

*ACTION SCEPTER II - Clinical Trials to Evaluate
Safety Outcomes in Procedural Sedation*

November 18, 2016

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1 P R O C E E D I N G S
2 (7:55 a.m.)
3 Welcome and Introductions
4 DR. DWORKIN: Good morning. I'm Bob Dworkin
5 from the University of Rochester. I noticed the
6 slide didn't spell out the acronym, and so I did a
7 little bit of research on the Web. SCEPTER stands
8 for, for those of you who don't have it in front of
9 you, Sedation Consortium on Endpoints and
10 Procedures for Treatment, Education, and Research.
11 SCEPTER is one of the initiatives that's
12 sponsored by ACTTION. I'm not going to unpack that
13 acronym, and we're all very pleased that you're
14 able to join us for what looks to be a very
15 interesting and important meeting over the next two
16 days.
17 Could I have the first housekeeping slide?
18 So I'm not going to go through all of this. You
19 can read it for yourself. The most important thing
20 is we all have cell phones and would really
21 appreciate it if you could put your cell phone on
22 vibrate or silence or something like that so that

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1 we don't hear your choice of ringtones. The
2 bathrooms are outside.
3 I guess another important housekeeping item
4 is that we are taping this meeting. ACTTION and
5 SCEPTER therefore are part of a public-private
6 partnership with the U.S. Food and Drug
7 Administration, and we put transcripts of all of
8 our many meetings on the Web so that everything is
9 publicly available and transparent. So just be
10 aware that anything you say for the next two days
11 will end up on the Web in several weeks.
12 This is the acronym for ACTTION. I just
13 wanted to on behalf of ACTTION welcome you-all and
14 just say a few words about what ACTTION is before
15 turning the meeting over to Dr. Denham Ward.
16 ACTTION is a public-private partnership with
17 the U.S. Food and Drug Administration. It takes
18 care of what could be thought of as four
19 therapeutic – it covers four therapeutic areas:
20 non-analgesia, pain medicine, anesthesia and
21 sedation; addiction medicine and treatment of
22 addiction disorders; and disease modification; and

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1 peripheral neuropathy. This meeting obviously
2 falls within the anesthesia and sedation component
3 of ACTTION.
4 This is the mission of ACTTION. ACTTION
5 supports with funding from FDA, industry and
6 various other sources, a range of activities. A
7 lot of those activities are focused on optimizing
8 clinical trials, as the slide says, but there are
9 other diverse activities, including developing new
10 measures and outcome measures for clinical trials,
11 developing diagnostic criteria. I'm not going to
12 go into all of that.
13 I think just to give you a sense of -- this
14 public-private partnership really was the idea of
15 the FDA's, and this, I think, is an informative
16 quote about why the FDA thought public-private
17 partnerships in these areas would be of benefit.
18 As Janet Woodcock and her colleagues,
19 including Ray Dionne who's here at the meeting,
20 said a number of years ago, "The science base
21 necessary to evaluate and predict safety and
22 efficacy is different from the science that

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1 generates the new idea for a drug, biologic, or
2 device."
3 Dr. Woodcock and Dr. Dionne and their
4 colleagues go on to say that NIH has a history, of
5 course, of funding research in the latter area,
6 basic science research that increases our
7 understanding of mechanisms and targets, and new
8 drugs and devices. But NIH does not have a history
9 of supporting research on the assessment and
10 prediction of efficacy and safety.
11 The FDA began the ACTTION public-private
12 partnership six years ago now, and a little bit
13 before that, began another public-private
14 partnership that many of you are familiar with,
15 which is Smart Tots. Those are two public-private
16 partnerships that grew out of this view of a gap in
17 what NIH funds and an opportunity of what FDA could
18 support to fill that gap.
19 That's just a little bit of the background.
20 As I said, we spent a lot of time on clinical
21 trials in all of those therapeutic areas, and
22 there's a lot more information about ACTTION and

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1 all of its activities at our website, which is
2 action.org.
3 So unless there are any questions, I'd like
4 to turn the meeting over to Dr. Ward and welcome
5 you-all again.
6 Denham.
7 (Applause.)
8 DR. WARD: Thanks, Bob.
9 Thanks, everyone, for working with me to
10 help put this meeting together.
11 Many of you were at the first SCEPTER
12 meeting, but I think not everyone, and it's
13 probably a good idea to go around and reintroduce
14 ourselves because this isn't a meeting where we're
15 going to sit in the audience and listen to somebody
16 come up and pontificate. This is a meeting which
17 we all have to contribute our ideas to reach the
18 goal of how best to look at adverse events in
19 sedation in clinical trials.
20 I'm Denham Ward. I'm an emeritus professor
21 of anesthesiology at University of Rochester and am
22 now professor of anesthesiology at Tufts, and I'm

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1 at Maine Medical Center. We can start with John
2 and go around.
3 DR. BERKENBOSCH: John Berkenbosch,
4 pediatric critical care at University of
5 Louisville.
6 DR. CARLSON: Doug Carlson, pediatric
7 hospital medicine and pediatric emergency medicine
8 at Southern Illinois University.
9 DR. MINER: Jim Miner. I'm emergency
10 medicine at Hennepin County Medical Center in
11 Minneapolis, Minnesota.
12 DR. DAHAN: Albert Dahan from Leiden in The
13 Netherlands.
14 DR. CHAPPELL: My name is Phil Chappell.
15 I'm from Pfizer. I work in CNS and drug
16 development.
17 DR. SEXTON: Anne Sexton, also from Pfizer
18 working in CNS and pain.
19 MR. WILLIAMS: I'm Mark Williams, and I'm at
20 University of Rochester.
21 DR. PANDHARIPANDE: Pratik Pandharipande,
22 Vanderbilt University, anesthesia and critical

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1 care.
2 DR. RIKER: Rich Riker from Maine Medical
3 Center, medical critical care and neuro critical
4 care.
5 DR. WUNSCH: Hannah Wunsch from Sunnybrook
6 Hospital, University of Toronto, intensive care.
7 DR. BHATT: Maala Bhatt, Children's Hospital
8 of Eastern Ontario, pediatric emergency medicine.
9 DR. CONSTANT: Isabelle Constant, I work in
10 Paris in children in anesthesiology and infancy
11 care.
12 DR. ROBACK: Mark Roback, pediatric
13 emergency medicine, University of Minnesota.
14 DR. GREEN: Steve Green, emergency medicine,
15 Loma Linda University in California.
16 DR. MASON: Keira Mason, anesthesiologist at
17 Boston Children's.
18 DR. ZHAO-WONG: Anna Zhao-Wong. I'm from
19 the Maintenance and Support Services Organization.
20 DR. PETIT-SCOTT: Rene Petit-Scott. I'm
21 with FDA.
22 AUDIENCE MEMBER: [Indiscernible], clinical

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1 reviewer, FDA.
2 DR. CRISAFI: Leah Crisafi. I'm an
3 anesthesia team leader in FDA's Division of
4 Anesthesia, Analgesia, and Addiction Products.
5 DR. SESSLER: Dan Sessler. I'm chair of the
6 Department of Outcomes Research at the Cleveland
7 Clinic and director of the Outcomes Research
8 Consortium.
9 DR. CONWAY: Aaron Conway. I'm a registered
10 nurse from Brisbane, Australia and [indiscernible],
11 Queensland Media Technology.
12 DR. GOZAL: David Gozal, I'm an
13 anesthesiologist from Jerusalem, Israel.
14 DR. ROCA: I'm Rigo Roca. I'm deputy
15 director of the Division of Anesthesia, Analgesia,
16 and Addiction Products at the FDA.
17 DR. URMAN: Rich Urman, anesthesiologist at
18 Brigham Women's Hospital in Boston.
19 DR. WEISS: My name is Mark Weiss, and I'm
20 an anesthesiologist at the University of
21 Pennsylvania and vice president of the Society of
22 Non-Operating Room Interventionalists and

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1 Anesthesiologists.
2 DR. GAN: TJ Gan. I'm chair of
3 anesthesiology at Stony Brook and also president of
4 the current American Society for Enhanced Recovery.
5 DR. DEXTER: Franklin Dexter, researcher in
6 anesthesia at the University of Iowa.
7 DR. KARAN: Suzanne Karan, anesthesiologist
8 at University of Rochester.
9 DR. LITMAN: Good morning. I'm Ron Litman.
10 I'm a anesthesiologist with the Children's Hospital
11 of Philadelphia and medical director of the
12 Institute for Safe Medication Practices. I'm the
13 ASA's representative here today.
14 DR. LERMAN: Jerrold Lerman,
15 anesthesiologist in Buffalo.
16 DR. CLARK: Randy Clark. I'm a pediatric
17 cardiac anesthesiologist working for the University
18 of Colorado at Children's Hospital Colorado. I'm
19 also the ASA's section chair for professional
20 standards, which includes the committees for
21 performance and outcomes measurement and standards
22 and practice parameters, among others.

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1 DR. DIONNE: Ray Dionne. I'm a dentist and
2 pharmacologist currently at East Carolina
3 University in the Department of Pharmacology.
4 DR. IRWIN: Good morning. Mike Irwin. I'm
5 professor of anesthesiology at the University of
6 Hong Kong.
7 DR. DWORKIN: Bob Dworkin, University of
8 Rochester.
9 DR. TURK: Dennis Turk, University of
10 Washington, Department of Anesthesiology and Pain
11 Medicine.
12 DR. O'CONNOR: Bob O'Connor from the
13 University of Virginia. I'm emergency medicine.
14 Good morning.
15 DR. TOBIN: Joe Tobin, professor emeritus,
16 pediatric anesthesia and critical care, Wake Forest
17 University.
18 DR. CRAVERO: I'm Joe Cravero. I'm an
19 anesthesiologist from Boston Children's Hospital.
20 I'm the chair of the Pediatric Innovation Research
21 Consortium and on the board of the Society of
22 Pediatrics Innovation.

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1 DR. WARD: And Ricky just walked in.
2 DR. TWERSKY: Hi. Ricky, Rebecca Twersky,
3 anesthesiologist at Memorial Sloan Kettering in New
4 York City. I have been involved with the pre-
5 ACTTION initiatives, and I'm glad to be part of
6 this group today.
7 DR. WARD: Thanks, everyone. Like I said, a
8 lot of people already know each other, but this
9 reinforces the breadth of expertise that we have
10 here across specialties and across continents.
11 We tried to organize this as a follow-on to
12 SCEPTER I, which was a meeting where we looked at
13 efficacy. I thought we would start with a review
14 of SCEPTER I.
15 As I hope you know, many of you are authors
16 on the two papers that came out of that. The first
17 paper was the literature review, the systematic
18 review of efficacy for sedation. The second paper
19 was really the recommendations that came out of the
20 first conference for how you do clinical trials to
21 measure efficacy.
22 The output of this conference is planned to

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1 be a paper on recommendations for how clinical
2 trials should be organized to measure adverse
3 events and how those adverse events should be
4 quantified.
5 We have a few changes in the schedule, but
6 nothing drastic, so we'll move things along with
7 that. Since everybody knows each other, I'm not
8 going to have any major introductions. We will
9 move from speaker to speaker without any major
10 discussion of who you are.
11 It's your meeting. So this isn't a meeting
12 to sit and listen to speakers. The speakers, have
13 been working with them, have an introductory
14 discussion, but most of their time should be spent
15 with a discussion from you, which is why there's
16 microphones on your desk. You don't have to get up
17 to go to a microphone. It's all there. We want to
18 get as much input to these ideas as we can during
19 this meeting.
20 Mark, who was the first author on both our
21 papers, we got him out of call, I think. He was
22 doing vascular cases all day on Monday, and he's

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1 going to review what we came up with for the
2 SCEPTER I meeting.
3 Presentation – Mark Williams
4 MR. WILLIAMS: Very good. Thank you very
5 much. Thank you, Dan, and thank you, Bob.
6 It's a pleasure to speak to you today. As
7 we discussed, this is a recap of the meeting that
8 many of you were at a couple of years ago now, so
9 we'll keep this brief so we can press on with the
10 important matters of discussing safety.
11 This was the overview of the interacting
12 components of sedation and sedation research as we
13 had it in our minds for the last meeting. As you
14 can see, the sedation efficacy and consistency of
15 the center and spreading out. The other important
16 components, we included clinician and patient
17 satisfaction within the efficacy and effectiveness
18 meeting at last meeting. The current meeting is
19 obviously on safety, and I imagine there will be
20 many meetings to follow.
21 Last meeting was held in D.C. not too far
22 from here in 2014 with 36 attendees across

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1 similarly today a range of specialties and a range
2 of adult and pediatric sedation experts, colleagues
3 from the FDA and industry as well.
4 The overriding impetus was that sedation
5 efficacy is very nebulous concept and consensus on
6 specific outcomes were certainly needed to
7 facilitate clinical trial design and ultimately
8 regulatory evaluations of sedation products.
9 The meeting consisted of, similar to the
10 setup of this meeting, several presentations, which
11 stimulated discussion following those
12 presentations. A systematic review was not
13 published at that time. The results were available
14 at that meeting, but the article had not yet been
15 published. Some discussion revolved around the
16 results of that review.
17 The priorities of sedation were felt to be
18 patient and clinician centered with overlapping
19 components of those priorities for this patient and
20 clinician. And reviewing the literature, there
21 were many goals of sedation efficacy of which we
22 touched on: sedation and sedation levels;

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1 particularly in pediatrics, behavioral components;
2 satisfaction; sedation timing and procedural-
3 related outcomes, and others such as pain and
4 recall.
5 We discussed sedation measures as positive
6 evidence for a lot of the sedation measures, which
7 unfortunately not a wealth of psychometric data to
8 support some of the measures. Similarly, in the
9 pediatric sedation scales, we discussed the
10 sedation measures with the most evidence of
11 validity and reliability.
12 The upshot of the two-day meeting was a
13 paper, which many of you are authors on, which was
14 really built around the domains of the -- we
15 borrowed from the Institute of Medicine -- four of
16 the six domains of the IOM's crossing the quality
17 chasm were used, being safe, effective, patient and
18 family centered, and efficient. For the first
19 paper, we focused on effective and patient and
20 family centered.
21 Many tools were discussed that could be used
22 to show sedation effectiveness, and we felt that

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1 procedural sedation, the procedure's satisfaction
2 really was a universal typical across sedation
3 trials as a way of measuring sedation
4 effectiveness. However, for a drug to be
5 classified as a sedative, we need some form of
6 defining it as having sedation properties. So with
7 that, a sedation scale was vital as well to be
8 included.
9 Moving on to patient and family centered,
10 the patient satisfaction was considered to be an
11 important aspect of assessing sedation, so that was
12 included in our recommendations. It culminated in
13 the recommended core outcome measures, which we
14 have in front of us.
15 For the sedation level in adults, the
16 Observer's Assessment of Sedation was recommended
17 for pediatrics, the UMSS. We also included the use
18 of additional rescue medications in there as well.
19 For proceduralist satisfaction, the
20 clinician's satisfaction of sedation instrument and
21 also observed pain scores as well.
22 For pediatrics, we had the Children's

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1 Hospital of Eastern Ontario Pain Scale and FLACC.
 2 For patient and family centered, including patient
 3 satisfaction, included two scales, the ISAS and the
 4 PSSI, which measure two separate components of
 5 satisfaction. They're used independently of each
 6 other. And for recall, modified Brice and the
 7 Numerical Rating Scale for Pain was considered
 8 important.
 9 I think for this meeting, we're hoping to
 10 have again presentations and discussion, and
 11 hopefully come out with some thoughtful
 12 recommendations, which can then lead to publication
 13 and further education of the sedation community.
 14 Okay, Denham.
 15 Q&A
 16 DR. WARD: We have some time for discussion
 17 on the majors that we have from the first meeting.
 18 Obviously, when we were looking at sedatives,
 19 effectiveness and safety, obviously, they're
 20 closely coupled, and most clinical trials would be
 21 looking at both simultaneously.
 22 MR. WILLIAMS: Yes.

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1 DR. WARD: Open for discussion and comments
 2 from the first meeting. Too early in the morning
 3 for anybody to --
 4 (No response.)
 5 DR. WARD: If not, we will keep a little bit
 6 ahead of schedule. As opposed to a continuing
 7 education meeting, where you want to make sure the
 8 talks start on time because people are coming from
 9 room to room, we're all in the same place at the
 10 same time. If we get ahead of ourselves, that will
 11 give us more time for discussion in other areas.
 12 We'll move on to the second set of talks,
 13 and Anna is going to be our first speaker to talk
 14 on MedDRA and the dictionary for reporting adverse
 15 events.
 16 Presentation – Anna Zhao-Wong
 17 DR. ZHAO-WONG: Good morning. Thank you for
 18 this opportunity to introduce, MedDRA, the adverse
 19 event reporting terminology at this conference.
 20 Again, my name is Anna, and I work for MedDRA
 21 Maintenance and Support Services Organization.
 22 These are the topics I'm going to go through

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1 today. We're going to do the introduction or
 2 overview of MedDRA, and talk about what is MedDRA
 3 and where is MedDRA used, and who uses MedDRA, and
 4 talk about MedDRA's features and how that
 5 facilitates adverse event reporting. Then at the
 6 end, I'm going to talk about the mappings of MedDRA
 7 or integration of MedDRA with other terminologies.
 8 The acronym of MedDRA stands for the Medical
 9 Dictionary for Regulatory Activities, and I'd like
 10 to do a quick polling. How many of you have heard
 11 of MedDRA?
 12 (Show of hands.)
 13 DR. ZHAO-WONG: Well, pretty good. How many
 14 of you have used MedDRA?
 15 (Show of hands.)
 16 DR. ZHAO-WONG: I expect some because we
 17 have industry colleagues and FDA colleagues.
 18 Excellent.
 19 MedDRA was initially created by the
 20 International Council for Harmonization -- we call
 21 it ICH -- in the early 1990s. ICH, just a quick
 22 introduction, is actually right now a legal entity.

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1 It's an organization put together by industry and
 2 regulators with the goal of setting standard
 3 terminologies and best practices so that we can
 4 increase efficiency and avoid redundant work.
 5 Because before MedDRA was established, in
 6 the world or in terms of adverse events, there were
 7 many terminologies used for adverse event
 8 reporting. So, for example, in the United States,
 9 we used to use COSTART. In Japan, they used to use
 10 JART. In Europe, they used to use WHO-ART.
 11 So in other words, for a new drug to be
 12 approved on the market by different regulatory
 13 authorities, that drug's data or the company who's
 14 submitting that drug adverse event data has to be
 15 coded in a variety of different terminologies.
 16 Although the clinical trial data is the same, but
 17 when they submit to different regulatory
 18 authorities, they have to code the same adverse
 19 event data in different terminology. So that will
 20 reduce the speed of the drug approval process and
 21 create a lot of redundant work.
 22 ICH was established, and the goal is let's

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1 set one standard terminology for everyone to use.
2 That way, we can all communicate. Because in
3 essence, MedDRA is the standard language that we
4 speak in the world of drug safety.
5 When we're using different terminologies,
6 we're like speaking different languages. Just like
7 if we have a conference, especially a WHO
8 conference, everyone speaks different languages, so
9 they have to have translators so that we can
10 understand each other. But with MedDRA, we all
11 speak the same language so that we can understand.
12 It doesn't matter where you are and to which
13 regulatory authority you submit your data to.
14 MedDRA is also used in the drug safety
15 monitoring, drug safety communication, drug safety
16 oversight.
17 With that, we call MedDRA a
18 clinical-validated terminology. It's used by both
19 the regulatory authority and the biopharmaceutical
20 industry, and it's used in data entry, what we call
21 data entry. It's the coding of adverse events.
22 And data retrieval analysis, of course, after the

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1 adverse events are standardized, then we can use
2 computer or all the tools they have to analyze the
3 data and retrieve the data.
4 Evaluation, to analyze is this drug safe for
5 patients to use as part of the drug approval
6 process and for presentation. For example, when
7 the companies submit their new drug application in
8 their adverse event section, they will use MedDRA
9 to present how the drug safety profile is for that
10 particular product.
11 Now, who or where is MedDRA used? MedDRA is
12 used in the entire product life cycle, including
13 the clinical trials and postmarket, when humans are
14 involved, which means the preclinical. The animal
15 testing stage is excluded. So from clinical
16 phase 1 all the way to the end of that product life
17 cycle, MedDRA is used to monitor and report adverse
18 events.
19 Naturally, all the regulatory authorities
20 would use MedDRA, especially in their databases,
21 safety databases, and these are some terms that
22 were used in the drug safety world. Like the ICSR,

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1 Individual Case Safety Report, would use MedDRA
2 when they do the reporting, and PSUR, period update
3 on the adverse events.
4 Clinical study reports in the investigator
5 brochures because the investigator brochures will
6 have an adverse event section.
7 Core company safety information, each
8 company for each product that they will have a
9 master sheet about that product, everything about
10 that product. That's what we call the core company
11 safety information. There's an adverse event
12 section. Of course, MedDRA is used there.
13 Marketing application for the new drug
14 application. Publications in prescribing
15 information will involve adverse event, and also
16 advertising. There are a lot of patient direct
17 advertising going on, and then on the TV, you will
18 hear the product names and drugs. At the end of
19 the advertising, you will hear they say very fast
20 all the adverse events that may be associated with
21 that product.
22 Then who uses MedDRA and how MedDRA is used,

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1 based on the ICH region? ICH is the organization
2 that initially created MedDRA. And actually when
3 they created MedDRA -- let me back up a little bit.
4 ICH is funded by what we call six parties in three
5 different regions. The three regions are the
6 United States, the European Union, and Japan. Of
7 course, in each region, there are two parties.
8 There's the regulatory authority, and there's an
9 industry association.
10 The three regions and the six parties funded
11 ICH, and after ICH created MedDRA, then the three
12 regions adopted MedDRA. So the first region is
13 United States. U.S. FDA, although does not mandate
14 the use of MedDRA, U.S. FDA uses MedDRA in its
15 internal databases.
16 Three FDA safety databases use MedDRA as
17 their adverse event terminology. There's the FAERS
18 for drug and biologics as a CDERS database, and
19 there's VAERS for vaccines as CBERS database. And
20 there's CAERS for foods, supplements, dietary
21 supplements, and cosmetics. So that's for the
22 CAERS database. Essentially, the MedDRA is the

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1 de facto standard terminology in the U.S.
2 Now, in Japan and the European Union, the
3 other two regions within the ICH, MedDRA is
4 mandated for use in the electronic reporting, and
5 of course, we have the biopharmaceutical industry
6 within the ICH regions.
7 Other than the biopharmaceutical industry
8 and the regulators, we also have MedDRA users in
9 other areas, in other countries beyond the ICH now
10 that more and more countries are adopting MedDRA.
11 For example, in North America, we're looking into
12 Mexico, and Canada already uses MedDRA. In South
13 America, Brazil is looking into use of MedDRA, and
14 in Asia, many Asian countries are doing that as
15 well, for example, South Korea, China, and
16 Singapore, so on and so forth.
17 Another important use in the MedDRA world is
18 the WHO drug monitoring center, the Uppsala
19 Monitoring Centre. UMC uses MedDRA in its VigiBase
20 so that VigiBase is using the same standards as the
21 regulatory database and industry database
22 elsewhere.

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1 We have a large number of academics. We've
2 got universities, research institutes. I would say
3 20 to 25 percent of all of our users are in that
4 category. We have toxicologists and others.
5 When we talk about worldwide, we have over
6 4,000 organizations in our MedDRA community.
7 MedDRA is an organization-based subscription. For
8 example, FDA is counted as one organization,
9 although within FDA, there are thousands, probably
10 tens of thousands of MedDRA users.
11 Pfizer has headquarters everywhere in this
12 world. They probably five or six headquarters, but
13 Pfizer is counted as one organization in the MedDRA
14 world. One Pfizer subscription is used for all
15 Pfizer staff worldwide.
16 Next, I'm going to introduce a little bit
17 about the features and structures of MedDRA to see
18 how that works for the adverse events. Now, what
19 MedDRA covers is described on this slide by this
20 big blue circle. Everything within the circle is
21 the information that is covered by MedDRA. Things
22 listed outside of the circle are the ones that

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1 MedDRA does not cover.
2 Let's take a look at the inside circle.
3 Now, because MedDRA is medical terminology, of
4 course, we can expect that MedDRA covers the
5 disease, disorders, the signs, and symptoms.
6 MedDRA also covers the labs, lab tests and test
7 results, and also medical and surgical procedures.
8 And in addition to that, we also cover the patient
9 medical, social, family histories.
10 In addition to the disease/disorder types of
11 information, MedDRA also includes medication
12 errors, product quality issues, device-related
13 issues, and then pharmacogenetic terms and
14 toxicology-related terms.
15 Also within MedDRA, there is a unique
16 feature called standardized queries. This is a
17 feature that MedDRA has to facilitate data
18 retrieval and data analysis for drug safety and
19 pharmacovigilance purpose. That's what we cover
20 inside of MedDRA.
21 Things we do not cover are listed also.
22 I'll start with the top left corner. MedDRA is not

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1 a drug dictionary. So when someone is reporting an
2 adverse event related to a drug, they need to
3 identify who is the patient, what type of drug the
4 patient took, and what happened to the patient.
5 So when identifying what type of drug the
6 patient took, they need to use a drug dictionary to
7 identify the drug, and then use MedDRA to describe
8 what happened to the patient. Did the patient have
9 a headache? Did the patient have a vomiting event
10 or some other events?
11 MedDRA does not have patient demographic
12 terms. This type of information is captured, but
13 captured in a column that does not use MedDRA to
14 code. MedDRA does not have clinical trial design
15 terms, so in MedDRA, you wouldn't find terms like
16 "double-blindness" or "placebo."
17 Moving to the right, because MedDRA is also
18 used to not only to report adverse reaction related
19 to drugs but also report adverse events related to
20 drug and device combination products, when trying
21 to identify the device, you need to keep in mind
22 MedDRA is not a device nomenclature. So to

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1 identify that particular device, the reporter needs
2 to use a device nomenclature to identify whether
3 it's a pacemaker, glucose pump, or some other
4 device, and then use MedDRA to describe what
5 happened to the patient.
6 MedDRA does not have a severity descriptor.
7 This surprises a lot of our users at the beginning
8 when MedDRA first came out. There was a why does
9 MedDRA include a severity descriptors? MedDRA has
10 all the adverse event terms, but because the
11 severity of a particular adverse event varies from
12 one clinical trial to another clinical, MedDRA has
13 a standard terminology to use for all clinical
14 trials.
15 For example, when we talk about a cancer
16 drug trial versus an antibiotic drug trial, the
17 severity will be very different between these two
18 trials. For example, if we both talk about
19 vomiting, the vomiting grade 2 in cancer drug
20 versus a vomiting grade 2 in antibiotic drug trials
21 are very different.
22 So that's why MedDRA does not have a

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1 standardized severity descriptor. That is left for
2 trials to decide, for that particular trial, what
3 is a mild, moderate, and severe for a particular
4 adverse event.
5 MedDRA does not have numeric value. For
6 those of you who just heard what I said, you said
7 hold on, wait a minute. You just mentioned MedDRA
8 has tests and test results. How come you don't
9 have a numeric value?
10 The test results in MedDRA are qualitative
11 results; they're not quantitative ones. For
12 example, blood glucose, we have blood glucose
13 normal, abnormal, increase, or decrease, and we do
14 not have blood glucose 40 milligrams per DL or 200
15 milligrams per DL, so that's the difference. And
16 MedDRA also does not have frequency qualifiers.
17 What does MedDRA look like? Now, we know
18 the scope of MedDRA, what's in, what's out, so what
19 does it look like? It essentially is a terminology
20 with five different hierarchic level, five tiers.
21 With these five tiers, we can start with a pretty
22 general level called system organ class.

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1 You can have system organ class like
2 according to the anatomical body system. You can
3 have cardiac disorders, renal disorders,
4 hepatobiliary disorders, gastrointestinal
5 disorders. You can also have a system organ class
6 based on the physiological system. For example, we
7 have endocrine disorders, metabolism disorders.
8 We can also have a system organ class based
9 on etiologies. For example, we have an infection
10 system organ class. We have neoplasm system organ
11 class. Then we have an additional system organ
12 class that's not disease and disorder oriented.
13 Like I mentioned in the scope, we have a system
14 organ class for social circumstances for our
15 patients' social and family histories. And we also
16 have a system organ class for investigation for lab
17 tests and test results. These are not disease
18 disorders system organ class.
19 We also have a system organ class for
20 surgical and medical procedures. So there are a
21 variety of different types of system organ classes,
22 and the total number of system organ classes is 27.

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1 Now, with that general topic in mind, on
2 top, when you go down the hierarchy, every level
3 you go down, then that general topic gets divided
4 according to either pathologically, or
5 anatomically, or physiologically, or clinically,
6 whatever makes sense. It gets divided into smaller
7 and smaller groupings. So as the level goes down,
8 the granularity increases.
9 So by the time you get down to the preferred
10 term level, that becomes a single medical concept.
11 So you could have a system organ class as cardiac
12 disorder, and when you come down to preferred term,
13 we're talking about concepts like bradycardia,
14 arrhythmia, those individual medical concepts.
15 That is what's at the preferred term level.
16 Under the preferred term, you said, well, we
17 have medical concept, that's done, right? No, we
18 have one more level underneath that. That's called
19 the lowest level term. The purpose of the lowest
20 level term is to provide different expressions of
21 that preferred medical term.
22 A lot of times one concept can be said in

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1 many different ways. That's why our language is so
2 rich. For example, you can have a preferred
3 medical concept called diarrhea. A lot of times in
4 the hospital or doctor's office setting, patients
5 don't usually say "diarrhea," right? They'll say,
6 "I have loose stool, watery stool," all of the
7 other different expressions of the same concept.
8 That why we have the lowest level term, to
9 allow those different varieties to be incorporated
10 into MedDRA. LLTs can be a synonym to the
11 preferred term or lexical variant to the preferred
12 term. For example, back pain can be also said as
13 pain back. We can have back pain as a preferred
14 term and pain back as a LLT. Then the other types
15 of LLT could be a quasi-synonym or sub-element of
16 that preferred term.
17 With the different variety of expressions at
18 the LLT level, that facilitates adverse event
19 coding. When patients are reporting different
20 types of expressions, the coder can easily find a
21 corresponding LLT within MedDRA. That's the
22 purpose of LLT, to allow coding adverse events to

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1 be linked to MedDRA, and that LLT will lead you to
2 a preferred term, a medical expression.
3 All of these relationships, the five levels
4 of relationships, are predefined in MedDRA to
5 facilitate a coding presentation and analysis. So
6 when an adverse event is reported to a
7 pharmaceutical company or reported to a regulatory
8 authority, if they have done the coding, what we
9 call the medical MedDRA coding, that means a linked
10 adverse event to a particular LLT.
11 These are the total 27 system organ classes.
12 As you can see, as I mentioned earlier, it not only
13 has disease and disorder system organ classes, it
14 also has other support system organ classes. So
15 based on the ICH guide, MedDRA is not only used for
16 adverse event reporting, but MedDRA can also be
17 used to encode patient medical histories, surgical
18 medical procedures, as well as lab tests and test
19 results.
20 That's an example of what a MedDRA hierarchy
21 looks like. This example uses as a cardiac
22 disorder, and it goes down. At the HLGT level, it

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1 breaks this cardiac disorder into a smaller
2 grouping, and as you go down the hierarchy, it
3 breaks even smaller, finer group. When it comes
4 down to the PT, it becomes a single medical
5 concept. Underneath that was a different
6 expression.
7 So now we know the LT is used for coding,
8 and then PT represents the medical concept. What
9 are these three levels for? Those are the three
10 grouping levels to help the subsequent data
11 retrieval and data analysis. So look for safety
12 signals because if you look the opposite way from
13 bottom up, you can tell that similar concepts are
14 grouped together at the HLGT level and then at the
15 HLGT level.
16 That way with the three levels on top, one
17 can then -- how should I say -- when you look down
18 the hierarchy, we're looking to the microscope,
19 right, to try and find the exact match of adverse
20 event. When we look up the hierarchal level, then
21 we're trying to gather the similar adverse events
22 together. That's when you do analysis. You want

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1 to see is there a signal, is there some safety
2 concern that related to this particular drug. Then
3 that's the time that we want to group similar
4 events together, and that's when we want to go up
5 to the hierarchy and to see if there's any
6 particular safety concern.
7 Because at the PT level, there could be many
8 types of arrhythmia, right? You could have
9 supraventricular arrhythmia, and you could have
10 ventricular-related arrhythmia, conduction
11 disorders. So at the PT level, you may not see a
12 strong signal because different types of arrhythmia
13 are coded to different PTs. But when you move up
14 the hierarchal level, then all the different types
15 of arrhythmia are grouped together, and that's when
16 you start to see a strong signal if that drug
17 really caused arrhythmia type of events.
18 MedDRA is also translated into many
19 different languages to facilitate the use of MedDRA
20 in non-English-speaking countries. Right now,
21 MedDRA has 11 different languages. English is the
22 master language, and then the English MedDRA is

<p style="text-align: right;">Page 41</p> <p>1 then translated into the other 10 different 2 languages. 3 All of these different languages are 4 connected through a 8-digit MedDRA code. Each code 5 represents one MedDRA concept, and that concept 6 then in turn is translated into all different other 7 languages. So this workgroup's work will be passed 8 down or adopted by other countries in the world. 9 Now, we start in the United States. Possibly in 10 the future, may be adopted by other countries. 11 MedDRA can then help to link the adverse events to 12 the different languages, other countries that use. 13 This is the last section I'm going to talk 14 about, the integration of MedDRA with other 15 terminologies. The first example I'm going to use 16 is the CTCAE. CTCAE is an adverse event 17 terminology created and maintained by the National 18 Cancer Institute, and it's used for the cancer 19 trials. 20 As I mentioned earlier, MedDRA does not 21 include severity descriptors. However, CTCAE, 22 since it's a specialized adverse event terminology</p>	<p style="text-align: right;">Page 43</p> <p>1 event terms are MedDRA terms with NCI-defined five 2 different gradings. So as of version 4 of CTCAE, 3 CTCAE is completely compliant with MedDRA. 4 I should add, CTCAE's terminology and 5 MedDRA's terminology, we both are maintained, and 6 we both evolve further down the road. So we work 7 closely. If CTCAE wants to add a new term to their 8 terminology, they will first look into MedDRA. If 9 their new term that they want to add exists in 10 MedDRA -- if it does, then it's easy to add. If it 11 doesn't, then CTCAE's maintenance organization, the 12 NCI, will contact us, and we can then add that term 13 to MedDRA so that they can add it, and then it's in 14 MedDRA. So the maintenance is important for both 15 terminologies. 16 This is the TROOPS tool that contains the 17 adverse event terms as well for the sedation 18 purpose, and we have received an initial draft of 19 the TROOPS terms. My colleague Judy Harrison did 20 an initial mapping. 21 A majority of the TROOPS terms mapped nicely 22 with MedDRA. There's only a handful of terms. For</p>
<p style="text-align: right;">Page 42</p> <p>1 and used in one kind of clinical trial -- so the 2 National Cancer Institute does have severity 3 descriptors in the CTCAE. 4 In their early versions of CTCAE, we created 5 a mapping between CTCAE adverse event terms and 6 MedDRA terms so that CTCAE and MedDRA can be 7 bridged together to facilitate NCI's research, and 8 then facilitate FDA's reporting and drug approval 9 process. 10 When NCI moved up to CTCAE version 4, what 11 we did is to actually synchronize CTCAE adverse 12 event terms with the exact MedDRA terms. Because 13 all the adverse event terms in CTCAE were in 14 MedDRA. They're just worded slightly different in 15 order to make this bridge easier. 16 So what NCI decided to do is just adopt 17 MedDRA terms as their adverse event terms. And 18 then NCI, based on the base adverse event terms of 19 those MedDRA terms, defined their grading from 20 grade 1 to grade 5, grade 1 as the most mild 21 adverse event and to grade 5, which is death. 22 In CTCAE, this base column, the base adverse</p>	<p style="text-align: right;">Page 44</p> <p>1 example, here I give the example, the sedation 2 complication, it does not have an exact match in 3 MedDRA. We have anesthesia complication, but not 4 the sedation complication, not at that level of 5 detail. So what we can discuss is to add this term 6 into MedDRA. That way the mapping will be nicely 7 bridged. 8 By doing the mapping with other terminology 9 also enriches MedDRA because MedDRA is intended to 10 meet the needs of our users. When we did the CTCAE 11 mapping, we added some additional terms to meet the 12 needs of the National Cancer Institute. The last 13 two years, we also did a mapping of MedDRA to 14 pediatric adverse event terminology that was 15 created by the NICHD. In that process, we also 16 added additional pediatric terms to MedDRA, so that 17 through these process of projects, MedDRA is 18 enriched in a particular area of the medicine. 19 We hope through this process and the 20 collaboration with your terminology, we can make 21 MedDRA better for the sedation society. With that, 22 I'll take any questions.</p>

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1 (Applause.)
 2 DR. WARD: Questions?
 3 DR. RIKER: Thank you for that great
 4 presentation. One of the things I didn't see in
 5 any of your information is the concept of
 6 causality. In all of our studies, when we're using
 7 MedDRA, there's also a column there, "probably
 8 associated, possibly associated." And I think the
 9 ability to separate -- just as an example, a
 10 varicocele bleeding patient is getting an EGD who
 11 gets hypotensive related to blood loss during the
 12 procedure. But that's not related to the
 13 procedure; that's related to the underlying
 14 disorder.
 15 So is there a place in MedDRA for causality
 16 to be assessed?
 17 DR. ZHAO-WONG: The causality is just like
 18 adverse events. They are disease/disorder terms.
 19 MedDRA does not particularly separate these adverse
 20 event terms or those causality terms. Since
 21 they're all medical terms, what is commonly done is
 22 it's in the different fields of the form.

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1 I'll give you an example. MedDRA is used to
 2 code medical histories. Many medical histories,
 3 just like a patient used to have cardiac
 4 arrhythmia, that's a history term. And in another,
 5 patient reported arrhythmia because he took a drug
 6 that caused arrhythmia.
 7 So they're both arrhythmia terms, but if
 8 that arrhythmia term is put in the adverse event
 9 field in the report, then it's an adverse event.
 10 If that arrhythmia term is put in the medical
 11 history field, then that's medical history.
 12 I think in causality in your case, the case
 13 report form, based on the design, if that disease
 14 is in the causality field, then that's a causality.
 15 If that disease is in the adverse event field, then
 16 it's an adverse event.
 17 Does that make sense? It's linked to the
 18 different fields in the report.
 19 DR. WARD: Why don't we wait for the
 20 questions? We're going to have a panel discussion
 21 with the whole first group, so let's hold the rest
 22 of the questions for the panel discussion.

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1 DR. ZHAO-WONG: Okay.
 2 DR. WARD: Thank you.
 3 So continuing on this idea of how we
 4 classify adverse events, Maala is going to talk
 5 about the Quebec guidelines for reporting pediatric
 6 sedation.
 7 Presentation – Maala Bhatt
 8 DR. BHATT: Thank you. It's really my
 9 pleasure to be here today to talk to you about the
 10 Quebec guidelines, which we developed several years
 11 ago now. And I don't think I adequately
 12 anticipated the diversity of the audience today, so
 13 I'd be very happy to take any questions, and I
 14 realize that we'll do that in the panel.
 15 Just to give you a little bit of background,
 16 we came about this process in anticipation of work
 17 that we were going to be leading in Canada through
 18 multicenter research looking at the safety of
 19 procedural sedation through a long-term
 20 surveillance study for adverse events.
 21 Before we embarked on that, we really felt
 22 like we needed a standardized list of definitions

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1 because in our review of the literature, everybody
 2 called the same event different things or they
 3 reported different outcomes for the same questions.
 4 So as a part of that process, we started out by
 5 looking if there were any existing databases that
 6 we could use, any taxonomies that we could map to,
 7 and really, we didn't come up with anything.
 8 We looked at trying to map our terms to
 9 SNOMED CT. We talked to Joe Cravero's group
 10 initially to see what they had used, and we really
 11 didn't find anything that we were satisfied with.
 12 What the end result was is that PERC, which
 13 is Pediatric Emergency Research Canada, who is
 14 leading this work, partnered up with PECARN, which
 15 is the collaborative emergency research network in
 16 the U.S., to develop a consensus panel. I invited
 17 Mark Roback to join me as the co-chair on that
 18 panel as we had been recently introduced by a
 19 mutual colleague. And we assembled a panel of six
 20 emergency physicians and two anesthesiologists with
 21 equal representation from the U.S. and Canada.
 22 What we came out with was standardized

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1 terminology and reporting for adverse events in
2 emergency department procedural sedation. It was a
3 consensus-based process, and I'll just describe a
4 little bit about the process to you and spend more
5 time talking about what we ended up in the formats
6 for our definitions.

7 The process was, we started off by
8 generating just a complete reference list from the
9 literature from the MEDLINE search from 1950 to the
10 first week of July in 2007 when we started our
11 process. From this list, we drafted a list of
12 sedation terms, adverse events, and definitions
13 found in the reference list articles, and we
14 compiled this and circulated it to the panel
15 members.

16 Eventually, we reached consensus on the
17 events to be routinely reported, and we did this by
18 way of electronic communication, teleconferencing,
19 and then finally, one face-to-face meeting in Mont
20 Tremblant, Quebec, which is why the guidelines were
21 dubbed the Quebec guidelines.

22 I'll just describe a little bit to you about

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1 how we ended up with intervention-based
2 definitions. In our search, we found that
3 different studies reporting on very similar things
4 reported very different definitions. For example,
5 in one of Mark's studies in 2004 in Denver, so at
6 an altitude, he deemed that oxygen desaturation was
7 a saturation less than 90 percent, no duration
8 specified. Sanborn in 2006 said it was a
9 desaturation greater than or equal to 5 percent
10 from baseline for greater than or equal to 1
11 minute.

12 I want you to pause to think about how
13 difficult that is to do in a clinical setting and
14 to see how many of us would actually calculate the
15 5 percent desat and also wait the 1 minute before
16 intervening. I come from a different lens in
17 emergency medicine. It might be a more realistic
18 thing in anesthesiology, but certainly in emergency
19 medicine, I haven't seen that happen.

20 Then Dr. Berkenbosch reported in 2004 that
21 desaturation was an O2 sat less than 90 percent for
22 30 seconds. So what you can see is that all of

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1 these definitions have a threshold, a number, and
2 then plus or minus a duration.

3 When we went rounds and rounds of
4 discussion, we thought that although they are
5 ostensibly very objective, because you have a hard
6 number and another hard number for a level and a
7 duration, there could be two scenarios where you
8 miss these things. If you have a precipitous fall
9 in an oxygen saturation and you intervene
10 immediately, you'll never actually fulfill some of
11 these definitions because you won't wait that 30
12 seconds or 60 seconds for it.

13 Then just as I said before, I think duration
14 is a really difficult thing to abide by or measure
15 in a clinical setting where you're really leaping
16 in to help your patient.

17 We didn't really feel like these definitions
18 were going to be able to give us standardized and
19 reproducible events, which is what led us to this
20 concept of intervention-based definitions.

21 Certainly, I think that they were controversial
22 then, and they still probably are a little

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1 controversial. But what they do require is that
2 for both the clinical event to have occurred and
3 for an intervention to be performed with the intent
4 of treating or managing that event. Every event
5 that does occur requires additional documentation.

6 That helps the researcher. These were
7 developed with the purpose of reporting in
8 research. That helps the researcher sort through
9 accuracy and severity based on the criteria used
10 for recognition and which interventions were
11 performed.

12 I'm going to go through a couple of examples
13 with you, and that might put this into a little bit
14 of perspective. I'm using oxygen desaturation as
15 the example throughout the next few slides, but
16 certainly, it applies to any of the adverse events.

17 We defined oxygen desaturation as oxygen
18 desaturation, and one or more of the following
19 interventions are performed with the intention of
20 improving the saturation. The interventions, as
21 you can see, range from very minor interventions
22 such as verbal cues and tactile repositioning to

<p style="text-align: right;">Page 53</p> <p>1 more important interventions such as the 2 application of positive-pressure, ventilation with 3 or without assisted ventilation and intubation. 4 Then if you do experience a desaturation, we 5 would require additional documentation, and that 6 additional documentation includes for oxygen 7 desaturation, what the baseline saturation was on 8 room air prior to sedation; if the patient was 9 pre-oxygenated; and if they were pre-oxygenated, 10 what method did they receive their oxygen by and 11 what the flow rate was; and then which 12 interventions were performed in response to the 13 oxygen desaturation so that this would allow the 14 researcher or the person sorting through the data 15 to understand for themselves if this would qualify 16 as an important event for them or not. Then 17 finally, what was the lowest reliable oxygen 18 saturation measure during sedation. 19 I'll use another example here, which is 20 apnea just to give you an idea of another 21 definition. It's the cessation or pause of 22 ventilatory effort, and one of more of the</p>	<p style="text-align: right;">Page 55</p> <p>1 terminologies to describe the adverse events. Some 2 studies called them type 1 and type 2 adverse 3 events. A lot of studies lumped adverse events 4 altogether even if they had different 5 pathophysiologic origins. 6 It's a clinically appealing category of 7 airway and respiratory complications, but if you 8 think about all of the things that go into that, 9 such as laryngospasm, partial airway obstruction, 10 central apnea, they all have different 11 pathophysiologies. And lumping them all into one 12 to look at, especially if you're going to look at 13 predictors of these events, I think that you'd be 14 missing some of the granular data. 15 What we did is we created nine main 16 categories, but we separated the events within each 17 of these categories so that individual events could 18 be reported separately. And if they were lumped 19 altogether, you would have an understanding of what 20 was contained in each of these categories. 21 For example, some of them only have their 22 one event such as oxygenation, vomiting,</p>
<p style="text-align: right;">Page 54</p> <p>1 following interventions were performed with the 2 intention of stimulating or assisting with 3 ventilation. 4 So again, it starts with very mild 5 interventions such as verbal cues and tactile 6 stimulation, but then advances to tracheal 7 intubation and the administration of reversal 8 agents. 9 The additional documentation here asks the 10 user to indicate the criteria used for recognition. 11 It could be visual confirmation, loss of a 12 waveform. And I think that this really helps the 13 researcher understand if it would qualify as apnea 14 according to them. Then again, which interventions 15 are performed. And we ask them to document all of 16 them that do apply so that we can understand what 17 the most advanced intervention was. 18 The second thing that we found was that 19 reporting of the adverse events was not 20 standardized. So as we mentioned, the studies that 21 were answering the same question would not report 22 on the same outcomes, and studies used different</p>	<p style="text-align: right;">Page 56</p> <p>1 aspiration, but others like ventilation contain 2 central apnea, obstructive apnea, and obstructive 3 apnea contains two subcategories of complete airway 4 obstruction and then partial airway obstruction, 5 and then finally, laryngospasm. 6 You can appreciate that if we just report on 7 ventilatory disorders or a ventilatory adverse 8 event, you really have no idea what's going on with 9 that patient. So I think it really was important 10 for us to separate out those things, especially for 11 emergency department procedural sedation where some 12 of these are more common than others and less 13 common than others. 14 Then as I said before, each of those adverse 15 events requires supplemental documentation, so 16 documentation that would help the researcher decide 17 on the severity of the event, and as well, the 18 accuracy and what was done to manage the event in 19 some cases. 20 For example, in vomiting, it's the only 21 definition actually that doesn't require an 22 intervention. So if you vomit, you vomit. It's</p>

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1 the expulsion of your gastric contents. But in the
2 additional documentation, we do ask whether an
3 antiemetic was administered to give us an idea of
4 how the event was managed.
5 Just brief, this is quite short compared to
6 the last one, but I would accept any questions.
7 Just to give you a little bit of reflection, we
8 just completed five years of data collection at six
9 Canadian centers for pediatric procedural sedation,
10 and we gathered about 6300 patients during these
11 five years, looking at the safety of procedural
12 sedation and specifically looking at risk factors
13 for adverse events.
14 Just reflecting on our definitions, looking
15 at the pros and the cons, I really do feel that the
16 intervention-based definitions give you
17 reproducible, objective events, and that they -- I
18 believe in the intervention. I believe in the
19 intervention over the threshold and duration. It
20 probably would have been a good idea for us to map
21 to MedDRA in retrospect.
22 I think that another pro is that the

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1 researchers can include only events that meet their
2 criteria for severe or important. So we think one
3 of the criticisms was that you captured every event
4 that may not necessarily be important to a
5 clinician or a researcher.
6 For example, I might have a lower threshold
7 to intervene than a colleague. So if an oxygen
8 saturation decreases to 95 percent, or even
9 98 percent, I might intervene with a verbal cue,
10 and that would be technically documented as an
11 adverse event, where you might not really think
12 that that's an important event.
13 By requiring the additional documentation, I
14 would have access to the fact that, okay, only
15 verbal cues were administered, and I would see that
16 the lowest oxygen saturation was 98 percent. So in
17 sorting through the data for research, you could
18 exclude those patients, but an advantage is I guess
19 it's more sensitive, so you don't lose any cases in
20 this way.
21 The downside, I think, through these five
22 years is that the documentation is really quite

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1 extensive. It's six pages of documentation if
2 you're going to document on every adverse event,
3 and I think it really does need to be incorporated
4 into your clinical documentation in order for it to
5 be successful.
6 We created a site-specific electronic
7 documentation form for each site that incorporated
8 clinical and study documentation into one form, so
9 that this was incorporated into the sedation
10 documentation at each of the sites, and I think
11 that went a long way towards people being compliant
12 with the documentation.
13 I do think, though, that there is an ongoing
14 need to educate people, the end users, of using
15 these definitions because they really are
16 intervention-based definitions. So just because
17 you need to have the event and perform an
18 intervention -- and the clinical staff did need
19 regular updates when we saw that some of the data
20 coming through was not as we expected, so they did
21 require ongoing education.
22 That is another thing after Mark's talk this

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1 morning, just about the dissemination. With the
2 publication in Anesthesia and Analgesia, I think
3 that the idea is that people across specialties
4 would use these outcomes. But the challenge
5 is -- we published in an emergency medicine
6 journal, and there have been a number of studies
7 that have used the definitions as outcome measures
8 in emergency medicine, but I don't think that these
9 definitions have spanned specialties. So I think
10 that that is a challenge when it depends on where
11 things are published and how things are
12 disseminated.
13 That's it. Thanks.
14 (Applause.)
15 DR. WARD: There's a little change in
16 schedule, and I'm not quite sure exactly how it's
17 going to work. I think we're going to go to common
18 and adverse events in adult sedation, and then
19 Keira and Steve are going to do the SIVA reporting
20 tool in the next session.
21 DR. PANDHARIPANDE: A little bit in this
22 session.

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1 DR. WARD: A little bit of both. So I think
2 these two are going to overlap a little, and then
3 we'll have our question and answer for all the
4 speakers in the first session after your talk.
5 Presentation – Pratik Pandharipande
6 DR. PANDHARIPANDE: Good morning. I thought
7 we'd change this format just a little bit to
8 introduce the problems first, and then perhaps the
9 solutions coming from Keira, Mark, and Steve in the
10 follow-up session. So we'll do a brief
11 introduction over here
12 I'm not going to try to spell out every
13 sedation-related adverse event because that list
14 goes on. Mark and Denham are going to do a review
15 again tomorrow morning on this one, so that's the
16 first part of this.
17 Quick disclosure over here, I do have a
18 research grant from Hospira, which makes
19 dexmedetomidine, in conjunction with an NIH RO1
20 that I have.
21 The important part over here is that I was
22 specifically told that this was supposed to be a

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1 discussion, and I'm not supposed to be just
2 presenting slides, so that's going to be the
3 format. It's a discussion format. I'm going to
4 have a few questions, and hopefully, the audience
5 will participate and respond.
6 I'm an ICU intensivist, anesthesiologist but
7 don't do much procedural sedation. So you-all are
8 the experts out there. I just have to ask the
9 questions. And then the basis of some of these
10 questions come from Keira Mason and Steve Green's
11 work, where they had published in BJA about the
12 reason why one needs to standardize definitions.
13 I'm going to use that as a framework for this
14 discussion.
15 Here we go. I told you it's going to start
16 with questions. The first important thing, I
17 think, as a group and as we think about
18 recommendations, et cetera, one probably needs to
19 think about what is the definition of a procedural-
20 related or sedation-associated adverse event.
21 I'm going to just put out the definition
22 that Keira and Steve had put out in their

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1 paper -- that's Keira Mason and Steve Green over
2 here -- in their paper in BJA. They looked at the
3 IOM definition. They looked at the WHO definition
4 and sort of came up with this definition, which is
5 more related based on their opinion and their co-
6 authors as far as something that would work well
7 for procedural-related sedation.
8 I'm going to stop right here, and let
9 you-all look at this and think about this. We can
10 start commenting on whether you feel that this is
11 an appropriate starting point for a definition, or
12 whether this needs to be modified as we think about
13 what our recommendations are going to be for other
14 folks. We'll start with Rebecca.
15 DR. TWERSKY: I guess my reaction is to the
16 first word, "unexpected." We know that when we
17 give sedatives and analgesics, that we're going to
18 have some sort of respiratory response whether it's
19 apnea or a delay in respiratory rate. So I
20 wouldn't necessarily consider that unexpected.
21 I think it is an adverse event if, again, we
22 come up with a definition of duration in the

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1 intervention. But I think we might consider
2 responses to the sedation that are adverse but are
3 not necessarily unexpected.
4 DR. WEISS: At the same time, to follow up
5 on what Rebecca was saying, that "cause or
6 threatened to cause." For example, if you're in a
7 GS, and you give propofol, if someone becomes
8 apneic for seconds, might slip their jaw for a
9 second when they breathe, that threatens to cause
10 an adverse event. But I don't feel that -- and I'd
11 intervene by definition. But then once I
12 intervene, and they breathe again, I don't consider
13 that to be an adverse event.
14 I'm wondering if there's an issue of
15 sensitivity and specificity. Are we capturing too
16 much? Are we capturing things that may not make a
17 difference, and then might alter the way we treat
18 patients, when in fact we have a hair trigger on
19 what we call an adverse event?
20 I don't mean to sound cavalier about that,
21 but if I put my finger on someone's jaw, and they
22 breathe 2 seconds later, I don't consider that an

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1 adverse event.

2 DR. PANDHARIPANDE: Keira?

3 DR. MASON: I don't quite agree with Rebecca

4 about the respiratory depression or whatever, that

5 when we're doing a sedation, that we necessarily

6 expect that we're going to have an adverse event.

7 I think the opposite: When we do a sedation we

8 don't expect, we're going to have an adverse event.

9 We anticipate that we will have some events. Maybe

10 we might have some respiratory changes.

11 Certainly, there are drugs that don't even

12 create respiratory changes, and you might have a

13 hemodynamic change. But I think it's what you

14 don't anticipate is going to happen that we are

15 really trying to capture.

16 DR. PANDHARIPANDE: Maala?

17 DR. BHATT: I was just going to make a

18 comment. I think that that indicates that you are

19 very high-skilled. So if this is to be adopted by

20 everybody, the small events are precursors to

21 bigger events.

22 So if we don't recognize them, if we don't

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1 see them as a -- you don't have to call an adverse

2 event, but if you don't see it as a complication or

3 a precursor to be a bigger event, I think that

4 people that are less well trained, or aren't

5 anesthesiologists, or practicing in a small

6 community where you might not do this as much, may

7 not see this as -- might not view it in the same

8 ways.

9 Does that make sense?

10 DR. PANDHARIPANDE: Joe?

11 DR. CRAVERO: I think this is all really

12 good work. I would just offer a couple of thoughts

13 of what we've talked about in our consortium for a

14 long time, which is it is hard to make definitions

15 that fit every type of provider, because as an

16 anesthesiologist, I may be providing what I'm

17 terming sedation with propofol.

18 Honestly, if a patient becomes apneic for a

19 period of some seconds during that case, almost

20 like the Geico commercial, for me,

21 positive-pressure ventilation is what I do, so I

22 don't necessarily consider that an adverse event.

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1 Even if there was apnea and I intervened with

2 positive pressure, it's part of my work every day.

3 I would offer -- and again, I'm not saying

4 this is correct, but this is the kind of

5 conversations that come up. That same care

6 delivery in a different setting with a much

7 different provider, or that same event that occurs

8 with an oral sedative having been delivered by a

9 nurse provider, where the patient becomes apneic

10 and there is a requirement for positive -pressure

11 ventilation is a slightly different situation.

12 I would also offer the kinds of things we've

13 talked about, which is these minor issues like

14 oxygen desaturations, that we are assuming are

15 precursors or harbingers of other bad events, there

16 are not a lot of papers that really help us

17 understand what a 10-second oxygen desaturation

18 less than 90 really means in terms of any kind of

19 outcome. In and of itself, it clearly doesn't

20 represent an adverse outcome.

21 Whether or not events like that are actually

22 connected to more severe outcomes, there are people

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1 in this room that are better outcomes and

2 statistical researchers than I am. But that

3 connection is not necessarily made in most settings

4 of sedation.

5 So I would just say while I think they're

6 important in one sense or another, we do need to be

7 careful about how generalized some of these -- at

8 least when you get into the weeds, it starts to get

9 kind of tricky.

10 DR. WEISS: Let me ask you a question then.

11 Are you saying then that leads to the possibility

12 of raising the idea that what might be considered

13 an adverse event in one setting is not an adverse

14 event -- with the exact same set of situations,

15 what might be an adverse event in setting A is just

16 not routine but not unexpected and not an adverse

17 event in another setting.

18 So it's not just the adverse event we're

19 dealing with, but the location and site with which

20 we're doing it that might also provide the

21 destination, what we're going after.

22 DR. PANDHARIPANDE: We'll let Doug respond,

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1 and then Dan Sessler.
 2 DR. CARLSON: When we look at existing
 3 taxonomies of patient safety events, most are based
 4 on outcomes -- and I think if we look at this, it
 5 may help a little bit, although this is the crux
 6 that gets to be difficult -- is that if you look at
 7 serious safety events, or temporary or permanent
 8 harm, you go back to whether there was a variation
 9 from standard care. And there has to be a
 10 variation in standard care to actually go into a
 11 safety event.
 12 Now, I agree that bad outcomes in sedation
 13 are always variations of standard care, but it gets
 14 back to apnea. If you have an apneic event and you
 15 are trained to do that or are expecting that,
 16 that's not a variation from standard care. So I
 17 think we have to be a little bit careful about
 18 saying that is the adverse event.
 19 On the other hand, I do think that those
 20 interventions should be proxies for precursor or
 21 potential near misses. It's balancing that of
 22 measuring all the things we do to intervene versus

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1 what is not standard care and separating it out
 2 that is the crux of the issue.
 3 If we look at outcomes and go backwards,
 4 there may be a solution, although not an easy one
 5 that I see.
 6 DR. PANDHARIPANDE: Dan Sessler?
 7 DR. SESSLER: In the previous version of
 8 this meeting, we had a problem in that events were
 9 considered to be serious or not on a highly
 10 contextual basis. For example, movement in some
 11 situation was considered absolutely fine as long as
 12 analgesia was okay. In other situations such as
 13 pediatric MRI, movement was a disaster, but you had
 14 no need to deal with amnesia.
 15 The way we got around that was making our
 16 primary outcome based on proceduralist
 17 satisfaction. And I wonder if we do something
 18 similar here, where complications are defined in
 19 terms of the context and who is performing it.
 20 Complication would be something that the
 21 proceduralist considers to be abnormal.
 22 An anesthesiologist is giving a little

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1 positive-pressure ventilation is not considered
 2 abnormal. That's absolutely fine. It's a nurse
 3 who is unprepared for this in a different context,
 4 maybe that is an adverse event.
 5 DR. PANDHARIPANDE: Training plus the
 6 context of the --
 7 DR. SESSLER: Exactly.
 8 DR. PANDHARIPANDE: We have one here, and
 9 then there, and then we'll get to you. Sorry.
 10 John Guerra? Sorry.
 11 DR. GUERRA: I think sometimes we get hung
 12 up a little on event versus adverse event, and two
 13 aren't necessarily the same. As an intensivist, I
 14 may be providing positive pressure as well during
 15 procedural sedation. That's okay. That's part of
 16 what I'm trained to do as well.
 17 Might I call that an adverse event? Maybe
 18 yes, maybe no. But at the same time, picking up
 19 those events, even if they don't lead to a patient
 20 outcome that is a problem, is important because it
 21 helps us in defining something that we haven't
 22 discussed yet, and that is, what's the skill set

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1 required at the bedside when a patient is
 2 undergoing procedural sedation.
 3 I think there's value in collecting both of
 4 those, and we can argue back and forth probably
 5 about expected/unexpected, adverse event/event, but
 6 yet defining those things helps us become probably
 7 safer sedation providers in the long term.
 8 DR. HERTZ: Also, what if you have two
 9 agents, and they're both resulting in these events
 10 that are readily managed, but one is doing it at
 11 twice the frequency? I think that's something that
 12 people would want to know when they're selecting an
 13 agent, what is the difference, and if you can't
 14 capture these things in some way, even if they are
 15 expected, how do you make a judgment about the
 16 overall utility, all of the different decisions
 17 that are made?
 18 DR. PANDHARIPANDE: Denham, and then Keira.
 19 DR. WARD: This is a great discussion, and I
 20 think you also want to think about, even though
 21 there's a lot of overlap, maybe importing as a QI
 22 system, where we're letting a lot of practitioners

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1 use a lot of different drugs that we want to keep
2 track of, maybe more like a postmarketing QI
3 situation, versus if we're designing a clinical
4 trial for a new agent in a phase 2/phase 3 type of
5 trial, how do we define adverse events
6 prospectively so we're collecting that data for the
7 approval process in a phase 3 clinical trial.
8 There's a lot of overlap there, but they're
9 somewhat different, too, in the kinds of adverse
10 events that we're going to be looking at because in
11 the QI situation, we're much less controlled,
12 right? We're going to be in different areas with
13 different practitioners doing different kinds of
14 administration, versus a phase 3 clinical trial,
15 it's going to be much more controlled: who's going
16 to be given the drug, how we're going to be
17 collecting the data, what kind of situations. It's
18 going to be in and, perhaps a lot more control over
19 the kinds of definitions of adverse events that
20 we're going to be able to collect.
21 Maybe, overlapping in the two concepts of an
22 adverse event and a QI type situation and adverse

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1 event in maybe a new drug, or a new technique, or
2 new device. We can discuss both, but I think we
3 want to keep the focus a little bit on the phase
4 3/2, maybe even phase 1, clinical trial, that I'll
5 talk about tomorrow, of a new drug or device going
6 through the regulatory process.
7 DR. PANDHARIPANDE: Thank you. Keira?
8 DR. MASON: I think when we're trying to
9 think about what is an adverse event, that maybe we
10 need to define what is sedation because my
11 definition of sedation is patient who is able to
12 maintain hemodynamic stability, maintain their own
13 airway on their own.
14 If that's what we're defining sedation as,
15 then any time somebody is doing positive-pressure
16 ventilation of any kind is a deviation from what
17 essentially the definition of sedation is. I think
18 it's irrelevant whether I feel comfortable ambuing
19 a patient because that's my skill set as an
20 anesthesiologist. That is not necessarily the goal
21 of what sedation is, so it's a deviation.
22 AUDIENCE MEMBER: So I was just looking at

Page 75

1 the wording of the definition. Is it possible to
2 put the first slide back up, the first question? I
3 didn't realize we were on 3 already.
4 DR. PANDHARIPANDE: Well, the group
5 discussion went longer than I'd anticipated.
6 (Laughter.)
7 AUDIENCE MEMBER: Whenever I look at these
8 things, I try and get rid of terms that you can't
9 really define that are too vague. Although I agree
10 with pretty much everyone's -- what they've said,
11 you can look at these kinds of definitions and say,
12 well, what would "unexpected" actually mean or
13 "undesirable"?
14 I would get rid of terms like that or even
15 the word "threaten," but I would combine just
16 simple facts like "responses that cause patient
17 injury," I think we can all that most people know
18 what discomfort means. And then Dan's
19 recommendation about the provider contextual is
20 great, and to combine those two things.
21 DR. PANDHARIPANDE: Rich?
22 DR. RIKER: I think if we think about the

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1 variety of patients, procedures, and adverse events
2 we're talking about, it's incredibly complex to try
3 to pull something that's going to apply across the
4 board. But I would really plead for us to have the
5 ability to understand what was sedation related and
6 what was either disease related or procedure
7 related. A patient gets intubated during
8 bronchoscopy, that might be an incompetent
9 proceduralist causing pneumothorax. That might be
10 over-sedation and apnea and needing intubation for
11 that. That might be an underlying disease process,
12 where the patient was on 80 percent oxygen but not
13 intubated prior to the procedure.
14 So having some ability to make sense of that
15 and assign that etiology to the adverse event I
16 think is another thing we really need.
17 DR. PANDHARIPANDE: Sure. Last person.
18 Mark?
19 DR. ROBACK: I think as we identify these
20 events, or adverse events, or adverse outcomes, we
21 need to consider what we're going to do with that
22 information at the end of the day.

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1 When Maala first presented her Quebec
 2 guidelines to Joe's group, we had this vigorous
 3 discussion, which was exactly like we're doing now,
 4 and it became very clear to us -- because in
 5 emergency medicine, we do sedation, but we don't
 6 necessarily do it every day, whereas the people
 7 that are doing it every day in their sedation
 8 units, they're going to be measured by their
 9 outcomes and their adverse events. So every time
 10 Joe does a jaw thrust, they're going to say that's
 11 a bad thing? Well, of course, we don't want that.
 12 So really considering what are the most
 13 important things to follow and with patient safety
 14 being the goal.
 15 DR. PANDHARIPANDE: All right. I'm going to
 16 move on to another question. This is just to get
 17 the discussion going, which I see we've gotten that
 18 goal taken care of.
 19 (Laughter.)
 20 DR. PANDHARIPANDE: This question leads to
 21 the next two presentations, which are going to be
 22 talking about the tools. We've already started

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1 introducing this concept that is it just I expect
 2 some apnea, I expect some of this.
 3 So when we think about definitions and
 4 recommending what definitions should be considered
 5 adverse event, should they be linked to events and
 6 thresholds? So you had an apnea period for X
 7 amount of seconds, or does it have to include an
 8 intervention?
 9 I'm just going to put up a couple of
 10 examples over here. All of you know this, but
 11 these are from the literature, in apnea for 30
 12 seconds or oxygen saturations less than 90 percent
 13 for 30 seconds. These kinds of numbers, they have
 14 disadvantages because there are no thresholds based
 15 on the fact that nobody has been able to show that
 16 this particular thing is associated with an
 17 outcome, which is some of the things that we've
 18 been discussing now.
 19 That's one way of doing
 20 it, is having event threshold base, and Maala has
 21 already discussed some of this about having an
 22 intervention-based definition. For example, would
 you consider apnea only to be an adverse event if

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1 you required masking or positive-pressure support,
 2 or an oxygen desaturation would be considered a
 3 true desaturation only if you required oxygen
 4 supplementation.
 5 Again, those seem to have some benefits, but
 6 there are some problems as well. Because if these
 7 are to be reported, do you think someone is not
 8 going to be reporting something because they don't
 9 want it to be an adverse event. So if I can get
 10 by -- I see the sats are now 89, I see they're 88,
 11 87. They will recover. Let me just give them a
 12 little bit more time, so those kinds of things and
 13 whether that causes a problem.
 14 I'm going to again open it up for questions
 15 because I don't want to show the scale yet.
 16 TJ?
 17 DR. GAN: So again, as you alluded to, the
 18 problem with that is that we all practice
 19 differently. We have different anxiety levels of
 20 when to intervene. One may intervene when
 21 saturation is 95 percent; others may intervene at a
 22 different level. So then you end up with a not

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1 very useful data because everyone intervened at a
 2 different time when you start intervening with
 3 blood pressure going down by how much for how long.
 4 So I think it's important to perhaps capture
 5 the raw data, so to speak, when the saturation
 6 drops X amount or blood pressure drops an amount.
 7 Then whether you intervene or not, that is again,
 8 as Dan has alluded to, is contextual. Some people
 9 intervene -- an anesthesiologist may intervene at a
 10 different level compared to the others.
 11 I think the problem with this, what you put
 12 up, is that it's going to be very difficult to sort
 13 out what the actual events mean.
 14 DR. PANDHARIPANDE: I know there were
 15 problems with what I put up. That was the whole
 16 reason I put it up, to start this conversation.
 17 We'll go next there, and then, Maala, you're
 18 next.
 19 DR. LERMAN: I agree exactly with TJ. I
 20 think the construct in which you're making your
 21 observation makes a difference. So I think you
 22 need to capture both groups of information. I

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1 think however arbitrary your initial thresholds for
2 identification of a "adverse event" may be is one
3 thing, an intervention suggests an increased level
4 of concern, and that raises the bar. You could
5 call it major to minor or otherwise.
6 For example, who in the audience would not
7 intervene if the patient's saturation were
8 80 percent? So it's pretty obvious, we're using
9 the 90 percent and below as just a buffer because
10 the next situation may become extremely concerning.
11 And if it gets to 80 percent, if you didn't
12 intervene, with a bradycardia, for example, you
13 almost certainly will be running into a problem
14 shortly.
15 It is totally arbitrary. It totally depends
16 on the individual and the construct in which this
17 occurs, and I think you need to capture both bits
18 of information. Individually, I don't think you
19 can ever come to a satisfactory conclusion about
20 what an adverse event is.
21 DR. PANDHARIPANDE: Maala?
22 DR. BHATT: Obviously, I have an inherent

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1 bias here, but I would agree that just having a
2 definition that includes an intervention and
3 classifying that, and lumping it all together, is
4 not useful information. But I think that I would
5 agree that you need both sets of information. And
6 I think that the required documentation that
7 follows in the intervention-based definition will
8 provide you with that.
9 I would still maintain that if you use the
10 thresholds, I think that you're not going to get an
11 accurate, reproducible event because different
12 people will intervene for different things. And
13 just because they are part of the study, I don't
14 believe that they will stand by and wait for that
15 threshold to become effective.
16 DR. PANDHARIPANDE: We'll do Rick, Denham,
17 and then John, and then the next speakers can come
18 up with some solutions.
19 DR. WARD: The next group is a panel, and
20 maybe we should take that right now, is to get the
21 speakers from the first session all up here. Maala
22 and Anna, you will be on the panel, and we'll just

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1 segue right into the panel.
2 DR. PANDHARIPANDE: Do you want them to show
3 the tool at least and then walk through the
4 world -- Mark, do you guys want to introduce the
5 tool and then -- do you mind that?
6 DR. DENHAM: Yes, briefly, because I want to
7 make sure we leave enough time for the panel
8 discussion.
9 DR. GREEN: Pratik, should we present the
10 World SIVA, the previous tool, but we'll wait for
11 the new one until after?
12 DR. PANDHARIPANDE: The next session, yes.
13 I think that might work out and give people time.
14 DR. WARD: We have a larger panel. So we're
15 doing the previous and the new too, correct?
16 Presentation – Keira Mason
17 DR. MASON: Steve and I actually worked on
18 this adverse event sedation reporting tool when I
19 was chair of the International Sedation Task Force
20 for the World SIVA.
21 What we were doing was trying to address the
22 problem that's already clearly been stated, that

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1 the challenge is defining sedation-related adverse
2 events, defining what the meaning of it is, and
3 also what the potential implications of these
4 events were. As we all know, when you read the
5 sedation literature, it's multi-specialty involved,
6 both adults, both children from all parts of the
7 world, both developed and developing areas of the
8 world.
9 The challenge is looking at the way that the
10 data was collected, the content of the data, the
11 definitions that were used to describe the events,
12 the interpretation of the events, and of course,
13 then what do they mean in the context.
14 Our goal was to come up with a standardized
15 set of definitions, originally, for the sedation-
16 related adverse events. The initiative that Steve
17 and I are here to talk about was, of course, the
18 World SIVA, which is the adverse event sedation
19 reporting tool, AE sedation reporting tool, and
20 then Mark's going to come up later and talk about
21 the evolution of the World SIVA tool into the
22 TROOPS, which we will talk about.

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1 The World SIVA International Sedation Task
 2 Force consisted of 25 physicians from 10
 3 specialties from 11 countries both adult- and
 4 pediatric-focused clinicians. They had to be not
 5 only doing sedation in their daily practice and/or
 6 also -- but definitely involved in sedation-related
 7 research.

8 We really had quite a collection of
 9 expertise, some of whom who are actually in this
 10 room today. We had a group meeting, multiple
 11 correspondences in terms of emails, in terms of
 12 trying to come up with and agree on these
 13 definitions of adverse events.

14 As you can imagine, it was very challenging
 15 because we had everyone from gastroenterologists
 16 who do just adults to the anesthesiologist who is
 17 overseeing literally technicians providing sedation
 18 in areas of Africa where there were no physicians
 19 or expert providers at all.

20 What we came up with was published in the
 21 British Journal of Anesthesia a few years ago. It
 22 was the "adverse event reporting tool to

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1 standardize the reporting and tracking of adverse
 2 events during procedural sedation."

3 Just briefly, I think the strength of this
 4 tool was that not only did we come up with agreed
 5 upon definitions for these adverse events, but
 6 again, beyond defining these adverse events, what
 7 were the interventions, and then also what was the
 8 potential risks involved and the outcomes of these
 9 interventions.

10 Then at the end, we came up with a
 11 descriptor of what was the outcome. Was it a
 12 sentinel outcome that had significant adverse
 13 events, or was it something that was just very,
 14 very minor and transient? Again, at the end of the
 15 tool, which had six parts, we had everything from a
 16 sentinel event, to a moderate event, to a minor to
 17 a minimal event.

18 The format of this tool was an evolution of
 19 the Quebec guidelines that Maala presented because
 20 we did go into the actual interventions that were
 21 needed to be performed.

22 I received an unrestricted educational grant

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1 from Hospira, and we actually put this on the Web.
 2 So this is an open access Web-based tool. It's
 3 meant for anybody in any area of the world. What I
 4 liked about this is that there were no HIPAA
 5 identifiers. But also for those who are in areas
 6 of the world where they aren't able to collect
 7 their sedation data in a standardized fashion or an
 8 organized fashion, they could with their user name
 9 and password be able to collect and pull up their
 10 data at any time. And especially for people who
 11 are -- like I was called from Saudi Arabia because
 12 they failed their International Joint Commission
 13 visit for sedation, they could potentially be using
 14 this to start tracking their adverse events.

15 There were challenges. Nothing is perfect,
 16 so one of the challenges that we saw that evolved
 17 into our new project, which was TROOPS and the
 18 formation of the new committee, which was called
 19 ICAPS, the International Committee for the
 20 Advancement of Procedural Sedation, it was based on
 21 our identifying that not all of the adverse events
 22 really were reflective of the outcomes, and that

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1 were certainly challenges, some of them because we
 2 hadn't necessarily organized by organ system.

3 Some people felt that they were doing the
 4 sedation tool for tracking and identifying minimal
 5 risk outcomes, which might not have necessarily
 6 been time valuable for them, and again, that there
 7 were some problems, like Maala had already
 8 mentioned and others, with identifying the
 9 thresholds.

10 For example, an oxygen desaturation, we
 11 couldn't agree. If you're sedating a patient in
 12 the cardiac cath lab who's already coming in with
 13 an oxygen saturation of 75, what is their
 14 desaturation going to be identified as, and for how
 15 long would that need to occur for it to be
 16 identified as an adverse event?

17 That was pretty much what we worked on for
 18 the AE sedation reporting tool.

19 Steve, do you have anything you want to add?

20 Presentation – Steve Green

21 DR. GREEN: Yes. I just want to add that
 22 last point about the thresholds and duration, a lot

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1 of feedback that we would get is everyone has a
2 different idea of what the threshold should be or
3 what the duration should be. So to incorporate or
4 to continue with some kind of definition, you're
5 guaranteeing that people are not going to be able
6 to agree on it over time.

7 Q&A and Panel Discussion

8 DR. WARD: Can we have all the speakers up
9 from the first session? You guys, too.

10 We can run over a little bit because I think
11 the session next time is going to be a little bit
12 shorter.

13 DR. PANDHARIPANDE: The TROOPS can be about
14 20 minutes.

15 DR. WARD: For TROOPS, yes. So we can go a
16 little bit longer.

17 The ideas that I come away with so far is we
18 do have some tools out there for classification of
19 adverse events. From my perspective, they're a
20 little more aimed at the QI situation where we have
21 a lot of practitioners doing different things, and
22 less towards the clinical trials situation where

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1 maybe we can specify the threshold and the duration
2 for the intervention in the design of the clinical
3 trial and specify what the signal is that keys the
4 intervention, that reporting the signal is
5 important, not just the intervention but actually
6 was it a saturation? Was it the patient reporting
7 nausea before they actually vomited as part of the
8 signal for giving the ondansetron as an
9 intervention?

10 I think there are some issues that we've got
11 some tools, but are the right tools and how do we
12 modify them if need be for the clinical trial kinds
13 of situation?

14 Opening it up for the panel and for
15 continuing the discussion that we've been having.

16 Mark?

17 MR. WILLIAMS: Just talking about provider,
18 the thresholds can be very provider specific. One
19 thing I've seen is what do people think about
20 having time outside of a specified threshold as an
21 outcome?

22 DR. BHATT: How is that different from

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1 duration?

2 MR. WILLIAMS: It can be provider specific,
3 so you can set that. It can go across different
4 specialties, their parameters. But maybe multiple
5 times throughout a sedation procedure, you can dip
6 below 92, 90 for 15 seconds, 30 seconds.

7 DR. WARD: Instead of one 30-second period,
8 maybe out of the 20-minute sedation, you've had
9 several segments of desaturations, none of which
10 lasted 30 seconds, but in total saw the
11 area-under-the-curve kind of concept.

12 MR. WILLIAMS: Does it matter more? Does it
13 not matter? Just a thought, a suggestion. Value
14 your opinions.

15 DR. PANDHARIPANDE: I just feel that it gets
16 more complicated if someone has to measure the area
17 under the curve where someone is out of the
18 threshold. As a reporting tool where you're saying
19 it's something that has to go across specialties,
20 across nations, I think there are challenges
21 associated with that.

22 MR. WILLIAMS: Certainly, across certain

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1 countries -- our institution, we have electronic
2 reporting. All our data is grabbed in
3 from -- especially the saturations, it's captured
4 every minute, so there might be a way of capturing
5 it much more frequently than that.

6 DR. WARD: Remember, clinical trials may be
7 different than a reporting tool in a QI situation.

8 I think Albert had a question here and
9 then -- Albert?

10 DR. DAHAN: In my research and focusing on
11 saturation is not really my aim. Saturation is not
12 the endpoint of -- or maybe it's an endpoint. It's
13 not the cause of the adverse event. The adverse
14 event actually is the patient is not breathing well
15 enough, and how do you cope with that is much more
16 important than looking at saturation. It's much
17 more complex than just breathing. It's a measure
18 of gas exchange.

19 So we are looking at actually breathing,
20 especially pattern breathing of the patient. It's
21 not very difficult to measure, but it takes some
22 training, takes some time.

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1 That's what we're doing currently. We're
2 looking at especially the variability of breathing.
3 If variability goes up, believe me, within a couple
4 of seconds or minutes, the subject patient might
5 stop breathing.
6 We're really much too much focusing on
7 endpoints rather on cause of the adverse event, in
8 my opinion.
9 DR. WARD: Any comments from the back
10 or -- Dan and then John.
11 DR. SESSLER: I guess one of the challenges
12 we face here is that we essentially do not have a
13 link between observed events and outcomes. In that
14 respect, it differs from blood pressure where we
15 now know what the association is between different
16 levels of hypotension and outcome and can evaluate
17 those associations across a variety of different
18 measures.
19 One paper that evaluated measures of
20 hypotension that have been reported, they found 140
21 different measures reported in 130 papers. This is
22 not really very helpful, but I guess I see the big

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1 problem here as a lack of link between events and
2 outcomes. We're saying that these are events that
3 might foreshadow problems and that if you don't do
4 anything about hypoxemia, eventually, you will get
5 into trouble, but we don't actually know where to
6 intervene.
7 I guess that brings me back to proceduralist
8 or sedationist and context as being really
9 important because what's an important event in one
10 context may really be completely unimportant in
11 another, and the danger is that we record a bunch
12 of events. It's technically easy to record events.
13 You can record every episode of desaturation, and
14 you can do more sophisticated things like area
15 under the curve or time-weighted average below some
16 threshold. But we still don't know what it means,
17 and what it means is going to depend very much on
18 who's there. That's especially true when you get
19 to interventions because an intervention that's
20 trivial for an anesthesiologist may not be in
21 another context.
22 DR. WARD: In the context of a clinical

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1 trial for a new compound, would that then -- we
2 will talk about some breakthrough issues later on.
3 Would that then change the indications and usage?
4 Like when propofol first came out, who could use
5 the drug based on the data that we got from
6 clinical trials?
7 DR. SESSLER: Right. Well, we have the FDA
8 people here who can comment, but I would assume
9 that if you're testing a new drug that the results
10 apply in context and the FDA labeling may reflect
11 that. But maybe you could help us, Leah.
12 DR. CRISAFI: I'll let Rigo go ahead.
13 DR. ROCA: This is Rigo Roca, and actually
14 Dr. Hertz is back there as well. We agree in the
15 context that when you get the data, you're able to
16 actually try to get a picture of what the safety
17 profile actually is and whether there are certain
18 events, as has been discussed before, that really
19 do not require a lot of intervention. That's
20 actually useful to know.
21 As Dr. Hertz mentioned, we would be able to
22 have information regarding the potential

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1 comparisons with different drugs, et cetera, and
2 that information we would try to put into the
3 package insert to inform you so that you know what
4 was seen in the clinical trial.
5 DR. WARD: John?
6 DR. BERKENBOSCH: I have comments and then a
7 question. First, I'm going to just say and I think
8 that there's little value in differentiating events
9 based on provider specialty. I think that's
10 unhelpful. It's divisive and probably not
11 constructive to advancing sedation-related clinical
12 trials.
13 The question I had for you, Maala, using the
14 Quebec guidelines, and there's a lot of value in
15 looking at the intervention part of it. What do
16 you do with all of the data that isn't collected,
17 that isn't recorded where maybe somebody's
18 hypotensive for a period of time, and the provider
19 thought, nah, I don't need to intervene because the
20 other ones look okay? I think that's still
21 potentially valuable data.
22 What do you do with that in the setting of

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1 reporting using the guidelines, or any
2 intervention-based guidelines, whichever one you
3 choose to use?
4 DR. BHATT: That's fine. I think that maybe
5 somebody else could chime in because my answer for
6 that is that we actually don't do anything with
7 that data.
8 We have a number -- so with propofol, if
9 they have a transient drop in blood pressure and
10 the practitioner doesn't feel the need to
11 intervene, we don't actually capture that data.
12 Because the thinking behind it was that if it is a
13 significant event, that there will be the need for
14 an intervention. You can't have hypotension that
15 gets worse and worse and worse without an
16 intervention, right?
17 So we don't have that data, and we don't
18 have -- I think what Mark was alluding to is the
19 electronic capture of vital signs that get stored.
20 Certainly, we don't have that at our center or any
21 of the centers that we worked at, but that could be
22 useful information with that respect.

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1 I'd be interested to hear what other people
2 think about, that thinking, because I think that
3 there is -- I definitely come from one way of
4 thinking, and there is a disconnect with
5 understanding what to do with that data or how
6 people feel about that. I'd be interested in
7 hearing what others think.
8 DR. RIKER: As we look at the individual
9 adverse events, we could come up with specific
10 interventions that might be a long list and would
11 vary by adverse event. But I wonder if a simpler
12 method might allow us to allow more flexibility. I
13 think about a rescue event like a jaw thrust or a
14 few breaths with a bag-valve mask or something like
15 that versus something that extends beyond the
16 procedure.
17 You go to the ICU, you get intubated, you're
18 on new antibiotics, something like that as just a
19 measure of what might be a minor or a simpler event
20 versus something that extends beyond the procedure
21 and requires a higher level of care or something
22 like that.

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1 DR. WARD: I think what we're hearing here
2 is, again, the reporting for a QI situation versus
3 a clinical trial situation may be somewhat
4 different, and at the different level of clinical
5 trial, do you need different levels of data?
6 Phase 2 trial, you really want to know all
7 the saturation data and maybe not -- maybe as
8 Albert pointed, saturation is too far down the
9 line. You really want to know more about the
10 actual ventilation. Saturation is actually a
11 fairly difficult parameter to measure.
12 Like Rick was saying, does the severe
13 outcomes, somebody gets admitted to the ICU because
14 they vomit and aspirate, that's clearly an adverse
15 event. But in a phase 2 trial, what are the kinds
16 of things that you're going to want to be
17 collecting there as opposed to a phase 3/phase 4
18 clinical trial?
19 Anybody on the panel?
20 DR. GREEN: I'll just weigh in. I think a
21 lot of this discussion about clinical QI is very
22 relevant to FDA because first we're deciding what

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1 are the things that are clinically important. Then
2 there may be another layer of data collection below
3 that that's needed for a phase 2 clinical trial,
4 but I think the first discussion tells you what are
5 the most important things that the end users are
6 going to care about.
7 DR. WARD: I think we get to the problem
8 that Dan has alluded to. We can get what the
9 adverse events are, but do we know what the signal
10 is in more of the physiological data that would be
11 predictive of it? We may know that for some of the
12 work that he's done in blood pressure. We may not
13 know that in some of the other possible adverse
14 events.
15 Ricky?
16 DR. TWERSKY: I think what would help is we
17 have on the dais panelists who have knowledge about
18 the registries that we've collected, and Joe
19 Cravero, and maybe you're going to be doing that
20 later. But I think what would help me in
21 understanding how we fill out these ambiguities by
22 learning about the robust information that has

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1 already been collected, again, it wasn't in the
2 clinical trials; it was in the context of clinical
3 care.
4 But to help us then narrow down these
5 questions that have been brought up as far as
6 duration, level, hypotension, hypertension, I'd
7 like to hear -- and you don't have the slides up
8 there, but that would help also to inform us what
9 you've seen from thousands of cases that you've
10 looked at.
11 DR. CRAVERO: If I can just say, Rebecca, I
12 will overwhelm you with slides.
13 DR. TWERSKY: Can't wait.
14 DR. CRAVERO: Minutiae detail on what we
15 found. And I think it does inform this
16 conversation a little bit, but the exact issues
17 that are being brought up here, I don't think are
18 changed hugely, that you have a large number of
19 very minor things that are reported and a very
20 small number of very major things reported in the
21 pediatric databases.
22 Like I said, I'll show you examples of our

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1 data, but I think the issues remain difficult in
2 terms of exactly what everyone has been saying
3 here: what represents an outcome versus a
4 complication? We have spent a lot of hours
5 discussing that, and I think this is a good
6 conversation. But we're running into the same
7 things that we've done when we tried to come up
8 with a consortium reporting tool.
9 DR. TWERSKY: Right, because I don't think
10 we'd want to be bogged down with minor events, and
11 that could be what's happening in your reporter
12 registries, or if you had the same experience.
13 Dr. Bhatt?
14 DR. BHATT: We are just about to publish our
15 first paper. Hopefully, I'll submit it while I'm
16 here at this conference. We separated things that
17 we didn't -- we reported on four major outcomes:
18 serious adverse events, adverse events that require
19 significant interventions, oxygen desaturation, and
20 vomiting because they were the most common things.
21 I think that when it's from an emergency
22 department perspective, it is more clinical, and I

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1 appreciate what Denham is saying with that. I do
2 think that the things that we report on, they're
3 not going to be the same things that you want to
4 report on in a phase 2 clinical trial.
5 I think that it's fair that you're going to
6 want much more granular, different information, and
7 I think that that's worth pursuing in terms of what
8 to report and how to capture that data. But I
9 would still maintain that I don't think that the
10 threshold duration is the answer there.
11 I think that there is another answer, but I
12 don't know what it is. But I don't think it's
13 threshold of duration.
14 DR. WARD: Other comments, anybody else want
15 to weigh in?
16 DR. ZHAO-WONG: When we talk about adverse
17 event definition, we need to keep in mind adverse
18 event versus adverse action. Adverse event is
19 actually an undesirable event regardless of
20 causality.
21 DR. WARD: We talk about more granularity of
22 the data because in a clinical trial, the more

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1 granularity you have, the more expensive it is,
2 too. I think it's nice to collect everything, but
3 that gets more and more expensive to collect
4 everything in a clinical trial.
5 You'd like to collect granularity of things
6 that are going to affect -- and that gets to what
7 Ricky was asking. What are the outcomes that are
8 actually occurring, and can we collect data earlier
9 in clinical trials that are going to be related to
10 the actual outcomes that we see in these QI
11 databases?
12 Hannah?
13 DR. WUNSCH: Just a comment on hoping that
14 looking at the long-term outcomes maybe answers
15 some of those questions. As someone who does a lot
16 of work on mechanical ventilation, we always talk
17 about patients who receive mechanical ventilation,
18 not require mechanical ventilation, and are
19 admitted to ICU not requiring intensive care for
20 the exact same reasons we're talking about, the
21 small adverse event category, you get the exact
22 same problem when you go to the next level, even

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1 though it feels like maybe it should be a more
2 concrete answer to some of these questions. I
3 think you just dive into the same problems.
4 DR. KARAN: I'd like to echo some stuff that
5 Dan was saying and that Albert was saying, is that
6 we're actually just not monitoring ventilation
7 right now in procedural settings. It's very hard
8 to assess what's happening before the intervention
9 or what's causing the desaturation.
10 So until we start monitoring, I'm wondering
11 whether we're going to borrow from our sleep
12 colleagues for their definitions for how we monitor
13 apnea and hypopnea with more of the ambulatory
14 monitors that are coming out in the future that
15 will be helpful, informative to then when we do the
16 trials looking for patterns and things like that.
17 And then eventually when we get to the FDA point
18 and we're going the lab-based trials, maybe one of
19 the limitations to applying it to the procedural
20 basis was can you actually use these monitors
21 because seemingly, we can't for some reason use the
22 respiratory monitors or the end tidal CO2 I think

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1 because of mostly cost or we're just unfamiliar
2 with it.
3 AUDIENCE MEMBER: We started using in a
4 whole different way flow monitoring, measuring
5 exhaled [inaudible -- off mic] in the air; very
6 cheap, very easy to apply, and it's usually very
7 good indication of the flow, [inaudible] much, much
8 cheaper
9 DR. WEISS: The other question then to me,
10 since that come up there, is the level of
11 monitoring the same in each of these areas that
12 we're doing? If there is not a different level, or
13 consistent level, or a base level of monitoring,
14 then we might be picking up different things
15 because of our ability or our inability to pick up
16 something that's happened.
17 DR. WARD: Picking respiratory, I think
18 there are other adverse events we're interested in
19 --
20 DR. WEISS: Right, but that's across the
21 board. If we all of a sudden have to have a
22 uniform way of picking up through our monitors, not

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1 just our own senses, what we're doing is, if we're
2 not all using the same monitors, we haven't
3 standardized it, then we're behind the eight ball
4 there.
5 DR. WARD: James and then Dan.
6 DR. MINER: I think one of the problems we
7 run into is when we look at devastating outcomes
8 that occur in the community, and we go back and
9 review for the root cause, it's usually a lack of
10 attention, just relying on the mechanical monitor.
11 They weren't dosing well.
12 If we go back and look at our clinical
13 trials, we protocolize [ph] our dosing very
14 closely, we have extra people watching to collect
15 our data, and we cause interventions that prevent
16 most of the bad outcomes. So we do all large
17 research trials. We don't find the bad outcomes
18 that we see in the community.
19 I think that's why it's really important
20 when we're collecting this data that we look for
21 interventions in smaller occurrences because we
22 extrapolate those. Well, this drug is going to

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1 require a lot of attention and a highly trained
2 person to do it safely versus this drug might not
3 because we can't even find anything when we're
4 watching closely.
5 DR. WARD: Dan?
6 DR. SESSLER: Mark's point seems really
7 important. We haven't discussed the minimal level
8 of monitoring that's required for these studies,
9 and I don't think we should get into specifying
10 specific monitors. But it would be reasonable for
11 us to say that in a study of sedation, you need to
12 measure saturation and ventilation and tidal CO2,
13 or a median tidal CO2 as a measure of ventilation.
14 But maybe we should specify that so that there's at
15 least a uniform dataset.
16 DR. WARD: I think we're going to be
17 listening to that discussion tomorrow, but
18 absolutely.
19 DR. CRAVERO: I believe even in our data
20 analysis, we've seen that there is, even with the
21 same monitors, variability in how well people
22 report. When you're talking about things like

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1 desaturations, a sophisticated electronic medical
 2 record and monitoring system data capture gives you
 3 much more detail than if you have someone observing
 4 and just marking down when they observed a
 5 desaturation for a certain amount of time.
 6 We've seen this when we do video analysis
 7 versus at the same time asking people to tell us
 8 about how many desaturation events, et cetera. You
 9 see different things based on video analysis versus
 10 the individual reporting. I think when you have
 11 electronic data capture, that obviously helps.
 12 However, there is artifact in there that needs to
 13 be considered as well.
 14 There is some subtlety when you're looking
 15 at minor issues. I think the issue about what
 16 monitors you have and how you are capturing that
 17 data does make a difference in terms of how well
 18 you capture adverse events or complications as
 19 defined.
 20 DR. WARD: Just as an aside, as a technical
 21 point, a saturation monitor is not a particularly
 22 great monitor. There's a lot of variation between

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1 whether it's on the finger or the ear, on the time
 2 delay that you get before the saturation is picked
 3 up.
 4 There's a lot of technical issues about
 5 using saturation. As Albert pointed out, there's
 6 really a downstream monitor to pick up a
 7 ventilation problem. Saturation may not be a
 8 particularly good design monitor to actually do
 9 that.
 10 DR. PANDHARIPANDE: A slightly different
 11 question, but for Anna over here. So as we're
 12 thinking about monitoring versus what are
 13 definitions of adverse event, when you think about
 14 MedDRA, when you look at regulatory requirements,
 15 when you look at industry studies versus
 16 investigator-initiated studies, so if you're going
 17 to have recommendations for clinical trials, which
 18 are done by investigators versus industry, what
 19 level of the MedDRA hierarchy would you consider
 20 reasonable?
 21 I'll give you that example. It's coming up
 22 in clinical trials. My DSMB for my NIH-sponsored

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1 study went back and said, "We'd really like you to
 2 use the MedDRA classification," and then specified,
 3 "We'd really like you in your 14-center study to
 4 use the preferred term," which is 21,900 terms to
 5 try and coordinate among 12 sites when I'm the only
 6 one who has gotten a subscription.
 7 How would you balance that? Would there be
 8 two different requirements for industry studies
 9 versus clinical trials that we are recommending
 10 investigators might do?
 11 DR. ZHAO-WONGA: I think MedDRA does have a
 12 large number of terms, and the different levels are
 13 used at different purposes for capturing adverse
 14 events, actually at the LLT level because of the
 15 maximum specificity. The preferred term and all
 16 the other four levels are for retrieval analysis
 17 purpose.
 18 But for sedation specific, not all 70 or
 19 20,000 terms apply. I think that's why it's a good
 20 idea to have term knowledge like TROOPS. There are
 21 terms that are specific for sedation, and if
 22 anything falls beyond that, I would expect a very

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1 small percentage of adverse events would fall
 2 beyond that, then the coders can look into MedDRA
 3 to find it.
 4 DR. PANDHARIPANDE: Just following up on
 5 that, so for example, if your patient under
 6 procedural sedation has an arrhythmia, that comes
 7 under the preferred term, which is under the 21,000
 8 terms right now. I could classify that in the
 9 organ system and say, well, it was a cardiovascular
 10 event, which then looking across probably a
 11 senseless reporting of cardiovascular event. The
 12 arrhythmia is important, but that means I have to
 13 drill down to the 21,900 terms.
 14 That's the balance I'm trying to say. As we
 15 recommend it for investigators, how do we try and
 16 get the balance between the two?
 17 DR. ZHAO-WONG: That's probably going to be
 18 between investigators and the regulators in terms
 19 of how they do reporting. But for CTCAE as similar
 20 comparison, they also have a group of adverse
 21 events that are commonly seen for cancer trials.
 22 Then their guidance is these are the commonly seen

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1 adverse events that you use. If anything falls
2 beyond, also possible for cancer trials, then you
3 select in MedDRA.
4 DR. WARD: Dan, then Jerry; Dan first, then
5 Jerry.
6 DR. SESSLER: It would be reasonable to
7 require continuous data acquisition. It's now
8 technically easy, and if you don't have that, you
9 miss events, and you miss the ability to do more
10 sophisticated analyses such as area under some
11 threshold.
12 DR. WARD: Jerry and then Anna.
13 DR. LERMAN: One of the topics that hasn't
14 emerged in the discussion at all is whether
15 awareness or recall is not an adverse event in
16 children who have sedation. Those who walk the
17 tightrope between avoiding all these bad
18 physiologic responses we've been discussing but
19 keeping the child on the table run the risk of
20 having awareness in a child. Probably more likely
21 to occur in a painful procedure, less likely to
22 occur in a non-stimulating sedation such as a

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1 radiologic procedure.
2 Yet it hasn't been raised as an adverse
3 event in any capacity and would suggest that
4 perhaps it's dismissed by this group. I guess we
5 need to broach the subject and put it in
6 perspective.
7 DR. BHATT: I could address that. In our
8 Quebec guidelines, we actually report unpleasant
9 recall as part of a measure of efficacy of
10 sedation.
11 DR. LERMAN: As which?
12 DR. BHATT: As part of efficacy, so we would
13 say -- oh, sorry, successful sedation. So we would
14 that a procedural sedation was not successful if a
15 child had an unpleasant recall of the procedure or
16 a recall of the procedure.
17 DR. LERMAN: But it's not an adverse event?
18 DR. BHATT: It's not classified as an
19 adverse event in our reporting, but it is reported
20 as an unsuccessful sedation. I guess an
21 unsuccessful sedation could also be seen as things
22 did not go well, an adverse event.

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1 AUDIENCE MEMBER: When you hear about TROOPS
2 later, awareness is part of that.
3 DR. CHAPPELL: May I make a comment from the
4 industry perspective on that issue you just raised?
5 We would typically report that it's lack of
6 efficacy and it would be as an adverse event.
7 DR. BHATT: Can you repeat that? Sorry.
8 Lack of efficacy.
9 DR. WARD: Lack of efficacy. It would get
10 reported as lack of efficacy or reported as an
11 adverse event.
12 Hannah, last question.
13 DR. WUNSCH: I just wanted to ask, getting
14 at this tension around different providers having
15 different thresholds and different abilities, has
16 there even been an attempt to incorporate just
17 provider anxiety or stress associated with an event
18 as basically being an adverse event and using that
19 almost as a way if you collect information about
20 who the provider is, that you can start to almost
21 adjudicate what's going on and what's causing
22 people to get stressed out as the provider, which I

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1 think actually is potentially a very important part
2 of this and could be very different certainly
3 across providers without having to say limit
4 certain sedation to certain types of providers.
5 I don't know if it's ever been discussed.
6 DR. WARD: I don't know much research in
7 that area in sedation, maybe. But in oncology,
8 there's the concept of tolerance of uncertainty and
9 tolerance of risk. And there's actually validated
10 measures of the provider's tolerance of uncertainty
11 and tolerance of risk, and that has impact on the
12 kind of conversation the oncologist has with the
13 patient as far as the kind of chemotherapy that
14 they're going to get.
15 Maybe a similar concept of tolerance of
16 risk, maybe one of the validated forms, validated
17 survey tools of tolerance of risk for the provider.
18 DR. WUNSCH: Or just even add an individual
19 event point, does the provider feel stress by this
20 experience.
21 DR. WARD: Mark?
22 DR. WEISS: There's a provider risk in that,

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1 too. Another thought might be, too, does the site
2 of the procedure influence what we consider an
3 adverse event as well, too? For example, sometimes
4 we have [indiscernible] people, and the
5 proceduralists will go up to the unit or the
6 bedside and do a procedure, an endoscopy.
7 Sometimes they'll say I would feel much more
8 comfortable if they were down in the OR, we have
9 more backup there, too.

10 How much does the site also influence what
11 we're dealing with as well

12 DR. WARD: I'll let the panel have the last
13 comments before we go on break.

14 (No response.)

15 DR. WARD: Let's take a break. I think
16 we've got enough time to take our 30-minute break,
17 so let's be back at 10:40 for the next session.

18 (Whereupon, at 10:11 a.m., a recess was
19 taken.)

20 DR. WARD: Great. It suddenly became quiet
21 as soon as -- speaking of duration thresholds,
22 there seems to be a threshold value that once you

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1 get the noise below a certain threshold, it falls
2 off quickly.

3 A little bit of change in the program. Mark
4 is going to present TROOPS, which is the new tool
5 that's available following on, and then we'll
6 continue to look at common adverse events both in
7 pediatric sedation that Joe will present and dental
8 sedation that Ray will present.

9 Presentation – Mark Roback

10 DR. ROBACK: Thank you, Dr. Ward.
11 Thank you all for the opportunity to
12 present. This is a really a work in production.
13 This is our most recent draft, and it's tracking
14 and reporting outcomes of procedural sedation.

15 Our goal is really to provide a standardized
16 and very practical tool intended for daily use to
17 record sedation-related adverse events,
18 interventions performed, and outcomes. We would
19 really like this tool to be for all procedural
20 sedation, all types of providers, all locations
21 outside of the operating theater, and for all age
22 groups. Ideally, this is something that can be

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1 incorporated right into the electronic health
2 records that most institutions have adopted or will
3 adopt soon.

4 This is the work of the International
5 Committee for the Advancement of Procedural
6 Sedation. Keira and Steve presented the World Siva
7 and ICAPS previously. Just to summarize, it's a
8 multidisciplinary, international, independent
9 consensus committee whose mission is advancing
10 optimal evidence-based practice for procedural
11 sedation and analgesia.

12 In this particular iteration of the
13 committee, it's all sedation researchers from nine
14 countries and five continents and representing,
15 much like this group here, the breadth of providers
16 of sedation. As we began to develop our tool, we
17 wanted to adhere to the Institute of Medicine's
18 Clinical Practice Guidelines We Can Trust.

19 Then as we started the process, we wanted to
20 develop our definitions, and we did it through a
21 general survey of the committee members. We based
22 it on the previous works that have been presented,

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1 the World SIVA and Maala's Quebec guidelines.

2 Once we had the consensus, process was
3 initiated. It was an internet-based questionnaire
4 using nominal group technique and the Delphi
5 method. We had sequential consensus generation
6 with vigorous online discussion much like has been
7 going on at this conference. We had sequential
8 generation of our consensus of this process.

9 All responses from members were displayed
10 anonymously. Revisions were based on ongoing
11 feedback by the group. The co-chairs Steve and
12 Keira served as moderators to guide the direction
13 of the consensus.

14 The provisional tool and definitions were
15 then submitted to outside professional societies
16 and procedural sedation interest groups. This
17 would be one of those, and we solicited external
18 feedback, which was reviewed by the committee.
19 Additional Delphi review and revision occurred, and
20 that leads us to the tool we have today.

21 A summary of what we learned in the process,
22 we really wanted the tool to be organized by organ

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1 systems because that's the way practitioners
2 organize their clinical information. Outcomes
3 other than adverse events really needed to be
4 included as well.

5 Based on the first publication from the
6 first SCEPTER meeting and some of the discussions
7 that had been going on, clearly, there's other
8 things that are very important, and we wanted to
9 emphasize the patient experience, talking about
10 comfort of the patient and recall of event. Just
11 recall of event wasn't seen as something that was
12 bad. Rather, an unpleasant recall of the event.

13 Then we also had great discussion about
14 events and thresholds versus interventions, and we
15 really wanted to have outcomes that were really
16 meaningful to practitioners.

17 We ranked our outcomes based on severity,
18 and as we present the primary tool today, the red
19 would be the sentinel outcomes. These would be
20 life threatening. They warrant immediate reporting
21 to sedation care systems, and this should receive
22 the highest level of peer scrutiny for continuous

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1 quality improvement.

2 Intermediate outcomes would be in yellow,
3 and these are serious enough to endanger patients
4 if not promptly managed or reflect suboptimal
5 sedation quality or patient experience. These
6 warrant timely reporting to our sedation care
7 systems and periodic peer scrutiny.

8 The first part of this is the primary tool
9 that would be used more for QI purposes and for
10 looking at populations of patients receiving
11 sedation, and we also wanted to recognize that we
12 needed to have more granular data for research
13 purposes, really building on all of the discussion
14 that's gone on today.

15 These had the sentinel and intermediate
16 outcomes as well, but we added the minor outcomes
17 and interventions thinking that they could be
18 important and should be studied.

19 This is the current draft of the tool, and
20 you can see that we start off with the initial no
21 adverse outcomes or events, and then if that's
22 checked, then you're essentially done. However,

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1 the next part if it's yes, I think it should be
2 emphasized that these were unplanned outcomes, and
3 so if what you're doing is part of your everyday
4 practice, that wouldn't be considered an adverse
5 event or outcome.

6 If you checked the yes box, then you go
7 through this table, and we have the intermediate
8 and the severe interventions and outcomes. The
9 first column then are our organ system, airway
10 breathing, circulation, neurologic, and then
11 sedation quality and patient experience.

12 Rob, if you could give us the online version
13 to show you how this might work. This is how it
14 would be in an electronic health record. That's
15 great. Go to airway and breathing. You can see
16 there that the definition then would come right up.

17 If you go over to apnea, there's also the
18 definition. The same with pulmonary aspiration and
19 laryngospasm.

20 If you can just scroll down a little bit,
21 you can see that it does give us the -- a little
22 bit further, please, down. There's the definition

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1 of the intermediate and sentinel events, and you
2 can see the first column, circulation, neuro. Now
3 we have sedation quality and patient experience.

4 Someone had mentioned we really care if the
5 adverse event or the event results in a change in
6 care plan. So if you could hover over
7 hospitalization or escalation of care, this would
8 be an important distinction to make as far as an
9 outcome.

10 If you could look at the far column, Rob,
11 maybe you can pull it over right. We thought it
12 was very important to recognize such things as did
13 the patient require restraint during the procedure
14 and the sedation. This is something that we want
15 to recognize as not optimal sedation. We also
16 define paradoxical response, unpleasant recovery
17 reaction or agitation, as well as important
18 outcomes.

19 Next slide, please.

20 Then the second part of the tool would be
21 for optional items that can be used for our phase 2
22 trials or for other research purposes. And then

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1 special clinical settings, if this is a new
2 sedation enterprise in an institution and they
3 wanted to more closely follow the care provided,
4 this could be employed.
5 Then you can see many of these interventions
6 that are taken from the Quebec guidelines and the
7 World SIVA tool, tactile stimulation, airway
8 repositioning, things that you may consider just
9 part of your everyday practice and not being an
10 adverse event.
11 In a phase 2 trial or perhaps in a sedation
12 unit that's just getting started, maybe they want
13 to know which drugs are leading to more of these
14 interventions and should this change the way that
15 we provide sedation in our specific setting.
16 The last slide then, we thought we would try
17 to identify strengths and advantages of our
18 proposed tool. Again, this is designed for
19 widespread everyday use. It facilitates the
20 standardization of sedation terminology, adverse
21 events reporting, and QI monitoring.
22 We thought it was really important that it

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1 reflect, much like this group, all patients, ages,
2 types, providers, and settings. It has to be
3 practical and be readily incorporated into current
4 clinical care processes if we're going to be using
5 this as a safety surveillance tool.
6 However, we also recognize the importance
7 for making it valuable for researchers as well, and
8 that way, you could easily transition from using it
9 as your safety surveillance, your QI project, and
10 then it can become a research tool by adding the
11 second portion.
12 Then the last piece, as we heard earlier
13 today about MedDRA compatibility, I learned a lot
14 about why this is important, especially as we look
15 at our partnerships with the private sector and
16 doing clinical phase trials.
17 Having MedDRA compatibility is something
18 that we really found would be important. We were
19 excited when Judy and Anna were able to show us
20 that this could be adapted and made MedDRA
21 compatible with only really minor variations.
22 So that is our proposed tool with the catchy

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1 acronym, but really our goal is to be able to track
2 and record outcomes of what we do with sedation.
3 Thank you.
4 (Applause.)
5 DR. WARD: We have a couple of questions now
6 before the panel. And my question is, how is it
7 going to be disseminated?
8 DR. ROBACK: How would this be disseminated?
9 I think much like what has been done with the World
10 SIVA tool, this could be made available as an
11 online access if you're willing to be part of the
12 project. And Keira and Steve could speak more to
13 how that worked.
14 DR. MASON: We could decide whether or not
15 we would accept industry sponsorship for this.
16 It's a fairly expensive project. Just getting that
17 tool online that I showed cost about \$50,000 to
18 have that all put online and interactive. But the
19 nice thing is that when you do this, it's going to
20 be all password protected, so you'll have your own
21 way of getting into the site, and it's going to be
22 data that you can access for yourself.

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1 DR. ROBACK: I think it would also be
2 important to approach the major electronic health
3 record providers and see how that could be
4 incorporated into their current formats.
5 Yes?
6 DR. URMAN: Is there any plans with this
7 tool to perhaps enable data sharing or
8 benchmarking, looking at other people's data even
9 if it's de-identified for research purposes, for
10 benchmarking, something that you're planning on?
11 DR. MASON: As the master users, obviously,
12 people have access to all the data.
13 DR. URMAN: All the data, not just your own
14 data?
15 DR. MASON: We as the masters of this will
16 have access to all the data.
17 DR. ROBACK: I think one of the really nice
18 features of what they've done with the World SIVA
19 tool is that you have this large repository, and
20 you as an individual institution will have complete
21 access to your own data so you can use that for
22 your own purposes. Then if you go through the

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1 process, you can become part of a bigger project
2 using these multicenter data points.
3 DR. MASON: I think World SIVA covers over
4 40 countries currently from developed and
5 developing countries participating. You'd be very
6 surprised. Some of the people in this room are
7 actually actively contributing.
8 DR. ROBACK: Maala?
9 DR. BHATT: I think the tool is great. I
10 think that it makes things very clinically relevant
11 and easy to document, and so I think that it's a
12 great evolution.
13 In reporting, if you're talking about a big
14 multinational study, do you have a comment on how
15 you will track denominator with this?
16 DR. ROBACK: I think that's a really good
17 point, and that's one of the limitations currently
18 of our system is that it's only numerator data.
19 Essentially people are sending in what they've
20 done, and those who are not sending it in, we don't
21 know.
22 I think what we would do is encourage each

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1 institution to say is this something that we want
2 to do and really try to get at can we get all of
3 the data because without the denominator, it's
4 clearly less valuable information.
5 DR. MASON: One thing that we did for the
6 World SIVA tool that we considered doing for this
7 tool is that for the World SIVA tool, if I was
8 going to log in today and put in one of my sedation
9 patients, it will ask me each time I log in to
10 estimate how many sedations I do a year.
11 So that's the best that we can do in terms
12 of establishing my denominator, and if it changes,
13 then at that point, I'll change the number as I
14 enter. But that is part of the log-in function
15 with the provider.
16 You could even have -- for example, if your
17 sedation team or your ER team wanted to be one name
18 and one password, you want to do it as a team, you
19 could. Then you could just estimate how many
20 sedations you as a team do for the year.
21 DR. ROBACK: One of the goals of making this
22 a practical part of your everyday workflow was just

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1 this purpose. So where I work at the University of
2 Minnesota, we have eight hospitals. We're the only
3 children's hospital. We would really like to think
4 that as an overriding part of the University of
5 Minnesota, that everyone participates, and that
6 it's required, and that it's not onerous, it's just
7 part of your workflow, and that way, we can really
8 get that important denominator.
9 Yes?
10 DR. O'CONNOR: Just two comments. Both
11 relate to money. The first one is that you
12 mentioned working with the electronic health record
13 vendors. If this were importable into the record
14 as part of your documentation that could be used
15 for your procedure, I think the user rate would
16 skyrocket.
17 The second thing is that I'd be in favor of
18 an outside vendor, but other data registries have
19 used subscription fees, for example, to pay for it.
20 I don't know if you've considered that or if that's
21 under discussion.
22 DR. ROBACK: I think those are very good

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1 points, and quite frankly, my part of it hasn't
2 been thinking too much about the finances. Dr.
3 Mason is the expert.
4 DR. MASON: I think one of the problems
5 about having subscription fees is that it prevents
6 the individual user from using it, and also, people
7 who really wouldn't -- and so a lot of them
8 take -- like if I wanted Children's to start asking
9 for money to pay a subscription fee, it just raises
10 the difficulty of accessing something that we're
11 trying to have people easily access.
12 But also, if we're making this a tool for
13 all people from all countries, I think that would
14 be a big barrier, certainly for people from
15 developing countries. That was never our intent,
16 and that's why we got a substantial fund from
17 Hospira after we developed it with no hands in this
18 at all. It was just a goodwill gesture.
19 DR. O'CONNOR: Those are great points. I do
20 think if we're willing to build any coding, it
21 would be adopted. Just making it a part of my
22 procedure.

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1 DR. RIKER: Do you have a handle on how long
2 it takes to enter the data? How intensive
3 time-wise this is?
4 DR. ROBACK: That's clearly a very important
5 part of this. I was just talking to John earlier
6 about what they're doing with the SPS. They're
7 done to 45 seconds on their tool. We haven't timed
8 it, but we envision this to be less than a minute.
9 That's been our goal.
10 DR. RIKER: Second point, as far as
11 benchmarking, so we've put together an
12 International Cardiac Arrest Registry, and when you
13 put your data in, you've got, any time you want it,
14 access to your own data. But you can also get
15 access to the unidentified every data. So it
16 doesn't tell you this is St. Joe's Hospital or this
17 is wherever, but it gives you the group data.
18 I wonder if procedurally specific data for
19 this kind of thing might be a helpful benchmark.
20 DR. ROBACK: I think that's a really
21 important thing to think about. If it's
22 de-identified, there's no reason you shouldn't be

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1 able to search upper endoscopy or whatever it is
2 that you're particularly interested in.
3 DR. WARD: Aggregate data.
4 DR. ROBACK: Aggregate data, yes.
5 DR. WARD: Speaking of data, Joe's going to
6 give us some real data related to adverse events in
7 pediatric sedation.
8 Presentation – Joseph Cravero
9 DR. CRAVERO: This is a great discussion for
10 me. I would just say we've been talking about
11 common and important adverse events within the
12 groups that I've been working with for at least the
13 last 15 to 20 years, and the discussions have gone
14 quite a bit like what we've done today.
15 What I'm going to try to do is just present
16 generally the data that we've had, and I'm not
17 trying to orient the discussion other than to say
18 this is what it is. I would encourage us to think
19 maybe about how this applies to clinical trials
20 specifically because I think there's a real issue
21 with talking about our research and our quality
22 data versus what we want to know from a clinical

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1 trial. As we're trying to start a new clinical
2 trial at our place, I see a real difference between
3 those two things.
4 Just for a quick comment, I do think
5 pediatric clinical trials are slightly different.
6 We understand that essentially all infants,
7 toddlers, young children, older children with
8 developmental delay require sedation in order to
9 contain their emotional and other issues around the
10 procedures that we do. We have to sedate kids for
11 non-painful procedures that you just don't do for
12 adults generally.
13 We really do have a slightly different
14 patient cohort that we're dealing with, and a lot
15 of these patients have very little pathology that
16 would impact on their sedation, whereas I think
17 again the majority of your adult patients have a
18 lot more comorbid issues and you're sedating
19 probably less for the MRI scans and more for more
20 invasive types of things like your upper GIs and
21 other stuff.
22 Just thinking about the fact that we are

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1 sedating kids in remote locations and that the
2 demands are slightly different for our kids than
3 adults.
4 I'm sorry. I have talked about this so many
5 different times in different groups. Many of you
6 have seen me talk about exactly what I'm going to
7 talk about here for a second, but they asked me to
8 give a talk. This is what I got.
9 I got to say what I usually say, which is I
10 would encourage people that the sedation literature
11 on clinical trials generally reports events that
12 range widely. They do record a lot of
13 physiological disruption, including O2
14 desaturation, which is the most common thing that
15 is reported, and as we've already discussed, I'm
16 just very uncertain about what it means.
17 They do talk about airway interventions, and
18 we do get reports on how many kids require
19 positive-pressure ventilation, et cetera, which I
20 would say is important and interesting. Maybe the
21 problem becomes when we start using taxonomy like
22 complication or adverse event.

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1 Within the PSRC, we've really tried to get
 2 away from that because it's so loaded that we now
 3 go toward what do we just want to know, and we now
 4 record things like what interventions were required
 5 during these sedations without any of the
 6 judgmental implications of using the idea of
 7 complication or adverse event.
 8 Whether an anesthesiologist is readjusting
 9 the airway or an emergency medicine person is doing
 10 that or whatever, rather than getting into is this
 11 a complication or not, we're just talking about
 12 what needed to be done in order to get MRI scans
 13 done with propofol -- that's what we want to
 14 know -- or dexmedetomidine, or whatever, and then
 15 you can make your own judgment about how important
 16 those reports are.
 17 Just give you a couple of examples, I don't
 18 use these as bad or good clinical trials, just this
 19 is the kind of thing we see in pediatric sedation.
 20 This was a report of propofol in the pediatric
 21 intensive care unit. It actually was a comparison
 22 of propofol versus ketamine for rather deep

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1 sedation -- I would call it general
 2 anesthesia -- in the intensive care unit with
 3 sedation provided by intensivists.
 4 In this particular case, the report was that
 5 12 out of 58 patients required airway manipulation,
 6 10 required positive-pressure ventilation, 3 out of
 7 47 of the ketamine group required positive-pressure
 8 ventilation, which is a little different for me. I
 9 think that's a fairly high rate for ketamine. 1
 10 needed to be intubated because of what was
 11 described as "difficult ventilation." It wasn't
 12 really described more than that.
 13 Again, I'm not trying to make judgments
 14 here. I'm just telling you this is the kind of
 15 thing that is reported in clinical trials
 16 concerning pediatric sedation.
 17 Another trial, again, in part of this trial,
 18 they actually recorded all the different types of
 19 interventions that were required. And I'm sorry
 20 for those of you who can't read this, but there's
 21 things like airway repositioning, apnea that
 22 required bag-valve mask, intubation, et cetera. So

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1 this is very typical of pediatric clinical trial
 2 reporting.
 3 I would offer a question as to whether or
 4 not you consider these things adverse events.
 5 10.6 percent of the ketamine group experienced what
 6 was thought to be discomfort during the procedure.
 7 Again, that may be considered more efficacy than
 8 adverse event. I think there's a little bit of a
 9 gray area there as to what's efficacy and adverse
 10 event reporting.
 11 23-minute recovery time for propofol,
 12 50-minute recovery time for ketamine. Again, our
 13 thinking in the pediatric sedation research
 14 consortium is very extended recoveries do represent
 15 an adverse outcome. You can argue whether that's
 16 actually true or not or is that really some measure
 17 of efficacy, but we do think that it's important to
 18 think about sedation regimens that require hours
 19 and hours of recovery. Is it a significant thing
 20 that we need to think about in a clinical trial?
 21 Vomiting, et cetera, similarly.
 22 Another clinical trial looked at -- this was

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1 an observational report -- of propofol used for
 2 emergency medicine provided elective sedation for
 3 hematology oncology procedures in pediatric
 4 patients. In this case, it was propofol procedural
 5 sedation.
 6 It was a prospective evaluation of 393
 7 sedations. They reported 5 percent of their
 8 patients had hypoxia as less than 90 percent during
 9 the procedure, 3 percent required airway
 10 manipulation, meaning jaw thrust or head tilt, and
 11 1 percent required positive-pressure ventilation.
 12 I think this is very typical of what we see
 13 with propofol and as a clinical trial outcome in
 14 children. Whether or not you consider any of these
 15 really complications or adverse events, I think we
 16 could again go on probably all day.
 17 The conclusion, as they almost always are in
 18 these clinical trials, is that drug X is safe and
 19 effective for procedure Y. In groups of 393, I
 20 would offer that that is a fairly small group to
 21 try to conclude that a given technique as a
 22 clinical trial can be generalized to the entire

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1 population of children undergoing procedures.
2 At Dartmouth -- and I think I've talked to a
3 lot of you here about our work there -- we really
4 tried to take a more human factors approach and
5 look at a very detailed analysis of the way
6 sedation is given. We came up with a way of
7 thinking about the goal, which is to get a child
8 through a procedure such as an LP, going from your
9 starting point to a similar ending point with the
10 same level of consciousness and health.
11 During the course of that procedure, you're
12 going to have side effects due to pain. You're
13 going to treat that with either morphine or other
14 types of sedatives, and you're going to be getting
15 yourself into side effects and/or adverse events
16 related to undersedation or side effects and
17 adverse events related to over-sedation.
18 So as part of this, we came up with this
19 Dartmouth Operative Condition Scale, which I think
20 I presented the last time we met, which judges the
21 conditions of the patient during a procedure based
22 on pain, stress, movement, consciousness, and side

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1 effects from the sedation, which we defined as
2 saturations -- I'm trying to read this. I'm
3 getting old -- and respiratory pauses, and then low
4 blood pressure. So we tried to incorporate all
5 aspects of the child's status related to the
6 sedation itself in one scale.
7 We have just submitted to pediatrics -- and
8 I think it's conditionally accepted -- a new scale
9 that will be the procedural sedation scale for
10 children or PS3, which has six levels from zero up
11 to 5, which considers the state of the child.
12 Either they are wildly out of control, experiencing
13 problems from undersedation, to a state where they
14 are out of control, experiencing too much sedation
15 and physiological disturbance in spite of
16 intervention as a zero. So there you are providing
17 positive-pressure ventilation, but the sats are
18 still abnormal. We grade it from low to high.
19 Again, during the DOCS validation, we tried
20 to define three zones with when you add up our
21 scores, you can either have a high score that's
22 associated with side effects from the procedure or

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1 undersedation and very low scores that indicate
2 side effects from the sedation itself. We've
3 published this work in A&A.
4 I would just offer you that when you do this
5 and look in a very detailed manner at the scores
6 that you get over time and overlay the time of the
7 procedure, you get a better idea of how you were
8 meeting the demands of the procedure with your
9 sedation than you do when you just have
10 intermittent reporting.
11 This goes a little bit to what we were
12 talking about before. We looked at this scale,
13 published a study looking at the scale over 110
14 different procedures, assigning DOCS score every
15 minute to their procedures. And we found that the
16 failure to achieve sedation was about 5 percent.
17 It was 8 percent when you didn't have expert
18 providers, and zero percent with expert providers,
19 defined as those people that provide sedation as
20 part of their professional work as a team, so
21 basically sedation service providers.
22 We found that there was huge differences in

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1 the time from beginning of the sedation to the time
2 of the beginning of the procedure, and that can
3 vary on the effectiveness of the sedation activity.
4 We almost consider this an adverse outcome when
5 you're waiting that long to start a procedure, but
6 it probably is better classified as effectiveness.
7 We did classify over-sedation events and
8 undersedation events, and I guess again, you could
9 call this all under the rubric of effectiveness.
10 But we think there really are problems or there are
11 complications associated with undersedation.
12 Again, going to what we were talking about
13 before, when we look in detail at these tapes, we
14 found issues related to low sats for significant
15 periods of time that were not recorded in the
16 record of the patient that had been sedated. We
17 found kids that were not fully recovered when they
18 were discharged, yet the recording from our nurses
19 or the nurses that were involved was such that they
20 indicated the patient was ready for discharge.
21 I think as we were talking before, the
22 definition of states, the electronic capture of

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1 data is going to be really important in clinical
2 trials to actually know that you're talking apples
3 to apples, oranges and oranges.
4 Under-sedated states, again, we could call
5 this efficacy. We were calling it adverse event at
6 the time, but we found that very commonly. I think
7 in pediatric sedation, the undersedation of
8 patients is actually a much bigger problem than the
9 over-sedation of patients if you look at outcomes
10 generally.
11 Just very briefly, I think many of you have
12 heard me talk about Pediatric Sedation Research
13 Consortium. It is a consortium of specialists
14 across the country. We have 48 institutions
15 involved, about 20 percent anesthesiologists, 33
16 percent intensivists, about 30 percent emergency
17 medicine, and 70 percent other specialists, largely
18 hospitalists now that are providing us information.
19 We do collect a lot of different data
20 elements in this project: patient factors,
21 procedure factors, sedation technique, care
22 providers, observed care, and in specific germane

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1 to this lecture, complications associated with each
2 sedation encounter. The complications that we
3 collect include apnea -- and I'm sorry. In blue
4 here are the definitions that we've had. And I
5 guess I'm not sure about the World SIVA effort, but
6 we found that being very specific when you are
7 talking about adverse outcomes is incredibly
8 important because if there's any way to
9 misinterpret something, people will. I'm not
10 kidding. Even death.
11 (Laughter.)
12 DR. CRAVERO: It's amazing the variability.
13 "Well, what did you mean by dead?"
14 "I don't know. I think it's fairly clear."
15 It's amazing. So over time, we've had to
16 really be very specific. And what we did
17 ultimately was our interface for our data
18 collection tool has a bunch of click boxes that you
19 click for the primary problem that you are taking
20 care of, the coexisting medical problems of the
21 child.
22 As was just indicated in the last lecture,

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1 this tool now -- by somebody who knows how to use
2 it and there's a lot of skill that comes with doing
3 it a lot of times. But you can fill out this tool
4 for the average pediatric sedation in less than a
5 minute. But if you hover over any one of these
6 things -- and I'm sorry, I don't have it active on
7 mine. But if you hover over any one of these, it
8 will give you the definition so that there is as
9 little confusion as possible.
10 I would say in clinical trials, this would
11 be absolutely critical that people understand when
12 you click laryngospasm, what exactly do you mean,
13 and when you say hypoxia, what exactly do you mean.
14 It just is a morass if you don't have that well
15 laid out.
16 Just to deliver on the promise of data,
17 we've published about 15 papers out of this effort
18 now. The first one was as exemplary as any of
19 them, talking about the incidence and nature of
20 adverse events during pediatric sedation. Data
21 collection at that time was 30,000. Now we have
22 almost half a million encounters in our database.

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1 At the time out of 30,000, we had zero
2 deaths, 1 cardiac arrest, 1 aspiration, 24 stridor
3 and laryngospasms, 21 unplanned admissions. So we
4 considered these indicators of major issues, and
5 it's not very ambiguous that there was a
6 significant problem when one of these things
7 happened. We were able to say that happens about 1
8 out of 1500 sedations in kids.
9 There were some less serious adverse events.
10 Stridor and laryngospasm, wheezing or apnea that
11 interrupted the procedure was 1 in 400. 267
12 vomiting, secretions, or desaturation episodes that
13 interrupted the procedure, meaning somebody had to
14 stop what was going on and address these issues,
15 about 1 in 100 sedations.
16 We did a similar kind of study looking at
17 the incidence and nature of adverse events using
18 propofol from a large group of our reporting
19 institutions. In this case, it was over 50,000
20 encounters, and again, just to give you a flavor, 6
21 emergency anesthesia consults, 29 emergent
22 intubations, 83 oral airway insertions, 192

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1 positive-pressure, bag-mask ventilation.
2 To the specific issue of clinical
3 trial -- and I'm sorry, John Berkenbosch over here,
4 suffered through discussions that we've had for
5 hours about this. We've really gotten away from
6 trying to determine was this really an adverse
7 event or wasn't it, was it expected, was it
8 unexpected largely because that language becomes so
9 difficult to be precise about that we have
10 ultimately decided we're just collecting this, and
11 that's what we're going to report. Then people can
12 make their own decision about whether or not this
13 represents an adverse problem or not.
14 I would argue for me in my job, the fact
15 that I had to insert an oral airway, not a big
16 deal, but that could be something that you want to
17 know in a phase 2 trial about the use of propofol
18 for sedation of children undergoing MRI scans.
19 That's what we've ultimately come down on,
20 and while the title of this talk was supposed to be
21 complications, I'm almost like I don't even want to
22 use that word because people start to get very

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1 uncomfortable with it. Clearly, there's a few
2 things we can say are complications, but a lot of
3 things that are ambiguous when you try to use that
4 language.
5 I'm going to skip through this because it's
6 sort of repetitive, but for Dr. Twersky, just so
7 you know --
8 DR. TWERSKY: I know you don't like --
9 DR. CRAVERO: You're getting it. I'm sorry.
10 We did consider inadequate sedation a
11 problem. This is rate per 10,000, and this is the
12 absolute number of problems that we recorded in
13 this 50,000 patient group. You can see we have
14 things like inadequate sedation, airway
15 obstruction, allergic reaction, apnea as defined as
16 greater than 20 seconds during the course of a
17 procedure, agitation at the end of a procedure.
18 There's a bunch of them here.
19 Interesting, I guess I'd just point out,
20 some things we did not include initially were
21 things like IV complications. We did not have this
22 as one of our elements to collect initially, but so

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1 many people were writing in that they had problems
2 with IVs during the procedure, that they
3 infiltrated or they couldn't get an IV started, et
4 cetera, that we then started to include IV
5 complications as one of the issues.
6 We also had to include, say, secretions. We
7 did not have secretions down as a problem during
8 your sedation, but people started writing this in
9 so often that we ended up having to include it. We
10 defined it as secretions that required you to
11 interrupt the procedure and suction in order to
12 maintain stability and easy respiration within the
13 patient.
14 I would say to you there are things that
15 come up, and again, is that a complication? I
16 don't know, but you probably want to know how often
17 that occurs with drug A versus drug B or drug
18 combination C. So I would say I'm not calling it a
19 complication, but I think it might be something you
20 want to know.
21 We did collect cardiac arrest data, and I'd
22 just say it's interesting. Again, cardiac arrest,

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1 you'd think that's clear, but then there's all
2 these things that happen like significant
3 bradycardia that was profound. Maybe there was
4 asystole, maybe not, but CPR and epi was given,
5 therefore, we considered it a cardiac
6 resuscitation.
7 Maybe not everybody would have gone to this
8 level with the heart rate of 25 or 30; maybe they
9 would. I'm not sure, but you have to be careful
10 about exactly what you call these things.
11 We had another 16-year-old athletic male who
12 was having a colonoscopy, got very bradycardic, and
13 was considered to have asystole for 30 seconds.
14 CPR and atropine was given, and the kid was back to
15 baseline in 30 minutes. So very recoverable
16 things, but clearly, here's a major problem that we
17 want to know about.
18 We also collected unplanned airway
19 interventions, which we have morphed now into just
20 airway interventions because we considered this
21 over time. The unplanned part of this just became
22 too hard to know. So now in the current

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1 publications, we just talk about what kind of
2 airway interventions were required.
3 We have a fairly recent paper looking at
4 major adverse events in relation to nil per os. We
5 published this in Anesthesiology just last year.
6 In this case, we looked at 120,000 patients
7 undergoing sedation, and then we looked at whether
8 or not they were meeting NPO criteria or not.
9 For the purposes of this talk, I just want
10 to say we had a fairly specific definition of
11 aspiration, and that is, you saw contents coming
12 out of the mouth during the sedation. And then
13 after the procedure, you had a change in status
14 that was significant, requiring oxygen, requiring
15 admission and/or x-ray evidence of a problem with
16 respiration that was not anticipated.
17 We also were recording major adverse events.
18 I would just say to you we decided from a
19 observational data collection that we're going to
20 stay with major complications which we define as
21 cardiac arrest, aspiration, unplanned admission
22 because it gets very fuzzy when you get into the

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1 very minor problems given all the things that have
2 already been discussed here today.
3 But when you look at aspiration and major
4 complications, I can just tell you that we were not
5 able to find a correlation between the patients
6 that were, in fact, meeting NPO criteria and those
7 that weren't. Now, we could get into a whole
8 discussion on this. There's all kinds of possible
9 confounders here. We did do multivariable
10 logistical regression to try to get rid of them,
11 but as far as we could tell, within this group, we
12 were not able to determine a direct relationship.
13 But I think more to the point of this talk,
14 we have tried to be very careful about how we
15 define adverse events and the reporting of things
16 mostly in terms of major adverse events that are
17 easily agreed upon.
18 I'm going to summarize here that I do feel
19 like pediatric sedation adverse event is slightly
20 different because of the nature of our patients and
21 the nature of our practice. If you're looking for
22 heart attacks, you're not going to find them

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1 really. If you're looking for more minor things,
2 you're going to find a lot of them.
3 How we consider them I think is an
4 interesting conversation to have in the context of
5 clinical trials and possibly getting away from
6 necessarily calling them complications. There are
7 many reported adverse events. I would suggest many
8 of them have little or no meaning from the outcomes
9 perspective, as we've already said.
10 There are many minor complications, and I do
11 think we need standardized definitions that include
12 some physiology with intervention. I obviously
13 agree with a lot of the conversation that's gone on
14 so far that's morning.
15 I guess I'll take questions when we have the
16 panel.
17 DR. WARD: You can take a couple questions
18 now.
19 DR. CRAVERO: Anybody have any questions?
20 I am obviously very steeped in this stuff,
21 and we've talked about this so much. I'm
22 interested in the conversation we've had so far

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1 this morning.
2 I do think there's a real difference, as you
3 pointed out earlier, between what we collect and
4 what we're probably interested in from the quality
5 improvement standpoint or from an observational
6 database standpoint and what I want to know as a
7 clinical trialist when I'm comparing one technique
8 or one drug to another. I do think as we go along
9 today or tomorrow, that kind of perspective needs
10 to be considered.
11 DR. WARD: Apnea was one of the more common
12 or cessation of breathing?
13 DR. CRAVERO: Right.
14 DR. WARD: Was there any definition of how
15 that's measured? That's actually without direct
16 physiological measurement.
17 DR. CRAVERO: Yes. We have it under -- if
18 you hover it, I think, but it's lack of air
19 movement for 20 seconds or greater, is our
20 definition of apnea. And it does not necessarily
21 imply central apnea or obstructive apnea, which is
22 obviously a problem.

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1 But when you're collecting data from 40
2 institutions, which you're probably not going to do
3 with a clinical trial, but my personal feeling is
4 it is very hard to get good data from a large
5 number of institutions. So you have to be very
6 cautious about the conclusions you make based on
7 data that comes from a real large variety. So we
8 did not try to get into the subtlety of was it
9 central or was it obstructive, just did you observe
10 lack of air movement by either your direct
11 observation or end tidal CO2 for 20 seconds or
12 greater.
13 DR. WARD: Dan?
14 DR. SESSLER: This reminds me a bit of
15 airway device evaluations, that the reason that
16 you're interested in a novel type of airway device,
17 let's say a video laryngoscope, is the hope that it
18 will save you when you get into a can't
19 intubate/can't ventilate situation, that is, when
20 your patient is trying to die, you hope that you
21 can reach for some device, and it will save you.
22 The trouble is that these events are very

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1 rare. Great that they're rare, but it makes it
2 really hard to study them. So there has never been
3 a study of any airway device that remotely
4 addresses what we're really interested in.
5 Instead what we have is lots and lots of
6 studies -- I'll admit to having done some of
7 them -- where you have intermediate outcomes such
8 as time to intubation. The trouble is that that's
9 not really relevant. It's not really interesting,
10 but there are hundreds of articles that evaluate
11 different airway devices with time to intubation as
12 the primary outcome.
13 I'm a little concerned that we have the same
14 potential dynamic here, where you look at something
15 like desaturation, which is only tenuously related
16 to the things we really care about, which are
17 serious complications, patients trying to die, and
18 your data are very encouraging because they don't
19 seem to be dying, but it tells you it's going to be
20 very hard to study.
21 But we need to be careful that just because
22 the outcome of interest is difficult to study, that

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1 we don't just slide into some outcome that's
2 actually not interesting and perhaps unrelated to
3 what we are interested in.
4 DR. CRAVERO: A couple of obviously great
5 points, Dan. I think there's a couple things from
6 our stuff, which is we preface any report that we
7 make that we are talking about high performance
8 sedation services functioning in primarily
9 children's hospitals but also large community
10 hospitals, very few small community hospitals. I
11 think people need to take that data for what it is.
12 It does not imply that this indicates what the data
13 would be if you looked at the entire country. I
14 think it's a good point.
15 Secondly, I think, again, you get to the
16 issue of what do people need and want to know in a
17 clinical trial. Our point in the Sedation Research
18 Consortium has been more what do people need to be
19 able to do and what do they need to understand
20 about sedation practice in children.
21 If you're providing propofol at the level of
22 200 to 250 mics per kilo per minute to children of

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1 a given age, what do you need to be able to do, and
2 what can you expect to see when you're doing that?
3 So you need to be able to recognize apnea. You
4 need to be able to open an airway, and rarely but
5 too, too rarely, you need to be able to provide
6 position pressure ventilation.
7 My thought is when you talk about clinical
8 trials, you probably want to know -- although I
9 would agree with you, that still doesn't really
10 tell me about the outcomes I'm most interested in,
11 like did anybody need to be admitted that shouldn't
12 have been admitted or did anybody die or whatever.
13 But it probably is important information when
14 you're trying to compare one drug to another.
15 So if I look at dexmedetomidine for a group
16 of patients versus propofol, I might want to know
17 how many times do you have to intervene with
18 dexmedetomidine versus how many times you have to
19 intervene with propofol when I want to think about
20 how I'm going to use that drug clinically, who's
21 going to use it, how are we going to use it,
22 et cetera, even though I would completely agree

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1 with you, it still doesn't tell me which drug is
2 safer. And I think we need to be cautious about
3 using that kind of language. I totally agree.
4 DR. SESSLER: It gets back to who's doing
5 the procedure, who's doing the sedation, and the
6 context of the intervention. So, for example,
7 something as simple as providing oxygen is a
8 disaster if you have to stop an MRI to put oxygen
9 on. In another context, providing
10 positive-pressure ventilation, if it's an
11 anesthesiologist doing that, it's trivial. It's
12 part of the job.
13 DR. CRAVERO: I would just say again, for us,
14 our whole effort, since we're a multispecialty
15 group, is to try to, as much as possible, get away
16 from the contextual part of it when we report
17 stuff, and just say this is what happens. You can
18 make the decision as to how important those things
19 are or how worrisome they are, but we're going to
20 tell you when you use this drug for this type of
21 intervention, this is what happens, at least in the
22 group that we see.

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1 DR. WARD: Rick?
2 DR. RIKER: I just want to jump off on Dan's
3 comment. So for rare events, I think maybe we need
4 to overtly say that a randomized trial is not the
5 gold standard or shouldn't be the gold standard.
6 For something that happens 1 or 2 percent of the
7 time to look at 99 percent of your data and not
8 find that event, maybe what we think of as a lower
9 quality type of study, a registry, a cohort based
10 on a specific outcome, and drilling down in that
11 situation may be better.
12 We did a propofol infusion syndrome study in
13 the ICU and wasted most of our effort on the wrong
14 patients. I think a careful consideration of what
15 the right research design would be for these
16 uncommon events is worth discussion.
17 DR. CRAVERO: I think you're right. For
18 pediatric section, that may not really be from a
19 clinical trial perspective, something you're going
20 to even be able to do. You're going to be able to
21 look at some of these outcomes because they come
22 with a frequency that you can actually look at and

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1 consider in populations that are possible to do
2 with clinical trials.
3 You can try to get a frequency for the
4 really rare events by using the kinds of things
5 you're talking about. But again, I would
6 personally like us to think about, if we're going
7 to be discussing clinical trials, what are the
8 reporting requirements and what do we think is
9 useful in that context, which I would say if you're
10 looking for neurological injury due to sedation
11 accidents, the clinical trial is not going to do
12 that for you. You're going to have to understand
13 that you're not going to get that out of this.
14 DR. WARD: Speaking of areas, another area
15 we maybe as a group doesn't necessarily think much
16 about as being done a lot is the dental sedation,
17 certainly an area in which those of us who have had
18 root canals and maybe a long time ago your wisdom
19 teeth taken out, have had to put up with dental
20 level sedation.
21 Ray has done a lot of work with that, and we
22 want him to talk a little bit about adverse events

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1 in dental sedation.
2 Presentation – Raymond Dionne
3 DR. DIONNE: Thanks for having me. I
4 retired from the NIH about three years ago. When I
5 look back at my career, I say, gee, I had a
6 successful career, but I accomplished almost
7 nothing. So I went down to East Carolina
8 University and was kind of wasting away going to
9 seed. And for the misfortune of society but for my
10 good fortune, opiate overdoses and deaths
11 associated with sedation have become noteworthy
12 recently. So it's given me a renewed career. I'm
13 sort of a born again crusader.
14 (Laughter.)
15 DR. DIONNE: I have one bad slide here. I'm
16 going to see if I can get it all there. This is
17 the problem with not having anybody to do my work
18 for me anymore. I actually have to do these
19 things.
20 You might ask yourself, why is even sedation
21 needed for dentistry because if you're of a certain
22 age group and a certain SES status, it's not a big

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1 deal anymore. However, the fear and anxiety about
 2 dentistry is still very prevalent in the
 3 population. It seems to originate in childhood for
 4 good reason. Those needles that you get seem to be
 5 about 6 feet tall, and they hurt quite a bit. Then
 6 all the stuff that follows after that can be very
 7 unpleasant as well.

8 It does appear to lead to the avoidance of
 9 dental care, and it's remained stable over the past
 10 50 years despite all the progress we've made with
 11 preventive techniques and improved restorative
 12 techniques. It also seems to be that if people do
 13 have high dental anxiety, which is about 15 or 20
 14 percent, they'll go to the dentist less frequently.

15 Now that we have some fairly good
 16 association data that suggests oral diseases are
 17 related to possibly cardiovascular disease and
 18 diabetes, there might be greater implications that
 19 just a little disfigurement and early onset of a
 20 denture or something like that. There may be more
 21 going on.

22 About 21 percent of patients in the survey

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1 we did a number of years ago said they would
 2 definitely go more often if they could get some
 3 kind of drug that would make it a little bit easier
 4 for them to tolerate.

5 One of the problems I've had since I became
 6 a dental educator in my new role is at first I
 7 thought I was going to shape their young minds. I
 8 got over that delusion about four lectures in. So
 9 now what I try to do is scare them at the beginning
 10 and hope they'll pay attention at least to the 15-
 11 minute mark or so.

12 (Laughter.)

13 DR. DIONNE: I did this little thing right
 14 before I was going to give a talk on anesthesia and
 15 sedation to the dental students, and I was startled
 16 to have this stuff pop up. This was like the first
 17 two pages of a Google search, and it talked about
 18 children being killed. Apparently, if you die
 19 undergoing a procedure in a hospital, that's a
 20 death. When it happens in a dental office, it's
 21 murder as portrayed by the literature, or by the
 22 public thing.

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1 One thing that caught my eye also was this
 2 handling of cases about questions about the state
 3 review process, which is down there. And I've
 4 recently discovered there's two states where
 5 there's a big controversy brewing where they think
 6 there's between 40 to 50 deaths in the last 5 or 7
 7 years, depending on what report, that have been
 8 swept under the carpet in both of these states.

9 And investigative reporting has suggested there's
 10 an issue there, but no one's been able to pry
 11 through the liability insurance data that's always
 12 closed and forgotten apparently, and the state
 13 data.

14 It may be that the things that we do see in
 15 the public domain only represent the tip of an
 16 iceberg that may be a lot bigger than I ever would
 17 have expected.

18 Then there's another thing that's implied by
 19 this is that there's been a growth of people who
 20 use sedation as an aggressive part of their
 21 marketing process to try to get people to come in,
 22 and this has become probably resulting in too many

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1 people being exposed to these procedures. Worse
 2 yet, the procedures that they're pushing are far
 3 removed from evidence based.

4 This is some old data that came from Charles
 5 Cote, who I always think of as a friend of dental
 6 anesthesia and sedation, but he always seems to
 7 publish the data that makes us look a little bad.

8 (Laughter.)

9 DR. DIONNE: This was some stuff he
 10 published related to case reports he could find in
 11 the FDA database that was available in the USP and
 12 then reviewed the literature. Here is the way
 13 he -- there was 95 cases, and because there were
 14 many things that contribute to any particular
 15 situation, he had far greater numbers.

16 What I tried to do for purposes of teaching
 17 is point out that these two leading categories are
 18 really drug and dose related. Our profession seems
 19 to be obsessed with training people to do
 20 resuscitation better, not to address possible
 21 preventive procedures associated with that.

22 Then there are procedures and methodology-

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1 related things, and then finally, there are
2 training-related things. Very often, the question
3 about the personnel arises because there is still a
4 standard within the dental community that if you
5 have a dental assistant who has taken one week of
6 training, they can be the surrogate for the
7 anesthetist/anesthesiologist as long as the person
8 who's the captain of the ship is trained up to that
9 level of anesthesia/sedation. But of course, the
10 captain of the ship is over here doing a procedure
11 and monitoring, and even the drug administration is
12 often done without full supervision. That's a
13 little bit of a problem as well.
14 When you look, this is old data, you can't
15 deny that dentistry seems to be the leading
16 perpetrator here. About a third of the deaths were
17 associated with dental procedures, so more likely
18 to have serious morbidity and mortality. Like I
19 said, my friend Dr. Cote points that out.
20 Actually, he wouldn't remember me if he walked up
21 and saw me, but I at least like to throw his name
22 out like that.

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1 All right. So what I did recently, I got
2 myself in front of a train that was going down the
3 legislative process at the American Dental
4 Association. They were going to put to a
5 resolution that was going to regulate or I thought
6 over-regulate the safest form of sedation, which is
7 nothing more than having people swallow a
8 benzodiazepine but ignore everything else.
9 I looked at the same strategy. Could I
10 scare the people by doing a little literature
11 search? I just did a literature search on deaths
12 in the dental office, and I was startled to get
13 600,000 hits. Now you know the ratio of meaningful
14 stuff and garbage is pretty high, but I started
15 plowing through this. And only in the first 500
16 reports I reviewed -- and then I had a second
17 person go through and do the same thing, and we
18 came up with some agreement on it -- was that there
19 were 42 deaths. I'm not going to extrapolate that
20 there's 20,000 based on this kind of mathematics,
21 but it's worth digging in. If epidemiology follows
22 big footprints, this may be a hint that something's

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1 going on.
2 If you looked at the age range, it was a lot
3 of kids, mostly less than 2, up to 89 years, so 28
4 out of the 39 where the age was reported were
5 children. As far as the modality used, general
6 anesthesia was associated with 20 of the deaths; IV
7 sedation, 13; oral, 5; and that was the modality
8 that people were going after. "We've got to stop
9 something. We've got to stop this scourge of oral
10 sedation that's causing all these problems." Only
11 2 of these were actually associated with triazolam,
12 which was the drug that was being implicated.
13 Nitrous oxide, which is hard to imagine
14 unless you have a plumbing problem, but if you give
15 enough local anesthetic with it, apparently you get
16 problems, and then 2 were not reported.
17 So then I looked at the practitioners, and
18 again, it's hard using reports in the public
19 domain, but for every one of these, there's usually
20 20 reports. If you read through all of them, you
21 can get some idea of what's going on.
22 Oral surgeons, who are probably the greatest

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1 users of general anesthesia in the dental
2 profession, although I think they only represent
3 about 6 percent of the total number of dentists,
4 were associated with 10 deaths. Pediatric
5 dentists, also frequent users of sedation, 7. But
6 what kind of surprised me is general dentists were
7 implicated in 13 of these deaths. Then others were
8 either not reported, but we're still digging on
9 that.
10 My bias, of course, is it has a lot to do
11 with the drug. So I looked as closely as I could
12 at the drugs. A lot of benzodiazepines reported.
13 Diazepine given alone at a reasonable dose usually
14 doesn't cause problems, but then they're almost
15 always associated with an opiate. And as the FDA
16 has pointed out in their recent warnings about the
17 combination of opiates and benzodiazepines, it's a
18 different picture when you put the two together.
19 General anesthetics were being used.
20 Chloral hydrates, which everybody tells me no one
21 uses anymore, somehow or other is still causing
22 reports of pediatric deaths.

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1 Then as far as the combinations,
2 benzodiazepine and opiate was almost always what
3 was reported, but then you had the multiple drug
4 combinations. Now, this is kind of an improvement
5 because I did a survey about 25 years ago, and it
6 wasn't uncommon to find people reporting that they
7 were using five or six drugs on a routine basis, so
8 at least things have done in a little bit better
9 direction.

10 The most problematic thing in this area,
11 which I don't know we design a safety endpoint for
12 this, is the single operator anesthetist. This is
13 still considered to be a professional entitlement
14 for some people. You have the person who is doing
15 everything himself, or if you're doing general
16 anesthesia, then you're obligated to have an
17 assistant, which as Cote did report one time, he
18 says, "That's like having a high school dropout
19 with one week of training" was the way he
20 characterized and saying that's equivalent to
21 medical anesthesiologist.

22 Then there were a surprising number that had

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1 a separate anesthetist/anesthesiologist, either an
2 RN, MD, or a DDS, and there are a small sliver of
3 dentists who get two years of anesthesia training
4 and are supposed to provide that service as
5 separate from the operator.

6 Causes of death were almost always either
7 respiratory depression or cardiac arrest secondary
8 to respiratory depression so that was pretty
9 common. If, in fact, there's any credibility to
10 this kind of crude way of doing things, something
11 may be going on that suggests there's a lot more
12 morbidity and mortality associated with sedation
13 than I ever would have imagined, and that it's kind
14 of being swept under the carpet right now by those
15 people who have the professional benefit by being
16 able to promote this as part of their repertoire.

17 What else might be going on here? This word
18 "sedation" always bothered me because I always
19 thought we were trying to produce anxiety
20 reduction. Even for a while in the dental
21 profession, they used to call it anxiolysis, which
22 was that category at the low end of the dose

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1 response, somewhere above nitrous oxide, somewhere
2 where oral sedation might fit in, but before you
3 get into parenteral and whatever. At least there
4 was recognition then.

5 This was a monster study we did, had 1,000
6 patients in a prospective, five sites. Got the
7 government to spend a lot of money on it, and I
8 thought once this study was published, well, my
9 work was done. When I came back years later and
10 looked again, nothing had changed on the basis of
11 what I had promoted or published.

12 This was a measure of efficacy. It wasn't
13 quite anxiety reduction, but it was a global
14 measure. What you could see is if you had a
15 placebo but always with local anesthesia, which is
16 an important distinction from a lot of the things
17 that are done in the medical world -- we almost
18 always have to give effective local anesthesia to
19 perform our procedures.

20 If you just gave them midazolam, titrate it
21 to a clinical endpoint that would be considered
22 sort of light sedation, you got a rating there. If

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1 you kept pushing midazolam every time the person
2 wiggled, you got a little bit of an improvement.
3 If you gave midazolam plus an opiate fentanyl,
4 seemingly in the same range of efficacy as judged
5 by the patient, and then finally if you produced
6 deep sedation with a combination of midazolam,
7 fentanyl, and methohexital, you got -- these were
8 all within the same range of efficacy as judged by
9 the patient.

10 However, when you looked at the observer's
11 rating, and we had the person doing the procedure
12 as well as a separate person who was just there to
13 observe the patient, clearly, they thought the more
14 CNS depression you produced, the better off the
15 patient was or the more cooperative they were or
16 the better sedation.

17 I always get a little nervous when we talk
18 about what the operator wants versus what the
19 patient wants when I see this because there's no
20 increase in benefit from the patient's point of
21 view, yet there is the potential risk associated
22 with giving two and three drug combinations, and

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1 that seems to be supported by that case report data
2 I just showed you.
3 The other side of the equation, is there
4 some safety consideration? Well, these are the
5 people that got the placebo or the two midazolam
6 regimens, and you don't have to be able to see too
7 far. Even with my 69.9 years of vision, I can tell
8 that that looks a lot different from that. And
9 these are the people who are having 100 percent
10 oxygen supplemental, by the way.
11 So respiration rate went down. Oxygen
12 saturation went down, and expired CO2 went up. So
13 it suggests then that the potential risk from these
14 drugs in combinations that depress respiration are
15 not providing any benefit to the patient if they're
16 admitted, just an anxiolytic drug and given
17 effective local anesthesia.
18 All right. So you'll say, well, that
19 doesn't make any sense because we know people are
20 having pain, the big joke about the endo, the root
21 canal procedures, the extractions and things like
22 that. And granted, if you're having it done with

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1 inadequate local anesthesia, that's a very painful
2 process. But if you do adequate local
3 anesthesia -- and it's not that hard to achieve in
4 the mouth, 95 percent success rate on the first
5 shot, by the second shot, it goes up to 99, and if
6 you're still missing, the third one is always
7 magical.
8 I one time was having a problem with a
9 patient, and I went to my colleague. I said, "Gee,
10 Dave, I don't know what to do. I've given this
11 mandibular block twice. Should I give him another
12 one?" He said, "Ray, there's two forms of
13 anesthesia, numb and not numb. You got not numb.
14 Give him another shot."
15 (Laughter.)
16 DR. DIONNE: So I overcame my anxiety as a
17 pharmacist and give the third shot. Magical.
18 Sooner or later, you're going to find it or it's
19 going to move around enough that you get it.
20 We did a study, and we were using at the
21 time a scale that Rick Gracely had developed, where
22 he had demonstrated that he could separate out

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1 sensory intensity, how much they felt, how bad it
2 bothered them, which he called unpleasantness, and
3 then their overall pain report.
4 So if you gave people local anesthesia and a
5 placebo and took out two teeth, you got that kind
6 of a pain report, not very high. This scale is
7 hard to interpret, but this was in the ballpark of
8 slight pain or slight sensory intensity.
9 If you gave them diazepam and then took out
10 two more -- you couldn't do a crossover here
11 obviously because the diazepam wouldn't go away in
12 that short period of time -- or if you gave them
13 fentanyl, there didn't seem to be any difference in
14 the sensory intensity.
15 However, if you asked them look at the
16 unpleasantness of the sensations, diazepam was
17 clearly having an effect, and this wasn't a recall
18 thing because we were asking them 30 seconds after
19 the procedure was over to give us these ratings.
20 Fentanyl did nothing because of course, there was
21 no clinical pain to speak of for it to relieve, so
22 it didn't do much.

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1 Then if you asked the patient overall what
2 was your pain during the procedure, diazepam
3 actually, using a category scale, took it down to
4 no pain reported, whereas fentanyl just had a
5 marginal non-significant effect.
6 This would suggest then in the context of
7 dental sedation with local anesthesia that just the
8 opiate alone doesn't give you much additional
9 benefit, but it does have the risk of respiratory
10 depression.
11 Having looked at this literature for a long,
12 long time, I tried to parse it out into what were
13 the factors that were determinants of safety, which
14 would be presumably the things we would try to come
15 up with as safety endpoints when we were trying to
16 design studies.
17 While no one believes me in the dental world
18 and I find this incomprehensible, I think the drugs
19 have something to do with safety.
20 (Laughter.)
21 DR. DIONNE: PhD in pharmacology, you didn't
22 waste your time, Dr. Dewey. I figured it out. I'm

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1 carrying that knowledge forward.
2 The doses obviously make a difference, root
3 of administration, parenteral versus oral. People
4 worry, oh, sure, if you load enough down there,
5 it's going to give so much sedation that they'll be
6 just as obtunded as they would be if they got
7 parenteral, but even then you got advantages of
8 slow uptake and the beginning of elimination.
9 The rate of administration, which was proved
10 by a dentist in North Carolina few years ago, where
11 he gave 10 milligrams of midazolam as an IV bolus,
12 and then he pulled out his butterfly and started
13 his procedure, and quickly found he was working on
14 a dead patient. While people still question me
15 about that, I think that one's pretty obvious.
16 Then the combinations of the drugs, one of
17 my colleagues years ago looked at single drug, two
18 drugs, and three drugs given for pediatric
19 sedation. He referred to the three-drug
20 combination as the "kid killer cocktail" because it
21 was always the one that was associated with the
22 significant morbidity and mortality, whereas the

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1 single doses of those or even two combined usually
2 didn't cause the big bad outcome.
3 Patient selection, preoperative value makes
4 a difference, obviously monitoring, premature
5 discharge, all these things. But for the purposes
6 of trying to focus in, I consider everything that
7 has an asterisk a preventive factor that maybe we
8 could use when we're trying to teach people or
9 ideally set some guidelines for how people do
10 things that we might take those into consideration.
11 If you take all that together, I have my
12 little pyramid here, which I always try to simplify
13 everything down to that level. I work on the
14 theory that the students only remember at most two
15 or three things that I say over the course of 50
16 minutes, so I try to make it real simple.
17 I try to point out that this is the
18 foundational things. And even in the most skilled
19 hands with the best training and experience, you
20 can't always overcome that finite incidence of
21 problems that happen.
22 There was a classic example in the dental

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1 literature years ago of a guy who cooked up his own
2 little technique, went around the world telling
3 everybody how great it was. He did it like 10,000
4 times, and the next case is when he had his serious
5 adverse event. And he had no idea how to treat it
6 because he'd never had one, and he wasn't trained
7 to that level. So he had a death, and the next
8 thing you know, I'm reading about his coroner's
9 inquiry that gets published in the British medical
10 journal or something like that.
11 So all that good 10,000 cases safely, still
12 if there's something that's inherently dangerous
13 about the method, it manifests eventually. And all
14 this stuff also, clinical judgment makes a huge
15 difference, and I don't know how we can come up
16 with a risk factor for that. Can't be giving the
17 guys MMPIs ahead of time.
18 This is where the balance is, I think,
19 between safety and therapeutic efficacy. I think
20 for purposes of moving forward, it'd be nice to
21 recognize that opiates do produce obviously a dose-
22 related decrease in respiration. General

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1 anesthetics obviously do. In the right hands, in
2 the right context, or with the right risk, explain
3 to the patient because very often, this is done
4 with the assertion that these techniques are safe
5 because I've used them my whole career.
6 There was one case report I read of an
7 80-year-old oral surgeon who had a death, and his
8 defense was, "I've been doing it this way for
9 50 years. I know it's safe and effective." Well,
10 that particular day, it didn't work out, and he had
11 a young kid.
12 That's the other thing that's a little
13 discouraging. You're used to seeing people that
14 have got medical indications for this. You read
15 these case reports, and it's just one picture of a
16 young kid after another with handwringing by the
17 parents and the journalism making a big deal out of
18 it. It gets a little depressing.
19 Local anesthetics, it's hard to cause
20 respiratory depression with that. In looking at
21 all the case reports, I could only find one that
22 seemed to be a very high dose of mepivacaine. The

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1 additive effects are obvious, but people tend to
 2 sort of ignore it. Then any of these things that
 3 result in decreased consciousness have the
 4 potential for causing respiratory effects.
 5 I think one of the possible strategies that
 6 I'm trying to lead up to but I'm not sure I have a
 7 clear case for it is that patient self-report of
 8 reduced anxiety is really the therapeutic endpoint
 9 for this. We're not doing major procedures. We
 10 just want to get someone over the hurdle.
 11 I have a trite observation. I'm now a high
 12 mileage kind of guy, and I've had about 12 things
 13 done in the last 20 years. I always say, "I just
 14 want local anesthesia and a little bit of oral
 15 sedation." And that works about 90 percent of the
 16 time, but if you can't get local anesthesia, my
 17 hand shoots up in the air. I say, "I want some
 18 fentanyl now or meperidine."
 19 I even had a hernia repair done halfway
 20 awake, and the only thing that was disconcerting
 21 about that is when I was listening, I realized that
 22 my surgeon was on the left side and I knew my

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1 hernia was on the right side.
 2 (Laughter.)
 3 DR. DIONNE: That was anxiety provoking
 4 especially when some strange voice said, "Well,
 5 what should I do with this?" My surgeon said, "Oh,
 6 I wouldn't touch that if I were you."
 7 Whoa, I didn't remember anything after that
 8 because my heart rate must have gone way up, and
 9 seemingly two hours later, I'm in the recovery
 10 room, and I'm looking down, and, "My legs are all
 11 there, but what about the other things that are
 12 down in that area?"
 13 (Laughter.)
 14 DR. DIONNE: All right. So if I'm accurate
 15 about this, sedation is really the observed
 16 manifestation of decreased consciousness. It
 17 doesn't necessarily translate into anxiety relief,
 18 although they are obviously correlated very
 19 tightly.
 20 Then I got this at the last meeting, and I
 21 honestly can't remember who it was, but it was
 22 someone from the patient-reported outcomes office

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1 who said that we really shouldn't be using observer
 2 assessment because it's not a direct measure of how
 3 the patient feels, functions, or survives. So for
 4 a clinical trial's point of view, then maybe that
 5 makes a difference at least in my little shallow
 6 end of the pool.
 7 I'm advocating then -- and we're looking at
 8 clinical trials but also change in clinical
 9 practices. Anxiolytic drugs are relatively
 10 selective so they make sense. The ability to
 11 titrate the dosage seems obvious, but when you have
 12 people that are using high doses of these drugs
 13 orally and they think they can titrate by waiting
 14 10 or 15 minutes and then popping another pill
 15 down, that causes potential for problems.
 16 The combinations obviously are prone to
 17 overdose, and then I think it's very problematic to
 18 have minimally trained dental assistants who are
 19 functioning as surrogates of convenience for the
 20 anesthesiologists.
 21 Just to prove that this isn't all just
 22 hyperbole, I dragged up this old data. And this

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1 shows you 0.25 milligrams of triazolam compared to
 2 what turned out to be 18 milligrams of IV diazepam.
 3 We were titrating the patients to the usual
 4 endpoint of dropping eyelids, slurring of speech,
 5 and what we would call moderate sedation. And then
 6 we looked at the anxiety change from baseline,
 7 specifically asking about anxiety. Well, even with
 8 that good local anesthesia I'm telling you about,
 9 the patients definitely knew something bad was
 10 happening, and they had a big increase.
 11 If you gave triazolam, you got about half as
 12 much anxiety report down to fairly low levels.
 13 Triazolam plus nitrous oxide, a little bit additive
 14 benefit, but the nitrous is so weak, when you put
 15 something really effective, it doesn't do that
 16 much. You can see nitrous alone, there's evidence
 17 at how weak it can be on its own.
 18 Then diazepam, in a small sample of
 19 10 patients per group, didn't actually achieve
 20 statistical significance, although it was obvious
 21 they were pretty well sedated. So it does suggest
 22 then a little dichotomy between -- oh, and the

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1 thing is these people look normal.
 2 If you give someone 0.25 milligrams, unless
 3 it's time to go to bed, it doesn't affect them that
 4 much. Give 0.5, like I tried one time, you don't
 5 remember the post-op instructions. It can be used,
 6 and in some of these studies, we did do 0.5. If
 7 you give it sublingually, you get a faster onset,
 8 greater peak effect, and you even get patients
 9 reporting more pain relief.
 10 So I think there's a difference between the
 11 anxiety relief and the appearance of sedation,
 12 which leads me then to some suggested endpoints and
 13 risk factors for outpatient sedation. It'd be nice
 14 to have some rigid criteria for percentage decrease
 15 or respiratory depression that we would say, based
 16 on clinical trials, based on these big footprints
 17 of deaths and whatever, we don't think this is what
 18 should be going on. And when we evaluate some new
 19 method, or if we ever get to the point where
 20 evidence-based dentistry is real, then we would say
 21 show us the evidence whether you have a safe
 22 procedure based on respiratory depression.

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1 I think it'd be a consideration to look at
 2 CNS depression as not good and the anxiety relief
 3 as the measure. And if you could have some way of
 4 measuring those two and show that there is some
 5 relationship between the respiratory depression,
 6 the CNS depression, and respiratory problems in
 7 morbidity and mortality, maybe that would be a
 8 reasonable endpoint.
 9 Then many people talked about the status at
 10 discharge where people send patients out the door.
 11 I was reading one case report where the patient got
 12 a phenomenal amount of sedation, had a long
 13 procedure, and then died in the parking lot. The
 14 dentist tried to claim it had nothing to do with
 15 him, and it was just that person's time to happen
 16 and stuff like that, 10 minutes later. So there
 17 has to be some status for discharge as an outcome.
 18 I think as a risk factor and I don't know
 19 how you measure this, I don't know how you
 20 legislate against it or whatever, but it seems to
 21 be logical that every place else in the universe,
 22 except for the dental community, thinks that having

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1 a separate anesthetist/anesthesiologist makes sense
 2 versus having a minimally trained dental assistant.
 3 Even had one time we were interviewing
 4 someone for dental school, and we asked them if
 5 they had any research experience, and they said,
 6 "Yes, I do this anesthesia. I'm the dental
 7 assistant, and sometimes I experiment with which
 8 drugs I give and how fast I give them."
 9 The captain of the ship was over there doing
 10 his procedure, not knowing that this little kid was
 11 squirting a little fast, a little slow, trying a
 12 couple drugs together and whatever. Imagine the
 13 maturity level of those people that are doing that
 14 kind of stuff.
 15 Finally, one of the things that always
 16 strikes me is the range of response you get when
 17 you try to look across the population. It usually
 18 goes from the full measure. Whatever is zero and
 19 whatever is 100, you can show that when you give a
 20 fixed dose of a drug, you get a full dose of
 21 responsiveness.
 22 It may be that part of the problem is

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1 because we always tend to treat for the worst case,
 2 we may be always picking the highest dose or a
 3 combination of drugs to try to achieve that outcome
 4 in everybody, where if we had some measure of
 5 individual response, then we could actually try to
 6 get to the point where we're just giving the safe
 7 amount of the drug to achieve the effective
 8 outcome. But again, it's hard to imagine other
 9 than for teaching purposes, but it'd be nice to
 10 arrive at that as something that we might try to
 11 capture in clinical trials.
 12 Lastly, the safety of these multidrug
 13 regimens used for sedation, it appears to be
 14 particularly problematic in the pediatric
 15 population if over two-thirds of those deaths that
 16 I picked up were in pediatrics and then another
 17 five or six were in people that were extremely old
 18 or shouldn't have probably been in the outpatient
 19 setting anyway.
 20 The young, healthy adults probably do okay
 21 because that's what they are, young, healthy adults
 22 who can absorb this stuff, but if we can get at

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1 some of this stuff, maybe that might be something
2 to consider in our clinical trials' design. That's
3 what I have to say about that.
4 (Applause.)
5 DR. WARD: We've got about 15 minutes before
6 lunch, so maybe we can get the other speakers back
7 up. And Randy, would you mind moderating the last
8 session here?
9 Q&A and Panel Discussion
10 DR. CLARK: I'm going to take moderator's
11 prerogative and ask the first question for Joe.
12 Over the course of the development of the
13 consortium, has the location of those sedation
14 procedures changed? I know early on, it was highly
15 ED specific. Is that still the case now that
16 you're up to half a million?
17 DR. CRAVERO: No. I think the bulk of the
18 procedures are done in sedation environments that
19 are specific for pediatric sedation. So most of
20 the institutions we collect data from have some
21 location within their hospital where they perform a
22 significant number of sedations.

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1 Now, the sedation team obviously needs to go
2 to the MRI scanner, needs to go to CT scanner,
3 et cetera, but most of the institutions do have a
4 location where they perform sedations. We do not
5 actually, within the data that I showed today, have
6 many emergent sedations. There is some in there,
7 but it's a relatively small amount that are done
8 actually in the ED as an emergent sedation. There
9 are sedation services that work within the ED
10 environment, but they're doing elective sedations.
11 I'm not sure exactly how to answer your
12 question. We do have a lot of data from emergency
13 medicine specialists. It's second only to the
14 amount of information we have from intensivists.
15 And even from the intensive care perspective, when
16 we collect information from intensivists, they are
17 not largely doing procedures on patients in the
18 intensive care unit that need an emergent procedure
19 in the ICU. If they're performing the procedure in
20 the ICU, it's because they have determined that a
21 bed location in their ICU is going to be used for
22 elective sedations.

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1 So it is a highly selective group, and I
2 think that's one point we need to constantly bring
3 up that it is very -- the groups that are
4 participating are highly motivated and highly
5 organized.
6 DR. CLARK: That's the lead-in to my real
7 question. If I understood what you said correctly,
8 you try to take context out of the reporting of
9 events as much as possible, and if I understood
10 that correctly, what do you think are the
11 implications of removing context for the design of
12 clinical trials?
13 DR. CRAVERO: Maybe the nuance of the
14 language is not good from what I said. I think the
15 context of what happens is very important, and
16 again, we've talked about this for hours and hours
17 and hours within our group.
18 I think what concerns me when you get to
19 clinical trial reporting is that the idea of
20 saying, well, this was a complication or an adverse
21 event because it occurred in this particular
22 environment, this was not an adverse event because

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1 it was another type of provider in a different
2 environment gets hopelessly difficult.
3 I would advocate personally that when you
4 talk about what goes on, it should be fairly
5 objective reporting of what was done during these
6 procedures performed with these medications to
7 produce sedation and try to get away from having it
8 be loaded with the idea of, well, because it
9 occurred in this environment with this particular
10 type of person, it should be considered this versus
11 that.
12 That's more what I'm talking about. But I
13 think when we talk about quality improvement and
14 safety of patients, I think what you're pointing
15 out can't be said enough, which is it's probably
16 more important to consider who's giving the drug
17 and what context they're giving it in than the drug
18 itself. But again, I think that's different when
19 you're talking about that versus clinical trials
20 where we have a specific drug modality either given
21 alone or in comparison to another.
22 DR. CLARK: Mark?

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1 DR. ROBACK: I really want to agree with
2 what Joe said, and the contextual point that really
3 matters --
4 (Laughter.)
5 DR. ROBACK: -- is the patients. When you
6 look at Maala's studies and our studies when I was
7 in Denver, emergency medicine for children, we are
8 sedating ASA 1s and 2s, 99 percent they're
9 receiving. They're healthy patients. They're
10 receiving deep sedation but for really short
11 procedures, whereas when you look at what these
12 guys have published, 15 percent ASA 3s and 4s,
13 they're getting MRIs that last 60 plus minutes.
14 That's the difference, and you're going to see
15 differences in your adverse events rates
16 absolutely.
17 DR. LITMAN: I haven't heard much today
18 about upper airway obstruction. Back in the 1990s,
19 Denham and I did a series of studies that showed
20 that when you sedate kids with very similar
21 sedatives that they use in the dentist's office,
22 what your real outcome is that's the most important

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1 is not really anything that has to do with
2 ventilation per se, but it has to do with
3 oxygenation.
4 Oxygenation really only goes down the tubes
5 when you have upper airway obstruction. There's
6 very little else that can cause it. You have to
7 screen out for people, kids and adults, with upper
8 airway obstruction, a propensity, like kids with
9 big tonsils or kids with colds.
10 I oversee in my practice a very large amount
11 of non-anesthesiology-driven sedation, and we're
12 there to help out and to take over airways that
13 become obstructed. Almost every time this
14 happens -- in fact, I would just go so far as to
15 say pretty much every time -- it's for one of two
16 reasons: Either the kid had big tonsils or I
17 should say some kind of pediatric sleep apnea that
18 we didn't previously know about, but all you have
19 to do is ask if the child snores at night -- it's
20 usually a pretty good clue -- or if they had a
21 cold, and they have some kind of upper airway
22 inflammation.

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1 I don't really think it depends upon the ASA
2 status per se, but it's the propensity to upper
3 airway obstruction. So if you're going to talk
4 about how to design a clinical trial, I really need
5 to go back to like something that Denham and I
6 talked about in the 1990s, which was how do you
7 find a drug that has the best ratio of depressed
8 consciousness to the ability to cause upper airway
9 obstruction.
10 That's not an easy task, of course, because
11 you have to figure out a way to measure upper
12 airway obstruction, which isn't easy, and to my
13 knowledge, the only drug that fits that favorable
14 profile still to this day like in the '90s is
15 ketamine. There's not much else.
16 DR. CLARK: Dr. Mason?
17 DR. MASON: I had a comment about dental
18 because I think when we consider the dental
19 sedation complications, it's a totally different
20 kind of beast because even the data that you
21 presented from Cote, that was before dentists were
22 even using pulse oximetry.

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1 When you look, for example, in 2012, there
2 was a closed claims database from a large dental
3 malpractice insurer that released their adverse
4 events, and of the sedation-related adverse events,
5 half of them ended up in death, and only 8 percent
6 of them had pulse oximetry.
7 Sp I'm not really sure that it's the drugs
8 that we're giving the dentists, and I frankly think
9 that the fact that the dentists haven't killed more
10 people is because the drugs that we give them are
11 relatively benign. Chloral's been around for a
12 century, but I think it's more important to
13 recognize that these patients aren't being
14 monitored. There's no vigilance. There's drug
15 overdoses. Patients are dying of just excessive
16 lidocaine in dentists' offices or improper dosing
17 rather than the drugs themselves.
18 DR. CLARK: We're going to have a discussion
19 on the regulatory and practical differences
20 affecting both medicine and dentistry a little bit
21 later, but that's going to be an interesting part
22 of that discussion.

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1 I think we had one over here first. No?

2 DR. KARAN: I also wanted to speak to the

3 dentistry thing. As somebody who is training

4 residents and has been asked by the school of

5 dentistry where I am to train dentists, new

6 recommendations to provide them some anesthesia and

7 sedation training, it's very hard to relate

8 anything that we're doing in the anesthesia world

9 to anything that the dentists are doing.

10 I've asked them, "Well, why don't you tell

11 me what you're doing in the community?" and there

12 seems to be a disconnect. And maybe that will

13 improve in the future, but certainly we can teach

14 them to be afraid, as you said, and for proper

15 monitoring.

16 As an anesthesiologist, I wonder if we're

17 being mandated, appropriately so, maybe to teach

18 them basic aspects of sedation, probably we're not

19 using or modeling what we do for dentists to safe

20 sedation for their training, for their requirements

21 now that their national organizations are

22 requiring.

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1 DR. DIONNE: The requirements have just

2 recently been increased to 60 hours of didactic

3 training and 20 cases for doing parenteral sedation

4 presumably up to the level of deep sedation. For

5 deep sedation and anesthesia, it's a more rigorous

6 criteria. For the people who want to call

7 themselves dental anesthesiologists, they have to

8 do two full years of training.

9 The pediatric dentists have a -- I'm not

10 exactly sure what their level of training is

11 because they're usually assuming that because

12 they're giving drugs orally, it's going to be okay.

13 But you look at a lot of these things, one of the

14 cases I found took place in a dental school clinic

15 with a so-called dental anesthesiologist

16 administering the drug, and quickly, when they

17 realized they had a problem, transported the

18 patient to the emergency room, and it was still a

19 fatal outcome.

20 Even with those standards that they have in

21 place now, that finite possibility or probability

22 that something's going to happen when you're using

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1 certain drug combinations still manifests itself.

2 I like the idea of scaring them because I

3 had a colleague years ago who told me he invited

4 everybody in his hospital in the schools to come in

5 and get anesthesia training as long as he was

6 supervising them carefully. I said, "Geez, that

7 sounds a little cavalier. I did three months of

8 anesthesia, and the only thing I knew at the end is

9 I was scared to ever do it again." And he said,

10 "That's the idea, Ray." It might be something to

11 that.

12 DR. CRAVERO: I'm actually going tomorrow to

13 a meeting of AAPD to talk about data collection in

14 a broader sense because there actually has been

15 some legislation, particularly in California,

16 that's going to require pediatric dentists to

17 collect some information on what they're doing and

18 report information on what they're doing. I think

19 in conjunction with that, we may see some

20 improvement overall in practice if we could

21 actually understand what's going on.

22 The problem without a pediatric -- and

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1 correct me if I'm wrong, but a lot of problem is

2 that we don't even know how many occur. There's no

3 general reporting of how many kids are getting

4 sedation and what is being used across the country,

5 total black box as far as that's concerned. All we

6 know is that every once in a while, there's a big

7 problem.

8 If I could just put a plug in there, I think

9 it's also important for us to recognize in terms of

10 clinical trials that there are little or no

11 clinical trials when it comes to office-based

12 pediatric sedation for dentistry. Chris Heard and

13 some people in Buffalo have done a couple along

14 with the dental people there, but there's just not

15 much there at all.

16 I think as a group of investigators and

17 people that are interested in this, it's almost

18 like something we should try to do more of is help

19 pediatric dentists with clinical trials on the kind

20 of meds that they use because right now, there's

21 very little to guide them. We've done, I think, as

22 a general population of researchers very little to

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1 help that.
2 If I could just push back on Ron just a
3 little bit, I think what you're saying is
4 absolutely accurate. We do have some studies that
5 look at different populations, particularly
6 obstructive sleep apnea since it's a problem that
7 is rampant and growing.
8 I think we need to recognize that the
9 problem of airway obstruction is going to be highly
10 dependent on the population that we look at and
11 that clinical trials need to report those
12 comorbidities if we're going to make sense out of
13 them.
14 What we will undoubtedly see, as has already
15 been reported, there are certain drugs that are
16 less likely to cause obstruction in a population of
17 patients with obstructive sleep apnea, whereas,
18 let's just put words to it, like propofol probably
19 is less of a problem in 4-year-olds that don't have
20 obstructive sleep apnea than it is in those that
21 do. And part of clinical trials should allow us to
22 understand what populations are most at risk and

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1 for that drug, for this particular trial, what are
2 we talking about.
3 I would say, though, that just looking at
4 things like snoring, we need to have much more
5 precise definitions of what the population is and
6 what we're talking about in order to make sense out
7 of those clinical trials. Because as you know
8 better than I, things like snoring sometimes can be
9 extremely sensitive but not very specific for that
10 problem.
11 I totally agree with you that the population
12 and the comorbidities influence trial outcome, and
13 we probably have not done as good a job as we
14 should of defining those comorbidities.
15 DR. CLARK: Go ahead.
16 DR. LIGHTDALE: I'm just going to notice, I
17 guess, that there is this inherent bias in asking
18 the question did an adverse event occur. It's
19 really in the eye of the beholder whether or not an
20 adverse event occurred.
21 Mark, I guess my question with the TROOPS
22 is, is there any thought to just collecting events,

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1 forget that first question, go straight into did
2 any of these happen.
3 DR. ROBACK: I think that's a great point,
4 and I was thinking about that as Joe was presenting
5 as well. These are events of interest or events
6 that we care about. It's just that we use adverse
7 events for so long.
8 I don't know, Steve or Keira, do you have a
9 thought on it?
10 DR. GREEN: I think just the idea of routine
11 quality improvement, if you're tracking these lists
12 of events, not all of them are clinically
13 important. So you're going to burden your quality
14 improvement process. The goal of TROOPS is to try
15 and pull out what is clinically important and
16 what's worth the time to track.
17 DR. LIGHTDALE: I'll just push back on that.
18 If nothing occurred, it would take zero seconds to
19 fill out the form, right? No events.
20 DR. CLARK: One last question.
21 DR. CHAPPELL: Phil Chappell from Pfizer.
22 I'm sitting here listening to the conversation from

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1 the perspective of drug development. I've been
2 struggling with this notion of the complex issues
3 that have been kicked around, how do you define an
4 event, and is it adverse or procedural related or
5 drug related or some interaction between the two.
6 But I think that within industry, we would
7 be forced to -- in an a priori way in a drug
8 development program -- make some decisions or set
9 some guidelines. An event of this nature would be
10 recorded as an adverse event. It may not be
11 related to the drug or the device under study, but
12 I doubt we'd be able to have something of an
13 agnostic description of the events that happened.
14 DR. CRAVERO: I would just say having dealt
15 with the data monitoring boards in the past,
16 clearly, you're going to have certain things that
17 are unambiguous, and I think that's what I just
18 tried to point out. From my perspective, the
19 things that a data monitoring board would need to
20 understand is that we have an unexpected admission
21 when we have a kid who required ICU level care or
22 was injured neurologically from a -- there's no

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1 question about that.
2 I think the question becomes when you have
3 events that do not raise to the threshold of what
4 an oversight board would need to know and
5 adjudicate the continuing of a trial or not.
6 That's a lot of what we get into, particularly in
7 the pediatric realm, which people want to know how
8 many times did you have to readjust the patient's
9 airway to keep it opened, but I don't think that's
10 something I would report to a data monitoring
11 board. I would report if I had to call 911 to help
12 me in my office.
13 But I get what you're saying. Certain
14 things need to be not judgmental or not left to the
15 provider, and we can be precise about saying it is
16 a major problem. I think the question becomes in
17 so many of the things that are reported in the
18 pediatric realm are not clearly a big problem, and
19 when you put language that makes it sound like it
20 was a problem like "complication," it starts to get
21 everybody uncomfortable. But I totally agree with
22 you. There are major issues that need to

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1 unambiguously be called adverse events or
2 complications.
3 DR. CHAPPELL: Right. Things like death or
4 an unplanned admission are pretty clear and pretty
5 distinct. The issues will arise, I think, in
6 deciphering and deciding what to record for things
7 that do not rise to that level. We may still
8 within industry be compelled to record all of those
9 events and place them in some category.
10 DR. CLARK: Dr. Ward? I'm sorry. Go ahead.
11 DR. ROBACK: I was just going to say that
12 that's the big challenge because the obvious
13 adverse events and outcomes are extremely rare, and
14 then if we want to capture all these other events
15 but we call them adverse events, is that going to
16 decrease reporting because people don't want
17 to -- this can become punitive, and I don't want
18 them to think I did something wrong.
19 DR. CHAPPELL: Exactly. One last comment,
20 and the person who spoke about MedDRA pointed this
21 out. There's a distinction between an adverse
22 event and what is now called an adverse drug

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1 reaction. For drug developers, it's the ADRS that
2 end up -- a description of the risk-benefit of the
3 product and so forth, or they carry the greater
4 weight.
5 DR. CLARK: Dr. Ward?
6 DR. WARD: I think it's time for lunch.
7 DR. CLARK: Time for lunch.
8 (Whereupon, at 12:19 p.m., a lunch recess
9 was taken.)
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22 AFTERNOON SESSION

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1 (1:21 p.m.)
2 DR. WARD: In organizing the program, this
3 morning was focused more on what's actually
4 happening out there. So I had a little bit more of
5 a quality improvement focus on how do we collect
6 real world data to see what the adverse events are.
7 Because if we're looking at something new in trying
8 to design clinical trials, then we need to design
9 them so that we're cognizant of what the real-world
10 problems are that we're trying to make sure the new
11 drug or technique might improve on.
12 This afternoon, I'm going to change the
13 focus to really what we are interested in more, and
14 that's if we've got a new drug or compound or
15 procedure, how are we designing clinical trials
16 that are best going to elucidate the true outcome
17 safety issues that that compound might have.
18 We're going to start off with Leah from the
19 FDA. I think what seemed to work the best this
20 morning is we'll hold questions until the panel,
21 and we'll get all three up on the panel. Frank's
22 going to chair the panel, and then we'll have a

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1 break. Then we'll have a panel discussion that
2 will encompass everything that we've talked about
3 today.
4 Leah.
5 Presentation – Leah Crisafi
6 DR. CRISAFI: Thank you, and good afternoon.
7 I get to do the after lunch talk which is always
8 fun. I'm going to be providing regulatory
9 perspective on evaluating safety and adverse events
10 in procedural sedation clinical trials.
11 I've divided my talk into four sections.
12 I'm going to start with the identification of drugs
13 that are approved for procedural sedation. I'll
14 spend some time talking specifically about
15 midazolam because it is an example of a drug where
16 serious safety issues were not identified until the
17 drug was used in the clinical setting.
18 I'll then present the main challenges in
19 evaluating safety in procedural sedation clinical
20 trials. And I'll end with a few slides that
21 include advice that we have given to companies
22 developing drugs for procedural sedation.

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1 This is a list of drugs that are approved
2 for procedural sedation and the year that they were
3 approved. The first three are clearly indicated
4 for procedural sedation, and whether etomidate,
5 ketamine and methohexital have indications for
6 procedural sedation may be somewhat debatable.
7 There are two reasons that I'm starting with
8 this list. First, I wanted to point out that there
9 does not appear to be much recent precedent in
10 terms of evaluating and establishing safety of a
11 drug for procedural sedation.
12 Second, I do want to briefly focus on
13 midazolam, which might seem like ancient history,
14 but I did not want to point out that not really a
15 lot has happened in the realm of establishing
16 safety of a procedural sedation drug since the time
17 of midazolam's approval. And I do think that
18 midazolam illustrates the importance of premarket
19 characterization of a procedural sedation drug's
20 safety profile.
21 It has been 30 years since midazolam was
22 brought to market in the U.S., if I'm doing the

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1 math correctly, and so I'll refresh everyone's
2 memories about that time by summarizing what was
3 being released in the news at the time.
4 Midazolam clinical trials were conducted
5 between 1980 and 1985 in settings where
6 resuscitative equipment was available, and there
7 were reportedly no deaths and no unexpected
8 problems in the clinical trials.
9 In March 1986, Versed was first marketed in
10 the U.S. and promoted as a drug for conscious
11 sedation, and in 1987, the manufacturer issued two
12 Dear Doctor letters, including a cautioning of the
13 reports of deaths among patients who had taken
14 Versed and the need for close monitoring of
15 patients who received it. It was also reported
16 that within 18 months after coming on the market,
17 the FDA received 86 reports of serious adverse
18 reactions, including 46 deaths.
19 The story goes on and includes a
20 congressional hearing and criticism of both the
21 company and the FDA, and a box warning for
22 midazolam was added because of these adverse events

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1 that were occurring in the clinical setting.
2 This may be too small to read, and perhaps
3 we don't need to read it, but this is the first
4 paragraph of the box warning. It identifies
5 midazolam as being associated with respiratory
6 depression and respiratory arrest, and it does
7 read, "In some cases where this was not recognized
8 promptly and treated effectively, death or hypoxic
9 encephalopathy has resulted."
10 I would like to make two points. First is
11 the critical importance from a patient and
12 clinician perspective of characterizing the safety
13 of a drug that causes sedation, particularly
14 because I think as we've already acknowledged
15 today, sedation does often go hand in hand with
16 cardio-respiratory depression. Second is how
17 important it is for drug developers and regulators
18 to strive to avoid repeating this situation, where
19 the potential for a drug to reliably cause serious
20 adverse events goes undiscovered in the clinical
21 trial setting.
22 I am hopeful that our discussions today and

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1 tomorrow will be a step towards characterizing the
2 safety of procedural sedation drugs such that we
3 will not ever again what we as a community went
4 through with midazolam.
5 Now, I'm going to move on to the challenges
6 related to the evaluation of safety in procedural
7 sedation clinical trials. So we have already hit
8 on many of these challenges in the discussion this
9 morning, and I look forward to continued discussion
10 about the challenges.
11 The first challenge that I really wanted to
12 talk about is the dynamic environment that is
13 procedural sedation. During the course of a
14 procedural sedation case, you often have changes in
15 the level of stimulation, and those directly impact
16 anesthetic requirement and cause changes in vital
17 signs over the course of the procedure.
18 Positioning changes can also result in
19 changes in vital signs, and those may be related to
20 what I'll call effective blood volume such as when
21 transitioning a patient in and out of lithotomy.
22 Position changes may also result in blood pressure

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1 readings that don't reflect blood pressure at the
2 vital organs such as during colonoscopy performed
3 in the left lateral decubitus position with the
4 blood pressure cuff placed on the upper or right
5 arm.
6 Another challenging element in the
7 procedural sedation environment, which also relates
8 to effective blood volume, is the possibility of
9 significant bleeding. Bleeding can cause changes
10 in blood pressure and heart rate that are not
11 related to any drug but rather a result of the
12 dynamic setting of study.
13 Each of these changes reflect the dynamic
14 environment, but is the clinical situation itself
15 irrespective of any changes related to giving an
16 investigational agent.
17 The next problem, if you will, is that your
18 clinical trial investigators are likely to be
19 experienced givers of sedation working in a very
20 controlled environment and being very cautious
21 because the drug in use has not been approved.
22 They're going to be constantly anticipating and

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1 evaluating changes in patient status and taking
2 steps to address those changes in order to prevent
3 the occurrence of adverse events.
4 This is distinct, perhaps, from the clinical
5 trial settings for most other types of drugs where
6 you have a defined patient population and a defined
7 intervention, that being administration of a study
8 drug, after which the patient is followed and
9 observed for adverse events.
10 So in the anesthesia setting, you have
11 continuous evaluation and intervention that can
12 mask or confound the identification of adverse
13 effects of a drug that would be identifiable in the
14 absence of that anesthesia provider who's doing
15 their job to provide continuous evaluation and
16 intervention.
17 The next challenge relates to the many data
18 points that are collected over the course of a
19 procedural sedation case. Most sedation drugs that
20 we use have the potential to cause respiratory and
21 cardiovascular changes, and one of the biggest
22 conflicts in procedural sedation clinical trials,

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1 as I think we're already discussing today, is the
2 distinction between characterizing a drug's
3 cardiopulmonary changes and determining the
4 incidence of cardiopulmonary adverse events.
5 This is a challenge because on one hand, we
6 really do want to be able to inform clinicians
7 about off-target pharmacodynamic effects of a
8 sedation drug, and we haven't been historically
9 considering any change in vital signs to be
10 necessarily adverse.
11 We are constantly reconsidering the criteria
12 for adverse until we do have well established and
13 universally applied criteria for adverse. The most
14 important thing may be the collection of complete
15 data so that we have the ability to determine after
16 the fact what to consider adverse.
17 Regarding the frequency of vital sign data
18 collection, we've been trying to take a
19 conservative approach, but it is not clear that a
20 change at one point in time should be considered an
21 adverse event. However, because we have been
22 worried about missing transient but potentially

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1 important changes in vital signs caused by short-
2 acting drugs, we have requested that sponsors
3 document lowest values observed during the course
4 of a procedural sedation case.

5 Ultimately, the minimum frequency of vital
6 sign collection during sedation clinical trials is
7 not established. Every 5 minutes is the American
8 Society of Anesthesiologists' standard. Although
9 it may not be a surprise to you that if we want
10 sponsors to provide vital signs' nadirs, we have
11 been less than satisfied with being provided data
12 points for only every 5 minutes.

13 Perhaps this isn't a one-size-fits-all
14 question. It could be argued that the
15 pharmacokinetic profile of a drug be factored in
16 determining the frequency of vital sign collection,
17 or it could be argued that phase 1 and not phase 3
18 is the time for identifying pharmacodynamic effects
19 of a drug as relate to basic cardiopulmonary
20 function.

21 At this point, I will digress and share with
22 you one sentence that I wrote during my first new

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1 drug application review in order to highlight our
2 concern about the provision of vital sign data in a
3 new drug application.

4 This is the sentence I wanted to share.
5 "For example, this submission does not include a
6 single blood pressure reading during a 100-minute
7 adverse event of hypotension during which study
8 drug was interrupted in a subject who ultimately
9 died."

10 This is a clinical trial that was conducted
11 in ICU patients, so the scenario is not exactly
12 something we could imagine encountering in the
13 procedural sedation setting. However, the concept
14 is 100 percent applicable, that in order for us to
15 be able to interpret what happens in the context of
16 an event, be it considered by the adverse by the
17 investigator or not, we need data.

18 Collection of this data needs to be
19 incorporated into the study protocol and carried
20 out by the investigator if we are to be in the
21 position to evaluate and confirm adverse events.

22 Moving on to the challenge of concomitant

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1 medications, there are some situations where
2 procedural sedation can be formed with only one
3 drug being administered. Factors affecting whether
4 one drug is sufficient would include the type of
5 procedure and the pharmacodynamic effects of the
6 one drug. However, it is much more common, as you
7 all know, for several medications to be
8 administered as components of procedural sedation,
9 and those concomitant medications complicate the
10 characterization of a drug safety profile.

11 There are two main issues stemming from
12 concomitant medication use. Those are first, how
13 do you ensure that the profile of the drug you are
14 studying is reasonably well reflected in what you
15 are capturing. In other words, are concomitant
16 medications making a significant contribution to
17 the safety profile because pre meds, rescue meds,
18 and analgesics can significantly contribute to
19 degree of sedation. They may be administered in
20 significant amounts and produce sedation in which
21 case, the safety profile may be more reflective of
22 the con med than of the drug being studied.

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1 Arguably more important, particularly as we
2 consider again the experience with midazolam and
3 its synergy with opioids, is the need to understand
4 the safety profile of the drug as it is going to be
5 used clinically. If a drug produces sedation but
6 provides no analgesia, it probably needs to be
7 studied in the setting of invasive painful
8 procedures requiring concomitant opioid
9 administration so that we can understand the safety
10 of the drugs in combination because their use in
11 combination is inevitable if the sedation drug is
12 to be used clinically at all.

13 Another challenge relates to the study of
14 procedural sedation drugs in high-risk populations
15 such as those with cardiopulmonary debilitation.
16 We generally want drugs to be studied across the
17 full spectrum of patients in whom they are likely
18 to be used, and I would argue that it is important
19 to include those who are debilitated to the extent
20 that they may tolerate a general anesthetic.

21 However, this is obviously a very high-risk
22 patient population, and challenges to study include

<p style="text-align: right;">Page 225</p> <p>1 the non-uniformity of the comorbidities in this 2 patient population as well as likely difficulties 3 in recruiting patients. 4 A final challenge that I think deserves 5 mention but I hadn't been thinking would be our 6 focus today, and probably we could spend more than 7 an entire meeting talking about, is how to 8 determine the safe setting for administration. 9 Our labeling for propofol, which I've chosen 10 because it's probably the most used drug for 11 procedural sedation today, states, "For anesthesia 12 or monitored anesthesia care sedation, diprivan 13 injectable emulsion should be administered only by 14 persons trained in the administration of general 15 anesthesia and not involved in the conduct of the 16 surgical diagnostic procedure. 17 "Sedation patients should be continuously 18 monitored, and facilities for the maintenance of a 19 patent airway providing artificial ventilation, 20 administering supplemental oxygen, and instituting 21 cardiovascular resuscitation must be immediately 22 available.</p>	<p style="text-align: right;">Page 227</p> <p>1 con meds than the study drug, but if they're 2 admitted from the anesthetic, then the safety 3 profile established may not reflect the safety 4 profile of the drug when it is used in the clinical 5 setting. 6 Fifth is the challenge of studying high-risk 7 populations where the establishment of safety of 8 procedural sedation drugs is no less important than 9 in ASA 1 and 2 patients. And last is the 10 determination of the minimum requirements of the 11 clinical setting where the drug is administered. 12 Now I'd like to move on to the final portion 13 of my talk, which is just a brief presentation of a 14 few fundamental pieces of advice that we routinely 15 give companies relating to the evaluation of safety 16 in clinical trials that I think this talk would be 17 incomplete without. They relate to the definitions 18 of what we expect to find in clinical trial 19 protocols and the minimum number of subjects we 20 require in a drug development program. 21 With regard to adverse event definitions, we 22 expect sponsors to incorporate the definitions for</p>
<p style="text-align: right;">Page 226</p> <p>1 "Patients should be continuously monitored 2 for early signs of hypotension, apnea, airway 3 obstruction, and/or oxygen desaturation." 4 My question that I will pose, but really may 5 be for another day is, is there a method of 6 evaluating a drug that would give us confidence 7 that training in the administration of general 8 anesthesia or resuscitative equipment are not 9 required for safe administration? 10 At this point, I would like to restate what 11 we find to be the major challenges with evaluating 12 safety in procedural sedation. First, procedural 13 sedation is a dynamic environment where changes are 14 not necessarily attributable to the administration 15 of a drug. Second is the continuous evaluation and 16 intervention of the investigator who's doing their 17 job by preventing adverse events. Third is the 18 large number of data points that need to be taken 19 into account in evaluating a drug safety profile. 20 Fourth is the issue of concomitant meds. If 21 they are a major element of the anesthetic, then 22 the safety profile may be more reflective of the</p>	<p style="text-align: right;">Page 228</p> <p>1 adverse event and serious adverse events exactly as 2 they are defined in the Code of Federal 3 Regulations. You can see those definitions on this 4 slide. The Code of Federal Regulations also 5 includes definitions for life threatening, 6 suspected, and unexpected, and ideally a protocol 7 will also include these regulatory definitions. 8 There is a guidance that's listed here that 9 we do find very helpful for identifying and 10 explaining the definitions that we do often point 11 sponsors to, and that's the guidance safety 12 reporting requirements for INDs and 13 bioavailability/ bioequivalent studies. 14 Regarding severity and causality 15 determination for an adverse event, we expect 16 protocols to include parameters for determining the 17 severity of an adverse event as well as the 18 relationship between an adverse event and the study 19 drug. 20 With specific regard to severity, we usually 21 point sponsors to the FDA guidance toxicity grading 22 scale for healthy adults and adolescent volunteers</p>

<p style="text-align: right;">Page 229</p> <p>1 enrolled in preventive vaccine clinical trials as a 2 resource for severity definitions. 3 While obviously not developed for the 4 procedural sedation population, we feel that it's a 5 good starting place for sponsors who have not 6 provided severity definitions that we think are 7 reasonable. 8 For those of you who are not familiar with 9 the vaccine guidance, I've provided this table as 10 an example of definitions that have been used in 11 the past and are found in the guidance. I want to 12 point out that the identification of categories of 13 mild, moderate, severe, and potentially life 14 threatening as we have here is consistent with what 15 we would expect a sponsor to define in their 16 protocol. 17 Regarding causality determination, when a 18 sponsor hasn't provided definitions that we think 19 are reasonable, we usually point them to the World 20 Health Organization Uppsala Monitoring Centre 21 system as an example. 22 I've provided this table from the WHO UMC</p>	<p style="text-align: right;">Page 231</p> <p>1 sedation with the majority of subjects exposed to 2 the highest dose and longest duration for each 3 sedation trial type. A final consideration with 4 regard to the size of the safety database is the 5 possible need for expansion if safety concerns 6 arise during clinical trials. 7 With regard to non-new molecular entities, 8 we have provided guidance that's very similar 9 excepting the 1500-subject requirement. Companies 10 have been advised of the need for at least 300 11 subjects per indication with the possible need for 12 expansion of the safety database if issues arise 13 during planned trials. 14 That is the last of the advice that I have 15 to share. I'm going to just move on to a brief 16 summary. 17 We first looked at the list of drugs that 18 are approved for procedural sedation and 19 established that there's not a lot of recent 20 history that provides insight into the regulatory 21 prospective on the safety evaluation of procedural 22 sedation.</p>
<p style="text-align: right;">Page 230</p> <p>1 causality assessment system just to give you an 2 idea of the causality definitions that have been 3 used in the past. The WHO UMC example includes 4 categories of certain, probable, likely, possible, 5 unlikely, conditional unclassified, and 6 unassessable unclassifiable. I would like to 7 emphasize that we don't require companies to use 8 the terms or the definitions provided here or in 9 the vaccine guidance, but we do expect that 10 companies provide reasonable terms and definitions 11 that provide the basis for consistent 12 classification within a trial of adverse events in 13 terms of severity and causality, and ideally, the 14 definitions are uniform across an entire safety 15 database and drug development program. 16 Moving on to the numbers of subjects 17 required for the demonstration of safety, we have 18 told sponsors that as per the International Council 19 for Harmonization E1A guideline, 1500 subjects need 20 to be exposed to a drug that is a new molecular 21 entity. We have also told sponsors that they must 22 study a minimum of 300 subjects for each context of</p>	<p style="text-align: right;">Page 232</p> <p>1 I presented the example of midazolam where 2 after five years of clinical trials, the risks of 3 the drug seem not to have been well characterized. 4 Then I presented the challenges in the evaluation 5 of clinical trials, and I look forward to continued 6 discussion about these challenges from the group 7 today and tomorrow. 8 Finally, I identified some of the basic 9 advice that we have provided sponsors relating to 10 safety expectations in procedural sedation clinical 11 trials, and that's it. 12 (Applause.) 13 DR. WARD: I think we'll save questions for 14 the panel. We began with the segment on the 15 regulatory perspective, and now a clinical trial 16 design perspective. 17 Presentation – Daniel Sessler 18 DR. SESSLER: I've been asked to discuss 19 clinical trials from the perspective of identifying 20 complications. I'm going to address several 21 different topics all bound together by the 22 challenge of studying complications.</p>

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1 Efficacy in a sense is easy to evaluate
2 because efficacy is usually a continuous outcome.
3 Furthermore, you have an efficacy outcome of some
4 sort in every patient. Complications are very
5 different because you don't expect them in most
6 patients. They're inherently rare.
7 You can look at mediators of complications,
8 so for example, hypoxemia as a mediator of
9 respiratory arrest or vomiting as a mediator of
10 aspiration pneumonia. So those events are a little
11 more common. Some of them are continuous and
12 therefore relatively easy to study or ordinal, and
13 the reason that those are relatively easy to study
14 is that you simply have more information than you
15 do for a dichotomous event.
16 The trouble is that the events we care
17 about, those rare but very serious complications,
18 are always dichotomous. They're things like
19 unexpected intubation, ICU admission, death. Those
20 are rare and dichotomous, and it immediately gets
21 you into trouble, and I'm going to illustrate how
22 much trouble you get into.

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1 Studies are often powered for a 50 percent
2 treatment effect or a 50 percent difference in the
3 complication incidence in this case. But that's
4 actually unrealistic because very few of our
5 treatments actually have 50 percent types of
6 effects. Twenty percent would be far more
7 realistic.
8 If you take an event that occurs at, say, a
9 10 percent incidence, which is very, very high and
10 fortunately, none of our serious events occur at
11 anything remotely resembling 10 percent, but to
12 design a study, a two-group parallel study, that
13 identifies a 20 percent reduction in a complication
14 that occurs in 10 percent of the cases, you need
15 5,000 patients. But most of our complications
16 occur at, say, 1 percent, and then you need 50,000
17 patients, or 0.1 percent for serious events.
18 Things like death, ICU admission are
19 probably less common than 0.1 percent, and
20 suddenly, you're talking about half a million
21 patients. So it is impossible to do randomized
22 trials that identify these rare serious

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1 complications.
2 Perhaps as a consequence, our literature is
3 full of fragile results. That's results that might
4 be statistically significant, but don't actually
5 give us very much information. I'll give you this
6 as an example. These are two lightly disguised
7 real studies, both of which were published in the
8 New England Journal of Medicine, granted, two
9 decades apart.
10 These were studies of a drug for prevention
11 of postoperative myocardial infarction. One of
12 these studies had 200 patients in it. There was 1
13 myocardial infarction in the treatment group, 9 in
14 the placebo group, relative risk about a 90 percent
15 reduction, and the p-value was 0.02.
16 The second trial had 4,000 patients. It had
17 200 events in the treatment group, 250 in the
18 placebo group, relative risk of 0.8. That's 20
19 percent reduction in myocardial infarctions, and
20 the p-value was exactly the same. It's 0.02.
21 Let me ask you, which of these do you trust?
22 Well, the answer is obviously, you trust the second

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1 one, and there are two reasons for this. One is
2 that a relative risk reduction of 90 percent is
3 biologically implausible. Nothing we do reduces
4 anything by 90 percent. It's not consistent with
5 our experience or biology.
6 The other problem is that the result is
7 statistically fragile, and what I mean by that is
8 if you add two outcome events to the treatment
9 groups in each of these studies, in the first
10 study, you go from 1 to 3 versus 9. That result is
11 no longer statistically significant.
12 If you do that in the second study, it does
13 not change the p-value out to the third decimal.
14 So that's a robust result. It's one that you
15 trust. The first is not.
16 Let me put it another way. These are the
17 results of theoretical studies, so we're reducing a
18 10 percent event to 5 percent in each of these
19 cases. So it's a 50 percent treatment effect,
20 already biologically probably implausible, but I'll
21 give you that.
22 Each of these results is statistically

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1 significant, so you could publish any of these
2 results, but let's look a little more closely at
3 them. Look at the bottom one, for example. The
4 95 percent confidence intervals here range from
5 about 0.25 to almost 1.
6 In other words, from a fourfold reduction in
7 events, which is biologically implausible, to
8 nearly 1, which is no effect at all. That study,
9 even though it has 500 patients, this is not a
10 small, inexpensive study. This is a 500-patient
11 study, but it still is giving clinicians almost no
12 useful guidance.
13 You do not know from that study over a
14 factor of 4 what the true treatment effect is. You
15 need 10 times as many patients. You need to get to
16 5,000 patients to shrink those confidence intervals
17 to a level that actually gives clinicians some
18 useful guidance about how to proceed that will
19 allow clinicians, for example, to calculate number
20 needed to treat.
21 Our literature is full of studies that are
22 wrong or can't be replicated. The reason I say

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1 that is that if you look generally in the
2 biomedical literature, about 90 percent of all
3 papers report at least one statistically
4 significant result.
5 If you look at very large NIH-funded
6 studies, all of which are done for extremely
7 compelling reasons, that is, good biological
8 mechanisms, good animal data, usually some
9 preliminary human data, so you look at those big
10 studies, two-thirds of them are negative.
11 The difference between 90 percent positive
12 and two-thirds negative is the error term. Those
13 are all the publications out there that are wrong.
14 The trouble, of course, is that we don't know which
15 ones are wrong and which ones are right.
16 Almost everyone thinks that p equals to 0.5
17 means that there is a 95 chance of replicating the
18 study. That is not at all what it means. P equals
19 to 0.5 means that there is only a 5 percent chance
20 that the observed distribution resulted from
21 chance. That is not at all the same thing.
22 Let me show you what that implies for

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1 replication. Let's say we do a study of an
2 intervention that is completely ineffective or
3 we're studying a drug and it has exactly the same
4 incidence of complications as your reference drug,
5 same thing. You expect to confirm the null
6 hypothesis. So you do the study, you expect to get
7 a result near zero.
8 Let's say you then repeat the study, so
9 exactly the same study, and you keep repeating it
10 over and over again. On average, you will get zero
11 because the intervention is ineffective, but you
12 won't get zero every time. You will get a
13 distribution of values around zero, and in fact,
14 you'll get a typical, normal distribution like
15 that.
16 What p less than 0.5 means is that the
17 observed values from one study are in the outer
18 2.5 percent on each end of this normal
19 distribution.
20 So let's say you do a study, and you get a p
21 equal to 0.5. So the observed value is at the X
22 there. That value then becomes your best estimate

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1 of what the truth is. You don't know what the
2 truth is, but that's your current best estimate of
3 the truth.
4 Let's do the same thought experiment again.
5 So we keep repeating the study over and over again,
6 exactly the same study over and over again. On
7 average, you will get a value at the X, but of
8 course, you won't exactly get X each time. You
9 will again get a distribution of values around X,
10 and in fact, it will be the same normal
11 distribution just shifted so that the center is at
12 the X.
13 Well, let's consider the implications for
14 replication. So looking at the lower curve, half
15 of these replication attempts will be to the right
16 of the vertical line, to the right of the X value.
17 Those values will more extreme than your original
18 observation. The p-value will be smaller, and
19 those will be considered successful replications.
20 That's the shaded part there. But the other half
21 will be to the left of the vertical line and the X.
22 Those values will be less extreme and will have a

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1 larger p-value. All of those studies will fail to
 2 replicate the original observation.
 3 So p equals to 0.5 does mean that you have a
 4 95 percent chance of replicating the study. It
 5 means you have a 50 percent chance of replicating
 6 the study.
 7 Well, 50 percent is a coin flip. That's not
 8 very good. A reasonable question then is, okay,
 9 how extreme a value do I have to observe in the
 10 first trial to actually have a 95 percent chance of
 11 replicating at p less than 0.5?
 12 You get the answer to that by shifting this
 13 lower distribution to the right until 95 percent of
 14 it is more extreme than your original X value, the
 15 vertical line. And then you take the center of
 16 that distribution, and you go back up to your
 17 original, and you find out that you need a p-value
 18 of 0.0003.
 19 Why on earth was p less than 0.5 identified
 20 as the threshold for statistically significant?
 21 It's really an accident of history based on a
 22 misunderstanding of what p-values mean. It never

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1 should have been the threshold. If the threshold
 2 for significance had been something like 0.001, we
 3 would have a lot fewer publications, and the
 4 publications we have would be a whole lot more
 5 reliable.
 6 A strategy for dealing with rare events is
 7 to use a composite outcome. The reason people use
 8 composite outcomes is that it reduces your sample
 9 size by increasing the baseline incidence of
 10 events. Remember, sample size for a dichotomous
 11 outcome is determined by baseline incidence and
 12 treatment effect.
 13 Treatment effect is part of the biology.
 14 You can't change that, but baseline incidence, you
 15 can change by broadening your definition of a
 16 complication or by stacking various complications.
 17 The most common reason people use composites
 18 is to reduce sample size. That's actually not a
 19 very good reason for using the composites. There
 20 are compelling reasons to use composites, and that
 21 is when a particular disease or condition is
 22 manifested many ways.

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1 Diabetes is a perfect example. You're doing
 2 a study of glucose control in diabetics. You could
 3 design the study with a primary outcome of
 4 end-stage renal disease. That's legitimate, but
 5 don't you think patients are also interested in
 6 blindness and amputations? Wouldn't you want to
 7 include that? And myocardial infarctions for that
 8 matter, wouldn't you want to include that in your
 9 analysis? So that's a legitimate reason to use a
 10 composite.
 11 The rule for a simple collapsed composite,
 12 that is, one or more, is that the components of the
 13 composite need to be comparable in terms of
 14 severity and incidence. For example, if you're
 15 evaluating, say, surgical infections, you could
 16 have a composite that includes deep sternal wound
 17 infection, sepsis, abdominal abscess, and urinary
 18 tract infection.
 19 Whoops. Urinary tract infection is 50 times
 20 as common and is 50 times less serious.
 21 Effectively, all you're evaluating is urinary tract
 22 infection. So you're not allowed to do that. If

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1 you're going to use a simple composite, you have to
 2 find things that are comparable in terms of
 3 severity and incidence, or you need to use special
 4 statistical techniques, which are readily available
 5 that either account for incidence and severity.
 6 Studies can be done with either superiority
 7 or noninferiority or rarely, equivalence. Most
 8 studies are done on a superiority basis. You want
 9 to see if a new drug, for example, for sedation is
 10 superior, that is, it's more effective or less
 11 toxic than an existing drug.
 12 But let's say the new treatment is less
 13 expensive, or maybe it's less expensive and you
 14 have good reason to believe it's safer and you want
 15 to see if it's at least as effective. Then you
 16 might do a noninferiority analysis. Noninferiority
 17 is the same as saying it's not worse, and it's okay
 18 if it's better. Doesn't have to be better, but
 19 it's okay if it's better.
 20 To do a noninferiority study, you have to
 21 set some clinically important delta because when
 22 you say not worse, you're not saying it's within a

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1 hundredth of a percent of identical. You're saying
2 that it's within some clinically meaningful amount.
3 Let's say efficacy is defined on some
4 sedation scale, and you say expect it to sedate to
5 3, but we'll accept 2.5 as clinically not different
6 from 3. Then you would say anything that's about
7 that good or better is okay.
8 Equivalence is rarely used. In fact, one of
9 the few indications for it is evaluating generic
10 drugs where -- correct me if I'm wrong -- I think
11 the FDA wants the new drug to be identical, not
12 better.
13 One way to enroll a large number of
14 patients -- and if you're going to look at
15 complications, you have to have a very large number
16 of patients -- is this relatively new study method
17 which I call alternating intervention. So far
18 there's one published paper, one study completed,
19 one that's in progress using this method.
20 It's not suitable for new drugs because it
21 has to be done under a waived consent, but when you
22 have two treatments -- let's say two standard ways

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1 of sedating people, but you don't know which is
2 best or which causes fewer
3 complications -- alternating intervention is a way
4 of enrolling very large number of patients, many
5 thousands of patients, relatively easily and
6 relatively inexpensively.
7 It's appropriate for quality type studies
8 where you have two interventions that are well
9 accepted, they are both approved, and you have to
10 convince your IRB that this is essentially a
11 quality study, that you want to evaluate, to
12 compare these two methods both of which are
13 accepted.
14 If your IRB agrees, then what you can do is
15 use one method for a period of time, say a couple
16 of weeks, and then you switch to the other method
17 for a couple of weeks, and then you switch back,
18 and you keep doing that.
19 So it is not a randomized trial. Individual
20 patients are not randomized to one treatment or
21 another. In fact, the treatment periods are not
22 even randomized; they just alternate. But you do

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1 this over a period of a year or two years or even
2 longer. Over time, there is no reason to believe
3 that patients preferentially get scheduled during
4 one 2-week block versus another 2-week block. In
5 practice, you end up with virtually identical
6 groups, which is after all, the point of
7 randomization.
8 What's nice about this is that you can
9 enroll very, very large numbers of patients quite
10 easily, and that's especially true if you're using
11 electronic data acquisition, and all or most of
12 your results can pull out of an electronic medical
13 record.
14 I'd like to point out that even very well
15 done studies that are technically done
16 appropriately, they're blinded and randomized, can
17 still give you results that are wrong. Attrition
18 bias is not a big issue for sedation studies
19 because people get their sedation and they go home.
20 It's done.
21 But in, say, chronic pain studies where
22 people need to participate for months on end,

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1 people getting less effective treatment drop out,
2 and they drop out in a non-random way. It's called
3 attrition bias, and that happens no matter how well
4 you've done the study.
5 With novel techniques or novel drugs, the
6 clinicians may not be as good. So they may be very
7 experienced at using an older drug and much less
8 experienced with a novel drug. In fact, if it's an
9 unapproved drug, this may be the very first time
10 they've actually used the drug. They're just not
11 going to be as smooth with it. They're not going
12 to know exactly how to titrate it. They won't
13 anticipate problems the way they will with a drug
14 that they've been using for years.
15 So you can end up with a result that the
16 novel drug doesn't look as good as the conventional
17 drug even if it's a better drug, and it's simply a
18 matter of experience. The clinicians aren't as
19 good at it.
20 Ancillary drugs may differ, and Leah
21 mentioned that. If a new treatment is less
22 effective, clinicians may make up for that by

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1 giving higher doses of ancillary drugs, and unless
2 you're very careful, you won't necessarily trap
3 that difference.
4 Then sedation levels may differ. So you may
5 give doses of two different drugs, and they may
6 even be set by protocol, but unless you have the
7 right dose, you will get the wrong results.
8 Dose really matters, and let me illustrate
9 that for you. So let's say you do a good quality,
10 blinded, randomized trial. It's well powered. The
11 95 confidence intervals are small. Most people
12 would look at this and say that's a pretty clear
13 result. The experimental treatment is clearly
14 better than the control. Anybody disagree?
15 (No audible response.)
16 DR. SESSLER: So these are the actual
17 dose-response curves. Of course, you don't know
18 the dose-response curve because for most of our
19 drugs, we don't know the dose-response curve.
20 So those are your original results, and I've
21 overlaid the actual dose-response curve. Notice
22 that the dose-response curves in this case are

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1 identical. They are simply shifted a little bit.
2 So the experimental drug dose-response curve has
3 shifted a little bit to the left. It's a little
4 bit more potent drug.
5 Well, let's say you used a higher dose of
6 the control drug, which you might. After all,
7 equivalent doses is not the same number of
8 milligrams. It's some clinical impression about 4
9 milligrams of this is equal to 45 micrograms of
10 something else. It's a clinical comparison.
11 You're saying we think these are comparable doses.
12 But suppose you got it wrong. Suppose you
13 had done the study a little differently with a just
14 little bit higher dose on the control group.
15 Suddenly, the experimental group looks
16 substantially worse than the control group. But
17 suppose you had given more of both drugs. Then
18 you'd be up where the curve saturates, and they
19 would look identical.
20 So my point is that dose matters, and we
21 rarely include this in studies. Almost all of our
22 studies have one dose of an experimental drug and

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1 one dose of a control drug, and you can get very
2 different results depending on where you are in the
3 dose-response curve. And this is a simple example
4 because the dose-response curves are identical.
5 They're just shifted. In fact, there's no reason
6 why they should be identical. One could be flat
7 compared to the other.
8 To summarize here, complications, at least
9 the complications we're really worried about, are
10 dichotomous and rare. Virtually no study is
11 powered to detect serious complications. And as I
12 explained right in the beginning, you essentially
13 can't.
14 I'm not saying this to blame investigators.
15 It's a function of the biology. When you're
16 dealing with very rare dichotomous events, it is
17 impossible to do studies that are large enough
18 because we can't study 50,000 patients, much less
19 half a million patients, in a prospective
20 randomized trial.
21 Now, in phase 4 studies when you can use
22 techniques like alternating intervention, then you

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1 can accumulate a large number of patients. It's
2 important that drugs that get approved go into
3 phase 4 studies. And midazolam is the perfect
4 example of why we need to do that. You can't just
5 approve a drug and say everything is fine because
6 the rare events can't be detected in clinical
7 trials. You will only see them afterwards.
8 Strategies that can help are composite
9 outcomes, and remember that dose really does
10 matter. Whenever possible, it is nice to include a
11 dose-response curve in studies. Thank you much.
12 (Applause.)
13 DR. WARD: We'll save the questions for the
14 panel.
15 Dr. Li from FDA will continue with some of
16 the issues that Dan has raised about how we look at
17 rare events in clinical trials.
18 Presentation – Bo Li
19 DR. LI: Good afternoon, everyone. My name
20 is Bo Li. I'm a statistician from the Office of
21 Biostatistics at the Center for Drug Evaluation and
22 Research of FDA. I want to thank the organizers

<p style="text-align: right;">Page 253</p> <p>1 for this great opportunity to share and learn. 2 Actually, this therapeutic area of sedation 3 drugs is new to our team, so this talk is pretty 4 much a landscape talk. So I will share some 5 general statistical comments on the quantitative 6 assessment of drug safety. I changed the title 7 later, a statistician's perspective working in FDA, 8 and the standard disclaimer. 9 Evaluation of safety is a critical part of 10 the drug review and approval process at CDER. I 11 will give an overview of the safety evaluation of 12 drugs and of the role statisticians play in that 13 process. In particular, I will focus on some 14 statistical considerations on these three items. 15 I think this is the wrong set of slides, but 16 let me continue on that. So first, I will talk 17 about the characterization of general adverse 18 events reported in your NDA or BLA. I'll spend 19 some time on meta-analysis of safety outcomes, then 20 the challenges and features when designing a safety 21 outcomes trial. 22 For the time consideration, I will skip the</p>	<p style="text-align: right;">Page 255</p> <p>1 new safety information often emerges after a 2 product is used in a wider patient population after 3 marketing. 4 In recognition of such limitations, FDA 5 continued to monitor and characterize the safety of 6 drugs through active and positive surveillance 7 programs. With that being said, drug safety 8 evaluation in FDA is continuing throughout the life 9 cycle of a drug or a biologic. 10 In the last decade, several high profile 11 concerns about drug safety led to the new 12 regulation, including FDAAA, which stands for Food 13 and Drug Administration Amendments Act of 2007. 14 FDAAA granted FDA new authority to require 15 postmarketing safety studies, and it changed the 16 label to include new safety information. 17 Under FDAAA, postmarketing requirements, a 18 PMR study can be required to assess the risk 19 related to the use of a drug. That may be required 20 at the time of approval or when new safety 21 information arises. Such studies include 22 randomized controlled trials, observational study,</p>
<p style="text-align: right;">Page 254</p> <p>1 sentinel item, and I will talk about a case example 2 for long-acting beta agonist, LABA, followed with 3 some closing remarks. 4 Safety data is continuously evaluated at all 5 stages of drug development, including the 6 preclinical, early phase, and late phase trials. 7 Before a new drug or biologic is tested in humans, 8 preclinical work occurs to determine whether the 9 product is reasonably safe for initial use in 10 humans besides its efficacy. 11 The next step is clinical development. One 12 goal is to get a safety profile for the drug in 13 humans. Safety evaluation continues from phase 1 14 to phase 3 trials. 15 For marketing application of a new drug or 16 biologics, FDA assesses whether the benefits of the 17 drug outweigh its risks. Knowledge about a new 18 product is always limited at the time of approval 19 due to brief duration, limited patient population 20 of clinical studies, or lack of sufficient 21 information of some potential serious risk to be 22 addressed appropriately in the product labeling. A</p>	<p style="text-align: right;">Page 256</p> <p>1 animal study, registry, et cetera. Before 2 requiring a PMR study, FDA must find that a 3 premarketing study is not sufficient. FDA must 4 require at least a burdensome study. 5 FDAAA also authorizes FDA to require a risk 6 evaluation and mitigation strategy, REMS, if it's 7 determined either during the initial product review 8 or at any point in the postmarketing period that 9 specific safety measures are needed to ensure that 10 the drug's benefits outweigh its risks. 11 FDAAA mandated the FDA create the Sentinel 12 Initiative, an active surveillance system based on 13 electronic health data. This surveillance system 14 is called active because the FDA has the ability to 15 initiate a query of the data. 16 A brief organizational chart of CDER. The 17 Office of Biostatistics is under the Office of 18 Translational Sciences and mainly collaborates with 19 three offices in CDER: the Office of New Drugs, 20 the Office of Surveillance and Epidemiology, and a 21 relatively new Office of Generic Drugs. 22 Since the time that FDAAA became effective,</p>

<p style="text-align: right;">Page 257</p> <p>1 FDA has substantially strengthened its safety 2 program for drugs. Expanded groups dedicated to 3 drug safety were established in CDER. In 4 particular, within the Office of Biostatistics, the 5 Division of Biometric VII, DB7, was created in 2009 6 to enhance the quantitative evaluation of drug 7 safety. DB7 provides support to both the Office of 8 New Drugs for premarketing safety assessment and 9 the Office of Surveillance and Epidemiology for 10 postmarketing safety assessment across the life 11 cycle of drugs and therapeutic biologic products. 12 In DB7, we evaluate and help design safety 13 studies, including clinical trials designed 14 primarily to study safety outcomes. Such clinical 15 trials could be either premarketing or 16 postmarketing. We review observational studies 17 submitted to meet postmarketing requirements. 18 When safety issues are raised by addressing 19 the information, a retrospective look at multiple 20 completed trials -- in other words, meta- 21 analysis -- may be required, and a statistical 22 analysis plan will be reviewed by us. We also</p>	<p style="text-align: right;">Page 259</p> <p>1 efficacy data and safety data collected to support 2 a marketing application. Randomized clinical 3 trials are the principal means of establishing the 4 efficacy claims of drugs. However, these trials 5 are limited in size and duration and exclude high- 6 risk populations. Lack of statistical power and 7 generalizability makes safety data included in an 8 NDA or BLA mostly used for exploration and 9 estimation purposes only. 10 The challenges also include the lack of 11 prespecification and adequate ascertainment of 12 adverse events. Safety endpoints are often not 13 adequately collected, precisely measured, or 14 adjudicated. 15 For evidence generation of efficacy, 16 clinical trials are assessed individually. 17 However, safety data are generally aggregated for 18 multiple clinical trials. A reason to pool trials 19 is that one may be able to provide a more precise 20 and a more reliable estimates of safety parameters. 21 Also, pooling data may allow conclusions to be 22 drawn that would not be seen by looking at the</p>
<p style="text-align: right;">Page 258</p> <p>1 review some prospectively planned meta-analysis to 2 evaluate specific safety concerns. 3 In addition, DB7 has expertise in the design 4 and statistical methods used in the sentinel 5 studies and some other FDA initiated 6 pharmacoepidemiological studies. When these safety 7 studies or analysis are completed, we review the 8 study report and look into the data and 9 interpretation of the results. All these 10 activities contribute to CDER's daily regulatory 11 decisions. Besides the review work, DB7 conducts 12 research of statistical methods in drug safety 13 evaluation to support drug development and 14 regulation. 15 Note that DB7 does not typically review the 16 general adverse events of NDA or BLA. We get 17 involved only when there is a focused or specific 18 safety issue that requires the expertise and 19 resources of DB7. But I will touch a little bit on 20 some statistical issues arising in the general 21 NDA/BLA adverse events reporting. 22 This table depicts the key differences of</p>	<p style="text-align: right;">Page 260</p> <p>1 individual trials. 2 The integrated summary of safety, SS, is a 3 section of the NDA that provides comprehensive 4 safety information collected throughout the drug's 5 development program. The goal of the SS is to 6 characterize the overall safety profile of the drug 7 and to identify risks that should be included on 8 the product labeling. 9 Safety parameters of interest typically 10 include those specified in the FDA guidance, those 11 that have priority, special interest, or concern 12 for the compound or the drug class, and those 13 identified during data review. 14 Some examples of safety parameters are 15 exposures, concomitant medications, deaths, adverse 16 experiences, lab measures, and vital signs. The 17 summary of the estimates of correctly selected 18 parameters should sufficiently describe the overall 19 drug safety profile. 20 We can characterize adverse events by 21 reporting crude proportions or incidence rates 22 adjusted by exposure or time to event. That choice</p>

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1 should depend on the trial design. For example,
2 for time-to-event trial, proportions may be less
3 meaningful.

4 Various methods can be used to make
5 comparisons between groups. These methods include
6 difference or ratio of proportions, difference or
7 ratio of incidence rates, hazard ratios, survival
8 curves, et cetera.

9 As we already discussed, pooling of safety
10 data from multiple trials may give us more insights
11 in the safety profile of a drug. From a
12 statistical perspective, a critical question is how
13 to pool data in scientifically sound ways. Rare
14 adverse events pose additional challenges for data
15 presentation in SS.

16 To explain the issues when pooling data from
17 multiple trials, I made up this hypothetical
18 example. Study 1 has two groups, treatment and a
19 control. The randomization ratio is 3 to 1, 300
20 patients randomized to treatment group and 100
21 randomized to the control group.

22 We are interested in the association between

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1 the treatment and some adverse event, AE. Number
2 of subjects with AE are 180 and 60 for the two
3 groups, respectively. So it's easy to calculate
4 the risk for each group. They are same, 60
5 percent. Thus the relative risk is a ratio of
6 them, which is 1, means a neutral effect.

7 Now, assume that we have a second trial
8 study 2, which investigated the same drugs and same
9 outcome. This trial has a balanced design, 1 to 1.
10 Each arm enrolled 200 patients, and each arm has 60
11 subjects with adverse events. So the risk of AE
12 for both groups are equal again. It's 30 percent,
13 resulting in a relative risk of 1.

14 We have two trials. Now, let's guess what
15 will be the combined relative risk if we pool the
16 data from the two trials. Intuitively, it should
17 be 1 because for each individual trial, it's 1.

18 A typical pooling of the same SS is just
19 crudely pooled across all trials. That means in
20 the pooled table, number of subjects, number of
21 adverse events are simply the sum of corresponding
22 numbers of individual trials.

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1 Data are pooled together as if it came from
2 a single study. Thus in this example, we got 500
3 subjects for treatment group, 300 for control
4 group, 240 subjects with adverse events in
5 treatment group, and 120 with adverse events in the
6 control group.

7 Risk can be as easily calculated; again, 240
8 divided by 500, which is 48 percent, and for the
9 control, that number is 40 percent. That ends up
10 with a relative risk of 1.2. 1.2 means that the
11 treatment is 20 percent more harmful than the
12 control. However, this obviously contradicts with
13 our intuition. It seems misleading.

14 This phenomena is called Simpson's Paradox.
15 What caused that is deferring randomization ratios
16 within a study and a different study populations
17 across studies. Recall that study 1 includes a
18 high-risk population with 60 percent subjects
19 having the adverse event randomized in a 3 to 1
20 ratio. Study 2 include a low-risk population. The
21 risk is 30 percent, and the randomization is 1 to
22 1.

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1 When we add the number of subjects from the
2 two trials for those on treatment, 300 out of 500,
3 300 from study 1 out of the total 500, which means
4 a 60 percent of the patients are high risk. For
5 those on control, in total, we have 300, but you
6 have only 100 from study 1 for the high-risk
7 population. That means only a third are high-risk
8 patients.

9 Crude pooling does not adjust for this
10 disparity, thus resulting in a bias or distorted
11 estimate of treatment effect. Crude pooling can
12 give misleading results from any factor that
13 impacts the adverse event proportion is
14 disproportionally representing the overall drug and
15 compared cohorts such as demographic factors like
16 age, gender, race, or other factors like deferring
17 time of study.

18 We can imagine a cardiovascular outcome.
19 Two studies studied the cardiovascular outcome, and
20 one is for younger population, and the other is for
21 the older population. They have a different
22 randomization ratio. If you mix them together

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1 crudely, that also will give you this target
2 estimate of the treatment effect.
3 A lesson we learned is that crude pooling is
4 not a proper way to combine data from multiple
5 studies. We should almost always perform analysis
6 stratified by trial. That means the overall
7 estimate should be a weighted average of a common
8 treatment effect or risk across trials.
9 Common traces or weighted method include the
10 so-called inverse variance weighting and
11 Mantel-Haenszel weighting. Both methods will lead
12 to a point estimate of the treatment effect and its
13 associated confidence interval.
14 We revisit this example. If we adopt the
15 stratified or weighted analysis, no matter which
16 weighting strategy we chose, we will get similar
17 estimate of the overall relative risk with a point
18 estimate of 1 as shown at the bottom of this slide.
19 We talked about the estimate of treatment
20 effect when combining multiple trials. Let's now
21 go back to the reporting of overall risk or
22 proportions in the combined data. In this example,

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1 the overall proportion of the adverse event for
2 each group as reported in this column highlighted
3 in yellow, are 48 percent for treatment and 40
4 percent for control, respectively.
5 These proportions themselves seem misleading
6 as one is higher than the other, but they should be
7 comparable. If the proportions are comparable
8 within each single study, an acceptable strategy
9 should lead to comparable overall proportions
10 between the treatment groups.
11 It's under debate which way is the best to
12 report the overall proportions for multiple trials.
13 One possible option is to estimate through
14 weighting again. Two common weighting methods are
15 Mantel-Haenszel or weighting by study size.
16 The overall risk estimated using the two
17 weighting approaches were shown here in these two
18 highlighted columns. Here is a type where it's not
19 in my new slides, but that means adverse event, not
20 death.
21 The overall risk estimated using the two
22 weighting approaches, for one method is 43 percent

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1 for both groups, and the other method gives us 45
2 percent for both groups. They are both comparable.
3 For rare adverse events, very likely
4 appropriate pooling is needed. Where events are
5 rare, inverse variance procedure may not work well
6 due variance estimate. We can consider other
7 methods like Mantel-Haenszel or something called
8 the Peto method.
9 Zero event trials are frequently seen in the
10 setting of rare adverse events. In this case, the
11 absolute effect measures like risk difference or
12 rate difference may be better suited than the
13 relative effect measures like risk ratio or rate
14 ratio. Imagine you'll have zeros in the cells.
15 You divide by zero, and that will give you
16 indefinite number.
17 In many cases, while a formal comparison
18 cannot be made, we can only report the estimate of
19 the risk of adverse event and its corresponding
20 confidence interval. When no events are observed,
21 the rule of three allows one to calculate an upper
22 bond on that risk. For example, in a sample of

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1 10,000 subjects with no adverse events, the upper
2 95 percent confidence interval for the risk would
3 be set at 3 over 10,000.
4 I will attach meta-analysis of safety
5 outcomes. If you search for the definition of
6 meta-analysis, there are a lot of different
7 languages. I personally like the definition given
8 in this November 2013 FDA white paper. "Meta-
9 analysis refers to the combining of evidence from
10 relevant studies using appropriate statistical
11 methods to allow inferences to be made to the
12 population of interest."
13 Note here the keywords here are "appropriate
14 statistical methods." Generally said,
15 meta-analysis itself is a statistical approach used
16 to combine results from different studies or trials
17 to evaluate some specific hypothesis.
18 The stratified or rated approach is like
19 when we have just the top [indiscernible]/ The
20 inverse variance, Mantel-Haenszel methods, they are
21 actually examples of meta-analytical methods.
22 Meta-analysis is often used when one single

<p style="text-align: right;">Page 269</p> <p>1 trial does not provide sufficient information, 2 which is common for the rare safety outcomes. 3 Meta-analysis can be used to estimate the treatment 4 effect of risk for a therapeutic intervention and 5 to quantify the uncertainty of the estimated risk. 6 By using all available data from multiple 7 trials in your meta-analysis, randomization within 8 each trial can be preserved. Statistical power is 9 increased by increasing sample size. In other 10 words, precision of the effect estimate can be 11 improved. 12 Again, this is an older slide, so I have a 13 lot of slides here for the meta-analysis, but I 14 will talk about a general summary of the meta- 15 analysis. I apologize for that. 16 We can do meta-analysis. More than one 17 study has estimated a same effect. Choice of 18 trials to be included in the analysis should be 19 blinded to the results of that trial. One needs to 20 evaluate appropriateness of study design and 21 conduct of each trial, including randomization and 22 blinding methods, patient population, outcome</p>	<p style="text-align: right;">Page 271</p> <p>1 assure adequate information was collected in an 2 unbiased way, especially in a trial not designed 3 for the outcome of interest. Many times data 4 extraction from multiple trials are challenging due 5 to inconsistent definition, collection, and the 6 measurement of safety outcomes, and also due to the 7 different structure or format of the trials. 8 I'll skip this, some methodology. 9 Based on what has been discussed so far, 10 assessment of safety in drug development program 11 has its unique methodological issues in the context 12 of secondary use of efficacy of clinical trials in 13 the context of rare safety events. Some rare 14 events may not be even observed, and collaboration 15 of information from multiple trials is often 16 needed. 17 Meta-analysis is a statistical tool to 18 synthesize the information from multiple trials. 19 To do a high quality meta-analysis, you may need to 20 team with necessary expertise, including 21 statistical, clinical, or sometimes informatics. 22 You may want to carefully develop a study protocol</p>
<p style="text-align: right;">Page 270</p> <p>1 ascertainment, comparator, patient follow-up, and 2 differential dropout. You remember garbage in, 3 garbage out. The quality of the meta-analysis 4 strongly depends on the quality of each individual 5 trial included in that meta-analysis. 6 I'll skip this. 7 Assessed clinical trial information is 8 unique to FDA. That means we can often get patient 9 level data of the trials, which is ideal for a 10 meta-analysis. The meta-analysis conducted outside 11 FDA are mostly based on the summary results of the 12 individual studies, which we call the trial level 13 meta-analysis. 14 Patient level data allows us to apply common 15 definitions of safety outcomes across trials to 16 conduct subgroup analysis, to conduct time-to-event 17 analysis to assess exposure and the follow-up 18 between groups, to conduct various sensitivity 19 analysis with all this detailed information. 20 To conduct a rigorous meta-analysis, 21 selection of trials should be made blinded to the 22 trial results. I emphasize that. We needed to</p>	<p style="text-align: right;">Page 272</p> <p>1 and a statistical analysis plan to conduct a 2 rigorous meta-analysis. 3 Carefully designed and conducted 4 meta-analysis can provide important input to FDA's 5 regulatory decisions. In general, when FDA 6 [indiscernible] for a prospective subject level 7 meta-analysis. 8 Now I'll spend some time on the safety 9 outcomes trial. Safety outcomes trial may be 10 requested premarket or postmarket. The risk can be 11 quantified only in a randomized clinical trial. 12 Most clinical trials designed to evaluate safety 13 are event driven, meaning the statistical 14 information contained in that trial is determined 15 by the number of events rather than the number of 16 subjects. 17 Such trial is planned to continue following 18 patients until a fixed number of events, let's say, 19 D events, are observed. The trial objective is 20 typically to rule out some amount of excess risk by 21 comparing the upper bound of the 95 percent 22 confidence interval against some prespecified risk</p>

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1 margin, let's say delta.
2 The D events are observed by following
3 subjects for a fixed period of time, and this
4 provides the number of patient-years. We can
5 imagine the highest annual baseline event rate is,
6 the fewer patient-years will be needed to observe
7 the fixed number events D. For rare safety events,
8 we may need more patient-years, which means larger
9 sample size, longer duration, so enriched
10 population may be considered in such cases.
11 For example, in a dedicated cardiovascular
12 outcomes trial, trials in which to observe patients
13 at a higher cardiovascular risk would require fewer
14 patient-years than trials conducted in low
15 cardiovascular risk populations.
16 This figure shows the relationship of the
17 risk margin and is the number of events needed when
18 power is fixed at 90 percent, type 1 error fixed at
19 0.5, and assuming the true relative risk equals 1.
20 In general, lower risk margin requires more events.
21 As the risk margin increases, fewer events are
22 needed.

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1 This is a table of results to show you
2 specific values of the risk margin under the number
3 of events. For example, if the goal is to rule out
4 a relative risk of 1.3, you will need 611 events.
5 However, if the risk margin is set higher at 2,
6 only 88 events would be needed.
7 I have another table, but it's not shown
8 here. I'll just describe it. So I have another
9 table which shows you a different background event
10 rates, like the rate is 1 percent or 2 percent,
11 which can be considered as rare events.
12 For example, if you have risk margin of 1.3,
13 you need 611 events. So if the background event
14 rate is 1 percent, that means you need 61,100
15 patient-years. That is huge.
16 That means if the background event rate is
17 low, the trial size to rule out excess risk can be
18 quite large. That's setting a small risk margin
19 for safety event that occurs infrequently would
20 likely result in too large of a trial to be
21 considered feasible.
22 In the end, the choice of a risk margin is

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1 highly impacted by the feasibility of conducting
2 the trial and completing it in a timely fashion.
3 Clinical considerations are necessary in how such
4 trials will ultimately be powered as well as
5 analyzed.
6 Another design feature that needs to be
7 considered in a safety outcomes trial is a choice
8 of a control arm. The choice of control can be
9 placebo, background therapy, or standard of care,
10 or even active control with a known safety profile.
11 We needed to consider knowledge of
12 background risk of the control. For example, a
13 control that has been under investigation for
14 possible risk would not be appropriate. We need to
15 consider tolerability of the control as it will be
16 studied over an extended period of time. That's
17 typical for a safety trial, also, ethics. For
18 example, it may not be ethical to use a placebo
19 control for a trial that is planned to continue for
20 multiple years.
21 Safety outcomes trial included the rules for
22 treatment discontinuation such as lack of efficacy

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1 after so many months of treatment or sustained
2 increases in vitals. Additionally, this event-
3 driven trial often has long duration that would
4 result in fewer subjects being in treatment at
5 study termination.
6 In order to assess the attributability of
7 the event to treatment exposure, the trials should
8 be designed to follow subjects while exposed to
9 treatment as well as after the discontinued
10 treatment. The statistical analysis plan should
11 document how to address the attributability as
12 well.
13 Study analysis includes all safety events
14 that occurred while subject was exposed to
15 treatment or off treatment. On treatment analysis,
16 a subject is censored at the time of treatment
17 discontinuation, plus typically, some predefined
18 event ascertainment window.
19 Such analysis does not count events after
20 the ascertainment window. These two analyses
21 differ in how they count events in the defined time
22 at risk. Overall, the assessment of the safety

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1 outcomes should include both analysis and
2 prespecify which one would be the primary.
3 These are some examples of safety outcomes
4 trial we currently see. We see a lot of
5 cardiovascular outcomes trials associated with the
6 use of antidiabetic drugs, which is due to this
7 2008 guidance.
8 I'll skip this. I'll skip sentinel.
9 The story of LABA, a little background.
10 LABA is a drug class indicated for the treatment of
11 asthma. They provide bronchodilation for 12 hours
12 or longer. Some large trials conducted in 1990s
13 suggested the LABAs are associated with adverse
14 asthma outcomes such as asthma-related death.
15 This resulted in a box warning that warns of
16 asthma-related deaths associated with LABAs and
17 specify that these drugs should only be used for
18 patients not adequately controlled on other asthma
19 controller medications or whose severity clearly
20 warrants initiation of treatment with two
21 maintenance therapies. LABAs are currently used in
22 combination with asthma controller medications like

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1 inhaled corticosteroids, ICS.
2 In response to the recommendations from the
3 November 2007 pediatric advisory committee meeting,
4 FDA initiated a meta-analysis to explore possible
5 associations of four LABA products marketed in the
6 U.S. with a composite endpoint of asthma-related
7 hospitalization, asthma-related intubation, and
8 asthma-related death. Another goal is to examine
9 the risks in subgroups, particularly in pediatric
10 patients.
11 In 2008, FDA requested sponsors of LABAs
12 submit trial level and patient level data for
13 asthma trials. These requests specified as the
14 including criteria for trials the adjudication of
15 asthma-related events, the format, and the
16 variables of the data to be submitted to the FDA.
17 In the meta-analysis, the risk effect was
18 estimated by Mantel-Haenszel risk difference, which
19 is a stratification method stratified by trial.
20 This statistical method makes use of trials with no
21 events by using this risk-effect measure of risk
22 difference instead of ratio.

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1 This forest plot shows the results of the
2 meta-analysis for the individual drugs, four drugs
3 here. Three out of the four drugs had a positive
4 risk difference estimates. Remember, to the right
5 of the Y-axis means it's bad for the drug. To the
6 left, it means the drug is variable.
7 Three out of the four drugs had positive
8 risk difference estimates for the asthma composite
9 endpoint. Only one drug had statistically
10 significant risk difference estimate, which is the
11 second one from the top. The risk-difference
12 estimate for one drug, the top drug, Advair, was
13 negative and not statistically significant.
14 Overall, you can see it's statistically significant
15 for that risk difference estimate.
16 The meta-analysis results by the age
17 subgroups is shown here. There was a general trend
18 among the age groups with high-risk difference
19 estimates among the younger age groups. Except the
20 older equal to 65 age group, the risk difference
21 estimates for all other age groups were positive
22 and statistically significant.

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1 This trend among the age groups for the
2 asthma composite endpoint was apparent when each
3 drug is considered individually -- it's not shown
4 here -- except in the case of Advair, the first
5 drug. This kind of trend is pretty much driven by
6 the asthma-related hospitalization. You can
7 imagine that may be the most frequently observed
8 adverse events in that composite.
9 Subsequently, the boxed warning of LABAs was
10 revised accordingly to reflect this new information
11 and current knowledge. This is for the pediatric
12 patients. "Previous trials and FDA meta-analysis
13 showed LABAs associated with asthma adverse events.
14 It's not known whether there are similar risks when
15 LABAs are added to ICS. Current available data are
16 inadequate to determine that risk.
17 "It's determined that this question cannot
18 be answered through re-analysis of existing data,
19 analysis of spontaneous reports of adverse events,
20 or epidemiological studies using existing
21 databases. Therefore, controlled clinical trials
22 are necessary."

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1 In April of 2011, the FDA issued a
2 postmarketing requirement to all manufacturers of
3 LABAs that are marketed for asthma in the United
4 States to conduct controlled clinical trials to
5 assess the safety of a regimen of LABAs plus ICS
6 compared with ICS alone. The trials are
7 multinational, randomized, double-blind and last
8 six months. The primary endpoint is a composite of
9 asthma-related death, intubation, or
10 hospitalization. Events are to be adjudicated by
11 an independent adjudication committee.
12 The agreed upon sample size of 11,700
13 patients in each trial will provide a 90 percent
14 power to rule out a doubling of relative risk.
15 That means [indiscernible] equals 2. The design
16 and conduct of all the trials are similar so that
17 the results of the four trials can be reviewed
18 jointly in order to evaluate rare events such as
19 asthma-related deaths.
20 To my knowledge, two trials have been
21 completed so far, and the results have been
22 published in the New England Journal of Medicine

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1 earlier this year. The study reports are under
2 FDA's review now.
3 Some closing remarks, during the last
4 decade, FDA has greatly increased its ability and
5 capacity to address the quantitative safety
6 evaluation of drugs through the successful
7 implementation of new regulatory authorities of
8 FDAAA and other key initiatives.
9 A safety system has been created to evaluate
10 FDA-approved drugs across their entire life cycle.
11 The quantitative assessment of drug safety focuses
12 on premarket and postmarket safety studies for
13 sound scientific basis.
14 Although great progress has been made, more
15 work still needs to be done. For example, use of
16 more refined data collection methods, encourage
17 prospective planning and the design for safety
18 assessment, and as always, the sponsors are
19 encouraged to contact FDA early to discuss their
20 research plans.
21 I missed the acknowledge and reference part
22 again. So that's my presentation. Thank you.

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1 (Applause.)
2 DR. WARD: If we could get our three
3 speakers back up for questions?
4 Q&A and Panel Discussion
5 DR. DEXTER: As the moderator, I'm going to
6 start with the question, and then audience people
7 can go from there. One of the things that struck
8 me is that Dr. Li talked about in terms of a long-
9 acting beta agonist, in terms of sample sizes of
10 11,700 for a trial, and it's definitely about 10-
11 fold larger than what we're talking about in terms
12 of the studies.
13 Dr. Crisafi, you mentioned in terms of one
14 of the issues was the issue of the frequency of
15 measuring vital signs.
16 Dr. Sessler, you talked about the whole
17 issue that we really need to have sample sizes of
18 15,000, but practically speaking, it's going to be
19 in the 1500-range initially.
20 I think that one of the things in terms of
21 rather than a pessimistic view, but rather
22 something we actually might be able to address, is

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1 the issue in terms of the frequency. So, for
2 example, if you measure vital signs or record them
3 every 5 minutes, that's a 300-second interval, it's
4 quite easy to go from 300 seconds to 30 seconds.
5 One of the things I was hoping you-all might
6 discuss, to think about the issue, is that if
7 you're going to use the nadir blood pressure, the
8 nadir saturation, the nadir respiratory rate as an
9 endpoint, that's exquisitely sensitive to the
10 sampling interval.
11 Is it feasible, as part of both the
12 discussion now and thinking about it broadly as
13 part of this meeting, to be able to come up at
14 least with recommendations in terms of the sampling
15 interval being something such as a 30-second range?
16 Do you want to start?
17 DR. SESSLER: I'll be glad to. I guess this
18 is part of the general topic of what I could call
19 curve descriptors because when you measure over
20 time, whatever the interval is, you get a
21 complicated curve. You can't possibly do
22 comparisons over lots and lots of time. It's not

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1 meaningful.

2 You have to break down this complicated

3 curve into something that you can describe either

4 as a signal number or as some limited number of

5 numbers. The simplest curve descriptor would

6 simply be the average, but you could use the

7 median. You could use the maximum. You could use

8 the minimum. You could use the area under a

9 threshold. You could do time-weighted average,

10 time-weighted average under a threshold.

11 Any of these might be appropriate in various

12 contexts. We've actually considered these in great

13 detail because we've been very interested in blood

14 pressure recently, and blood pressure is one of

15 these things where you get lots and lots of

16 measurements, particularly if you're tapping into

17 electronic records.

18 So you can have hundreds to thousands of

19 measurements per person times 500,000 people. You

20 get lots and lots of numbers. How do you deal with

21 them? We've actually looked at many different

22 types of curve descriptors to find ones that are

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1 strongly associated with various outcomes of

2 interest.

3 Now, the problem here is that we lack that

4 association. We don't know, for example, the

5 extent to which hypoxemia predicts things that we

6 care about. Nonetheless, I think we can take

7 frequent measurements, term them into a curve

8 descriptor. Once you do that, it's normally not so

9 sensitive to how many measurements you make.

10 Nadir is, and that's an exception because

11 you get random values. Any single value is not

12 perfect. Every value has an error associated with

13 it as a technical error in many cases. And if you

14 look for the lowest value of saturation, you will

15 find some very low value that may have nothing to

16 do with the patient, and furthermore, it may be

17 maintained for, say, 3 seconds, which is not

18 physiologically plausible or interesting.

19 With the exception of nadir, if you're using

20 something like area under a threshold of 90, it

21 actually doesn't make very much difference how

22 often you measure. I'm a fan of measuring

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1 frequently, and I don't see any reason not to.

2 There's no need to write these measurements down by

3 hand. They are electronic data. They can stream

4 onto a disk perfectly easily, and then you know

5 exactly what happened.

6 You'll get the wrong values if you depend on

7 people to write it down by hand. You will get

8 wrong values in a non-random way because people

9 looking at a complex signal like saturation that's

10 going up and down all the time will pick a value

11 they like and write it down. So I think you should

12 just measure it electronically and then evaluate it

13 with some objective electronic curve descriptor.

14 DR. DEXTER: Others? Any other comments?

15 DR. CRISAFI: I agree with everything that

16 you said, and in terms of collecting nadir values,

17 I agree that a drop to a certain level that

18 sustained for only a few seconds really isn't

19 clinically meaningful.

20 But we're very concerned about missing

21 important things, and I think it will be great if

22 we can figure out what those important things are

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1 that we need to capture and give us the nice buffer

2 so we have good information, useful information,

3 and not extraneous information.

4 DR. SESSLER: Right. That's the advantage

5 of well-designed curve descriptors is that even if

6 you don't recognize that a saturation of 63

7 maintained for 4 seconds is an artifact, it doesn't

8 actually contribute very much to area under a curve

9 because it gets bounced by everything else that

10 happens.

11 DR. RIKER: Let me make a provocative

12 statement. The ICU literature is growing with

13 papers where surrogate physiologic outcomes,

14 PaO2/FiO2 ratio, cardiac output, some other

15 parameter of something bears no relationship to

16 outcome or may even be opposite more meaningful

17 outcomes such as functional evaluation, mortality,

18 length of stay in the ICU, time on a ventilator, et

19 cetera.

20 Let me challenge the concept that a single

21 isolated vital sign ever means anything that's

22 important to us as clinicians.

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1 (Laughter.)
 2 DR. CRISAFI: We need to characterize a
 3 profile of a drug, and when you have a drug that's
 4 very short acting, if you ignore those dips as a
 5 drug is re-dosed, you may not have an accurate
 6 description of what the drug is capable of doing
 7 during a sedation case.
 8 DR. WUNSCH: If you wanted to answer that
 9 before I go on a slightly different question,
 10 that's fine.
 11 DR. SESSLER: I was just going to say the
 12 opposite is also true, that we've all seen patients
 13 who get what I call the dipsies. Their blood
 14 pressure goes down a little bit and recovers
 15 spontaneously, and this keeps happening, and then
 16 they crash. Okay? No particular dip was
 17 important. They recovered on their own, but it
 18 was, in fact, still meaningful. So there's no
 19 simple answer here.
 20 DR. DEXTER: In addition, when we think of
 21 sedation, very often we're talking about the ASA 1
 22 patient in the office-based setting as compared to

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1 the ICU patient.
 2 Yes?
 3 DR. WUNSCH: I just wanted to go back to the
 4 original question you posed using the example of
 5 blood pressure, whereas I think a lot of the
 6 answers were talking about pulse oximetry because
 7 that is a continuous monitor that can be downloaded
 8 as frequently as you want.
 9 I just wanted to raise the point that when
 10 we're talking about sedation and monitoring, that
 11 to get anything more than every minute or two is
 12 going to start talk about having arterial lines in
 13 people, and when you're talking about thousands and
 14 thousands of patients, then you get into real risks
 15 that go with upping your monitoring to do that,
 16 whereas something like pulse oximetry and our other
 17 monitors are not invasive. I think it's important
 18 maybe that we make that distinction when starting
 19 to talk about how we monitor people.
 20 DR. LI: I have a comment. Sometimes when
 21 we're looking at the vital signs to fully
 22 characterize the safety profile of a drug,

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1 especially for the safety outcomes we are not
 2 familiar with, we need to analyze such data.
 3 For example, in the dedicated outcomes
 4 trial, you power the trial by the specific safety
 5 outcome, which is usually a hard endpoint like the
 6 deaths or cardiovascular events, something like
 7 that, for some hypothesis testing purpose.
 8 DR. DEXTER: Dr. Cravero.
 9 DR. CRAVERO: I just want to say this is
 10 like an awesome session. Really, all these talks
 11 were great. I'd love to steal all the slides, but
 12 I will ask some questions instead.
 13 Dan, I was just wondering -- again, great
 14 talk -- one thing you didn't talk about was the
 15 difference between clinical and statistical
 16 significance. I think it was implied in a lot of
 17 what you said, but particularly where we have large
 18 studies, we can have large odds ratios with very
 19 little real clinical effect.
 20 I personally see a lot of studies that I see
 21 published based on large odds ratio changes but
 22 with very little real clinical effect, and I was

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1 wondering if you would maybe just give your take on
 2 that.
 3 For Leah, I had one question, too. I'm just
 4 going to throw out my questions. That is, you gave
 5 a definition that the FDA has for adverse events.
 6 It clearly doesn't jibe completely with what we've
 7 talked about here, and I'm wondering if you could
 8 give us an idea of what you think we need to do.
 9 What is the FDA looking for from a group
 10 like this concerning that very important issue,
 11 which goes to how we study these things and do
 12 clinical trials?
 13 Bo, I was just wondering, you made a real
 14 separation between efficacy and safety. I would
 15 suggest that in the field of sedation, those two
 16 things sometimes overlap. For instance, if a
 17 patient is moving wildly during a procedure, it
 18 could lead to safety issues, and therefore, I don't
 19 know that there's an easy, a bright line between
 20 efficacy and safety in this particular field. I'd
 21 be interested in your comments on that. Maybe Dan
 22 could start.

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1 DR. SESSLER: Okay. I guess the first one
 2 was for me, so I will start. This is an excellent
 3 point. There absolutely are clinically differences
 4 that cannot be detected statistically, and this
 5 happens in trials. That was the whole point of my
 6 talk, is that when you're dealing with rare events,
 7 you essentially cannot find them in any normal
 8 sized clinical trial.

9 On the other hand, when you go to
 10 epidemiological or history-based analyses, you have
 11 the opposite problem where it's very easy to find
 12 statistically significant associations that may not
 13 represent clinically meaningful effects.

14 It depends on what outcome you're looking
 15 at. If it's something like death, a lot of people
 16 would say almost any relative risk is important.
 17 But if you're looking at less important outcomes,
 18 that may not be true anymore.

19 Generally speaking, clinical trials suffer
 20 mostly from inadequate power and fragile results,
 21 but they're well done. They're internally
 22 consistent. Registry studies often find

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1 statistically significant results that are not
 2 clinically meaningful.

3 The real problem with registry trials is not
 4 that, though. It's confounding and bias, and they
 5 creep into unknown extents every time you do an
 6 observational study. I'm much, much more worried
 7 about confounding and bias than I am about
 8 statistical error in registry studies.

9 DR. CRISAFI: Regarding the definitions and
 10 identifications of things that are considered
 11 adverse, we have these prescribed definitions that
 12 are in the Code of Federal Regulations. We expect
 13 sponsors, companies to use the definitions that are
 14 codified.

15 I think we have the opinion that since we
 16 don't have thresholds that are universally agreed
 17 upon, or interventions that are universally agreed
 18 upon, as really clinically important, clinically
 19 significant, we feel like everything -- until we
 20 have some consensus about what really is and is not
 21 clinically meaningful from an adverse event
 22 perspective, till we have that consensus, we feel

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1 like everything probably should be considered
 2 adverse.

3 Sharon is raising her hand.

4 DR. HERTZ: I guess I actually just want to
 5 explore the question a little bit more because I'm
 6 looking back at the definition. Where do you think
 7 it is not --

8 DR. CRAVERO: I just think it's fairly
 9 general. We haven't been able to come to agreement
 10 in this forum -- and not that we've talked about it
 11 too long, but -- as to what represents a
 12 significant -- if you want to read it, the
 13 definition is just very general. That's my
 14 concern.

15 A group like this perhaps needs to help try
 16 to define how we should look at that definition
 17 because anyone of us -- we could take 20 people in
 18 this room. We read that definition, we may report
 19 different things because how we're interpreting
 20 what's written there.

21 What I'm wondering is what is the FDA
 22 looking for from a group like this to try to help

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1 further elucidate what they're talking about there.

2 DR. HERTZ: I don't know if someone is
 3 controlling the slides can put up Leah's slide -- I
 4 think it's 12 if I have the same version that came
 5 over.

6 There's no wiggle room on these. These are
 7 required by law in a clinical trial. From a
 8 clinical trial perspective, this would be a dumping
 9 of data, and that's okay. All the adverse events
 10 are expected to be reported. But I think the key
 11 here today and what you're saying is --

12 DR. CRAVERO: Can I just say, we haven't
 13 been able to agree on what's an adverse event.

14 DR. HERTZ: Okay. I'm thinking back to some
 15 of the anesthesia applications I've seen, and I'm
 16 understanding a little bit more now.

17 DR. DEXTER: If I may do this as sort of a
 18 moderator, you have a patient in which the plan is
 19 to give sedation during which they're going to be
 20 doing some sort of an upper endoscopy, some
 21 bronchoscopic procedure, in which it's totally to
 22 be expected that there will be hypoxemia

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1 transiently as part of the procedure. You just
2 kind of then stop the procedure transiently.
3 Is that an adverse event when the saturation
4 transiently goes below 90 percent? There is no
5 practical way to differentiate between the drug and
6 the procedure.
7 DR. HERTZ: Right. So I think the challenge
8 here is to do a number of things. One is to figure
9 out how to measure these events. For the purposes
10 of regulation, everything is going to get reported.
11 It needs to because -- that's a separate issue, but
12 for the purposes of these studies and understanding
13 the products, once you have decided how to measure
14 them, then you need to decide -- hopefully, this
15 group will have -- so there's the measurement, and
16 then there's the relevance of it.
17 If you report every desaturation, you report
18 every desaturation. It doesn't mean the drug's
19 bad, especially if it's behaving in clinical
20 context the way it's expected. In fact, it's
21 determined that, for the most part, the background
22 rate of hypoxia in the setting of bronchoscopy

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1 hasn't been exceeded. That's a discussion of the
2 relevance of the things that are being recorded.
3 All those hypoxic events are not necessarily
4 counted against the drug, and even better, if
5 there's an active control, you compare them. And
6 if there's no difference, the whole signal goes
7 away. But it's still reported and discussed
8 because what's important and interesting about that
9 information is what if it's considerably less
10 common with the new drug or more common with the
11 new drug, then would be considered normal standard
12 of care or as exhibited by the active comparator.
13 So the reality is even if the event of
14 hypoxia is an expected event, in excess, it becomes
15 an adverse event, and we don't know that until it's
16 been recorded and considered in context. And
17 that's where this group is important, is how does
18 one do that. It's a two-step process. There's a
19 measurement, and then there's an endpoint. And
20 translating measurements into endpoints is much
21 trickier in this context than in most because of
22 the continuum between safety and efficacy.

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1 So that's the key. How do we gather enough
2 information to understand what if the hypotension
3 associated with the study drug is deeper than the
4 hypotension with the standard of care?
5 So those are the kinds of challenges that we
6 have in terms of getting so much data we don't know
7 what to do with, wanting data that is feasible or
8 not in terms of quantity, how to analyze it. These
9 are the things.
10 So it's that intersect of coming out with
11 measurements, outcome measurement instruments, and
12 then possibly using that data, some other type of
13 relevance instrument, where we want to quantitate
14 it. That's where I think, like going back to this
15 morning, perhaps that could help the difference
16 between understanding a drug used in an outpatient
17 suite for a procedure, in an inpatient suite for a
18 procedure, in the OR, and in the ICU. It's all
19 going to be context driven because that's how you
20 guys will interpret these adverse events when
21 you're using it, and that's how we need to know it
22 behaves when we're looking at the overall balance

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1 of risk and benefit.
2 DR. DEXTER: Dr. Sessler?
3 DR. SESSLER: I couldn't agree more. All
4 drugs, all interventions, everything we do has
5 potential complications. The outcome of a
6 randomized trial is not that there are
7 complications. It's the difference in
8 complications between the two groups and therefore,
9 it's perfectly okay that a procedure like
10 bronchoscopy causes hypoxemia, but if one drug ends
11 causing a lot more hypoxemia than the other, then
12 that's interesting.
13 Along those lines, I think it's helpful to
14 predefine clinically meaningful differences, and
15 that's something that investigators are beginning
16 to do, but it's not actually been routine in the
17 past. People would just look for a difference and
18 hope they find some statistically significant
19 difference. And if they do, they write a paper
20 about it saying, okay, there's a difference.
21 If you predefine a difference and then you
22 end up with a small difference -- and this happens

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1 in pain studies all the time. You end up with a
2 difference of 1 point, 2 points out of a 11-point
3 Likert scale. Is it clinically meaningful even if
4 it's statistically significant? Probably not.
5 DR. DEXTER: Yes?
6 DR. CHAPPELL: I have a follow-on to this
7 comment. We routinely, or in many trials at least,
8 in addition to collecting all the adverse event and
9 vital sign data we're required to collect, we'll
10 predefine adverse events of special interest, and
11 they will often have criteria for what is held to
12 be or considered a clinically meaningful effect.
13 Sometimes it might even have requirements that
14 patients be terminated from the study or other
15 steps taken if the situation arises.
16 That might be one way to address the need.
17 On the one hand, it would be comprehensive to
18 collect all this data. On the other hand, to be
19 able to target effects that are likely to be
20 clinically relevant and meaningful.
21 DR. DEXTER: Why don't we finish here, I
22 think. Yes, please.

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1 DR. LI: My comment to the question for me,
2 I think Sharon and Phillip already addressed a lot.
3 I think in some contexts, you have a clear cut of
4 safety and efficacy, but in some contexts, if you
5 don't understand the drug very deeply, then you
6 don't have a clear cut of that.
7 For example, you have common adverse events
8 that may be expected for some compounds for some
9 populations, and then sometimes you have the
10 adverse events of special interest that was defined
11 a priori, which you may know a lot or may not know
12 a lot. And sometimes you have unexpected serious
13 adverse events.
14 For example, that Avandia story, that's
15 unexpected. I think the cardiovascular harm, which
16 was shown in that meta-analysis, was unexpected.
17 That's why FDA has this 2008 guidance for the
18 anti-diabetic drugs to evaluate their
19 cardiovascular safety.
20 Now, we are seeing some cardiovascular
21 outcome prior for diabetes drugs powered for
22 superiority. So that means the sponsor may want to

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1 test if we have cardiovascular benefit.
2 So I agree to some extent. It's a
3 continuum. Sometimes there is a clear cut.
4 Sometimes there is not.
5 DR. DEXTER: Do we stop --
6 DR. WARD: You can do some more questions.
7 DR. DEXTER: Yes, you have a question?
8 DR. HERTZ: I just want to ask a question
9 about the minimum clinically important difference.
10 I am more familiar with analgesic studies than
11 anesthesia studies because, frankly, we get more.
12 We often see a group mean difference in
13 treatment effect that's rather tiny. You said you
14 were questioning the relevance of a 1.1 difference
15 on an 11-point scale, and sometimes we see a group
16 mean of difference of well less than 1, 0.5, which
17 is pretty big for most of our studies for a variety
18 of reasons. But I don't think a patient would ever
19 say, "My pain is down a half a point. I'm feeling
20 a lot better."
21 So I think what's really important when we
22 think about clinically important differences is to

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1 separate what we mean on an individual basis and
2 what we mean on a group treatment difference.
3 For instance, with blood pressure, when we
4 see blood pressure studies and we see a difference
5 of 2 or 3 millimeters of mercury, that's considered
6 pretty big on a population scale. But again,
7 that's within the range of noise for having the
8 person rush in a little bit late or even if it's
9 just the normal fluctuation. We would never make a
10 therapeutic decision based on 2 to 3 millimeters of
11 mercury on an individual.
12 So as you think about how to put these
13 measurements into context, it depends how you
14 choose to look at the data. If you look at average
15 changes and you think that's relevant, then that's
16 what's different, what's meaningful from a group
17 perspective. If you're looking at responder
18 definitions in individual amounts that count as
19 useful, and then you're going to count the people
20 who have a useful or whatever change, that's
21 another way to look at it.
22 I think it's just important for us to

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1 remember that there's two ways of looking at
2 minimum important clinical difference, individual
3 versus group.
4 DR. SESSLER: That's certainly true. Some
5 of these may be the wrong types of studies. Maybe
6 they should have been noninferiority studies to
7 start with because it sounds like you're getting
8 that kind of result, and a new drug that's
9 noninferior to another one may still be preferable
10 under some circumstances.
11 DR. DWORKIN: I disagree with you. If
12 you've got a drug where you've replicated
13 statistically significant superiority to placebo
14 and the delta is 5 out of a 100, 5 millimeters on a
15 10-centimeter VAS, and this drug is very safe, very
16 well tolerated, has a novel mechanism of action,
17 and is relatively inexpensive, I would argue that's
18 a contribution to public health.
19 There's no threshold for what is clinically
20 meaningful at the group difference level absent a
21 consideration of all of these other factors like
22 safety and tolerability and cost, novelty, et

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1 cetera, et cetera, et cetera. A 0.5 delta, or 5
2 millimeter delta, obviously is not clinically
3 meaningful if the drug is less well tolerated and
4 riskier than what's on the market.
5 So the group difference that Sharon was
6 describing, we don't have any thresholds for pain,
7 which is all I know about, because the context of
8 that delta is so important, primarily safe in
9 tolerability, with all these other factors.
10 DR. SESSLER: Right. I was making an
11 argument there. But sure, a new drug that cost
12 10 times as much with an unknown safety
13 constellation has to be a lot better than just
14 equivalent. On the other hand, in -- I do lots of
15 thermal regulation studies.
16 If you have a new warming device that's less
17 expensive, you have no reason to believe that it's
18 dangerous, I would say all it has to be is as good
19 as our current warming systems. What approach you
20 use is very much dependent on the circumstances.
21 DR. DEXTER: Yes?
22 DR. WARD: Just a follow-on that you gave

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1 the illustration that we need a dose-response curve
2 when we're looking at the effect. Unless we've got
3 a single dose, you can't really tell. But you also
4 need to have a dose-response curve for the adverse
5 events, because if you don't have the dose-response
6 curve for the adverse events, you may find two
7 drugs that look better that fall into with what you
8 just said. You really need both dose-response
9 curves.
10 DR. SESSLER: Oh, absolutely. The
11 dose-response curve is going to be different for
12 every effect of the drug, and you have to look
13 differently at different effectiveness measures and
14 separately at different adverse events. We never
15 do this. So the dose-response curve, it's very
16 easy for me to draw them on a slide, but in fact,
17 we don't know what they are.
18 DR. DEXTER: Let's take the last question.
19 TJ?
20 DR. GAN: I think one of the problems with
21 what I'm trying to raise is that I think the
22 instrument of measurement that we have, it's very

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1 rudimentary. We talk about the VRS score and 1.0
2 to 10. The fact is that patients interpret very
3 differently. So a score from 9 to 6 or 7 is very
4 different from a score of 4 to 1, although the
5 extent of the difference is the same, but it's
6 very, very different.
7 So in a way, we haven't really taken into
8 account what the individual patients think about
9 the drugs. We just look at because of our
10 constraints and limitations of the score that we
11 have. Another one is the nausea score from zero to
12 10. Again, we know that that is very different,
13 and patients interpret it very differently.
14 I think the whole thing may be a little bit
15 flawed because we just don't have good instruments.
16 DR. DEXTER: Let's end it there, and say
17 when it comes to efficacy measures, that different
18 scales have advantages and disadvantages in terms
19 of their interpretation perceptually.
20 DR. WARD: Let's take a half hour break, and
21 we'll come back with a panel. We'll wrap up for
22 the day.

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1 (Whereupon, at 3:23 p.m., a recess was
2 taken.)
3 Panel Discussion
4 DR. WARD: I thought we'd spend the last
5 hour today -- from my perspective, I think this has
6 been an incredibly productive and interesting
7 meeting. I hope it all has been for you. Tomorrow
8 we will focus more on some of the individual
9 adverse events.
10 One of the key things that I heard today
11 that I really liked as an organizing event -- I
12 think it was Susan that said it -- is we really
13 have two instruments. We have a measurement
14 instrument that's going to be collecting the data,
15 and we have a relevance instrument that may be
16 context patient and provider specific that then
17 filters the measurement data to decide what the
18 relevance of it is for particular adverse events.
19 I like that concept of thinking about how we
20 measure what the relevance and incidence of adverse
21 events are.
22 This is the time for anything we've talked

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1 about today, both comments from the audience,
2 questions and comments from our panelists. I want
3 to start out as the moderator with a couple of
4 questions for the panel, but for everybody, too.
5 The first one is, if I'm doing a clinical
6 trial for procedural sedation, and particularly
7 looking at adverse events in it, should a blinded
8 control group always be included in a clinical
9 trial of a new procedural sedation, or should
10 I -- many of the clinical trials I see for
11 procedural sedation drugs are, let's just try the
12 drug in a set of procedures. We'll measure its
13 efficacy, and we'll measure its adverse events, as
14 opposed to a randomized controlled trial in which
15 we've got a control group. Clearly, it can't be a
16 placebo. It's got to be an active control. If so,
17 if we should be recommending that, what's the
18 active control?
19 So I'll turn that over to anybody in the
20 panel who wants to --
21 DR. SESSLER: Well, to be a trial, it has to
22 have a control group. What the control group

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1 should be, it depends. If you have no available
2 treatment for a condition, it's acceptable to use a
3 placebo; otherwise, most people would say you
4 should use your best available treatment as the
5 control group and then compare your novel entity to
6 that.
7 DR. WARD: What's the best available
8 treatment?
9 DR. SESSLER: What is best?
10 DR. WARD: What's the best available
11 treatment in a clinical trial for procedural
12 sedation?
13 DR. SESSLER: I guess the investigators and
14 clinicians can decide that, and it's going to be a
15 highly context specific answer.
16 DR. CRAVERO: I would sort of agree. I
17 wrote an editorial about trying to raise the bar
18 for clinical trials in pediatric sedation a while
19 ago. I don't think there was anything profound
20 about it, but I think it goes a little bit to this,
21 which is, number one, in pediatric sedation trials,
22 it is often just as you described.

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1 They're called trials, but really, it's an
2 observational report of the last 100 whatever I did
3 with whatever drug I used. And they're not
4 terribly helpful, yet that's what gets reported, as
5 I think I tried to outline a little bit today.
6 I do think what was brought up earlier today
7 which is awesome, is that there is a real dose
8 issue as well, and the comparison is always made
9 with whatever the investigator has chosen as the
10 comparative drug and dose. Yet oftentimes, I would
11 look at the trial and say, that's really an
12 inadequate dose.
13 There's a million different examples we
14 could all use, but we know, for instance, the
15 efficacy of a drug like dexmedetomidine at a
16 certain dose in children is pretty low, yet there
17 are reports of it used at much higher doses.
18 I would throw it out there. I don't know
19 what the right answer to that particular question
20 is, but if you're going to use a low dose of that
21 drug and compare it to something else, you're going
22 to get one result, whereas if you used what has

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1 been reported as a much effective dose of the
2 comparator drug, you're going to get a different
3 result, and Dan reviewed that very nicely.
4 I think there should be a comparator group,
5 and there should be a comparator group that has
6 some data behind it that reveals that that is an
7 effective way of using that comparator drug.
8 DR. WARD: Hannah?
9 DR. WUNSCH: You mentioned the word
10 "blinded" in your question, and I think that raises
11 all kinds of issues in terms of kind of handcuffing
12 providers who may be, for instance, comparing
13 sedatives with very different qualities, and where
14 it really is just not practical, or really safe in
15 a sense, to be asking providers to be titrating
16 things. And this gets back to the dose issue where
17 often you're not really sure whether doses are
18 equivalent or not.
19 So although I completely agree that to say
20 that it's a trial is to have two arms, I'm not sure
21 blinded needs to be in there, and maybe shouldn't
22 for some of the safety reasons.

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1 DR. WARD: Any comments from the panel?
2 DR. SESSLER: It's often not possible or
3 practical to blind a study, but let me just clarify
4 the wording. If it's a trial, you have to be
5 comparing two different things. Normally, that's
6 randomized, blinded if practical. It doesn't have
7 to be randomized. So an alternating intervention
8 study is a type of trial even though it's not
9 randomized.
10 A case series is not. That's an
11 observational study. A retrospective analysis is
12 an analysis. It's a study, but it's not a trial.
13 DR. WARD: Rich, and then Jerry.
14 DR. RIKER: I guess I would say I don't know
15 that we should recommend a single drug or a single
16 approach to procedural sedation because the
17 specific qualities that we're trying to attain are
18 so different from procedure to procedure. Movement
19 okay, yes or no. Recall, yes or no.
20 I like the idea of looking at the available
21 evidence and looking for a proven comparator, one
22 that many people would agree is an accepted

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1 standard. But I don't think we should go into the
2 weeds of making a drug recommendation.
3 DR. WARD: Jerry?
4 DR. LERMAN: Two points. The first is,
5 unfortunately, many of the drugs we have for use in
6 anesthesia, except perhaps the inhalational agents,
7 have never had a dose-response study actually
8 performed on the drugs for any outcome, efficacy or
9 otherwise. So before you even get into the
10 sedation realm, the expected effect of the drug has
11 never been studied.
12 So you do have -- and I see it on editorial
13 boards that I sit. We get all kinds of people
14 submitting papers, and they picked arbitrary doses
15 because everybody else uses them. However, that's
16 all flawed. And the primary problem is we've not
17 got those dose-response studies, and we should be
18 doing them as part of the FDA approval of the drug.
19 The second thing is I beg to differ with
20 those on the panel who say you can't blind any of
21 these studies because the notion that you don't
22 know what drug you're giving isn't actually

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1 necessary to blind a study. The observer, if
2 they're recording an effect, need not know what the
3 hypothesis of the study is or what their
4 actual -- the key elements and the outcome are.
5 They can record all kinds of extraneous data.
6 If they don't know what you are actually
7 seeking, then actually the study is blinded. Now,
8 if the operator is also making those judgments
9 based on the drug that person is giving, then that
10 makes it more complicated, so you have to have a
11 distinct observer. That person unaware of the
12 hypothesis or specific issues that you're looking
13 at makes it a blinded study.
14 DR. WARD: Yes, I think those are good
15 points, Jerry. A couple of studies that I've done
16 in the past, for the original study on
17 dexmedetomidine, we actually did a dose response
18 for dexmedetomidine, both on effect and side
19 effects, so there are some things in the literature
20 with that.
21 DR. LERMAN: But not in children. That's
22 the whole -- that's what we're talking about.

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1 DR. WARD: In children, okay.
2 DR. LERMAN: With inhalation agents, we did
3 determine MAC values in all the agents
4 before -- well, halothane was on the market for
5 10 years before George Gregory found the math for
6 it, the measure. So we do have that disadvantage.
7 DR. WARD: It is possible to do the blinded
8 study. I've done a study in which I was giving the
9 drug behind a shield, and nobody else knew what
10 drug was being given because they couldn't see it.
11 You have to do a few things, but I think it is
12 possible to both do dose response and blinded.
13 DR. MASON: I think it also depends on the
14 drug. If you're comparing ketamine to anything,
15 it's not going to be valuable to blind because
16 you're easily going to tell, or dex, it's going to
17 cause drop in heart rate.
18 So I think the sedative drugs in general
19 seem to have different enough properties that it
20 would be really not possible for somebody not to
21 guess what they're giving.
22 DR. LERMAN: If they actually don't know the

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1 drug, they can guess as much as they want, they're
2 blind.
3 DR. WARD: Yes. I would just say that
4 there's a big difference between guessing and
5 knowing, and you'd be amazed at the number of times
6 the guesses are wrong even though you think they
7 should be able to tell what the drugs are.
8 Comments from the panel?
9 DR. SESSLER: I agree. People are not
10 nearly so good at guessing the drugs as they think
11 they are. Observer blinded is a good way to go if
12 you can't blind everyone, but the more people you
13 can blind, the better.
14 We typically keep our statisticians blinded,
15 also. So they do their analysis on a group A/group
16 B basis. So you might think statisticians are
17 completely objective, but they're making decisions
18 all the time. Is a value an artifact, or is it
19 real? How are we going to do a particular
20 analysis? We just keep them blinded.
21 DR. WARD: I don't know what the study was.
22 Oh, it was on using sham orthopedic surgery versus

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1 I think it was for knees. And that was so blinded
2 that the authors wrote two versions of the paper
3 before they knew the results. They wrote a version
4 of the paper if it was a positive result, and they
5 wrote a version of the paper as if it was a
6 negative result before they unblinded the results.
7 Not only were the statisticians blinded, but
8 writing the paper was blinded.
9 DR. SESSLER: We often write the paper
10 before the results are available.
11 (Laughter.)
12 DR. WARD: They actually wrote two papers.
13 They actually wrote and agreed upon two papers, one
14 with a positive result and one with a negative
15 result, and agreed that when they unblinded and got
16 the result, they couldn't then change the paper.
17 That was the paper that they were going to have to
18 submit.
19 DR. SESSLER: That was a classic article.
20 DR. CRAVERO: I obviously totally agree with
21 the comments. I would only say that lacking good
22 PK/PD data on all of these sedatives in the next

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1 10 years, when we see clinical trials, it would
2 just be nice if people would recognize that what
3 they did was kind of arbitrary and try to use the
4 available evidence, such as it is, to choose a
5 reasonable comparator. I don't think that's always
6 done. That's my only point.
7 DR. SESSLER: I would love to see the FDA
8 require good dose-response curves before drugs go
9 into clinical trials, that it go from a very small
10 phase 1 dose escalation study into a formal
11 dose-response curve, and then go on to phase 2 and
12 phase 3 studies.
13 DR. HERTZ: Me, too. I would like to
14 require that, too.
15 DR. WARD: Susan, you want to make some
16 comments? Go ahead.
17 DR. HERTZ: I would love to have the ability
18 to require that.
19 DR. WARD: Mark, and then Albert.
20 DR. WEISS: At the end of Dan's talk, which
21 was really wonderful -- Dan, and I talked to you
22 about some of that, too. I want to hear the

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1 group's thought about this, too.
2 Dan talked about a new drug that might
3 really be more efficacious but it costs X times
4 more, so what's the value there. And I'm wondering
5 if we need to consider economic considerations as
6 part of maybe efficacy because when you're in
7 private practice, they might say that a certain
8 drug is better, but the hospital will tell you,
9 you're not going to get that drug because it costs
10 this much more.
11 I'm wondering if maybe this is part of the
12 conversation that we have as well, or maybe the
13 conversation will be eventually made for us.
14 DR. WARD: Albert and then --
15 DR. DAHAN: I think the idea of doing PK/PD
16 studies, and I wonder whether you should do two
17 dose-response curves because we often titrate to
18 effect. So if you keep measuring your plasma
19 concentration, you measure your effect. You do
20 have in every patient that you test a dose
21 response. When doing that, you don't need that
22 many subjects at all to get a good result.

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1 DR. WARD: Comments?
2 DR. DEXTER: I want to just comment on the
3 issue of the economics. When it comes to the
4 sedative agents, one of the -- when I say
5 challenges, I don't mean a negative or positive;
6 it's just one of the issues -- is that very often,
7 the economics is more dependent on the context of
8 use than it is on anything of the property of the
9 drug.
10 For example, if you have a particular
11 gastroenterologist, pediatric gastroenterologist on
12 a particular day, and there are three hours of
13 cases in the operating room, it makes no difference
14 if one drug is faster than other. It's a fixed
15 cost.
16 In contrast, if you have exactly the same
17 drug with exactly the same profile, and now you put
18 it into a room where the pediatric
19 gastroenterologist has 10 and a half hours of
20 cases. In that circumstance, it's probably purely
21 a variable cost.
22 One of the issues in terms of considering it

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1 is separately the issues in terms of timed
2 reductions, which can oftentimes be done at the
3 same time as an efficacy study, although you have
4 to consider as part of the trial whether it's a
5 realistic measure of time differences.
6 That's different from the economics of the
7 drug. So therein lies one of both the features of
8 sedative agents as well as different anesthetic
9 agents, is focusing really on time as an endpoint.
10 DR. SESSLER: Cost-effectiveness studies age
11 quickly because costs change quickly over time, and
12 they may also be very different from one hospital
13 to another. Different hospitals with different
14 bargaining powers simply pay different amount for
15 drugs.
16 DR. DEXTER: That's why you measure the time
17 difference as an endpoint, which don't really age.
18 They can somewhat differ depending upon the
19 workflow, but generally are very stable, homogenous
20 among centers. The economics of it differ
21 dramatically, not only among hospitals and over
22 time but just between two different operating rooms

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1 in the same hospital and the same day.
2 DR. CRAVERO: I do think it's an interesting
3 question with respect to safety, though, concerning
4 the specific goals of this particular conference,
5 or this particular gathering, which is if we have
6 drug A that is clearly more costly from the
7 perspective of the time that it takes to recover or
8 other aspects of the drug, the actual acquisition
9 costs and everything else as Frank just said, that
10 would go into cost analysis versus another drug.
11 Yet by the definition of some of the things we
12 talked about this morning, it has more requirements
13 for airway repositioning or more desaturation
14 episodes, yet no meaningful outcome differences.
15 Do you say, well, how do I consider that?
16 I'm not sure what the answer is, but we haven't
17 discussed that. If the drug was three times more
18 expensive but had fewer desaturation and airway
19 repositioning requirements, how do you put that
20 into context? I don't know. And it probably does
21 age fairly quickly.
22 DR. DEXTER: I was going to say also, airway

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1 repositioning depends in part on the level of the
2 provider. Are you referring to a pediatric
3 anesthesiologist? Are you referring to an
4 assistant in a clinic? So that has an enormous
5 effect in terms of thinking about these adverse
6 events.
7 DR. WARD: Back row.
8 DR. TOBIN: Having been a previous FDA
9 advisory committee member, part of our introduction
10 to the axioms of the FDA were to ensure the public
11 safety. It had nothing to discuss about
12 pharmacoeconomics or cost analysis.
13 So I think in a regulatory environment,
14 remember, the FDA doesn't set the price. The FDA
15 doesn't recommend what the competitive advantage
16 price is. The FDA is to ensure the public safety.
17 The sponsor decides on the price and what kind of
18 premium discount you're going to get if you're
19 buyer A or buyer B.
20 I think cost analysis is critical, but that
21 should all be done postmarketing because we as
22 providers need to understand if this drug is 10

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1 times more expensive but it's going to save us some
2 turnover time, that might still be a pretty
3 significant run for the money to use the shorter
4 acting, quicker agent, or if the actual number of
5 rare but catastrophic adverse events was reduced by
6 50 percent.
7 But that's what regulatory's responsibility
8 is, to take a look at that data, not look at the
9 pharmacoeconomic data. That may change in the
10 current political climate, but to me, unless I'm
11 misrepresenting what I was taught as an advisor to
12 the FDA, that's your job.
13 DR. WARD: Jenifer?
14 DR. LIGHTDALE: I'm just going to return
15 quickly to two points actually. One is the
16 blinding, and as the pediatric gastroenterologist
17 in the room, I'll point out that we're talking
18 about procedural sedation. So certainly, there are
19 cases where the proceduralist is actually
20 administering the sedation, which we can talk
21 about, but there's also many of these situations
22 you have a person administering the sedation and

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1 you have a proceduralist. You have a whole other
2 person there who can be totally blinded. You want
3 to remember that, and think about that creatively,
4 I think.
5 I'm really intrigued by this issue of the
6 cautious investigator, the person who -- sedation
7 is fascinating, right? You're not giving a drug to
8 somebody and they walk out the door, and maybe that
9 adverse event happens while they're at home. The
10 adverse event is happening right there in front of
11 a provider trained to rescue them, and perhaps to
12 try to keep them at some equilibrium so their heart
13 rate doesn't go up and their blood pressure doesn't
14 go down.
15 We have to capture what we're doing, or
16 we're going to miss the fact that somebody's
17 working really hard to create the noninferiority,
18 if I articulated that.
19 DR. SESSLER: Excellent point.
20 DR. LIGHTDALE: Thanks, Dan.
21 (Laughter.)
22 DR. WARD: Comments?

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1 DR. WUNSCH: I just think that goes back to
2 the ongoing theme today of this issue of different
3 providers who will intervene at different times in
4 different ways, and some who may sit back and let
5 the O2 sat sit at 88 percent for an hour, if
6 they're comfortable with it, versus someone else
7 who's fussing when the sat starts to drop a little
8 bit. So it's returning to the theme
9 earlier in the day of that issue of recognizing
10 different intervention thresholds and also just the
11 amount of work that goes into a sedation as you're
12 pointing out.
13 DR. WARD: Along that same line, the
14 question also that I had was how should high-risk
15 patients be incorporated into clinical trials, and
16 that also has to do a little bit with the nervous
17 observer. If I've got a patient that I don't think
18 I can intubate and I'm doing a procedural sedation,
19 I'm going to do it a little differently than if
20 I've got a young healthy person that if they stop
21 breathing, no big deal. I can ventilate them. I
22 can intubate them. I can rescue them okay.

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1 A sleep apnea patient, as Ron pointed out, a
2 pediatric patient with big tonsils, should we go
3 out of our way to make sure that the clinical
4 trials include patients that are at high risk?
5 DR. SESSLER: I'll be glad to comment. I
6 guess this is part of the general discussion of
7 internal validity versus generalizability.
8 Clinical trials generally have good internal
9 validity, which means that if you repeat the trial,
10 you expect to get the same result.
11 One way that you control that is by
12 minimizing variability. Investigators want to
13 minimize variability anyway because for continuous
14 outcome, the determinants of sample size are
15 baseline variability and treatment effect.
16 Treatment effect is the function of biology.
17 Variability, you can control by whom you enroll in
18 the trial.
19 If you look from a sponsor's perspective, a
20 maker of a drug or of a device, for example, wants
21 to have people in the study who are most likely to
22 benefit and least likely to be harmed, and are

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1 relatively similar so that they don't impose much
2 variability. That maximizes your chances of
3 getting a statistically significant result with a
4 manageable number of patients.
5 Those results are then taken by clinicians
6 broadly and extrapolated to the whole world, and
7 that's where you get into a problem because people
8 take results from a highly selective clinical trial
9 where not only the patients were selected, but the
10 procedures were very well controlled and
11 extrapolate that.
12 Experience has shown that these things
13 actually don't extrapolate very well. In the real
14 world, drugs are less effective and more toxic than
15 they are in the original clinical trials, and the
16 reason mostly has to do with selection.
17 Your point's really important. If you don't
18 have representatives of the entire relevant
19 population in your trial, you will get a result
20 that does not apply to the entire population.
21 DR. WARD: Yes?
22 DR. SEXTON: It would seem to me, though, if

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1 the drug is not approved, it's really not an
2 appropriate time, that the risk-benefit ratio for
3 someone with a compromised airway who's an ASA
4 class 3 or 4, before you know much about the drug
5 is not the time to give it to that individual. So
6 I would say don't enroll them in your study.
7 DR. WARD: So I guess my question would be
8 how much do you need to know about the drug. And
9 in these kind of drugs we're talking about, the
10 efficacy is usually pretty straightforward. Either
11 they provide sedation, or they don't provide
12 sedation.
13 If you've got a drug that you've got enough
14 so you know it works, it provides sedation, is that
15 a pretty early point that you want to move right
16 ahead and let's look at the sleep apnea patients,
17 let's look with the kids with the big tonsils,
18 let's look at the patients who are at higher risk.
19 At what point should that occur?
20 DR. SESSLER: That's why studies are phased,
21 so in the initial phase, you're quite careful about
22 whom you put into a trial, but by the time you're

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1 getting to phase 3 and you're trying to convince
2 the FDA, and more importantly perhaps clinicians
3 broadly, that this is an effective and safe drug,
4 then you really should try to include the relevant
5 population.
6 Too often, the relevant population is not
7 included. It's in fact a subset of people most
8 likely to benefit and least likely to be harmed.
9 DR. WUNSCH: I would think you would want to
10 be maybe at the point where you know something
11 about your risk profile of the drug beyond just
12 whether or not it can create sedation.
13 For example, if you're dealing with a
14 patient who's marginal in terms of their airway,
15 and it turns out it is a drug where the risk
16 profile errs on the side of more difficulty with
17 airways, then obviously, that may not be the group
18 that you then go next to, to assess. Similarly, if
19 it's a drug that's shown a fair number of
20 desaturations, your COPD patient who's already
21 satting only 88 percent may not be the patients
22 you're enrolling.

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1 So I think there probably would have to be
 2 some matching of at-risk patients and what is
 3 already known, and there would need to be enough
 4 known, about a new drug to feel confident that
 5 you're not compromising marginal patients, which
 6 probably puts you maybe one step beyond is it
 7 effective at causing sedation.
 8 DR. WARD: With the caveat of what Dan just
 9 said, generalizability is not all that great. It
 10 may look as like a nice, safe drug as far as the
 11 airway is concerned in people with normal airways
 12 and be horrible in a patient with a -- and you
 13 wouldn't have any idea that that was going to
 14 happen because of the generalizability.
 15 DR. SEXTON: That's probably one of the
 16 reasons the FDA requires postmarketing studies.
 17 That just seems like an appropriate time. Now,
 18 granted, I'm speaking from the point of the medical
 19 monitor, so I don't really prefer to have your
 20 patient be at tremendous risk and have to deal with
 21 that adverse event. That frightens me. Or it's
 22 not safe for the patient, or it doesn't seem like a

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1 good risk-benefit.
 2 At least postmarketing, we're talking about
 3 the rule of three before. So if you have a rare
 4 fatal event, you've got to give that drug to an
 5 awful lot of people before you see it. So that
 6 would make me err on the side of caution in the
 7 clinical trial.
 8 DR. WARD: Randy?
 9 DR. CLARK: There's an aspect of this
 10 generalizability that we touched on this morning
 11 when we were talking about sedation in dental
 12 patients. Most of these trials are done in our
 13 acute care hospitals in the United States. The
 14 federal Medicare conditions of participation create
 15 a regulatory floor that all of these hospitals have
 16 to work under, and they're very specific about who
 17 is administering these drugs in what context, what
 18 the preoperative preparation is, interoperative
 19 monitoring, and post-anesthesia evaluation is.
 20 There's no similar construct for what takes
 21 place in either physician offices or in dental
 22 offices, and those frequently then go to the states

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1 where they may be regulated by different boards.
 2 For example, in Colorado, we have a sunset
 3 review portion of all of our practices boards, and
 4 whenever the dentistry boards come back up for
 5 sunset review, we in anesthesiology are always
 6 asked do you want to get into the issue of how
 7 dentists are providing sedation and anesthesia.
 8 It gets to be a very politically complex
 9 issue, but I think we base a lot of the work that
 10 is done in dental offices on these clinical trials
 11 that are done in a very different environment with
 12 very different people.
 13 I know that it was mentioned in California
 14 because of one of the recent complications there.
 15 A patient bill of rights is being looked at that
 16 would require in dental offices the same standards
 17 of care that might be required in an acute care
 18 hospital.
 19 DR. WARD: Any other comments on this kind
 20 of area?
 21 (No response.)
 22 DR. WARD: I think one issue is if we're

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1 talking about rescue versus failure to rescue,
 2 because a lot of the complications are failure to
 3 rescue complications. In a well-designed clinical
 4 trial like Randy was saying, even high-risk
 5 patients in a well-controlled situation in which
 6 you could measure the need to rescue, would really
 7 give you a measure of, boy, we need to rescue a
 8 high percentage of patients who had airway
 9 obstruction.
 10 That would give us a signal that if it's
 11 being used in a less well-regarded situation, in
 12 which rescue might not occur, that that would be a
 13 much more dangerous area.
 14 I agree with you. There's a trade-off. At
 15 what point in what you know about the efficacy, do
 16 you then start aiming for the adverse event trials.
 17 So along that line, my third question
 18 is -- because we heard about event-driven clinical
 19 trials to look at adverse event. What's the role
 20 of event-driven clinical trials in sedation to look
 21 at outcomes? The panel or anybody? I don't see
 22 those very often.

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1 DR. DEXTER: The study, which was done for
2 pediatric radiology in Toronto, was very good in
3 terms of the type of provider. Just the basic
4 ideas week by week, and that's very standard or
5 every other day, the study which was done for
6 pediatric sedation in Finland, where they
7 alternated every other day.
8 DR. WARD: Did they look for events? Was
9 the size of the trial designed to look at
10 occurrence of events?
11 DR. DEXTER: I don't think so. I think it
12 would be inadequate for events. I think it was
13 designed, both of them, in terms of time.
14 DR. WARD: Is there a role for event-driven
15 trials for adverse events?
16 DR. SESSLER: Since the incidence is unknown
17 when you start, you could end up with a pretty big
18 trial if you're not careful. I'm not sure that
19 there's a big role for it here.
20 All survival curve analyses are event
21 driven. So whenever you have a trial where the
22 outcome is, say, cancer recurrence, the sample size

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1 is not determined by the number of patients
2 enrolled. It's determined by the number of outcome
3 events, that is, the recurrences that happen.
4 There certainly are lots of event-driven studies
5 out there. I'm just not sure I see a huge role for
6 it here.
7 DR. CRAVERO: It is really difficult,
8 particularly in the pediatric realm because even at
9 Boston Children's Hospital, where we have a high-
10 risk population -- I'm almost surprised when I see
11 somebody who actually has four chambers in their
12 heart.
13 (Laughter.)
14 DR. CRAVERO: But even in that particular
15 setting, when we try to come up with a risk
16 stratification construct for our patients, we can
17 select our certain characteristics that we know
18 statistically make somebody more risky. But even
19 putting that together, we come up with risk groups
20 whose absolute risk is still relatively low, and
21 you would need a great big trial.
22 Even of kids with Fontan physiology having

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1 sedation for their MRI or whatever, the actual
2 number of events, although it's orders of magnitude
3 higher than it would be for other people, still
4 relatively low.
5 So I would agree, it's really hard to do
6 that kind of a study at least in the pediatric
7 population. I think in the adult population where
8 there's a lot more comorbidity and perhaps more
9 events to look at, you're talking about a different
10 situation.
11 DR. WARD: Other questions from -- we've had
12 a busy day. I don't mind getting through 15
13 minutes early. Is everybody all --
14 DR. CLARK: I'll just respond to Joe's
15 comment about ventricles. At Denver, we have an
16 active adult congenital cardiac disease program
17 where cardiologist cross both sides of the street
18 between University Hospital and Children's, we have
19 the two ventricle patients taken care of at
20 University Hospital, and the one or fewer ventricle
21 patients at Children's.
22 (Laughter.)

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1 Adjournment
2 DR. WARD: Thank you all. Dinner tonight at
3 7:00. I think it's been a very successful,
4 productive day. I look forward to the second one
5 tomorrow. So we'll see you-all at dinner.
6 (Applause.)
7 (Whereupon, at 4:24 p.m., the meeting was
8 concluded.)
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