead  
20 of looking for true quality.  
21 So if we're trying to improve the quality of  
22 clinical trials, it probably makes sense for us as

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1 a group to talk a lot about the last two and not so  
2 much about the first three because they're all the  
3 same in a way: fabrication, falsification. And if  
4 you make it like a police article, where it's all  
5 about how to police more, that's not really, in my  
6 opinion, what we need. We need to just be better  
7 at what we do.  
8 (Applause.)  
9 DR. DWORKIN: I agree, Neil. I originally  
10 had a big red box around these two, and we could  
11 put a red box around this also because that's where  
12 training is targeted. Training is targeted at the  
13 patient not doing a very good job of reporting  
14 their pain. And then, of course, training is  
15 targeted at the carelessness, poor training,  
16 recording errors, misunderstanding, incompetence  
17 down there.  
18 So I think we actually, as you heard from  
19 the applause, we all agree with you that we need  
20 training; we need standardized training; we need  
21 evidence-based training, and that's hugely  
22 important.

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1 Lee?  
2 DR. SIMON: I'm interested that no one has  
3 actually referred to a problem, which is ubiquitous  
4 in the orthopedic community in pain trials,  
5 particularly when you're using devices that have  
6 been invented by the person doing the study.  
7 I've been involved in a couple of trials  
8 where the inventor of a drug was a study site, and  
9 the patients he recruited actually knew he was the  
10 inventor of the drug and wanted to make him happy,  
11 and all had a response, including those responding  
12 on placebo. Therefore, the studies failed.  
13 This is a training issue. We should know  
14 that if we are invested in such an event, that we  
15 should not be the person carrying out the trial of  
16 studying that product. But nowhere up there is  
17 actually this been said. And because it's  
18 ubiquitous in the orthopedic community, it perhaps  
19 isn't something that people recognize because it's  
20 clearly not the right thing to do. But nobody  
21 keeps saying it.  
22 DR. DWORKIN: Somewhere up here is kind of

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1 making sure we've done our best so the patients  
2 have realistic expectations, and this is something  
3 that's making --  
4 MALE SPEAKER: Removing bias.  
5 DR. DWORKIN: Exactly. S that's up here  
6 somewhere. We can put that in.  
7 Laurie, you had your hand up.  
8 MS. BURKE: I was just going to say that I  
9 think under site 1, 2 and 3 really belong under 5.  
10 They're like subsets of systematic error that need  
11 to be addressed. I don't know.  
12 DR. DWORKIN: Yeah. We based some of this  
13 on publications in the literature, and so we'll go  
14 over that. That's right, they are systematic but  
15 they seem in another level of kind of illegal.  
16 MS. BURKE: I'm reacting to the suggestion  
17 that we don't want to make this all about the fact  
18 that there's so much fraud in the clinical trial  
19 world. These are exceptions rather than the rules.  
20 DR. DWORKIN: One thing we can obviously do  
21 is combine 1, 2, 3 and make it just one subsection,  
22 kind of, fraud, fabrication, misconduct rather than

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1 splitting them out. I just wanted to put down the  
2 definitions for fabrication, falsification that  
3 comes from, I think, the article by Biogen. But in  
4 the article, we will not make it look so lopsided  
5 as Neil and you both pointed out.  
6 Other omissions, additions, et cetera? Bob?  
7 BOB: Well, in the service of just maybe  
8 stating the obvious, the word "fidelity" isn't up  
9 there, and maybe it's similar to "quality." The  
10 basic premise of designing a study, developing a  
11 protocol, and then following it, and knowing that  
12 you've done what you said you were going to do in  
13 the service of producing replicable methods and  
14 results, I think that that really is a core  
15 principle of value -- or I mean of quality, excuse  
16 me.  
17 So it comes to things like it's really about  
18 designing the trial and developing a protocol  
19 that's going to prevent problems as a really  
20 fundamental premise about this enterprise.  
21 Then in terms of correction, identification,  
22 you want a protocol that's going to help you

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1 identify problems so that you can correct them.  
2 And then the correction, I think, it's important  
3 that it's transparent when that occurs and that  
4 there's thought about that.  
5 Of course, it's important at a local site to  
6 be able to move clinically with good clinical  
7 practice in mind and the patients', human subject,  
8 protection in mind to act, to deviate from a  
9 protocol, if you will, on behalf of the patient  
10 care.  
11 But having said that, I think that it's  
12 fundamentally important that these mid-trial  
13 corrections, if you will, are really carefully  
14 considered in the context of that overarching  
15 concern about the fidelity of the trial.  
16 DR. DWORKIN: I think that -- right.  
17 BOB: So it's maybe just restating --  
18 DR. DWORKIN: I think the most  
19 challenging -- the most challenging column here, in  
20 some ways, is exactly this midstream correction,  
21 and it should be prespecified ideally, transparent.  
22 What we heard yesterday from Paul, from Sharon is

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1 it's got to be extensively, clearly documented.  
2 This is going to be the most challenging part of  
3 the manuscript to draft, I think, that column of 9  
4 or 10 recommendations. Dave?  
5 DAVE: Just to be clear, you're not going to  
6 include the company, the planning, the  
7 sponsor -- it's kind of interesting because it  
8 means that you're really putting all the onus on  
9 the patient and the site, and that you don't really  
10 think any of the risk to quality sits with the  
11 biopharmaceutical company.  
12 DR. DWORKIN: No. Isn't that this? Have  
13 they designed the right study that prevents --  
14 DAVE: Okay. I'm sorry.  
15 DR. DWORKIN: Yeah. No. I think the  
16 company is -- actually the company is responsible  
17 for all of this because this should all be in the  
18 protocol, right?  
19 DAVE: Okay.  
20 MALE SPEAKER: Just to follow up to David's  
21 point, obviously, the data comes in from the  
22 patient. The site does something with it. Then it

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1 gets put into a database, then it gets programmed,  
2 then the statistical analysis, then the endpoint,  
3 the final results. We're not really going -- to  
4 David's point, we're not thinking we can correct  
5 those aspects of data quality and data process.  
6 DR. DWORKIN: Right. So the first version  
7 of the slide had after the word "execution" in  
8 parentheses, it said "not analysis and  
9 interpretation."  
10 MALE SPEAKER: Not analysis. Okay.  
11 DR. DWORKIN: Because analysis and  
12 interpretation, I think, would be a whole other  
13 meeting. So this is really just about what happens  
14 before the database is locked and the statisticians  
15 take over.  
16 Trudy?  
17 DR. VANHOVE: Bob, where would you put like  
18 a bad medical monitor? Because you have a  
19 brilliant protocol, and the medical monitor,  
20 however, gets calls, and he lets in patients that  
21 really don't meet the eligibility criteria. But  
22 he's kind of like -- he's not very strict. It's

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1 just a bad medical monitor. Where would that go?  
2 MALE SPEAKER: Carelessness.  
3 DR. DWORKIN: Mike!  
4 MALE SPEAKER: I was just going to say, the  
5 last two comments remind me that maybe it's patient  
6 site, but you also have the people who are  
7 responsible for overseeing the study. It isn't  
8 just designing it. It's overseeing the conduct.  
9 And I think that's what you're starting to hearing  
10 from people.  
11 DR. VANHOVE: Yes.  
12 DR. DWORKIN: So there's a third or a  
13 fourth, depending on what we do with design,  
14 category of oversight, absolutely. That's an  
15 omission.  
16 MALE SPEAKER: Bob Kerns mentioned the  
17 fidelity with the protocol, which is essentially  
18 capturing that point. Bob Kerns talked about the  
19 fidelity of the protocol, as are people following  
20 the protocol. A bad monitor is not following the  
21 protocol.  
22 DR. DWORKIN: No. You can have a rogue

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1 monitor who isn't doing his job, and that's  
2 not -- the job of the monitor isn't really  
3 specified in the protocol. It's specified I guess  
4 in SOPs of the CRO.  
5 FEMALE SPEAKER: Oversight makes sense.  
6 DR. DWORKIN: I think oversight makes a lot  
7 of sense. Yeah.  
8 Lee?  
9 DR. SIMON: So just to go back to your issue  
10 about this mid-trial column -- and Laurie and I are  
11 probably the only leftover people from former FDA  
12 as opposed to any FDA people here. It's really  
13 critical not to make anybody who reads this paper  
14 to believe that they have carte blanche to  
15 manipulate issues that come up or become evident in  
16 the mid-trial or ongoing review.  
17 I can't tell you the numbers of times that  
18 I've actually had to see, on both sides of the  
19 table, where we see a data set that it suddenly  
20 dawns on them something is not right. And they  
21 don't understand that the trial then is obviated  
22 based on how much they do or what they do.

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1 So it really is -- we have to be really  
2 careful not to give people the sense that this kind  
3 of tweaking is de rigueur and welcomed. It may not  
4 be welcomed.  
5 DR. DWORKIN: That's right. I could even  
6 imagine -- it's late in the day; we don't have to  
7 think about this -- that we could recommend, in  
8 certain settings, we as a group think it's  
9 perfectly reasonable to call up a patient and say,  
10 "Mr. Jones, it looks like you didn't fill out your  
11 diary yesterday or you didn't take your medication  
12 yesterday." And we might say that, but it's going  
13 to be followed by, "However, for registration  
14 trials, the regulatory agency needs to be kind of  
15 contacted to ensure that this is acceptable." We  
16 will stick that in after any recommendation where  
17 we think it could be problematic at either FDA or  
18 EMA.  
19 DR. TURK: So that's like a black box  
20 warning?  
21 DR. DWORKIN: that's our black box warning,  
22 exactly.

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1 Rick?  
2 RICK: That's what I was actually going to  
3 address, is that mid-trial correction piece is I  
4 think going to be very problematic. Analysis,  
5 sure, we can talk about what we did wrong and how  
6 to address it for future studies. But for  
7 mid-trial correction, we want to be careful, as has  
8 been said, what we can correct.  
9 We can retrain monitors if they're letting  
10 patients in as exceptions in the protocol. We can  
11 retrain -- there's a lot of things we can retrain,  
12 but there's a lot we can't. So we just have to be  
13 very careful when we write that section, what  
14 passes muster for mid-trial correction and what we  
15 should address.  
16 DR. DWORKIN: So just out of curiosity, how  
17 many people in the room think it would be -- forget  
18 about FDA for the time being. How many people in  
19 the room, just as investigators, researchers, think  
20 it would be reasonable and acceptable to call the  
21 patient and say, "Mr. Smith, yesterday, you didn't  
22 complete your pain diary, and we hope that, you

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1 know, from now on, you are more careful about  
2 that."  
3 MALE SPEAKER: If it was written in the  
4 protocol.  
5 FEMALE SPEAKER: You can write in the  
6 protocol --  
7 MALE SPEAKER: If it was prespecified in the  
8 protocol.  
9 (Crosstalk.)  
10 DR. DWORKIN: Okay. But Sharon also said  
11 yesterday that in no circumstances would it be  
12 acceptable to call Mr. Smith and say, "Hey,  
13 yesterday, you said your worst pain was less than  
14 your average pain."  
15 (Crosstalk.)  
16 DR. DWORKIN: I'm not going to say  
17 they're -- well, I'll tell you, if I'm drafting  
18 this article, I'm not going to say there are two  
19 different issues until Sharon says to me that  
20 they're two different issues because of exactly  
21 what Lee said. I don't want us to make  
22 recommendations that it turns out the FDA doesn't

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1 agree with.  
2 MALE SPEAKER: But Bob --  
3 DR. DWORKIN: So we all agree that there's  
4 no problem with calling the patient and saying you  
5 didn't complete your diary.  
6 MALE SPEAKER: If it's in the protocol; only  
7 if it's in the protocol. It's got to be  
8 transparent, and you can plan them.  
9 (Crosstalk.)  
10 DR. VANHOVE: Exactly. I mean, very often,  
11 it will say if the patient hasn't filled it out for  
12 two days, there's going to be a call. It's written  
13 down, it's prespecified, and you follow that.  
14 DR. DWORKIN: But Trudy, what I'm saying is  
15 if -- the way I understood Sharon yesterday is even  
16 if it was written in the protocol that you call the  
17 patient to say the patient's worst pain cannot be  
18 less than average pain --  
19 MALE SPEAKER: But that's asking them to  
20 change the data.  
21 (Crosstalk.)  
22 DR. VANHOVE: So she had a problem with you

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1 going back and saying, "Hey, does this correct a  
2 score?"  
3 MALE SPEAKER: And she backtracked a little  
4 bit on that, Bob, in the break. You should get it  
5 from her.  
6 DR. DWORKIN: It might be that you're all  
7 right. I'm just saying I don't want to write that  
8 and publish it until we confirm it.  
9 MALE SPEAKER: Of course.  
10 DR. DWORKIN: We all agree.  
11 (Laughter.)  
12 Raymond?  
13 DR. CHEUNG: I think in the conduct of the  
14 study -- and we talk about there are opportunities  
15 for training -- you don't need to necessarily  
16 reference that I know that you're doing it wrong.  
17 But as part of the training, that you can always  
18 remind people, are you taking your medication; are  
19 you filling out your electronic diary? I don't  
20 think that that would -- I think that might be less  
21 of a problem.  
22 DR. DWORKIN: That was clearly not a

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1 problem, but what many of us wondered about is that  
2 kind of retraining on a regular basis all of the  
3 patients is obviously much more cumbersome, costly  
4 than targeted intervention. But targeted  
5 intervention might not be acceptable.  
6 Dave?  
7 DAVE: Yes. [Inaudible – off mic]. Part of  
8 medical monitoring in so many clinical trials to  
9 do -- there's a difference between training and  
10 coaching. And I think what's happening right now  
11 is we're combining those two things.  
12 If you say to somebody, I saw what you did,  
13 right, and you're doing it wrong; let me tell you  
14 how I think it should be done, that's coaching. I  
15 think training is to just say, "You have to fill  
16 out your diary every day." That's fine to get a  
17 notification that you need to fill out your diary.  
18 Those are different things. It's making  
19 sure that they're adhering to the protocol design  
20 is absolutely legitimate. And I think if you need  
21 to spend some time and say, well, I want to make  
22 sure you understand the difference between least

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1 pain, worst pain, and average pain, you can do  
2 that. You can train them on that. That's a  
3 difficult concept for some people to get.  
4 But you can't go, "Oh, I saw that you wrote  
5 something that was really crazy yesterday; go  
6 change it because it was wrong." I think that's  
7 what Sharon was referring to.  
8 MALE SPEAKER: Yes, exactly.  
9 DR. DWORKIN: I blame Lee for all of this  
10 because --  
11 (Laughter.)  
12 DR. DWORKIN: I was just agreeing with Lee  
13 that we don't want to make a recommendation that's  
14 going to end up biting some sponsor six months down  
15 the line because they read our article, and they  
16 think something is acceptable when it isn't.  
17 So I hope that we can all agree that we just  
18 want to make sure that our recommendations are  
19 either acceptable or unacceptable, and that we know  
20 what they are before we make them.  
21 Ajay?  
22 DR. WASAN: I think it's really important in

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1 this section to define context. And obviously, the  
2 context of an FDA phase 3 trial, such iterative  
3 processes, you have to have very tight parameters.  
4 But on the other hand, there's the opposite view,  
5 not for the FDA registration trials but some other  
6 kind of trials. Let me give you some good  
7 examples.  
8 Obviously, there's agreement that the best  
9 science is done as an iterative process. Let's say  
10 your outcomes you're looking at are physiological  
11 outcomes, so QST changes or fMRI changes. Those  
12 are some of the studies that Rob and I do for  
13 instance, and that you use the clinical trial as a  
14 mechanism to look at changes in physiology, and  
15 that's your main outcome.  
16 If someone is not adhering and you found  
17 out, it's kind of good that you talk to them about  
18 it. If they don't do their rating scales and  
19 something's bizarre about them, actually, since  
20 you're not primarily testing efficacy, you're  
21 actually trying to look at physiological outcomes,  
22 it's actually better that you have these iterative

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1 changes.  
2 You got to be careful too, right? You don't  
3 go overboard and fundamentally change and  
4 compromise the primary outcome you're looking for,  
5 which may be physiological.  
6 So I think we have to be really just careful  
7 on the context and define the context in which --  
8 DR. DWORKIN: That's exactly the kind of  
9 language we will have. Depending on the context,  
10 targeted intervention retraining may be  
11 appropriate, but in regulatory contexts, don't  
12 assume it is without getting approval from the  
13 regulatory agencies. That's the kind of language  
14 I'm imagining. It's what Dennis said; it's a black  
15 box warning. Other comments? Laurie?  
16 MS. BURKE: I think it might be an overkill  
17 to try to have a mid-trial column. You might just  
18 want to have this mid-trial considerations  
19 paragraph, and then -- the considerations are to  
20 change -- change your processes midstream are  
21 usually a bad idea, but there may be a reason to do  
22 something if you notice something that would deep

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1 six your whole program.  
2 DR. DWORKIN: SP I agree that I hope that we  
3 end up with fewer than 36 cells --  
4 (Laughter.)  
5 DR. DWORKIN: -- either by deleting a  
6 row -- I mean a column, as you suggest, or by  
7 combining, as I just suggested, some of the rows.  
8 I would hate for the ultimate manuscript to go in  
9 with an Excel spreadsheet that I can't do myself  
10 with 36 cells in it.  
11 Yes, John?  
12 JOHN: To say something that may already be  
13 obvious, but I think the point is that studies can  
14 be designed to monitor certain things and implement  
15 certain changes if things are found. You design  
16 the study -- I mean as David was just saying, it's  
17 completely reasonable to encourage a continued  
18 enrollment and filling out the forms. And if you  
19 know that people are not filling out forms, that  
20 you contact them.  
21 I don't think anybody would object to that,  
22 but it ought to be written in the protocol, which

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1 brings me to the second point, which I think Laurie  
2 would -- is partly what she's saying. And  
3 certainly, Sharon said yesterday, is be sure that  
4 you're upfront and transparent about what you do.  
5 And if you're in a registration trial, before you  
6 make any mid-trial corrections, you damn well  
7 better talk to the registering agency.  
8       Honestly, I don't know how  
9 clinicaltrials.gov works in this score, but if you  
10 change the protocol halfway through, somebody is  
11 going to be upset unless you -- and I think you  
12 need to go there and actually make the change there  
13 as well as a change. I'm not sure. But my point  
14 is transparency is really key.  
15       DR. DWORKIN: Other comments?  
16       MALE SPEAKER: The only thing is you can't  
17 always anticipate, right? When you're doing  
18 science, you can't anticipate all the problems, so  
19 you just -- that's the other caveat too. You can't  
20 prespecify -- unless you say a general term, "If  
21 there's something that comes up I can't think about  
22 right now, then I reserve the right to make some

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1 changes."  
2       (Laughter.)  
3       MALE SPEAKER: I think John is right. I  
4 mean, everything you do -- the protocol is it.  
5 Everything needs to be in the protocol, but part of  
6 being in the protocol is that the study will be  
7 monitored. And part of monitoring a study is to  
8 ensure that things are followed.  
9       As you were just mentioning, you may not be  
10 able to know everything that won't be followed, but  
11 part of the job is to make sure they adhere to the  
12 protocol. That's what the protocol is.  
13       If they don't adhere to the protocol, that  
14 actually is really bad, and you don't need to have  
15 somebody -- you don't need to have extra provision  
16 from the FDA saying that you have to -- it's okay  
17 to adhere to the protocol and make sure that the  
18 sites and the patients adhere to the protocol.  
19 That's what a protocol is.  
20       What I would say is, under there rubric John  
21 mentioned -- even if you can't predict it  
22 precisely, the point is we know with the protocol

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1 is trying to do. I'm hard-pressed to find an  
2 instance where you could do an intervention that  
3 would be -- as long as you're not changing the data  
4 or coaching the patient, I think you're fine.  
5       DR. DWORKIN: Trudy?  
6       DR. VANHOVE: I totally agree. I would say  
7 data falsification, if you identify that but you  
8 can't correct it, or you don't let the FDA know  
9 that, hey, I've got these patients that reenrolled  
10 10 times or whatever it is, or misconduct, then  
11 what? Okay, you identified it, and what are you  
12 going to do?  
13       DR. DWORKIN: I don't know.  
14       DR. VANHOVE: You can't correct anything.  
15       MALE SPEAKER: That's what's going to be fun  
16 about writing this paper.  
17       DR. VANHOVE: I totally agree.  
18       DR. DWORKIN: I think the issue -- and Paul,  
19 you've been silent. But the issue of what's  
20 appropriate when these things are identified in an  
21 ongoing trial -- I said this already -- I think  
22 it's the most challenging part of this paper to

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1 write. Just because you've anticipated some of it  
2 in the protocol, it doesn't mean what you say in  
3 the protocol was automatically right. If I write a  
4 protocol today saying I'm going to deal with  
5 missing data using LOCF, that doesn't mean I  
6 then -- I'm going to get a drug on the market using  
7 LOCF.  
8       So yeah, we have to put the best things we  
9 can in our design, but we need to make sure what it  
10 is that's going to be acceptable to the regulatory  
11 agencies, unless I'm missing something. This goes  
12 back to Lee's point. We just can't run the risk of  
13 misleading people that something is acceptable when  
14 it might not be.  
15       MALE SPEAKER: I think we definitely need  
16 Sharon to weigh in on some of this. Usually,  
17 statisticians aren't asked for this type of level  
18 of what's appropriate for a mid-trial correction.  
19 I think hitting the high points here have  
20 been -- we're more -- in the past, we've  
21 traditionally been much more focused on the site  
22 investigator and trying to train that individual



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1 rather than the actual subject. So that might be  
 2 something that needs to be discussed. How far do  
 3 we want to go in terms of interventions with  
 4 subjects?  
 5 I personally happen to agree that it's fine  
 6 to remind somebody, you haven't been taking your  
 7 drug; you haven't been filling out something.  
 8 Going further saying, do you need some help filling  
 9 out your patient-reported outcome statement is a  
 10 little -- that's starting to stretch things, and  
 11 it's going a little too far.  
 12 DR. DWORKIN: Well, that's inevitable. What  
 13 if they haven't completed it for three days? Can  
 14 you remind them that they haven't completed it?  
 15 Trudy, I completely agree that -- so Dennis  
 16 and I are doing a trial now on fibromyalgia. It's  
 17 NIH-funded. Of course, we would. All I'm saying  
 18 is I don't know with a hundred percent certainty  
 19 that Sharon would say of course. She might and  
 20 then we're all in agreement.  
 21 I think we're beating a dead horse here.  
 22 Are we beating a dead horse, Dr. Turk? Yes.

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1 DR. TURK: Yes.  
 2 DR. DWORKIN: Rob?  
 3 ROB: Again, just to remind, in any trial,  
 4 you may uncover violations, or deviations or  
 5 errors. You can always, first of all, query. And  
 6 as long as you're transparent in everything you do,  
 7 you can identify. If you were to identify a  
 8 patient who you thought was fraudulent, you could  
 9 still transparently suspect that, put that patient  
 10 and their data into a separate list and say, look,  
 11 we suspect or we're worried about the data for some  
 12 reason. And you could analyze it separately.  
 13 Obviously, it's not the intent to treat.  
 14 But if you come with violators or deviators  
 15 of any sort because of urine drug screens or faulty  
 16 data, if you can document it and be transparent  
 17 about it, you can analyze it, do a sensitivity  
 18 analysis. I think the FDA would welcome that.  
 19 But as long as you're transparent about any  
 20 errors -- and you can make mid-trial corrections as  
 21 long as you're transparent, I think, almost at any  
 22 level. But it may have implications depending on

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1 the impact or the type of corrections you're making  
 2 in a study.  
 3 DR. DWORKIN: Other comments?  
 4 (No response.)  
 5 DR. DWORKIN: Are we done early? Andrew?  
 6 DR. RICE: It was just the issue of  
 7 unannounced blood sampling as another measure of  
 8 adherence.  
 9 DR. DWORKIN: Yes.  
 10 DR. RICE: We might ought to put that just  
 11 as a one-liner. You can reference David Simpson's  
 12 study where we did it. He was the first author  
 13 under pros and -- we discussed the pros and cons of  
 14 doing that.  
 15 MALE SPEAKER: Yes, and Bernard actually  
 16 referred to some data suggesting that they were  
 17 kind of dramatic important differences between what  
 18 you got when you did announced versus unannounced.  
 19 DR. DWORKIN: Phil?  
 20 DR. CONAGHAN: Bob, I'm just a little  
 21 concerned about the generic versus specific pain  
 22 issues and almost the selling of this paper, as it

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1 were, how you make it related to pain.  
 2 A lot of the things we discussed are not  
 3 just relevant to pain studies. They're relevant to  
 4 lots of different trials. So to make this pertain  
 5 to a pain audience, I'm assuming some way you're  
 6 going to have to make examples that always relate  
 7 to a pain study when you're writing your  
 8 manuscript.  
 9 Is that what you've got in mind already?  
 10 DR. DWORKIN: Yes, absolutely. I mean  
 11 that's right. A lot of this is very generic about  
 12 clinical trials and not pain. Some of it is going  
 13 to be very pain-related like training people how to  
 14 do zero to 10 pain diaries, et cetera.  
 15 The issue you identified hasn't been a  
 16 problem with other IMMPACT papers that were  
 17 100 percent generic. We have an IMMPACT paper with  
 18 recommendations for how to deal with multiple  
 19 endpoints in a clinical trial, and it's really all  
 20 about statistical approaches to multiplicity.  
 21 I don't think there was anything specific  
 22 about pain in that article. And I think those

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1 articles are -- there haven't been many of  
 2 them -- are largely generic or maybe 70 percent  
 3 generic, are viewed by the reviewers and editors as  
 4 educational. That's I guess the way we've thought  
 5 about it.  
 6 But this will have, I think, 25 to  
 7 35 percent pain, specific material in pain  
 8 examples. So I don't know that it's a major  
 9 problem.  
 10 DR. CONAGHAN: The other element that I  
 11 think is part of good recommendation papers is to  
 12 highlight at least some of the priority research  
 13 agenda, which you normally like to get in. And if  
 14 you got some time now, I'm thinking of a couple of  
 15 things.  
 16 For example, even the training issues you've  
 17 brought up to me are not well evidence-based. The  
 18 issues of training people to use VAS or NRS scores  
 19 or whatever, we need to see the evidence base to  
 20 just make some difference after you've  
 21 psychometrically adjusted these scales.  
 22 That's just one example, but perhaps while

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1 you've got people here, a quick thought of what the  
 2 juice is for research recommendations would be  
 3 good.  
 4 DR. DWORKIN: Yes. We'll definitely have a  
 5 table with a research agenda that tends to kind of  
 6 write itself, because as we're writing most of the  
 7 paper, there are all these places, as Mark was  
 8 saying, where we're going to saying the evidence is  
 9 minimal or lacking. And that then becomes an item  
 10 in the research agenda.  
 11 So there will be definitely be a research  
 12 agenda that's driven by the holes in the evidence  
 13 underlying our recommendations or considerations.  
 14 Dennis?  
 15 DR. TURK: I was going to respond to the  
 16 first part of your question, which was about if  
 17 it's broader than just the pain, will it get sort  
 18 of seen or will it be picked up or observed or  
 19 would that information get out there?  
 20 In the past IMMPACT and ACTION papers, all  
 21 of which have -- 99 percent of which have appeared  
 22 in the Pain journals, they've ended up getting

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1 cited in over 600 different journals across the  
 2 entire spectrum. So somehow or other, even though  
 3 we're putting it in the Pain journal, it gets  
 4 picked up much more broadly than we maybe  
 5 anticipated.  
 6 DR. DWORKIN: Actually, that's the opposite  
 7 of what, I think, Phil was suggesting. If the  
 8 paper is 70 percent generic, it actually has a  
 9 larger audience than -- so that's actually an  
 10 interesting kind of --  
 11 DR. CONAGHAN: Those issues are really  
 12 important for all trials.  
 13 MALE SPEAKER: But my point was that even  
 14 though we're putting it in a Pain journal, it gets  
 15 picked up.  
 16 DR. DWORKIN: Yes. Other comments?  
 17 (No response.)  
 18 Adjournment  
 19 DR. DWORKIN: All right. I wish I had one  
 20 of these timers that counted down five seconds.  
 21 You will be hearing from us because the way this  
 22 works, and many of you are very familiar with this,

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1 is a manuscript will be drafted. Everyone who's  
 2 been here will be listed as a co-author. You are  
 3 completely free to ask us to take your name off it,  
 4 and we're happy to do that. If you don't, you will  
 5 be involved in multiple revisions of the paper  
 6 before it gets published as an article somewhere.  
 7 Thank you very much, Valorie and Andrea for  
 8 coordinating a wonderful meeting. Thank you all,  
 9 and especially the presenters, for your  
 10 participation, your ideas, your thoughts, and your  
 11 terrific presentations, and have a good safe flight  
 12 home.  
 13 (Applause.)  
 14 (Whereupon, the meeting was adjourned.)  
 15  
 16  
 17  
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 19  
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 21  
 22

	<b>120 (1)</b> 113:6	<b>30 (4)</b> 67:21;113:8;248:6,14	202:17	<b>abuse-deterrent (1)</b> 118:2
<b>\$</b>	<b>12-week (2)</b> 236:12;237:1	<b>3-0 (1)</b> 99:20	<b>70 (2)</b> 321:2;323:8	<b>academe (1)</b> 7:21
<b>\$1 (1)</b> 112:2	<b>13 (1)</b> 189:20	<b>300 (4)</b> 116:9;137:1;188:4;	<b>70s (1)</b> 6:10	<b>academia (2)</b> 36:10;156:22
<b>\$100,000 (1)</b> 151:3	<b>139 (2)</b> 136:4;213:1	248:13	<b>79 (1)</b> 213:1	<b>academic (44)</b> 38:4;62:6;70:10;
<b>\$20 (1)</b> 116:11	<b>14 (2)</b> 6:11;235:4	<b>33 (1)</b> 81:22	<b>8</b>	72:11;74:18;87:13,20;
<b>\$200,000 (1)</b> 151:3	<b>141 (2)</b> 136:5;213:1	<b>35 (2)</b> 157:13;321:7	<b>8 (2)</b> 202:16;247:20	100:16;109:14,15,18,19,
<b>\$400 (1)</b> 116:10	<b>15 (4)</b> 52:5;113:12;174:22;	<b>36 (4)</b> 266:3;268:5;312:3,10	<b>80s (1)</b> 6:10	20;113:7,11,14,17;
	278:22	<b>36-cell (1)</b> 288:4	<b>81 (1)</b> 106:9	114:11,19;115:6;116:3;
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