

*ACTION SCEPTER-III - Clinical Trials to Evaluate
Patient-Centered Outcomes in MVPs in the Adult ICU*

March 28, 2019

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1 P R O C E E D I N G S
2 (8:03 a.m.)
3 Welcome and Introductions
4 DR. DWORKIN: Good morning. I'm Bob
5 Dworkin, and I'll give you a very, very few minutes
6 introduction to what ACTTION is. ACTTION is a
7 public-private partnership that was established by
8 the FDA in 2010. They're not here. I don't see
9 them.
10 The people who were incredibly instrumental
11 in getting this going and continuing it were Bob
12 Rappaport, who's now retired from the FDA, and
13 currently Sharon Hertz, the director of the
14 Division of Anesthesia, Analgesia, and Addiction
15 Products, and Allison Lin, who I think will be here
16 later today. And lots of other people from the FDA
17 have been involved in supporting and helping out
18 with ACTTION since 2010.
19 So what is ACTTION? It's a public-private
20 partnership. The FDA, its notion of public-private
21 partnerships is to get everybody working together
22 to accomplish something. So the initial mission of

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1 ACTTION was to -- and I'm not going to get this
2 right. But the essence of the initial mission of
3 ACTTION was to figure out how to accelerate the
4 development of improved treatments for acute and
5 chronic pain, improved being either better
6 efficacy, or better safety, or both within a couple
7 of years.
8 Within a couple of years, I think around the
9 2012-2013 time frame options, ACTTION's scope has
10 expanded to include three additional therapeutic
11 areas: sedation, addiction medicine, and
12 peripheral neuropathy. So since about 2012,
13 ACTTION has tried to figure out, as a
14 public-private partnership, how do we accelerate
15 the development of improved treatments and
16 interventions across those four different
17 therapeutic areas.
18 I haven't figured out how to kind of analyze
19 this in a quantitative way, but my gut feeling is
20 about 40 to 50 percent of ACTTION's activities now
21 are pain, and the other three areas of addiction,
22 medicine, sedation and peripheral neuropathy are

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1 split equally with the remaining 50 to 60 percent.
2 In the FDA's view, a public-private
3 partnership brings together all the relevant
4 stakeholders, and ACTTION I think has been quite
5 successful in involving individuals from
6 professional societies. For example, Denham was
7 the ASA's first representative to the ACTTION
8 executive committee. Jim Eisenach, who many of you
9 know, is the current ASA representative to the
10 ACTTION executive committee.
11 We have participation of multiple
12 professional societies, academic investigators from
13 around the world, and patient advocacy groups;
14 pharmaceutical and device companies provide support
15 and of course government agencies, not only the
16 FDA, but NIH, CDC, and occasionally DEA. And we do
17 our very best to get international participation,
18 specifically from the EMA, but also from other
19 European initiatives.
20 The mission has remained the same, so with
21 respect to the mission, I think our focus across
22 the four different therapeutic areas of pain,

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1 sedation, addiction, and peripheral neuropathy has
2 really been clinical trials. How can we optimize
3 and improve the design of randomized clinical
4 trials across those different areas of medicine?
5 How can we optimize the design, the outcome
6 measures used, the statistical approaches to
7 analysis, and make sure that the data are
8 interpreted correctly? That's not the entirety of
9 what ACTTION has done, but the bulk has really
10 focused on clinical trials and improving their
11 design and execution and analysis.
12 The other thing I should say before I end is
13 we've also done our very best -- and we think this
14 is incredibly important -- to encourage the
15 participation of junior investigators whenever
16 possible and in any way possible. We provide
17 support every year for a 4-day pain school that's
18 held outside of Montreal, Canada, where 30
19 trainees, both basic and clinical, spend 4 days
20 learning about how to do pain research.
21 We're doing the same thing this summer with
22 a preclinical boot camp in Dallas, Texas. With

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1 respect to initiatives like this meeting, and
2 publications, and systematic reviews, we do our
3 best to get junior investigators involved. So if
4 you have a junior colleague who would like to get
5 involved in any of ACTTION's activities, please,
6 please just have them shoot me an email, and we'll
7 figure out a way to plug them into something that
8 they would be interested in.

9 I think I've said everything. I'm looking
10 at my notes, two other things. Just in terms of
11 funding, ACTTION has been financially supported by
12 a series of grants and contracts from FDA. We've
13 had two contracts and two 5-year cooperative
14 agreement research grants.

15 As I said, we also get support from
16 pharmaceutical and device companies. We've had a
17 little bit of philanthropy, not much philanthropy
18 but some, and even less royalties. But the bulk of
19 the funding is really industry support and FDA
20 support, and we've just actually submitted another
21 contract application to FDA.

22 Finally, this is the first time I'm saying

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1 this publicly, so it pleases me to be able to say
2 that last week, ACTTION got its 100th publication
3 accepted for publication, so we're really proud of
4 the milestone.

5 (Applause.)

6 DR. DWORKIN: Thanks very much. We're
7 really proud of the milestone of having published a
8 hundred articles since ACTTION was launched by the
9 FDA in 2010.

10 Before I sit down and shut up, any questions
11 about ACTTION?

12 (No response.)

13 DR. DWORKIN: Okay. The only other thing to
14 say is it's ACTTION with 2 T's, and our website is
15 action.org, and there's a whole lot of information
16 on the website. Thanks very much.

17 DR. WARD: Thanks, Bob.

18 A nice introduction to what ACTTION is and
19 what we're trying to do. I got involved with it
20 when I was his department chair when he came to me
21 and said I want to put in this thing to the FDA to
22 get some money. And I said, "That's a great idea

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1 if you want to get money." But then I got more
2 involved with it when it expanded to sedation.

3 I think maybe we'll start out -- after the
4 cocktails at dinner last night, it sounds like
5 everybody knows everybody, but I don't think that's
6 quite true. So maybe let's start with Rick Riker
7 and go around and introduce yourselves. There is a
8 list of all our participants and I guess any other
9 comments that you want to make.

10 DR. RIKER: Rich Riker, clinical and
11 neurocritical care at Maine Medical Center in
12 Portland. What a tremendous group we have here.

13 So thanks. I'm glad to be here for sure, from the
14 same Maine Medical Center and our clinical
15 pharmacists, and honored to be here.

16 DR. FRASER: Gilles Fraser from the same,
17 Maine Medical Center. I'm a clinical pharmacist
18 and honored to be here.

19 DR. WARD: David?

20 DR. GOZAL: David Gozal. I'm from
21 Jerusalem, Israel. I run the sedation service at
22 Hadassah University Hospital.

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1 DR. SESSLER: Dan Sessler, Cleveland Clinic.
2 I'm a trialist.

3 DR. FLOOD: Pamela Flood. I'm from
4 Stanford. I do anesthesia and pain medicine, and
5 I'm also a grateful former ICU patient.

6 DR. SHAFER: Steve Shafer from Stanford
7 University.

8 DR. VAN CLIEF: I'm Martha Van Clief. I'm
9 at the Food and Drug Administration.

10 DR. BAZINI: Alla Bazini, also FDA.

11 DR. EGAN: Talmage Egan from Salt Lake City,
12 University of Utah.

13 DR. BALAS: Michele Balas from The Ohio
14 State University, College of Nursing.

15 DR. DEVLIN: John Devlin. I'm a critical
16 care pharmacist from Northeastern and Tufts Medical
17 Center.

18 DR. ABSALOM: Good morning. I'm Tony
19 Absalom. I'm an anesthesiologist from Groningen in
20 the Netherlands.

21 DR. MAZE: Mervyn Maze, UCSF,
22 anesthesiologist.

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1 DR. SUN: Lena Sun, pediatric
2 anesthesiologist and SmartTots. I'm at Columbia
3 University.
4 DR. EGEROD: Good morning. Ingrid Egerod,
5 I'm a professor of nursing at the University of
6 Copenhagen.
7 DR. BROWN: David Brown, and I'm here
8 representing ICU patients, and I'm a recovering
9 academic.
10 (Laughter.)
11 DR. AITKEN: Leanne Aitken. I'm a professor
12 of critical care at City University in London, and
13 I do also have an appointment still in Australia at
14 Griffith University.
15 DR. NEEDHAM: I'm Dale Needham. I'm a
16 professor of pulmonary critical care at Johns
17 Hopkins and then outcomes research and work in the
18 medical intensive care unit.
19 DR. COLANTUONI: Elizabeth Colantuoni,
20 biostatistician at Johns Hopkins.
21 DR. DEXTER: Frank Dexter, University of
22 Iowa. I do economic studies, managerial

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1 epidemiology studies.
2 DR. COURSIN: I'm Doug Coursin. I'm an
3 internist/ anesthesiologist/intensivist at the
4 University of Wisconsin. I'm looking forward to
5 the polar vortex leaving town so I can get my kayak
6 and water. Thank you.
7 (Laughter.)
8 DR. TUNG: Avery Tung,
9 anesthesiologist/intensivist from University of
10 Chicago.
11 DR. SPIES: Claudia Spies, anesthesiologist
12 and intensivist from Berlin.
13 DR. BURRY: Lisa Burry, ICU pharmacists at
14 University of Toronto and Mount Sinai.
15 DR. SKROBIK: My name is Yoanna Skrobik.
16 I'm from Montreal. I'm an intensivist and recently
17 a pharmacology degree.
18 DR. SHEHABI: Good morning. I'm Yahya
19 Shehabi from Monash University. I'm a critical
20 care physician and an intensivist, and I'm sorry I
21 missed the dinner last night.
22 DR. DWORKIN: Bob Dworkin.

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1 DR. TANG: Wing Yu Tang, Pfizer. I'm the
2 health economics and outcomes research lead for our
3 targeted hospital grants.
4 DR. PANDHARIPANDE: Pratik Pandharipande,
5 anesthesia and critical care from Vanderbilt
6 University Medical Center.
7 DR. HOPKINS: Mona Hopkins, professor of
8 psychology and neuroscience at Brigham Young
9 University and an outcomes researcher at
10 Intermountain Medical Center.
11 DR. GIRARD: Tim Girard. I'm an intensivist
12 at the
13 University of Pittsburgh.
14 DR. KRESS: JP Kress. I'm pulmonary and
15 critical care at the University of Chicago.
16 DR. URMAN: Rich Urman, anesthesiologist,
17 Brigham and Women's Hospital in Boston.
18 Presentation - Denham Ward
19 DR. WARD: Great. Thank you.
20 Just as a little introduction, what we're
21 going to try to do in the next couple of days,
22 we've got a great group of people with a variety of

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1 interests, outcomes, statistics, critical care,
2 pharmacology, and at least three continents that I
3 heard. So I think we've got a group that should
4 give us an interesting discussion.
5 We all know about how a new compound makes
6 it to be used in our intensive care units, from
7 discovery of the compound, through FDA approval,
8 and post-clinical trials. What we're interested in
9 this meeting is the phase 1 to 3 clinical trials.
10 The past meetings have discussed that aspect of it.
11 As mostly phase 3, but as JP actually wrote
12 it in a prospective, there seems to be a little
13 lack of high-quality phase 1 and 2 trials
14 occasionally before we end up with a phase 3
15 clinical trial. It's not just a new compound. I
16 think we're also discussing possible devices with
17 possible protocols, anything that would change our
18 practice in the ICU; what's the evidence that we
19 need to generate in order to change that practice
20 so we all believe it?
21 There are a lot of perspectives to this.
22 What we want to try to do at this meeting is take

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1 as many of the perspectives as we can. Obviously,
2 a clinical trial design is just at the early end of
3 this, and you still need good clinical practices to
4 collect the data, and you have to have the right
5 outcome measures. But it's different whether
6 you're sitting at the FDA, you're a practicing
7 physician, you're in pharma, or even more
8 importantly, you're a patient in the public and
9 what's your interest in the right kind of
10 treatments when you're unfortunately a patient in
11 the ICU.

12 So SCEPTER, as Bob alluded to, has been a
13 sub-consortium in ACTTION. If you ever need an
14 acronym developed, I know who you need to go to.
15 In these days, it's very upon important -- as we'll
16 see, most of the ICU clinical trials have acronyms,
17 and if you get stumped, please email Bob. He will
18 definitely easily come up with an acronym for you.
19 Bob came up with this acronym for us, Sedation
20 Consortium on Endpoints and Procedures for
21 Treatment, Education, and Research.

22 We've done a little bit already. This is

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1 the third SCEPTER meeting. We've published two
2 systematic reviews on procedural sedation. For
3 procedural sedation, we decided to divide it up
4 into a pediatric and adult for the systematic
5 reviews. We did hold two consensus conferences on
6 procedural sedation.

7 For those conferences, we lumped them
8 together, pediatric and adult, but divided up
9 efficacy and safety in two separate conferences, a
10 little different than what we decided to do for
11 this meeting, which is divide up this meeting for
12 adult in one meeting and in pediatric for a second
13 meeting that we're planning on.

14 That's probably why Lena is here, because
15 she's going to help me put together the pediatric
16 sedation meeting, and John Berkenbosch, who was
17 with us for the SCEPTER I and II meetings, is very
18 interested in doing that, and he was unfortunately
19 not able to make this meeting.

20 We published our first paper in
21 Anesthesia and Analgesia on Patient-Centered
22 Outcomes in Clinical Trials of Procedural Sedation.

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1 Part 1 was efficacy. That paper immediately got an
2 editorial by John Butterworth, and not an
3 altogether complimentary editorial. He ended up by
4 saying what is this group that has the presumption
5 to actually make a recommendation for something.
6 But he nailed it because at the end of his
7 paragraph saying what does it actually speak for,
8 he said, "Alternatively, should we regard these
9 recommendations as well-intended advice from a
10 group of interested investigators and consultants?"
11 And my letter back was, "Yep, that's exactly what
12 this group is."

13 I think it's an advantage. We're not
14 representing any particular organization. We're
15 not representing any particular agenda other than a
16 group of, as he put it, well-intended interested
17 investigators and consultants. There's a lot of
18 expertise in this room in a variety of areas, but
19 there shouldn't be any particular political
20 agendas, and I think less so for this meeting than
21 there was for the procedural sedation meeting.

22 The next paper, part 2, was safety -- the

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1 first one was efficacy. We didn't get an editorial
2 for part 2, but it was selected as the article of
3 the month. So we moved from a critical editorial
4 to a complimentary article of the month selection
5 for our two papers.

6 In the first two meetings -- and I want to
7 suggest we think of something similar for this
8 meeting -- we took the IOM reports that talked
9 about the healthcare quality domains: safe,
10 timely, patient-centered, effective, efficient, and
11 equitable.

12 We decided for procedural sedation that
13 equitable and timely weren't necessarily important
14 areas, so it shouldn't be any issues about either
15 of those for procedural sedation, but the other
16 four were important, to be safe, patient-centered,
17 and effective. And efficient was perhaps a little
18 less so, and we didn't address efficiency quite as
19 much. That may be more important in ICU sedation.

20 Patient centered is both patient and
21 clinician centered, and there is overlap. This was
22 a slide we used for the SCEPTER I and II meetings.

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1 There are things that the patient is very
2 interested in. These pretty much apply to the ICU
3 sedation also, things that the clinicians are
4 interested in, and a lot of overlap. So when we
5 say patient centered, it has to be patient
6 centered, and it also needs to be centered about
7 what the clinician needs, but the clinician side is
8 the efficacy and efficiency side.
9 ICU sedation is complex. I'm not an
10 intensivist. I'm an anesthesiologist, respiratory,
11 physiologist, clinical trialist mainly in phase 1
12 type clinical trials. But I've learned a lot in
13 last I guess almost 9 months in organizing this
14 meeting, and I've done a tremendous amount of
15 reading and a few emails from new and old friends
16 to help me figure out what's going on.
17 This review paper by Reade in the New
18 England Journal back in 2014 had a diagram that I
19 couldn't resist putting up on how complex ICU
20 sedation is. One point I want to make is pain and
21 agitation, unpleasant awareness, is the important
22 pieces that analgesia and sedation is trying to

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1 accomplish in the ICU.
2 We've had a lot of discussions before the
3 meeting about delirium. For the purpose of this
4 meeting, delirium is truly an important outcome,
5 but it's not something that we're really going to
6 have to be able to discuss about treatments for
7 delirium, per se, either preventive or treating
8 once it's right. But clearly it's a piece of the
9 important employment outcome of ICU sedation and
10 analgesia.
11 We didn't do a systematic review before this
12 meeting like we did on SCEPTER I and II, and that
13 was because my friends said, well, we've really
14 already done that, and this was last fall, saying
15 the paper's going to come out; it's going to come
16 out soon. And in fact it did. It came out last
17 last fall.
18 So the PADIS guidelines published in 2018
19 really provides a lot of the details and systematic
20 review that we perhaps would have done prior to
21 this meeting if we hadn't been so lucky for the
22 PADIS guidelines to come out, and we're fortunate

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1 that many of the authors of these guidelines are
2 here with us today.
3 That's what we'll start out with, with our
4 first panel being, really, a discussion of what
5 PADIS found that perhaps could be improved
6 methodologically and why there are things that
7 PADIS recommendations couldn't have been made
8 because there wasn't methodologically adequate
9 studies to provide the evidence.
10 Housekeeping, Valorie, who you all met at
11 the front desk, is standing and can wave back
12 there. If you need anything, she'll fix it for
13 you. By the way, the places at your desk, a red
14 light goes on if you start talking. This meeting
15 is being recorded and transcribed, so when you make
16 a comment, please talk into the microphone. Make
17 sure the light comes on so we can get the
18 recording. Speak clearly and, please, every time
19 give your name.
20 By the end of the meeting if you don't know
21 who you are already, we will know who you are by
22 the end of meeting, but the transcriptionist

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1 doesn't. And when I go back and read the
2 transcript, it's nice to know who it was that made
3 that comment, so please say your name before you
4 make your comment.
5 I guess it goes without saying that this is
6 being recorded and transcribed, so you may want to
7 be careful what you say. In fact, Bob, do we put
8 it up on the Web?
9 DR. DWORKIN: Yes.
10 DR. WARD: Yes. So it will actually be put
11 up on the website for the public. It's actually
12 buried a little bit, so it's not easy to find, but
13 it is on the ACTTION website. So you may want to
14 be a little careful if you don't want your comments
15 put out there for everybody to find on the
16 internet, anyway.
17 Please sign in daily at the registration.
18 These are Val's things. Obviously, silence your
19 cell phones. It's being audiotaped; directly in
20 the microphone. Restrooms are outside to the left.
21 WiFi, select the Western meeting rooms on your
22 browser, and ACTTION with 2 T's is the access code.

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1 Lunch and dinner is upstairs where we had dinner
2 last night in the Mayfair Court. Our breaks will
3 be done right here.
4 Any questions, comments, concerns what we're
5 going to try to accomplish in the next two days?
6 (No response.)
7 DR. WARD: Okay. Nobody's had enough coffee
8 yet.
9 Our first panel, Doug is going to moderate,
10 and John and Yoanna are going to review where we
11 are at this point from what PADIS came up with to
12 get us started as the background.
13 Presentation - Douglas Coursin
14 DR. COURSIN: Good morning. I'm Doug
15 Coursin, for the record. I'm taking my blazer off
16 for my friends from Vanderbilt, but I do have a
17 tie. I wasn't sure as a moderator what the role
18 really was. I also wasn't sure if I was allowed to
19 have slides. And I figured by the end of this we
20 might be PowerPointed to death, so I was going to
21 take a shot at doing it without slides.
22 A discussion moderator is a person whose

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1 role is to act as a neutral participant in the
2 discussion. I have no biases, nobody's paying me
3 to be here, know nothing as Alfred E. Neuman once
4 said. But I try to hold the participants to a time
5 limit and try to keep them from straying off the
6 topic of the questions being raised.
7 Fortunately today, we have two of the
8 world's experts in sedation and a host of other ICU
9 related issues. They have significant experience
10 in study design, reporting studies, guideline
11 development, and publications in this area, and I
12 will introduce them in a minute.
13 This is a broad area. And just to provide a
14 little historical perspective, we live in the
15 ongoing tsunami of guidelines. There was a
16 guideline how to get here today, how to get on the
17 metro, and how to get into the hotel. And we often
18 encounter competing guidelines.
19 These guidelines were developed initially in
20 2002, and there are two survivors of the three
21 generations. I'd like to recognize my good friends
22 from Portland, from Maine Medical Center, Rich

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1 Riker and Gilles Fraser, who managed to give birth
2 and participate strongly in all three generations.
3 In the late '90s, early 2000, the first
4 generation was pulled together with a collection of
5 experts, and the focus was purely on sedation and
6 analgesia. Like so many other guidelines, I think
7 ACLS is the best of all of them. I expect in
8 another generation or two, they'll cover all of
9 critical care. But in the case of the sedation
10 analgesia ones, the whole area of delirium, altered
11 mental status in our critically ill adults became
12 an additional focus.
13 One of the buzzwords, which I think really
14 is the core to what we're going to talk about here
15 today and tomorrow, is patient comfort and safety,
16 because I find when I participated, they jettisoned
17 me after the second generation; probably a good
18 move. I'd either lost so much hair and my beard
19 turned so gray that I just couldn't stand up to the
20 pressure
21 As they expanded things, they began to look
22 more at the spectrum of what we do with our

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1 critical care patients and what the critical care
2 patient brings to us with their comorbidity, their
3 mental status to start with, and the like. In the
4 third generation, they expanded from the SAD
5 guidelines -- sedation, analgesia, and
6 delirium -- to the PADIS guidelines, and to this
7 they added in immobility.
8 I think the elegant work that Mona and
9 others have done and the Australians have done,
10 they're encouraging us to get people the heck out
11 of bed and get people to maintain at least their
12 musculoskeletal function as best they can and
13 maintain their respiratory function as well, but
14 also I think moving the clavicles up for us to more
15 aggressively address our cognitive function in the
16 intensive care unit.
17 With that, they added the "S" to the PADIS,
18 and that is sleep, which is a whole other topic to
19 discuss, an incredibly complex topic, and I don't
20 think is going to be a particular focus of the
21 group here.
22 So I just wanted to provide, the first

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1 guidelines came out in 2002. The next gestation
2 was incredibly prolonged and painful. It came out
3 in 2013. John and Yoanna did a spectacular job in
4 herding an incredible cross section of cats to
5 produce an expanded deeper guideline.
6 Each of the generations, in the first one,
7 we didn't have anything like Cochrane analysis or
8 grade, or PICO, which I think Yoanna and John will
9 talk about. That came out in the second
10 generation. That allowed us to focus and that
11 facilitated trying to come up with evidence-based
12 guidelines.
13 The problem with all of that has been
14 where's the evidence? Show me data. Not the
15 money, but show me the data, and show me the data
16 in my patients, whether it's in Portland, at Tufts,
17 or across the border with our friends in Montreal
18 and elsewhere, what is the data? And what's your
19 population like in it at all? Medical ICU, or
20 adult surgical ICU, or God forbid, it's a
21 subspecialty ICU.
22 Critical care is becoming more diffused.

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1 It's, unfortunately, in my humble opinion, likely,
2 if we're not careful, to be more siloed. We're
3 likely to have the CT surgical group, and the
4 neurosciences group, and the widget group over
5 here. We really need to work within that context
6 because my drug that I advocate for may be totally
7 reasonable in my population but not yours.
8 I think another thing that we have to take
9 into account as we look here is that most of the
10 drugs, save one that Mervyn and others developed,
11 was never developed for the ICU. It was imported
12 from someplace else. And I think from a
13 development viewpoint, if I was a pharmaceutical
14 executive, what would be my motivation to develop
15 an ICU drug?
16 I think coming away from that, one of the
17 things I'd be interested from the experts here to
18 discuss is what do we really want in this
19 hodgepodge of sedative, analgesic, anti-delirium,
20 comfort-inducing medication? What are the
21 indications? We haven't even gotten into the whole
22 area that we have limited PK/PD data on many of

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1 these drugs. We extrapolate them from much
2 smaller, much more tightly controlled studies in
3 healthy volunteers or in much briefer exposures.
4 We give opiates for prolonged periods of
5 time. Surprise-surprise; we see side effects. We
6 see tolerance. We give sedative medications, and
7 hypnotics that may cause physical dependence or
8 potentially withdrawal. These become incredibly
9 complex.
10 So I think the things that Yoanna and John
11 can also point out to us is how they came about to
12 come up with a host of recommendations but they
13 really nicely identify what are our gaps in
14 knowledge, and they are not insignificant. I think
15 as we come out of a meeting and a lively discussion
16 like this, that's really something we want to focus
17 on as we try to move ahead and the future studies
18 with the expertise of methodologists,
19 biostatisticians, and of course clinical experts
20 across the spectrum from physicians, nursing,
21 pharmacists, physical therapy related individuals.
22 Critical care for those who don't practice,

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1 it is a team sport, and there's good data that as a
2 team sport we do well if we have team leaders and
3 team expertise. But most importantly, we do our
4 best work when we have good communication.
5 So just in closing, I'd raised the following
6 questions that I hope we can address at this
7 meeting, if I can find where I listed them. What
8 do we want from the medications and
9 non-pharmacological interventions and protocols
10 that we generate?
11 What properties would the ideal agent, or
12 agents -- if they're going to be pharmacologically
13 mediated or non-pharmacologic approaches, what
14 would they look like? What would they give us?
15 What's likely the best way to get at developing
16 something new or taking what we already have and
17 identifying the right patient, the right
18 intervention, and the right outcome?
19 With that, I'll close, try to maintain my
20 neutrality, and turn to the experts. Our experts
21 today, Yoanna Skrobik from McGill in Montreal. She
22 has so many titles and degrees I can't go into all

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1 of them. At some level, She's a molecular
2 genomicist. She's an intensive care physician.
3 She's becoming increasingly an addiction
4 specialist, which I think is very germane to our
5 practice in the ICU considering the average ICU
6 patient is receiving what, Gilles? Would you say
7 10 to 14 medications a day?
8 DR. FRASER: That's the bottom.
9 DR. COURSIN: Many of them as continuous
10 infusions; many of them with very under-recognized
11 central nervous system effects, and I think we need
12 to keep that into account.
13 Our other expert -- and they were the
14 co-authors, and John was really the driving force
15 in this and had agreed, last night I heard, to do
16 the next generation. Thank you very much, John.
17 (Laughter.)
18 DR. COURSIN: On behalf of the board of
19 directors of SCCM, we thank you. John is a
20 professor at Northeastern and a professor at Tufts
21 Medical School and brings a wealth of knowledge.
22 Yoanna, I think you have slides for us.

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1 DR. MAZE: Can I just ask a question of you,
2 Doug?
3 DR. COURSIN: Yes.
4 DR. MAZE: As an interloper who hasn't been
5 involved in either the previous iterations, I'd
6 like to understand how you went from SAD, to PAD,
7 to PADIS, because I think that is clearly not the
8 end of the acronym.
9 DR. COURSIN: Rig
10 DR. MAZE: And I say that because if you now
11 have, as you've identified, a post-injury
12 condition, surely there's something you've missed
13 doing or not doing in that critical care period.
14 DR. COURSIN: Mervyn, I think you've hit a
15 nail right on the head, and I'll have the other
16 speak to this more eloquently than I can. But SAD,
17 I think the beginning, which was sedation and
18 analgesia, and they tweak out from that the use of
19 paralytic agents, neuromuscular blockers.
20 There's a whole guideline on this, and I
21 think Gilles and John and others from the PharmD
22 world would agree that the use of the paralytic

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1 agents in the ICU has gone like this [gestures]
2 over the ensuing two decades, unless you're
3 occasionally using something like cisatracurium,
4 therapeutically, not just to paralyze patients,
5 with really severe ARDS.
6 So they started I think with a very specific
7 focus, and I think we had a naive -- Gilles and I
8 were heavily involved in that first iteration with
9 Judy Jacoby, a former president of SCCM and a very
10 gifted PharmD. Our focus was, well, we came from
11 an era where everybody got high-dose morphine,
12 high-dose valium, and high-dose vecuronium.
13 Probably 10 to 20 percent of our patients
14 back in the '90s were being paralyzed, so everybody
15 worried what could be worse than paralyzed and not
16 adequately analgesed [ph] and sedated, and we began
17 to see a lot of very strange things occur. We have
18 of course all the issue with tolerance to the
19 morphine. You give a big slug of valium. You give
20 valium or lorazepam as an infusion. It's dissolved
21 propylene glycol. You have issues with renal
22 dysfunction, metabolic acidosis, and then you have

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1 drugs that have extremely long either lives or very
2 active metabolites.
3 Then you look at vecuronium and you look at
4 the world that we lived in at that time with renal
5 dysfunction with a drug that has 3 active
6 metabolites that are renally excreted. So we
7 started to see these very weird post-paralysis
8 myopathies, any one of the number of things.
9 We also got lot smarter in the way we
10 ventilated people, and we woke up to the fact that
11 maybe it wasn't such a good thing to have people
12 just flat in bed, stone cold, not moving. We very
13 simply moved to one of the key bundled pattern
14 things, which is unless you can't do your patient
15 care at least at 30, so you limit the aspects of
16 aspiration pneumonia. You limit the development of
17 ventilator-associated or hospital-acquired
18 infections.
19 So I think the first charge, what we very
20 simply thought -- and correct me if I'm wrong,
21 Gilles or Rick, we thought, well, let's get a
22 handle on sedation analgesia. Let's come up with

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1 some recommendations. Propofol was just coming
2 into its own. Etomidate had fallen off the map
3 because of its issues that you and others looked at
4 with adrenal steroidogenesis.

5 We now have a short-acting benzo that,
6 quote/unquote, "did not have active metabolites,"
7 which is not true, and those active metabolites
8 were never going to be a problem when, one, hydroxy
9 midazolam actually can accumulate. But we were
10 used to giving midazolam in the operating room as a
11 pre-med, a couple of milligrams or in the endoscopy
12 suite and get on your way home after your
13 colonoscopy. We were given 10, to 20, to 30
14 milligrams an hour of midazolam, not for an hour or
15 two, but for days.

16 Our length this day over the last 20 years
17 has gone like this [gestures]. Our length of stay
18 in a major medical center is under 4 days. Now,
19 that doesn't mean that you're not critically ill
20 when you go out the door, buy you may go out the
21 door with a trache in place that we percutaneously
22 put in, and you're either going to go upstairs to

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1 our intermediate care unit where you can be
2 ventilated on a trache, or you're going a mile away
3 to our LTAC, long-term acute care hospital.

4 So I think what people saw then, I think
5 Pratik, and Tim, and Wes Ely and others, Yoanna,
6 folks from Britain and the continent, started to
7 point out that people had really strange recoveries
8 when it came to delirium and cognitive function. I
9 think it started to come out that delirium wasn't
10 just me up here acting out or going into
11 withdrawal, but that it was a hypoactive delirium,
12 that this was very common, that we were
13 under-recognizing it.

14 Just editorially, I have good opinions that
15 tell me we grossly under-recognize pain in the ICU.
16 We also grossly under-recognize what the patients
17 and the families perceive of things and how their
18 needs to communicate may have changed.

19 So I think what happened in the second
20 generation, two big things. One was people became
21 aware that delirium and post-op cognitive
22 dysfunction was a major issue potentially in the

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1 ICU. What was the role of sedative and analgesics,
2 either inappropriate utilization of them or
3 prolonged utilization, or any one of a number of
4 factors, in playing a role in delirium.

5 I think one of the things you are expert in
6 and I know very interested in is what about all the
7 other things that have gone on, comorbidities,
8 inflammatory processes, surgical procedural
9 intervention, that in and of themselves may create
10 a delirium situation or a post-ICU cognitive
11 dysfunction.

12 DR. DEVLIN: I didn't mean to interrupt. I
13 was just going to add a couple of thoughts, too.
14 Sorry.

15 DR. COURSIN: A couple of what?
16 DR. DEVLIN: I was just going to add a
17 couple of thoughts additionally.

18 DR. COURSIN: No, please interrupt if
19 you --

20 DR. DEVLIN: No, no. I didn't mean to
21 interrupt. Sorry.

22 DR. COURSIN: Okay.

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1 DR. DEVLIN: I think the other thing with
2 guidelines, that we firmly believe it's an
3 instrument for change, right? We want to be making
4 change at the bedside for all these things, and
5 they're so interchangeable that we felt, when we
6 went to the Board of Regents at SCC and to propose
7 this plan for having five sections, including a
8 large immobility section and a sleep section is,
9 again, the interchangeability in clinicians at the
10 bedside don't necessarily put them into these
11 particular buckets: why is the patient awake at
12 night; why do they have the ICU cardiac weakness,
13 et cetera?

14 The other thing that really came out from
15 PAD 2013 was we had questions not necessarily
16 focused on immobility, but Gilles and I worked on
17 the part where we were looking at ways to reduce
18 delirium, and of course JP Kress' landmark study
19 had come out in terms of early mobility, and we put
20 that in the context of the guidelines as a way to
21 reduce delirium. But obviously the far bigger
22 question is we need to really tackle this

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1 immobility thing.
2 So obviously with Bill Needham's leadership
3 and many others, that's why that's all included,
4 and we felt if we don't do this, these are bedside
5 patient-derived issues. Again, the PADIS
6 guidelines are all focused on patient symptoms.
7 That's what PADIS stands for.
8 We thought if we didn't bring that context
9 in here, even though realizing -- for example, with
10 sleep, that there's just so little data and such a
11 complex area, that if we didn't start to define
12 that, and point out gaps, and drive people forward,
13 at least it's going to help clinicians think about
14 these things and what they should or should not do.
15 Sorry. I didn't mean to interrupt, but
16 those are just some important --
17 DR. COURSIN: No problem.
18 DR. DEVLIN: -- that sort of came along.
19 DR. COURSIN: Just for Denham's benefit,
20 that was Mervyn Maze asking us about other areas
21 and how this expanded, and John Devlin weighing in.
22 DR. WARD: I can recognize Mervyn's voice.

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1 DR. COURSIN: Okay. Excellent.
2 (Laughter.)
3 DR. COURSIN: But I think one additional
4 piece to the development of both SAD guidelines and
5 then the PADIS guidelines was that they began to
6 bring in a way to try to come to a collective
7 recommendation and a quality of that recommendation
8 to answer very focused questions that had not been
9 undertaken in the first one. That's a very
10 interesting process. The panelists will address
11 both the PICO approach and the use of grade because
12 it's not as if there aren't issues with that or
13 controversies.
14 There's always the age-old issue in any of
15 these of getting a collection of experts together
16 and having the wallflower up against a strong
17 personality or the aspect of we really don't have
18 much data, but our constituency wants a
19 recommendation.
20 I think one of the final things I'd comment
21 on is I'm quite interested as an observer to see
22 how these guidelines are actually applied, and I

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1 think that has some unintended consequences
2 regarding either people's development of protocols
3 or people's interpretation of the guidelines,
4 particularly when John and Yoanna spent so much
5 time with the collective group trying to say what
6 is the basis of the guideline and what is the
7 quality of data from this guideline, and how should
8 we interpret that?
9 As you look through their pages of
10 discussion on these, there aren't a lot of really
11 high-grade 1A recommendations, and I'm interested
12 in my own community to see how relatively
13 conditional low or very low database guidelines,
14 how they're applied in my institution. In very
15 short order, in the world of protocolization, they
16 get chiseled in stone, so as an outgrowth
17 additionally of the PADIS guidelines, SCCM has put
18 together A, B, C, D, E, F of a bundled guideline
19 approach or extrapolation from guidelines, and I'm
20 really interested to see what comes next, E, F, G,
21 H. I'm trying to think of things for X.
22 DR. SKROBIK: I'd like to say, Doug, we've

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1 infiltrated them.
2 DR. COURSIN: Okay. Excellent. So we'll go
3 from there.
4 Yoanna, I believe has some slides and
5 overview and discussion, and I appreciate people's
6 questions, and hopefully we can provide some useful
7 information. Yoanna?
8 Presentation - Yoanna Skrobik
9 DR. SKROBIK: Thank you. My name is Yoanna
10 Skrobik. I have the privilege of having been
11 invited to vice chair the PADIS guidelines with
12 John. It's daunting to stand in a room of people
13 this smart, and it's daunting to summarize, in what
14 I think is a short period of time, what I would
15 like to be a summary of what we did in the
16 guidelines and an invitation to come up with an
17 actionable methodology, or two, to invite the next
18 generation to do better or to do differently.
19 So I would like to invite all of you who are
20 doing something else to set that aside for maybe 15
21 minutes and listen to the content of what we did,
22 in summary, but more and more in the discussions

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1 that we've had, what we didn't do, and try and
 2 perhaps come up with one or two suggestions of your
 3 own so that when we come together into these
 4 groups, rather than have a speaker and content, to
 5 open up the discussion.
 6 We are not just privileged speakers. There
 7 are a lot of smart people here. As I was coming up
 8 to this magnolia flower-filled neighborhood, I was
 9 thinking about the privilege of what money buys and
 10 how lucky we are to have the partnership that was
 11 set up by Dr. Denham and others to think; the
 12 luxury of being able to step back.
 13 So I hope to be able to honor the people in
 14 this room and the process by at least helping with
 15 one or two deliverables, and considering how many
 16 ideas I have in my head and how chatty I am, it is
 17 going to be a challenge. So what I would like to
 18 do is summarize very briefly what we did and
 19 highlight what we're proud of.
 20 When we brought it rehabilitation, the
 21 reason that John said GP's important work, some of
 22 us had small children also, so we thought if you

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1 move people, they're going to be more relaxed, and
 2 then they're going to sleep better at night. It's
 3 artificial to dissociate sedation and sleep. We
 4 said we wouldn't address sleep today, but you all
 5 know that in the clinical environment, one of the
 6 most important reasons to administer sedatives is
 7 sleep.
 8 So all of those topics, as Dr. Maze said,
 9 our confluent, and as Dr. Egerod softly pointed out
 10 to me last night, it's not perfect, and there's
 11 some uncertainty.
 12 I think we were delighted to have patients
 13 both as collaborators and c-oauthors because we
 14 learned so much, and we brought in experts from
 15 Europe and Australia to a traditionally American
 16 bastion. Dale sweetly pointed out that we had not
 17 included other continents, but I think that it was
 18 something to be proud of that we had at least
 19 broadened it a little.
 20 We were particularly also proud of saying
 21 not only what is but what isn't, and saying why it
 22 isn't, because we thought that was really

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1 important. So it's the first guideline to do that
 2 within the SCCM. In the supplemental material, we
 3 hid in the 84 pages of the online supplement, we
 4 also published how people voted on each of the
 5 recommendations. We snuck comments into the grid
 6 because we thought it was really important to not
 7 be proscriptive, and if we were going to consider
 8 the reality of contextual and clinical variability,
 9 it's not true that there's always one right thing
 10 with a capital R and capital T.
 11 So those were our attempts to do better. We
 12 also came up with some new questions. What I
 13 wanted to stay in the retrospective after all that
 14 work, we realized that we had gone over some of the
 15 topics anew, and some we had not, and I'll give an
 16 example of that over the next slides; 37
 17 recommendations. It was 2 ungraded practice
 18 statements and 32 ungraded statements, and I'll
 19 speak to that very briefly.
 20 We use the grade method for ranking data,
 21 and therefore favored RCTs. We did not consider
 22 qualitative data. We didn't find a way to

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1 integrate the patient experience in a way that was
 2 methodologically sound, and we acted as if when
 3 intervention in a heterogeneous population actually
 4 applies to other people.
 5 We finalized PICO questions and came up with
 6 what we produced in 5 electronic databases, 2
 7 awesome librarians, a lot of people who supported
 8 the effort on every level, and we had the
 9 discussions in the five sections.
 10 Each of the discussions were attended by
 11 John and I, or both, and then came together for the
 12 final wrap-up in Hawaii in 2017 and spent a day and
 13 a half hammering out what it was we meant, because
 14 one of the things we learned the most clearly in
 15 the process is that in the communication piece lay
 16 the clarity in the final recommendations. So part
 17 of it had to do with explaining how we had written
 18 was actually intended, and I think we achieved that
 19 We had a lot of agreement, but it wasn't
 20 perfect. I really like the fact that it wasn't
 21 perfect because there are reasons to do things
 22 differently, and I think we should celebrate that

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1 diversity. I want to acknowledge that without
2 John's rigor and enthusiasm, because I've always
3 wanted to have what he puts in his coffee in the
4 morning, we would not have had the performance
5 metrics that we had.

6 We delivered the guidelines on time and with
7 a hundred percent participation in each of the
8 recommendations regardless of whether people agreed
9 with them or not. And I think that is to the
10 creditor of our fearless leader. I think we also
11 honored the ICU survivors, and I'll never be sure
12 whether we did it enough, but we tried.

13 We used PICO questions for the
14 recommendations that we made, and I wanted to give
15 you two examples of how we did that that are
16 relevant to the sedation issue, and then give you
17 one more recommendation to think about.

18 The pain assessment and management question,
19 should a protocol be used, was one of our PICO
20 questions. We said you have to differentiate
21 between analgesia first and analgesia-based
22 sedation, meaning you do your analgesia first and

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1 then say, "Ooh, do you still need sedation?" We're
2 playing you soft music or rap music, if that's what
3 you prefer. We're massaging your feet. Do you
4 want a drug on top of that, versus using an
5 analgesic as a sedative.

6 When John and I were discussing this more
7 recently, we thought, well, that would be an
8 opiate, wouldn't it? Would we have phrased it the
9 same way now that opiates are front and center as
10 being potentially problematic and potentially
11 problematic in terms of their effectiveness as
12 analgesics.

13 So we then delivered improbably this good
14 practice statement that pain should be guided by a
15 routine pain assessment. I think it is actually
16 extraordinary that all we could do is come up with
17 a good practice statement because it would seem
18 humanistically that it doesn't make sense to do
19 anything else.

20 So you see where I'm highlighting all of the
21 caveats because if you use a framework that
22 requires RCTs, what kind of caregiver wouldn't want

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1 to palliate pain? In fact, the data suggests that
2 not only don't we evaluate it very well, but we
3 don't manage it all that well.

4 So here we are talking about sedation and
5 analgesia for sedation, and maybe the analgesia
6 part and opiate part are not so straight forward as
7 we thought. So we suggested -- and this is the
8 content of the guideline -- that there be an
9 assessment driven and protocol based approach, but
10 we lumped analgesia and analgesia-based sedation.

11 The process that we used meant that all of
12 the patients ranked things according to priority,
13 so the pain part before giving sedation was hugely
14 important to patients, and I just want to highlight
15 that. If patients thought that that was so
16 important and we say we're doing patient-centered
17 care, how are we going to incorporate that in what
18 recommendations actually say or don't say? Where
19 is the place for the patient's voice?

20 I'm switching gears now to the actual notion
21 of managing agitation and sedation. We've come to
22 understand -- thanks to the work of several people

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1 in this room, probably the most
2 compellingly -- that sedatives are actually not
3 very good for you short term; not long term. We
4 have some notion that long term, they may increase
5 cognitive dysfunction, but how and so on.

6 We state in these guidelines that a specific
7 indication for giving sedatives is imperative.
8 Nobody asks the question. Your patient rolls in,
9 they get delivered a drug, but we stated that pain
10 should be addressed first and then sedatives should
11 be given; that there should be a reliable scale;
12 and that adverse events should be thought about.

13 In the gaps that we identified -- and this
14 list is very long -- pathophysiologic state, so
15 inflammatory states were blood-brain barrier
16 permeability may not be the same for drugs that are
17 potentially toxic like sedatives; reduce drug
18 clearance; PK/PD that have been studied extensively
19 in children but not in adults; drug-drug
20 interactions, which some of us have modestly been
21 interested in and every pharmacist knows about but
22 aren't necessarily integrated into how we practice;

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1 how individuals respond.
2 I think Pam Flood rattled me. She described
3 the subjective sensation of getting dexmedetomidine
4 versus propofol during one of the panel guideline
5 meanings and described her husband's reaction to
6 the two drug exposures. We had no room in our
7 guidelines for integrating how you feel, so all of
8 you who have taken an opiate, a sedative, know that
9 different ones do different things to you. Where
10 is that in the way that we practice, and does it
11 really matter? Does how you feel about it matter
12 at all?
13 Of course, genomic epigenomic factors are
14 huge because we are starting to understand that
15 they play a huge role in drug metabolism. All
16 caveats that we listed with specific, we were not
17 able to address or answer these questions.
18 We looked at short-term outcomes in the 2013
19 guidelines. We tried to look at long-term outcomes
20 in the 2018 guidelines to speak to Dr. Maze's
21 question, and we hit the wall of the lack of
22 information, and the lack of precision, and the

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1 lack of rigor of consistency across studies and how
2 that was done.
3 We looked at all the topics in all the
4 sections based on rank order. The experts said
5 this is what we think is important, and then we
6 handed it to the patients. So the order, for
7 instance, for the pain section was dramatically
8 altered by the patients; most of the others were
9 not.
10 Here are the most important ones for the
11 sedation group. Sedation and clinical outcomes was
12 considered to be the highest ranking, and then the
13 sequelae of lighter versus deeper sedation. I'll
14 speak to the light versus deep sedation because it
15 also highlights some of the questions.
16 We are looking at 15 years of literature.
17 We were able to find 8 RCTs and 3 observational
18 studies. So we're making recommendations for the
19 universe based on a relatively small amount of data
20 and end up saying we should be using lighter
21 sedation versus deeper station, but we don't know
22 what light means, and Pratik could talk about this

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1 for an hour and a half, I'm sure, if he was so
2 inclined, but he's not.
3 How do you define where the harm line is?
4 Is it an average, over 48 hours, or is it one
5 moment where you're completely -- the anesthetists
6 in this room will tell you that you get
7 post-operative cognitive dysfunction.
8 How is that different from the exposure of
9 the sedatives or the opiates that we given in the
10 intensive care unit where we give more drug longer
11 than most places. How that changed over time and
12 impacts people in the long term is also not clear,
13 and how do we describe what happens to patients?
14 I was listening to Dr. Brown casually say
15 describe the fallout from the intensive care
16 experience that he had and that his family
17 experienced. How do you measure it and how do you
18 say that it matters?
19 Judy Davidson from the family-centered
20 guidelines taught me that 25 percent of families
21 from ICU survivors are not back at work 6 months
22 later because they are too burdened by the caring

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1 and the psychological fallout of having had someone
2 you love go be near death. How do you measure that
3 economically? We're looking at hospitals costs.
4 What about the impacts on society, and should that
5 matter? So we didn't go there, and I think that
6 there's the patient specific factors.
7 When we asked the specific questions, we
8 said for medical and surgical ICU patients, so
9 non-cardiac surgery patients specifically, should
10 we use propofol or benzodiazepines, or
11 dexmedetomidine versus benzodiazepines, or
12 dexmedetomidine versus propofol? We sat and
13 talked. They said, okay, so it's meaningful. What
14 would make you choose one or the other?
15 That was one of my favorite discussions.
16 What do you think? What does your nurse manager
17 think? If you're occupying your bed for 4 more
18 hours or 4 less hours, it doesn't change the
19 nursing shift. And the definition that we came up
20 with were an agreement between the patients and the
21 clinicians saying if you lighten up in that much
22 faster -- 4 hours faster is what we decided,

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1 completely, and I think it was reasonable but we
 2 made it up -- what do we think is a significant
 3 shortening of extubation time?
 4 The patient answers to this were the most
 5 interesting man. They said, "Well, I don't really
 6 care." So it highlighted that all of our metrics,
 7 duration of mechanical ventilation, mortality, the
 8 patient said, "Well, if I am better and I have to
 9 spend one more night on the ventilator, then I
 10 don't really care." I was thinking, "My God, and I
 11 couldn't talk and express myself," so there you go.
 12 So much for my understanding.
 13 So the recommendation was that we use either
 14 propofol or dexmedetomidine because benzodiazepines
 15 had problems associated with them that are well
 16 described. But we were not able to define what
 17 long-term and patient-centered outcomes were, and
 18 the meaning to survivors was something that we
 19 couldn't quite put our finger on. We learned from
 20 Pam and others that patient perceptions were
 21 something that we were not able to methodologically
 22 capture, and the pharmacology piece was hugely

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1 missing.
 2 Costs were the subject of huge discussions
 3 also. Here we were with an Australian, or two, or
 4 three, and Europeans, and Canadians, and the
 5 Americans. I don't need to tell you that melatonin
 6 costs a very different amount in each of these
 7 places; that each of the drugs cost something
 8 different in each of these places and how does that
 9 compute into what you end up deciding.
 10 I think Dale has also highlighted the Third
 11 World's application of what we say. They're cost
 12 limited in a way that we don't consider, and the
 13 whole question of analosedation and patient
 14 subgroups. These were the gaps who identified for
 15 the sedation choices.
 16 I want to acknowledge all of the people who
 17 made this possible. It was hard work, and when I
 18 was on phone calls with a group beside my dying
 19 father, there were times when I wondered what I was
 20 doing there. My father was a man who liked things
 21 that would be delivered so that they would serve to
 22 build something else, and I think that all of the

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1 people in the PAD guidelines who spent these five
 2 years with us all had moments where they could have
 3 and would have been doing something else and chose
 4 to contribute.
 5 So I would like to think that we can honor
 6 this work and take it a step further, and I would
 7 particularly like to thank the patients who were
 8 not only part of it but engaged to the very
 9 delivery of the manuscript and contributed to it
 10 even more through that. Thank you.
 11 (Applause.)
 12 DR. SESSLER: Dan Sessler. Did you address
 13 how to measure sedation?
 14 DR. SKROBIK: Pratik, I don't know if you
 15 would like to speak to that. We had addressed the
 16 scales in the previous guidelines, so we had done
 17 the psychometric qualities of the sedation
 18 measurements. How to measure sedation is a wider
 19 question than that. Pratik led the sedation group.
 20 I don't know if --
 21 DR. PANDHARIPANDE: Pratik Panharipande just
 22 for the recording purposes. We did tackle it with

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1 regards to the scales, and because there was no
 2 difference between evidence between the 2013
 3 guidelines and the 2018 guidelines, which
 4 recommended using either the SAS or the RASS as the
 5 two scales with the greatest psychometric
 6 properties, we did not address that separately in
 7 the 2018 guidelines because there was new evidence
 8 to suggest anything should change with regards to
 9 that.
 10 The area that we tried to delve in deeper
 11 was within the context of the scales, how do you
 12 define light versus deep sedation? I'll touch on
 13 some of that tomorrow as well, but that was an area
 14 of debate and a fair amount of discussion because
 15 the literature doesn't clearly articulate what is
 16 the best definition for that. In each of the
 17 studies that targeted light versus deep levels of
 18 sedation either used different scales or used
 19 different cutoffs for that.
 20 So in general, we taught, based on what we
 21 read, somewhere between a minus 2 to plus 1 on a
 22 RASS scale and equivalent [indiscernible] on other

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1 scales was what people defined as light sedation.
 2 But again, that was an area that was relatively
 3 nebulous because none of the studies actually
 4 targeted that. So that would be an area that we
 5 will discuss tomorrow as far as what may be ways to
 6 try and determine what is a definition of light
 7 versus deep sedation.
 8 DR. DEVLIN: The other thing to add -- this
 9 is John Devlin -- Rich Riker led an important
 10 descriptor question, too, on objective sedation
 11 assessment as well. It wasn't an actionable
 12 question, but I think it was a great summary of
 13 where we're at in some of the pluses and minuses of
 14 incorporating that in the ICU. I just wanted to
 15 add that.
 16 DR. COURSIN: Denham?
 17 DR. WARD: Denham. Thank you. This was a
 18 great summary, and it brings lots of questions if I
 19 was sitting here with a new drug in my pocket that
 20 I wanted to get approved. I'll just start with one
 21 to follow up with Dan's.
 22 I've decided to use RASS as my measure in my

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1 clinical trial for a new agent. How much do I have
 2 to worry about the training and quality assurance
 3 of my people who are measuring RASS? Do I have to
 4 in my clinical trial -- my experience came from
 5 procedural sedation, and Roche when they came out
 6 with midazolam and flumazenil and advocated the use
 7 of the MOAS system, they actually had a training
 8 video that they produced.
 9 You had quite a long training video. Then
 10 they had examples at different levels of scores,
 11 and you had to score them and compare it to the
 12 experts' scoring. Then as you used the scale,
 13 there was a quality assurance program to go through
 14 and make sure that your clinical trial person was
 15 actually using the scale properly for that.
 16 So if I'm designing a clinical trial and
 17 using RASS for my sedation measurement, how much do
 18 I have to worry about the training and the quality
 19 assurance of the people who are making that
 20 measurement?
 21 DR. SKROBIK: I think at the sake of
 22 sounding like I'm always making things more

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1 complicated, if you don't know that your pain
 2 assessment was done properly, how are you even
 3 going to go down the sedation road? The data that
 4 we have that are current from Lisa Burry's work and
 5 others in the Netherlands, and in Canada, and in
 6 the community, and in academic centers, suggests
 7 that nurses assess pain maybe 50-60 percent of the
 8 time in ICU patients. And when they do, their
 9 documentation of it is different than what the
 10 patient reported.
 11 So to answer your question, I think I would
 12 add a layer to it and say you would have to mandate
 13 in every sedation protocol that pain be measured
 14 first and that it be tracked because in the same
 15 way that I think I drive a car better than --
 16 MALE VOICE: Doug.
 17 (Laughter.)
 18 DR. SKROBIK: -- we all have the sense we do
 19 things well.
 20 MALE VOICE: You've got your license?
 21 DR. SKROBIK: I came close to losing it on
 22 the way to the airport. This was not Yoanna

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1 Skrobik.
 2 So if we measure what we're doing and then
 3 compare each other in a trial specifically -- if
 4 you're doing a multicenter trial, I think it would
 5 be interesting to say how often and how reliably
 6 are you measuring whatever it is that your bedside
 7 metric is, and I would hope that that would improve
 8 the overall pattern of care.
 9 DR. COURSIN: If we could just hold on a
 10 second. Steve and David and Claudia I know have
 11 questions. I'd just like to make two comments.
 12 One, Dan, I think you're absolutely on the money
 13 having a standardized and reproducible technique,
 14 and I think there are three others in the audience
 15 I'd like to hear from about that in the studies
 16 they've done, SEDCOM and others
 17 I think the other issue is, is there
 18 something available objective in the way of a
 19 neuromonitor that would give us -- and I think that
 20 is a whole hand grenade verse of conversation.
 21 But Pratik and Rick and Gilles, in your
 22 studies, in multicenter studies, how did you

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1 control for the quality of SAS or RASS, if you
2 happen to be a Richmond guy or a Maine Medical
3 Center guy, in your analysis? How did you control
4 for the quality of their subjective scoring?
5 DR. RIKER: Riker. For SEDCOM, as part of
6 our startup meeting, we actually had the folks from
7 Vanderbilt who developed or validated RASS and
8 developed CAM-ICU, spend time with each of the
9 research teams to train them in that process. We
10 didn't do secondary confirmation of reliability or
11 anything like that at each site. We didn't go that
12 far, but it was included as far as our startup
13 meeting for training.
14 DR. COURSIN: Sir, yes? You had a comment
15 to that?
16 DR. SHEHABI: I just wanted to add, Rich, I
17 think it's very important that the sites get
18 trained specifically on site to control the quality
19 of conducting a pain and sedation and delirium
20 assessment. Like what Rich did in SEDCOM, in sites
21 where we ran it in 74 ICUs around the world, the
22 team visited every single center to train them on

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1 how to conduct these tests.
2 We left them with videos that they can use
3 at the bedside with PowerPoint presentations, and
4 then we had a study monitor who visited every
5 single site at least twice during the conduct of
6 the study for the quality control of the data and
7 how they're doing it. I think that's very
8 important in terms of making sure that the
9 frequency visits are done as supposed to be done
10 and they're done in a standard fashion across all
11 sites in a large multicenter trial.
12 DR. SKROBIK: Can I ask, other than the
13 social engagement that you make when you connect
14 live, do you think it's feasible to do that more
15 cheaply through electronic platforms or through
16 more pragmatic -- we talk about the cost of doing
17 RCTs and how huge it is for results.
18 DR. SHEHABI: I think it took quite a while.
19 It took us two years in doing that. We introduced
20 the site in a target fashion, so they were not all
21 started on April 1, and we had multiple people who
22 were doing that, visiting the sites. Like for

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1 example, at the Malaysian site, there were 11 sites
2 there. It would have been impossible to do that on
3 a video call.
4 That engagement at the beside training for
5 the research team and the senior clinicians was
6 very, very critical for them to understand what
7 they're expected to do. Even in the UK, the sites
8 there preferred onsite training, so we conducted at
9 least 5 centralized meetings in the UK for that
10 purpose.
11 DR. COURSIN: I want John just to get a
12 chance to jump in.
13 DR. DEVLIN: I think the other thing that
14 Yoanna and I have had a lot of discussions, two
15 particularly with delirium assessment, is nurses I
16 find want to know does my patient have delirium or
17 they don't, and they're challenged, and it can add
18 a little bit of stress to them as "I'm not really
19 sure."
20 I think it's important through the education
21 to give them that knowledge that it's okay that
22 they're not sure exactly what the RASS score is if

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1 the patient's CAM positive, but then to seek out
2 someone else in the unit because this could be a
3 night nurse who might be maybe a better trained
4 colleague that can really help.
5 Certainly in the research I've done it at
6 Tufts, we've really promoted that, and it seems to
7 have prevented a lot of not able to assess or not
8 really sure. I haven't done research on it, but I
9 think it's helped the validity of some of the
10 assessments or at least let the investigators know
11 the next day that they weren't sure. That was just
12 one thing to add.
13 DR. COURSIN: I think in part your local
14 research coordinator has to be working. I'm in a
15 unit probably typical of this group. We have 93
16 nurses in our unit, and we have float nurses and we
17 have nighttime replacements. So it's not a small
18 thing, but I think you need a series of champions
19 as well.
20 I just wanted to give Claudia a chance in
21 the back. She's patiently been waiting to comment.
22 Thank you.

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1 DR. SPIES: Thank you. I have one comment
2 to the discussion right now. We're doing a study
3 now with the German Ministry of Health involving
4 several centers. And our impression was in the
5 beginning that all these measurements on sedation,
6 analgesia, and delirium didn't work if you really
7 tried to give it by guidelines or give it by
8 e-learning.
9 So we implemented a blended learning concept
10 where we have e-learning as a beginning so people
11 know what they are talking about. So that's very
12 important because of the different professions
13 involved at the patient's bedside. And even the
14 relatives and the patient, him or herself, are
15 always concerned. So if you train the people, they
16 perform better.
17 Second, we have a simulator-based concept,
18 so people are not corrected at the bedside. They
19 don't feel annoyed. Sometimes they feel annoyed if
20 you do that. So I think that's not good to do it
21 that way. So we have a simulator-based concept,
22 and at the end you do supervising at the bedside.

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1 This at least decreases the inter-rater. Also the
2 inter-rater, we have a lot of variability in that
3 setting, and I think it's very important that
4 we -- some think we do the same things, but we
5 don't.
6 The other point I would like to address to
7 the methods of the studies. If you want to address
8 pain, I think you need a pain measurement, and
9 that's not done in many of the studies. The second
10 point, if you want to try sedation, you need -- all
11 the things that are not clearly stated in the
12 beginning. And that's giving you a lot of
13 confusion because sometimes if you measure pain,
14 you measure side effects of sedation and not pain
15 itself. So this is complicated, and I think there
16 are a lot of things we need to consider together to
17 release all that out.
18 DR. SKROBIK: If I could just add to that, I
19 think the other caveat that we thought about later
20 is that the notion of benzodiazepine withdrawal,
21 for instance, is not something. In children and in
22 the pediatric population, opiate withdrawal and

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1 benzodiazepine withdrawal are routinely measured.
2 In the trajectory of an ICU with all of the
3 drugs that we deliver, we actually don't test for
4 it very often in adults. To my knowledge, there
5 are two or three studies describing it, suggesting
6 that the incidence is as variable as 15 to
7 50 percent, so not an insignificant amount, and I
8 think in the don't knows, I think that's part of
9 it.
10 In Canada, there are three provinces now
11 that have electronic registries where you can't
12 close your days charting if you haven't done the
13 pain measurements and the sedation measurements.
14 I'm not sure the content of what's written in there
15 reflects what the patient actually has or doesn't
16 have, but I was grateful enough to be part of the
17 quality assurance of setting it up for the delirium
18 component and for the three components of sedation.
19 So there are ways to make sure that the assessments
20 are done, and in each of those platforms there's an
21 uncertainty box.
22 DR. COURSIN: You have to be careful, I

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1 think, of the old VA jokes that the patient had
2 normal vital signs an hour after they were declared
3 dead. Any of the experts who are boots on the
4 ground in developing these scores in the audience
5 for implementing or making sure that they're
6 implemented have comments? Michele?
7 DR. BALAS: Michele Balas. I think one of
8 the things that we talked about significantly on
9 working with the PADIS is the importance of
10 conceptual clarity in what the symptom is that
11 we're measuring or the syndrome.
12 For example, one of the most frequent
13 reasons clinicians report giving benzodiazepines
14 for is for anxiety, and many of the studies that
15 we've reviewed or that we include that involve
16 sedatives have rarely measured anxiety. Anxiety
17 gets lumped in with agitation. Agitation sometimes
18 gets lumped in with hyperactive behaviors, and
19 sometimes the patient that's deemed agitative is
20 actually having a normal response to being
21 restrained and having 15 tubes put in their body.
22 So I think it's really important. From a

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1 clinical trials perspective, I absolutely agree
2 that fidelity monitoring and the inter-rater
3 reliability is something that we definitely need to
4 build upon in the ICU community, but also the need
5 for that conceptual clarity when we're looking at
6 the symptoms; not just the outcomes but the
7 symptoms that we're looking at.
8 DR. COURSIN: Thank you.
9 Steve, you were jumping in, and, David,
10 we'll get to you. Steve's been patiently waiting,
11 and so has David.
12 Steve Shafer?
13 DR. SHAFER: I'd like to step back for a
14 second. Steve Shafer from Stanford. I'm not an
15 intensivist, but certainly your paper from last
16 year in Critical Care Medicine is just a wonderful
17 piece of work outlining both recommendations but
18 also the gaps in the knowledge.
19 One of the things that jumps out to me is
20 there are so many gaps in the knowledge and so many
21 things. I went through and made a list of all
22 things where it says low-quality evidence. And

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1 since we're here to talk about clinical trials, I
2 think that one of the things we're here to talk
3 about is how do you fill in this low-quality
4 evidence that really dominates both sedation and
5 analgesia, particularly, in my view, the sedation
6 piece? Because it costs money to fill in this
7 evidence, and the question is what's the economic
8 driver for it?
9 I can envision several economic drivers. If
10 there is a new drug that a company can come forward
11 with, that will drive more studies. Hopefully from
12 the company's perspective, it will be studies that
13 show favor of the drug, but it will give us more
14 information to fill in these knowledge gaps.
15 The problem is the drugs that we have are
16 generic. They all come out of anesthesia, and
17 there have been a number of attempts in the last 20
18 years to come up with the next generation of
19 propofols and dexmedetomidines, and other
20 sedatives, and nobody's done it because the market
21 isn't big enough and the regulatory path seems too
22 burdensome. And frankly, the drugs we have are

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1 awfully good, so they set a high bar.
2 That's one of the drivers. I don't see that
3 happening. Other drivers would be physicians,
4 perceive a gap in care. And I'm not one of these
5 physicians, but I don't get a sense that our ICU
6 doctors are saying we have these huge gaps in care.
7 You've identified the gaps and the knowledge, but
8 are the physicians saying -- the boots on the
9 ground in the ICU -- we need these gaps of
10 knowledge filled or there's an economic gap.
11 We could do better and we could pay for this
12 work if we could save money by doing these things,
13 and that would fund the studies. What is the
14 economic driver to fund the research to fill the
15 pretty overwhelming knowledge gaps that you
16 identified?
17 DR. SKROBIK: I think that what you speak to
18 is exactly that. We have a 4 percent error rate
19 across our medical systems no matter where or how
20 you look. We don't acknowledge it. We don't talk
21 about it. We don't apologize for it. We don't fix
22 it. So in addition to saying we are not perfect,

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1 you want us to say and maybe we don't deliver, and
2 it doesn't make sense.
3 On the other hand, you talk about making
4 money from an intervention. How much money would
5 you save if you delivered the care according to
6 whatever simple metrics? Not the sexy new molecule
7 that is going to make my wrinkles go away, but the
8 delivery of what the patient expects.
9 I don't know where that answer lies because
10 when I listen to your question, I would think that
11 incentives to make people more accountable for the
12 delivery and the costs of the care might be an
13 interesting perspective.
14 DR. DEVLIN: I just wanted to add really
15 quick, I think with the caregiver, it's a really,
16 really good point you brought up. I think it also
17 depends on the paradigm perspective of the
18 clinician, what they feel is the goals of care and
19 whether they truly are well versed on some of the
20 dangers of deep sedation and the mobility, not
21 being able to mobilize patients and as such.
22 Obviously, in the U.S. at least, we're

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1 dealing with a system where we're focused on the
2 cost of care in the hospital, but obviously this
3 spills over post-ICU, and readmissions, and
4 everything else.
5 DR. COURSIN: Steve, one observation I'd
6 make -- you've raised excellent points. Who's
7 going to spend half a billion dollars to bring a
8 drug to the market place that doesn't have the
9 multiplier of the next generation of statins, or
10 Z-Pak. The second piece to that, though, I think
11 that for the most part, in critical care, we are
12 pretty satisfied with what we have and what we have
13 that comes out.
14 I think where we have real blind spots
15 are -- what we've clearly outlined nicely how the
16 patient and their families are functioning, and in
17 a sense, the ICU with the shortening of stays and
18 whatnot, and the throughput that we have, a lot of
19 the problems that we're discussing here, they're
20 out of sight or out of the mind to the critical
21 care patient at the bedside.
22 I don't realize that 25 percent of families

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1 are not back to a functional state working. Their
2 quality of life is impacted a year later, and we
3 haven't even gotten to the root cause analysis of
4 what about the huge percentage of patients in the
5 United States, anyhow, who shouldn't be within
6 5 miles of an ICU, but yet get admitted? So I
7 think those are key issues.
8 JP, you had popped up with something. I
9 wanted to make sure I didn't oversee it.
10 DR. KRESS: One thing -- and maybe we'll
11 talk about it later -- this gap in what we
12 currently have and what we're seeking in terms of
13 quality there or continence and the
14 recommendations. I think it's important that if
15 you look at the way that the grading system for
16 these consensus statements is used, it's a really,
17 really high bar to get a strong recommendation.
18 If you look at the published guidelines for
19 many, many different areas, what percentage of
20 grades are low quality or weak recommendation
21 compared to strong? I would submit it's probably
22 more than 10 to 1, and maybe that's because the

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1 system is intentionally stringent.
2 If we're trying to improve on the quality of
3 our recommendations with better data, that's a
4 really high bar to jump over. Having sat through
5 these meetings and these consensus guideline
6 writing, you almost have to hit a grand-slam in a
7 particular area to get a strong recommendation. So
8 if we're hoping to get the next generation of these
9 guidelines with all strong recommendations, I think
10 it's almost, if not certainly, impossible based on
11 the system we use to give studies and
12 recommendations grades.
13 DR. DEVLIN: That's such an important point,
14 JP. I think the other thing too is we're framing
15 our guidelines, PADIS, for all critically ill
16 adults. This is just one example. So then we
17 downgrade things when there's not a patient
18 population that's been well studied, which is all
19 different subtypes of patients of critically old
20 adults. So that's an automatic downgrade when
21 there could be a great randomized study and a good
22 answer potentially in a subgroup of, say, a certain

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1 type of surgically critically ill patients. We ran
2 into this all the time in our guidelines.
3 DR. SKROBIK: Could I just speak to the
4 grade comment? We have huge discussions over the
5 grade methodology over these guidelines, and I
6 think it's a very interesting and important point.
7 I'm not sure how it influences trial design because
8 if we're going to be asking the questions within
9 the trials, perhaps that imperfect metric should be
10 set aside altogether because in itself, it is the
11 best tool we have so far. But for the very reasons
12 and many others that you've point out, it has major
13 limitations.
14 DR. COURSIN: Dan Sessler?
15 DR. SESSLER: It's true that with some
16 current systems, it's hard to make strong
17 recommendations, but that's not a fault of the
18 system. It's because we don't have the underlying
19 data, and there is a bit of a history of groups
20 coming out with fairly strong recommendations that
21 didn't hold up, and you only have to look at the
22 recent World Health Organization recommendation on

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1 supplemental oxygen, which defies available data,
 2 so there's a lot to be said for being rigorous.
 3 Along those lines, you presented a very
 4 formal way of developing consensus of doing a full
 5 systematic review, grading everything, voting,
 6 recording how people voted, making sure that people
 7 don't vote if they have a conflict, which might
 8 even be defined as having done for relevant
 9 research in the area.
 10 DR. COURSIN: And we did do that.
 11 DR. SESSLER: Okay. That is becoming a
 12 standard. It's the way we develop the Canadian
 13 Society of Cardiology guidelines. It's not what
 14 we're doing here, which is just something to think
 15 about. I mention it because I was involved in a
 16 PCORI consensus process and papers, and we got huge
 17 pushback from reviewers that basically said this is
 18 no longer the way it's done, and frankly, I think
 19 the reviewers were right.
 20 So going forward, we might think about doing
 21 this a little more formally so that we are at the
 22 current standard of care.

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1 DR. SKROBIK: I think it can be said of
 2 patient representation, if I could just add that,
 3 because Dale has done some very elegant work using
 4 groups of patients that were representative of
 5 populations in using Delphi rounds and going
 6 through a very rigorous process.
 7 We got slammed in the guidelines for having
 8 randomly apparently selected patients who just
 9 happened to wander in and want to donate that much
 10 volunteer time. Can we agree? It couldn't have
 11 been -- if you would have asked a representative
 12 sample to do this thing, they would have told you
 13 where you can get off the bus.
 14 I think the most elegant response to that
 15 was Cheryl Misak's, who said, "What is your
 16 presentation anyway?" And who speaks for whom and
 17 under what auspice? And I think what Dr. Ward was
 18 talking about earlier, benevolence is not a
 19 small -- it shouldn't be set aside.
 20 Pratik and I had a very lively discussion
 21 over the day yesterday in terms of what
 22 intellectual conflict of interest means. The key

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1 is the transparency and the communication. If you
 2 can say we did this transparently, this is what we
 3 did, this is exactly what we did, you can knock it,
 4 but you know what it was.
 5 The communication among those who share
 6 ideas the way we are has to be about the content
 7 and not about your opinion and whether somebody
 8 should be getting sedatives. We had one
 9 interesting intervention, and that was why would
 10 you give somebody a sedative anyway? You say that
 11 to most people, and --
 12 DR. COURSIN: David, I wanted to give you an
 13 opportunity. I apologize. David Brown.
 14 DR. BROWN: Again, I'm going to wear my
 15 patient hat a little bit more and family hat. I
 16 noticed -- and Yoanna, a great job on
 17 summarizing -- it was only survivors, and I wonder
 18 about the families of deceased ICU people to bring
 19 to bear because my experience in this area of
 20 working with people with advanced illness, one
 21 person has an advanced illness, the whole family
 22 has the advanced illness. Maybe I missed it.

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1 DR. SKROBIK: We had both, but we didn't
 2 declare it up front.
 3 DR. COURSIN: Dr. Shehabi?
 4 DR. SHEHABI: Yahya Shehabi. I think in
 5 terms of the recommendations, I think it's
 6 important to link that to the outcome looked at and
 7 make a recommendation. I think when it comes to
 8 the sedation group -- and Pratik, you could speak
 9 to that -- I think we made the bar very high in
 10 terms of the outcome.
 11 Instead of saying we're going to accept a
 12 short and mechanical ventilation to make a sound
 13 recommendation for X versus Y, which now it has to
 14 reduce 90-day mortality, or it has to do reduce
 15 such and such and such at 6 months. I think that
 16 probably what led to a lot of recommendations being
 17 made conditional, a low recommendation, because
 18 there's just simply no data on that.
 19 DR. DEVLIN: Yes, and that's a really
 20 important concern. That's one of the things
 21 obviously grade requires, is we did vote on our
 22 highest priority outcomes for our PICO question,

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1 and there was some pushback as people get familiar
2 with the data, and later on as we're trying to make
3 recommendations, "Well, can we just change some of
4 these?" And we were basically, no, we can't, but
5 that's such an important point, because the data,
6 it did drive a lot of lower-level quality
7 recommendations.
8 DR. COURSIN: Pam?
9 DR. FLOOD: I'll add on to what David said.
10 I want to recognize --
11 MALE VOICE: Could you speak into the mic,
12 Pam?
13 DR. FLOOD: Sure.
14 DR. COURSIN: That was Pam Flood.
15 DR. FLOOD: I just want to add on to David's
16 comment -- Pamela Flood, Stanford -- that we are
17 absolutely -- particularly those in this room who
18 are ICU survivors -- not a representative sample.
19 Not only have we survived, we survived intact, and
20 we were relatively healthy academic physicians
21 before all of this happened. So what's important
22 to us and our families might not be important to

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1 everyone, and other things might have greater
2 importance.
3 DR. EGEROD: This is Ingrid Egerod. I'm a
4 qualitative researcher, and I have some concerns
5 about the way the patient representatives are used
6 in research because we discussed this at length
7 about whether it's representative when we do our
8 qualitative research. I have a feeling that that
9 whole layer of discussion has disappeared when we
10 have patient representatives, and patients suddenly
11 become a representative to a much larger degree
12 than they really should.
13 In qualitative research, we always put in
14 all these important discussions of can this be
15 generalized and so on and so forth. I think that's
16 another thing that we need in research, is to
17 really define or discuss how to use patients and
18 families so it makes sense.
19 DR. COURSIN: If I could, Dale Needham, with
20 your expertise, would you comment for us on that?
21 DR. NEEDHAM: This is Dale Needham from
22 Johns Hopkins. I do think, and I did perhaps say

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1 to John and Yoanna, sure we have some patient
2 representation, but it's pretty tiny. I think that
3 our knowledge in how to do this is evolving. When
4 I present in an hour or so, I'll talk about one
5 approach that we had to try to have in a formal
6 consensus methodologies and Delphi, and try to have
7 about a quarter of our representatives be patients
8 or families.
9 I think we've still got lots of ways to
10 learn and how to do that, and I was sharing some of
11 that with John and Yoanna as well, but I'm not sure
12 that we know the answer yet. But I think it's
13 important that we continue to bring this up to
14 ourselves, continue to think about how we should do
15 that and recognize that often patients are going to
16 talk about an experience of one person, and we need
17 to put that in context, too.
18 I've seen sometimes where I think we just
19 give too much weight to what might be an outlier or
20 one representation. I say that just because the
21 research that I've done for 15 years looks at
22 long-term outcomes of ICU survivors. So we've done

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1 assessments on thousands, thousands of assessments,
2 so I think I have a little bit of a feel. Of
3 course, my bias as well, but sometimes one voice
4 may not always be the representative.
5 So that's a couple of thoughts, and I think
6 when I present, I'm happy to share some of our
7 learnings and thoughts that have come out of that.
8 DR. COURSIN: I want to get Leanne Aitken's
9 thoughts as well. I'm sorry. I'm trying to get
10 both of you.
11 DR. AITKEN: That's okay. Leanne Aitken.
12 Some of you may not be aware, but within the UK
13 research funding environment, you basically won't
14 get any government funding without a reasonable
15 patient and public involvement process, and that
16 includes some sort of consultation with PPI, as
17 well as PPI members as co-applicants on the grant
18 with you.
19 In the current study that I'm a co-app
20 on --
21 DR. SKROBIK: Sorry. What's PPI?
22 DR. AITKEN: Sorry. Patient and public

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1 involvement.

2 DR. SKROBIK: Not protein, pumpkin --

3 (Laughter.)

4 DR. AITKEN: No. And there's another PPI

5 related to insurance. It's not that either. In

6 the current study that I'm a co-op on that's

7 comparing dexmedetomidine versus clonidine versus

8 usual sedation, through our PPI process, one of the

9 outcomes that was considered most important to a

10 group of about 20 was how well the patient could

11 communicate with the family member.

12 We would never have thought of that. We

13 would never have put emphasis on it. That's a

14 single example, but I think it's an important

15 example of how we do need to think differently and

16 make sure that we get that voice. Now, we have a

17 group of between 18 and 20 that we consult with

18 regularly, and we have two patients and public on

19 our co-op team, but that's the process throughout

20 the whole of UK government-funded research.

21 DR. SKROBIK: If I could just speak

22 to -- this is Yoanna Skrobik -- the reproducibility

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1 within this small effort, what struck me was the

2 cohesion between the 5 patient representatives that

3 we had, who the exception of their preference of

4 depth of sedation spoke with one voice despite

5 their different experiences. I know it's not the

6 thousands that Dale refers to and not the long-term

7 outcomes, but within these specific topics, I was

8 struck by the homogeneity.

9 DR. COURSIN: Ingrid, you had a comment?

10 DR. EGEROD: Yes. I just wanted to add to

11 that, that I think one of the problems is that

12 we're trying to generalize and maybe we should just

13 accept that we can't generalize and that that's

14 okay.

15 What we're doing is we're giving a lot of

16 good examples of what might be meaningful to

17 patients, but we're in a different paradigm, and I

18 think we really need to keep remembering that it's

19 all right that they're not completely

20 representative. People are different.

21 DR. COURSIN: Mervyn, you had a comment?

22 DR. MAZE: Yes, and this is not meant to get

Page 91

1 into wordsmithing, but I want to ask about the way

2 that a recommendation is framed either in the

3 negative or the positive. And I'll give an example

4 of what you've said, but I won't read word for

5 word. You say something must not be used in all

6 patients. How does that differ from it is useful

7 in some patients and start defining what that some

8 is?

9 DR. SKROBIK: I think that's an excellent

10 point, and on the last slide that I showed, the

11 subgroup comments spoke to that, the gaps being if

12 people are all different in terms of pathology and

13 in terms of how they respond to whatever

14 intervention, being pharmacological or not, how do

15 you tailor?

16 You're not looking at a cohort with an

17 average when you're looking at the patient in front

18 of you, and if that subgroup hasn't been studied or

19 that personality profile hasn't been studied -- the

20 Israelis published a beautiful study looking at

21 whether being a controlling person made you more

22 likely to develop delirium. I have to say it was

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1 one of my favorite papers.

2 So how do you make that transition? And I

3 think that's where the -- subgroups specifically,

4 because we made recommendations for pain management

5 in the previous guidelines based on two studies in

6 two very specific subpopulations, and said opiates

7 were all the same because 2 opiates were compared

8 in each of those studies; so an imperfect example

9 of how you make a recommendation.

10 DR. MAZE: But are you therefore saying that

11 unless the subgroup is not identified, that it's

12 better to frame it in the negative?

13 DR. SKROBIK: No. I think you should think

14 about it and just express it clearly. This is a

15 very personal opinion, not the SCCM; this is a very

16 personal opinion. I think you get so caught up in

17 the naming of the conditional strong, weak, blah,

18 blah. If you have the patients to not read the

19 summary but read through the content of what

20 created that recommendation, then you get an idea

21 of what you're talking. Based on these two groups

22 of this profile of patients, these were the

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1 results.

2 You can then take that away and apply it in

3 your patient or not. But we live in a world where

4 medical information triples every 10 years. So you

5 take the guideline and you take the summary because

6 you couldn't possibly be an expert in sedative

7 exposure, and mechanical ventilation, and -- you

8 couldn't. So you take it, and the problem is in

9 the summarizing of it and in the words that you use

10 in the summary.

11 DR. DEVLIN: Again, another thing with grade

12 is you're forced to make your conditional

13 recommendation for or conditional recommendation

14 against, or strong for or strong against. That's

15 where you're parsing this divide of risk versus

16 benefit and all the other factors that came into

17 the recommendation space. So we have some that

18 look like they're negative and then some that are

19 positive, and that's simply how --

20 DR. SKROBIK: But if it could have

21 consensus, it's artificial.

22 DR. DEVLIN: We had a comment in the back.

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1 I'm sorry.

2 DR. TANG: Hi. I'm Wing Yu Tang, and I have

3 much more experience on more of the real-world data

4 on research side. So I'm very curious per a lot of

5 the comments being made about generalizability, and

6 certainly sample sizes I think comes into play as

7 well, in terms of generalizing either

8 subpopulations or small populations to a much wider

9 and generalizable audience.

10 We also talked about things like

11 productivity and absenteeism, which we capture a

12 lot as well, that are more I would say real-world

13 outcomes that aren't necessarily typical clinical

14 trial endpoints. These are actually realities that

15 I would say are limitations that sometimes clinical

16 trials can have.

17 So I'm really interested in thoughts

18 about -- we talked a little bit about qualitative

19 research, but there's obviously a really growing

20 number of real-world data, phase 4 studies, other

21 kinds of prospective works which are targeting much

22 more larger sample sizes, and the maturity of it

Page 95

1 clearly is evolving quite rapidly. And I'm

2 wondering thoughts about where that falls into the

3 current discussion on generalizability.

4 DR. COURSIN: Comments on that? Claudia?

5 DR. SPIES: Maybe surely. I'm also heading

6 the whole medical society development in Germany

7 for the guideline development, and there's a lot of

8 discussion also with the Guidelines International

9 Network on the quality of the guidelines. I

10 learned a lot from our guideline from this

11 networking that AWMF is having 180 medical

12 societies included. The Guidelines International

13 Network is a huge society giving standards and

14 including all the stakeholder representatives to

15 qualify a guideline.

16 At least from my perspective and doing a lot

17 of guideline research a lot of times, I'm mainly

18 stuck in the methodology. I think it's very

19 important that we have these people who help us

20 really to qualify our guidelines and really to get

21 that implemented because only with them is it

22 possible to get that implemented.

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1 My question is, is that moderated, all the

2 guideline development here in the U.S., by

3 Guidelines International or by a U.S. specific

4 guideline network that's really having all of these

5 people involved. One has to look at the throughput

6 model at the end, or the patients, the relatives,

7 the organizations, the system. It's very context

8 specific before an intervention goes. And because

9 it's not so easy to understand, I think it's

10 important I think to use that help people have in

11 different other guideline developments.

12 DR. DEVLIN: Yes, I can speak to maybe just

13 a little bit of that. There's a great working

14 group that obviously postulates and promotes the

15 ways clinical practice guidelines should be done.

16 Cochrane is involved as well. But there could be

17 inherent biases from those, those organizations.

18 Currently, from what I've seen talking to

19 other critical care organizations, is it's a little

20 bit fractured in terms of the societies that

21 support these guidelines have their agendas for

22 doing them. I don't think there's a lot of

Page 97

1 cross-talk. Even within SCCM, I'll be honest,
2 there's varying level of methodological support and
3 the focus of how these guidelines are done. So
4 there's just an incredible amount of variability in
5 quality and how they're done. These are really,
6 really big issues from that practice guideline
7 thing.

8 The one other comment I wanted to make,
9 which I think goes back to the comment there is,
10 when we're looking at choice of sedation, this came
11 up a lot within our group is, we're focusing a
12 question on which sedative the patient is to get in
13 the ICU, but that patient stay obviously could be
14 quite dynamic throughout the ICU stay, and maybe
15 there's a choice of sedative that's better on day 3
16 than the first day they get intubated if they even
17 need the sedative, and that dynamic process is not
18 brought into the guidelines at all.

19 We do bring it up as a gap, but I think it's
20 a really important one for this group because most
21 of the studies, you randomize patients to one
22 sedative or the other, and you keep that sedative

Page 98

1 going unless there's an adverse event, or a safety
2 concern, or they're extubated.

3 DR. COURSIN: Thanks, John.

4 As the moderator, we're coming kind of
5 toward the end of this session, and a question
6 comes up, a very logical one, about longitudinal
7 database follow-up.

8 Frank, any comments on that as far as
9 creating these databases and looking at them over
10 time, particularly with evolving practices or
11 competing guidelines?

12 DR. DEXTER: Frank Dexter, Iowa. I
13 understand longitudinal databases for endpoints
14 such as work or something like that, but it's
15 really hard, if it's difficult to measure something
16 even in a randomized clinical trial, to begin to
17 think about longitudinal measurements. I kind of
18 find that to be very difficult. Even if you were
19 to say take databases that already exist currently,
20 if you can't in a randomized trial measure
21 something reliably, having more data isn't going to
22 make it reliable.

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1 DR. COURSIN: Dan?

2 DR. SESSLER: Data quality also tends to be
3 poor in registries and controlling for confounding
4 is challenging. That's not to say that registries
5 are useless. We do lots and lots of registry
6 studies, but they sure don't have the reliability
7 of a controlled trial.

8 I think the point that even controlled
9 trials in this environment are difficult is valid
10 and important, and a solution to that is not a
11 registry.

12 DR. COURSIN: Thank you. I'd like to keep
13 going on with that, but I have one final kind of
14 burning question I'd selfishly like to ask. I'm
15 going to direct this to Steve.

16 Steve, you outlined what are the problems;
17 where are we unhappy with things; who's going to
18 pay for this? It would seem to me the key action
19 items coming out of this meeting would center
20 around clearly identifying what we need, whether we
21 can fill the gaps in or not, but what do we need
22 and who the hell's going to pay for it, and who's

Page 100

1 the advocacy group?

2 The force I would try to get out there, the
3 last data I looked at 1.4 percent of the gross
4 national product is spent on critical care in the
5 United States. That's a lot of dough. Is there a
6 way to leverage what we're talking about here in a
7 manner that we could make effective collection of
8 data, analysis to that data, and implementation?
9 Steve?

10 DR. SHAFER: I'm looking up to the session
11 that I'll be moderating at 4:30, and that's the
12 same question I've had, which is when we're talking
13 about clinical trial designs, you can't really talk
14 about that in the assumption that there's unlimited
15 funding. And a clinical trial design has got to
16 identify a problem worth solving, and the worth, I
17 hate to say this, has got to be defined in dollars
18 or whatever the currency is, but it's got to be
19 defined.

20 DR. COURSIN: We'll vote on Brexit later
21 today.

22 (Laughter.)

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1 DR. SHAFER: Yeah.

2 DR. SKROBIK: Dollars and glory, no? Is it

3 not dollars and glory?

4 DR. SHAFER: Somebody's going to write a

5 check, and they aren't going to write a check for

6 your glory.

7 DR. SKROBIK: No, write a check so that your

8 finding -- so there's the academic and journal

9 driven study; wow, we have this new thing. Nobody

10 does granular metrics.

11 DR. SHAFER: That will motivate all of us to

12 put in our time and effort, the glory part, because

13 we don't really do it for money; we do it for the

14 contribution we make. But in terms of funding the

15 cost of doing a study, if we can identify -- here's

16 the cost of not knowing. The cost of not knowing

17 is X, and it's going to cost some number smaller

18 than X to fill in that gap and give you this

19 return.

20 So I think we have to identify the costs in

21 that -- and as you say, 4 percent is a big number,

22 but what is the cost of not knowing -- what are the

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1 costs of these gaps in knowledge and gaps in

2 practice?

3 DR. COURSIN: Pam?

4 DR. FLOOD: I was just going to add to that,

5 that in a way, it's fortuitous, even though it's

6 sort of horrible. But at least in the ICU, there's

7 a big pot of money. We're spending an enormous

8 amount of money in ICU, end of life, and hopefully

9 not quite end-of-life care. The concept that this

10 could be done more efficiently and better means

11 that there actually is money to be saved there.

12 DR. COURSIN: And again, I'm looking for how

13 do you garner the issues and get an advocacy group.

14 And the real people we're looking at who seek glory

15 that could make this happen is the political force.

16 And what does this group see as a way to pool the

17 data together and the conversations here and get

18 that kind of information out there.

19 Well, there seem to be a few comments.

20 We'll start here.

21 Rick?

22 DR. RIKER: Riker. I think one of the

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1 things, Steve, in response to your comment, as

2 clinicians, I would be interested in a study -- we

3 see this resource costs versus outcome benefit or

4 whatever. There are four quadrants. So I'd be

5 interested in a new approach if it got as good

6 results for less money or less resource

7 utilization, or if for similar costs, I got better

8 outcomes.

9 Those are the kinds of things we're looking

10 at to make decisions about what do we do with our

11 patients. If there's not a new drug that comes

12 down the pike that the pharmaceutical industry is

13 going to pay for, for the research within our own

14 societies, or our governments, or AHRQ, whatever we

15 use for pathway, we've got to look for those kind

16 of outcomes.

17 DR. COURSIN: David Brown?

18 DR. BROWN: I think one of the big

19 challenges for all of us is \$550 million a year is

20 spent in lobbying in this city on healthcare.

21 DR. SKROBIK: How much?

22 DR. BROWN: \$550 million is spent on

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1 lobbying in healthcare. Almost all of it is spent

2 to keep the system the same because there are so

3 many people making so much money inside the system.

4 So that very idea that Rick brings up, is that

5 generating the political will to make a change,

6 you're stepping on so many toes.

7 So I think, Doug, you're exactly right.

8 You've got to use political maneuvering, and you've

9 got to have a face to it. There's a group here

10 that our firm's a member of, C-TAC, Coalition for

11 the Transformation of Advanced Illness Care. Dave

12 Longnecker is their chief of strategy. It's

13 focused on better end-of-life care, and there may

14 be something for some of the critical care groups

15 to have a little larger role in that group. It's a

16 nonprofit spun out of AAMC.

17 DR. COURSIN: Dr. Shehabi?

18 DR. SHEHABI: The Australian Ministry of

19 Health and the Medical Research Council, which

20 provided a lot of funds for the ANZICS Clinical

21 Trial Network investigating an ICU. I've recently

22 looked into the return on its investment into the

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1 clinical trials by ANZICS clinical trial group, and
2 the biggest return was learning what not to do in
3 ICU.
4 The point that Yoanna made -- I think you,
5 Doug, made that point first, that a lot of what we
6 do in ICU came to us from outside ICU and wasn't
7 actually designed for ICU. So it's really
8 important to examine what is it that we're doing
9 and what is it that we need not to do because
10 that's where the real saving is.
11 DR. WARD: Thank you.
12 DR. TANG: Just for the record, I think it's
13 important that was noted before about health
14 economics being an important player and balancing
15 that conversation so that you can translate
16 appropriately clinical outcomes to what it means it
17 health economics, I think that's definitely an
18 arena.
19 The reason I brought up earlier about the
20 ideas of real-world databases and registries is not
21 to say that it is in any way going to replace or
22 even the supplementary, but it's offering more data

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1 points to consider when we're talking about
2 actually seeing how these patients are flowing
3 through, and if we're not capturing them, how we
4 can better capture them, and the idea of creating
5 that more as a baseline of how we look at things
6 rather than pointing at all of the concerns.
7 The idea is that we really want to make sure
8 we have as wide as data possible. And if we have
9 already these infrastructures that speak to
10 insurance with claims and we have EHR databases,
11 can we look at those as different avenues that are
12 less resource intensive to add to more of that data
13 information and system forum?
14 DR. COURSIN: Thank you. We're at the
15 little after 10 o'clock mark. I didn't want us to
16 fall behind. I wanted to thank Yoanna and John for
17 their expertise. I had told Denham I would do my
18 best to get this shy group going, and I appreciate
19 your coming through for us.
20 DR. WARD: We do try to have fairly generous
21 break times. A lot of the discussion takes place
22 not in the formal meeting setting but over a cup of

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1 coffee. So I hope we can continue these
2 discussions over the next half hour and then come
3 back at 10:30, where we will continue with the
4 panel discussions. Thank you, and thank you,
5 panel.
6 (Whereupon, at 10:02 a.m., a recess was
7 taken.)
8 DR. WARD: After that nice background
9 discussion of where we are and where are the gaps
10 both in evidence and methodology, I really wanted
11 to start back to the patient's perspective. I
12 think that's one of the pieces, when you talk about
13 patient centered, that can drive a lot of parts of
14 understanding what we need to do to fill the
15 evidence gaps and what the right methodology is.
16 There was a lot of great comment of incorporating
17 patients in clinical trials, particularly using
18 qualitative research methods to understand the
19 patient's perspective.
20 We've got two speakers and a panel before
21 lunch, and I would like to start out with Dave
22 Brown.

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1 Presentation - David Brown
2 DR. BROWN: Thank you, Denham.
3 We're going to be talking about patients and
4 families in the ICU, and our previous discussion
5 was on a population you're in now, which is going
6 to be one patient and one family, and I'm going to
7 tell you my story.
8 I'm an outlier. If you see me weaving and
9 bobbing a little bit up here, it's because my
10 critical illness neuropathy knocked off some of my
11 proprioceptive function, and so that I can keep my
12 feet on the ground, I move a little bit side to
13 side. It's especially bad if they turn the lights
14 out. It's an amazing process that we almost never
15 talk about. It's not so much what to do, but what
16 to avoid and side effects.
17 Cures. Diseases come with a lot of side
18 effects. You can see that I'm an old chair. I'm a
19 former chair. I led a lot. There's actually
20 faculty in the room here that I was blessed to work
21 alongside and others that I've been blessed to work
22 alongside nationally. But I now run a little firm.

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1 What we're going to do today is talk about
 2 patients, and more importantly families, from what
 3 I learned, and then I'm going to share with you
 4 some heartfelt lessons that I think I take away
 5 from this.

6 Now, my declaration of interest, I'm the CEO
 7 of a firm called Curadux. I wanted to call that
 8 from Doc and the Family, but a Japanese guy owned
 9 the domain name, and I couldn't buy it from him, so
 10 I Latinized the English care guide, and that's what
 11 Curadux is. I'm a board member of NeuroTherapia,
 12 which is a unique molecule, a cannabinoid 2
 13 compound that we've worked on for 15 years that
 14 just had IND approval, and we hope to get in
 15 phase 1 trials by June for Alzheimer's. It's a
 16 very unique drug.

17 I'm an academic medical insider. At the
 18 time of my illness, I was one of the directors of
 19 the American Board of Anesthesiology. I sat on the
 20 ACGME's executive committee. I ran the RRC for
 21 many years. My clinical background is pain
 22 medicine and anesthesiology. So that's who I am.

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1 Here is a graphical cartoon of where I was.
 2 I started out first in the Air Force; then went to
 3 Virginia Mason; then to Mayo, where I ran their
 4 quality program; and then to Iowa, where Frank
 5 Dexter and I worked together; then to MD Anderson
 6 Cancer Center; and then to Cleveland Clinic, which
 7 is where I had my most notable certificate, and
 8 that was my critical illness and multiorgan
 9 failure. Then I went on after that to do two years
 10 of graduate work at Loyola in Chicago in bioethics
 11 and health policy in preparation for what I'm doing
 12 now.

13 Now, I'm going to sit, and the star of this
 14 about 4-and-a-half-minute video is actually my
 15 wife.

16 (Video played and transcribed.)

17 "DR. BROWN: The story goes back 35 years.
 18 I was active duty military in the Air Force. We
 19 were on the southwest side of town, and we got
 20 gunshot and knife wounds, frequently transfusing
 21 many, many units of blood. At one of those points,
 22 it's theorized that I had a needle stick, and back

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1 then we didn't know the term hepatitis C.
 2 "The FDA approved a new treatment regimen
 3 that gave me a larger opportunity to be cured if I
 4 went through the chemotherapy.

5 "KAREN: The first day it was fine, and then
 6 looking at the number of pills he took every day
 7 was shocking, and they affected him emotionally,
 8 physically. He couldn't get up the stairs anymore
 9 without crawling. It was very, very difficult.

10 "DR. BROWN: Then as we got about 5 and a
 11 half months into the 7-month course, I developed
 12 sepsis and required admission to our surgical
 13 intensive care unit.

14 "KAREN: I remember the first night he was
 15 in the ICU. It was like being on Mars. They don't
 16 speak my language. The noises are very strange. I
 17 remember asking what am I supposed to do?

18 "DR. BROWN: Time [inaudible]. I spent
 19 3 and a half weeks unconscious, had a heart rate
 20 somewhere north of 140, and I [inaudible] had
 21 pancreatitis, and my liver took a vacation. Of
 22 course, there were concerns that I bled into my

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1 head. Then I had respiratory failure. I had more
 2 than 6 organ systems out, so that predicts somewhat
 3 around 100 percent mortality.

4 "My family had a couple different
 5 discussions about end-of-life care and whether to
 6 do not resuscitate or should [inaudible]. I found
 7 it very interesting in a very detached professional
 8 way to watch myself dying.

9 "KAREN: I remember just thinking, just tell
 10 me what are the odds here? The wonderful nurse
 11 asked if I wanted to lay down with him, and I
 12 thought it was the last time I'd ever lay next to
 13 him. My decisions were based on more than medical
 14 knowledge. It was based on the hopes I have, and
 15 the prayers I have, and the faith that I have,
 16 realizing I didn't know the outcome.

17 "DR. BROWN: Then, late on a Friday night in
 18 one heartbeat, I became myself. I became
 19 cognitively intact. I became myself just as fast
 20 as you can snap your fingers. The first phrase I
 21 typed out was, 'I've never been more alive.'
 22 People walked with my family. That was very

Page 113

1 important.

2 "KAREN: And your family is very important.

3 Every person is different with different

4 challenges. So I would say equip yourself before

5 you meet a circumstance that will require

6 tremendous fortitude and faith.

7 "DR. BROWN: Caring for the family, letting

8 them know that we're going to protect their loved

9 one, we're going to do our very best, was keenly

10 important. To know that the family of that

11 individual is a human being with God-given dignity

12 that that human being has [inaudible], sometimes a

13 patient will tell me what they're worried about,

14 and I can put a hand on their shoulder and say, 'A

15 year ago, I was where you were.

16 "There's really nothing so beneficial and

17 almost a sacred commitment that we have with our

18 patients, to respect them and try to relate their

19 pain. I always considered myself very empathetic,

20 and I thought I was, and I probably was. But this

21 illness has raised my degree of patient-focused

22 empathy to another level. If I followed the book

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1 to give me a little boost till morning. My

2 secretary sent a car for me, and I laid down in the

3 back until I got to the hospital. Then I was sent

4 to the emergency department even though I was on my

5 way to the ICU, because that's what we did at the

6 Cleveland Clinic. You couldn't be admitted

7 directly from any office to the ICU. Is that

8 patient centered, 6 hours in the ED?

9 This is a week later. We don't know quite

10 what's wrong with me yet. This was the day they

11 figured it out. I had vasopressors. My heart rate

12 was north of 140. My respiratory rate was about

13 40. And I also looked as if was developing a

14 viable proliferative disorder with a node biopsy

15 positive for a lymphoma. Oh, and by the way, my

16 EBV titer was greater than 5 million per cubic

17 millimeter, so I had developed from my

18 immunosuppressed state an EBV. We don't know if it

19 was just simple EBV sepsis or EBV hemophagocytic

20 syndrome. That was a weekend.

21 So overall, you've heard a little bit from

22 the video. I had hepatitis C for 35 years. I

Page 114

1 on algorithms, I'd probably be dead."

2 DR. BROWN: This was used by the Cleveland

3 Clinic in part of their empathy series. Just some

4 framing for you out of the patient experience. I'm

5 in my own ICU, so everybody in there worked for me

6 at the time. I have a daughter that's a doc, a son

7 that graduated from Georgetown Law. My wife's

8 really smart. I had all the advanced directives

9 done. Our money was in a trust. I had planned

10 ahead. Everything was planned ahead, a real

11 connected medical insider, and our family

12 struggled.

13 So I'll tell you a little more about me.

14 This is my hepatologist note the day I was

15 admitted. You see in the upper left, blood

16 pressure's 78 over 45 in his office in a

17 wheelchair, and that's the night before I knew I

18 was failing, so one of my buddies came over from an

19 outlying hospital near where I lived on the west

20 side of Cleveland.

21 Started an IV, hung the first bag of

22 lactate, and then I hung the next 2 bags of lactate

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1 picked it up in the military and had done pretty

2 well. And I thought, my family, probably I'll die

3 of heart disease before hep C will get me, so I

4 kind of avoided it because I'm genotype 1, which is

5 what most of us in the U.S. are, and the cure rate

6 was about 25 or 30 percent with the old chemo.

7 Well, the interferon, ribavirin, and a

8 protease inhibitor moved that up to about

9 80 percent. Let me tell you, if you ever get

10 offered interferon, don't take it.

11 (Laughter.)

12 DR. BROWN: Find another way. But I had the

13 DIC for 4 days. My platelets were about 18,000.

14 That's why they gave me contrast through the

15 portable CT to see if I'd bled in my head, and they

16 knocked my kidneys off at that time with

17 hypertension. I was delusional through much of

18 this. I can tell you, for part of the time, I was

19 in the ICU, delusional unconscious, for 3 and a

20 half weeks. I was in a European ambassador's place

21 with China plates on the wall. I've never been

22 able to find those China plates in that ICU room.

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1 Also, I will speak to you in a moment about
2 a piece I wrote for Anesthesiology in the Mind to
3 Mind section, and I'll tell more of that story.
4 But the most suffering I had in the ICU was every
5 time an alarm went off in my room, it signified to
6 me and my delusion that one more patient was
7 entering an unethical research trial I was leading.
8 It's not an exciting run. That actually caused
9 more suffering than any of the physical things I
10 had.
11 Intubated and ventilated, I had ARDS. I had
12 a 50-pound weight loss, and that will become
13 important in just a moment. My marrow wasn't
14 working. My albumin was 1. I had what looked like
15 a term belly that had to have ascites drained.
16 Having that much ascites with ADRS and a 50-pound
17 weight loss is an exciting run.
18 So here's what I think I learned out of
19 this. When you lose 50 pounds out of your core,
20 every time these wonderful nurses turned me to
21 clean me, because I was incontinent of anything, my
22 shoulders and my hips subluxed. And I came up to

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1 my critical care docs and nurses afterwards and I
2 said, "Do you guys know about that?" They said,
3 "No. Nobody ever lives that is in that setting."
4 So that was painful. In this morning's
5 discussion, I am betting that it looked like that
6 was agitation when it was actually really severe
7 pain on shoulders and hips. I had an 8 o. tube cut
8 at 22 centimeters, and it's like breathing through
9 too small a straw. If you think of an
10 anesthesiologist intubated with ARDS, that's a bad
11 setting because you understand it.
12 Then after the nurses and respiratory
13 therapists come and suck your tube out, they suck
14 your FRC right out into that tube. Now, you have
15 to cough back up your FRC, but you don't have the
16 core muscle strength to cough, so you feel like
17 you're suffocating, and it hurts, and you're short
18 of breath.
19 Nasojejunal tubes, they hurt. They're sewn
20 in so they don't pull out. Fluid overload between
21 dialysis. When the young nephrology fellow comes
22 by and says, "Oh, your numbers look pretty good

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1 today; I don't think we'll dialyze you," "I just
2 wonder why I'm short of breath?" They were going
3 to treat my numbers rather than treat the patient.
4 I can tell you waking up -- I'm still in the
5 ICU 7 years ago today. I was extubated 3 days ago.
6 I'm in the ICU. I wake up in March Madness.
7 There's not much better time to wake up than
8 watching basketball from a warm bed in dialysis
9 where they take 2 or 2 and a half liters off of
10 you. You breathe better. They feed your graham
11 crackers and orange juice and put warm blankets
12 around you, and they're very kind individuals in
13 dialysis.
14 Three weeks into my ICU admission, 3 and a
15 half weeks about, I have a dream. I don't think
16 it's a delusion because I'm an old pilot, and I
17 flew right up until my chemotherapy. I flew the
18 airplane you see in the lower right all over the
19 country. I rarely flew commercially. I flew
20 myself. But I'd had a dream over the previous
21 decade, not flying, but they're in trouble.
22 I walk up, take the right seat, pull back on

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1 the stick, avoid the high line wires, squeak the
2 wheels onto the runway. I have this dream, and as
3 you can see there, it was actually 2:40 when my
4 eyes opened up, and I'd been out of it for 3-plus
5 weeks. I became myself. I became this guy, very
6 weak, but cognitively I thought I was intact.
7 Here's what was going on, on that day. I
8 had no sedation at the time I woke up. I was not
9 on sedation at the time I woke up. But during my
10 ICU admit, they used propofol or dex. They used
11 some benzos early on. And that comment I made in
12 the video, I remembered to this day, I woke up. My
13 nurse was a former army medic from Iraq war and
14 went to nursing school, barb wire, weightlifter;
15 couldn't scare him at all.
16 Jose came into my room. His eyes got about
17 this big, and I got the alphabet board out, and my
18 little old tremulous fingers typed out, "I've never
19 been more alive. Call my wife." And then it
20 really got exciting because I became -- I talked
21 about lobbyists here in DC. I became the principal
22 lobbyist at the Cleveland Clinic for extubation of

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1 one single individual.
 2 (Laughter.)
 3 DR. BROWN: I had had such an up and down
 4 course, they didn't quite trust me. "I think we'll
 5 just -- we don't want to do it. Let's let him
 6 prove himself."
 7 I wrote this article. It's in the October
 8 13 issue of Anesthesiology, Fantastic Delusions,
 9 Futility, and a Family's Love. My wife is an
 10 English major in her first life, and she tells me,
 11 I wrote in the genre of stream of consciousness,
 12 and it goes through all the kinds of things I was
 13 thinking. It tells a little bit of the story.
 14 My son, who is an attorney, his sister, his
 15 older sister, who's a physician, told him the first
 16 night I was admitted, bad things happen in
 17 hospitals at night. He never left my room at
 18 night. He caught 3 drug swaps that probably would
 19 have hurt me over those 3 and a half weeks. But he
 20 asks me, "What do you want us to do?" And I said,
 21 "Let's do the next thing."
 22 When they could rouse me out of the

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1 delusions, I had mostly a detached clinical look at
 2 my condition. My wife went to the family consult
 3 room on two occasions where they talked about end
 4 of life. My critical care team thought I was
 5 suffering too much, and certainly it's gone on, and
 6 on, and on. Should we just provide comfort care?
 7 And my wife actually said, "Let's give him a couple
 8 more days. He's always been a fighter." Well, I'm
 9 very thankful that she did.
 10 This is the story of -- that's not a
 11 delusion. That's my recurring dream of saving the
 12 aircraft. I have to tell you, during my illness,
 13 my auditory function was maintained pretty well. I
 14 have lots of intermittent memories of hearing even
 15 though my face was masked with unconsciousness or
 16 delusions. We know in anesthesia we always say
 17 don't talk about patients even when they're
 18 anesthetized because auditory function often is
 19 maintained. Well, I can tell you, even in critical
 20 ill patients, auditory function is maintained even
 21 though I couldn't speak into the world.
 22 Being extubated, I still can feel the

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1 emotion of being extubated. I was an old hurdler
 2 in college, and I actually used to be pretty fast
 3 before the neuropathy. But I still remember
 4 occasionally they'd make me run 400 meters because
 5 they needed somebody for the relay, and I had
 6 fast-twitch muscles, I didn't have slow-twitch
 7 muscles, and I needed a shorter distance. And I'd
 8 finish a 400 meter and just be gasping, and then it
 9 felt so good to stop. Being extubated is the same
 10 thing. It feels so good because they pull that
 11 tube out.
 12 Hippocrates had it right. I could sit down
 13 right now. I won't, but I could. It's more
 14 important to know what sort of person has the
 15 disease than to know what sort of disease the
 16 person has. If I have a criticism of modern
 17 healthcare -- and I have many as a patient. I get
 18 care at the VA hospital. I get care at Mayo. I
 19 get care at Cleveland Clinic. I get care at
 20 Marshfield Clinic. So I sample lots of different
 21 centers.
 22 If you look at me in my medical record, I

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1 look like a walking dead man because they keep
 2 every comorbidity in there so they can up-code when
 3 the reimbursement structure allows them to. So
 4 I've had to create my own personal health story to
 5 share with physicians when I have to meet with them
 6 so that they find out I still get 17,000 steps a
 7 day, and my dog and I go hiking quite a bit, and I
 8 actually am pretty active.
 9 Carl Hug, many of you know Carl. Carl sent
 10 me an email. This happened in March of '12 for
 11 perspective. This was in October of '12, we were
 12 getting ready to go to the American board. And you
 13 can see what Carl said. He said, "You screwed up
 14 my ICU lectures." He taught ethics down at Emory.
 15 He said, "I always thought after 7 days, we ought
 16 to just provide comfort measure, and you taught me
 17 something. I look forward to seeing you."
 18 Roger Williams was a PhD biochemist at the
 19 University of Texas, and I think he hits it pretty
 20 right when you're thinking about me as the patient.
 21 Medicines for real people, statistical humans, are
 22 of little interest. What happens is we let our

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1 policy discussions get too close to individuals'
2 bedsides.
3 I'm going to tell you now about my family.
4 I have 4400 pages of ICU records from the Cleveland
5 Clinic. A little secret, I'm in my own ICU. I'm
6 everybody's boss. When I was most critically ill,
7 10 days my vital signs were identical in the
8 record. Do you suppose somebody was cutting and
9 pasting? Do you suppose?
10 (Laughter.)
11 DR. BROWN: I can't validate it. My
12 daughter, she and I have always been fairly close.
13 I used to coach her in long jumping. She's a
14 pediatrician and did special needs pediatrics at
15 MCW. Here's what she posted. She's the Facebook
16 generation. "Nurses are angels sent from God.
17 Certain doctors can be angels when they listen to
18 you and actually come examine your family member
19 rather than making decisions from outside the
20 room." If I reflect on what's most missing in
21 intensive care units, it's time; what's missing in
22 all of medicine, but intensive care, it gets

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1 amplified because of the critical nature of it.
2 Text message. My children saved all their
3 text messages. I have 20 hours of recordings at my
4 bedside that my son used his iPhone. He worked on
5 Capitol Hill for six years, so he's all attuned to
6 that kind of stuff. My son, Cody, daughter, Sarah,
7 they're going back and forth. "He's going for a
8 pancreas ultrasound. Is this all pancreatitis?
9 No."
10 Ten days. "It doesn't look like Pops has
11 much more time left; supraclavicular node." She
12 concludes, "I think he knows his lymphoma won't be
13 treatable. I'm trying to do what dad taught me to
14 do for a patient rather than do to a patient." And
15 this old father doesn't even remember that I taught
16 her that, but I take credit where credit's due.
17 Now, my daughter is a pediatrician. What do
18 pediatricians do? They worry about kids. I had
19 two grandsons at that time. I now have four all
20 out of this family. She wanted to bring the boys
21 to see me before I died. So that you can see the
22 punch line is she never been happier for following

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1 her gut and kind of forcing the children into my
2 room to say goodbye.
3 The point I'd make here in this group is if
4 a family member has an advanced illness, everybody
5 in the family has an advanced illness. The ICUs
6 often are exclusionary of -- because we're busy. I
7 mean, we're that way. But it really was important
8 to her.
9 My daughter also finally said, "Can we get
10 one doc to be the quarterback, at least in
11 communicating? Because everybody's telling us
12 slightly" -- it's that telephone game. You whisper
13 to one person, and what comes back around. Family
14 really wants to have a single individual to share
15 the message.
16 Later in the course, I'm still uncertain if
17 I'm going to live at this point. I'm really sick,
18 and my daughter says, "I can list by name the ones
19 who've made our stay comfortable." So if you think
20 families don't know what it means to them, they do
21 know. It's a very personal journey.
22 Agitation, sleep, and PADIS guidelines, my

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1 son slept in the recliner in the corner of my IC
2 room for almost 3 and a half weeks. He says from
3 my nonmedical perch, he needs some peace and quiet.
4 Every time they leave him alone, his numbers get
5 better. I can tell you, after I recovered, I was
6 back at work in 60 days. I'd actually showed up
7 the first 3 weeks after my illness.
8 I drove to the Dairy Queen 2 weeks after I
9 was discharged. That was the test, 2 miles from
10 our house. I was on weight gain diet because the
11 dietitian told me eat a thousand extra calories a
12 day. And I can tell you, if you ever get in the
13 position I was in, I was on an apple fritter times
14 2 daily diet, a thousand extra calories. The only
15 hard part of that diet is stopping.
16 (Laughter.)
17 DR. BROWN: Even now when I walk by the
18 bakery and I see a fritter lying unattended, I
19 struggle.
20 They would text ventilator settings back and
21 forth. My daughter had to go home to her practice
22 and her family. This was on the day that I

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1 awakened. He says, "Dad's communicating; told the
2 ICU doc, 'I won't fail. Extubate me.'" And I have
3 to tell you, I had the little minimal strength to
4 extubate myself. I refused to extubate myself
5 because it was my unit and I wanted to set an
6 example.
7 (Laughter.)
8 DR. BROWN: I think that's crazy, but that
9 was inside thinking. Since this is an ICU sedation
10 conference, my wife would send emails blast every
11 evening. She's an introvert actually. So she
12 would go home and sleep. My son would stay.
13 Daughter would go. She'd send an email blast, and
14 on this one on the 24th, the night I woke up it
15 says, "I think he bothered his doctors so much,
16 they put him on sedation for their sake, not for
17 me." And I would bet you she had that parsed just
18 about right.
19 So let me tell you now lessons learned, and
20 I'll get off the stage. Algorithms aren't always
21 expert. Physician judgment, two physicians in
22 particular probably saved my life. Many

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1 contributed to saving it, but two in particular
2 were not going to give up. And it's not that they
3 beat me, but they saw further ahead than some of
4 the busy docs did during this.
5 I've told you before, utilitarianism, we all
6 let it creep next to the bedside. We all let it
7 creep next to the bedside. Everybody needs an
8 advocate. Often you need more than one advocate.
9 It may be your nurse that night, it may be your
10 family member, it may be a physician the next
11 night, but you all need an advocate.
12 These thoughts are what I came up with my
13 first week home after coming. "Care for me as a
14 unique human being. Look me in the eye." And I
15 say that mainly, the 7 months that I went through
16 chemo with interferon and my hemoglobin was about 6
17 and a half or 7. My white count was often down in
18 the 200 range. So I was getting intermittent
19 Neupogen and erythropoietin.
20 The most meaningful experience I had was one
21 of the laboratory techs that drew my blood weekly.
22 She'd gone through an osteogenic sarcoma when she

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1 was 18. She was now about 28, and Gina and I,
2 she'd always take me. She wouldn't let anybody
3 else take me, and that was probably one of the most
4 meaningful experiences in that illness, was having
5 that personal connection.
6 "Don't harm me if you can help it. Don't
7 let pain overwhelm me. Provide me with cutting
8 edge care yet appropriate for me, my values and
9 goals, and my finances." We almost never talk
10 about that, but these were my thoughts the week
11 after I got home at night. And I logged it in just
12 so I wouldn't forget and start to make it sound
13 better than it was.
14 This isn't my slide. This is out of the
15 Harvard Business Review. In December '14,
16 Drs. Mate and Compton-Phillips, Dr. Mate lost a
17 mother at MGH, falling through the cracks after a
18 hip fracture, I believe was what the setting was.
19 The problem in our healthcare system, it's
20 fragmented. Somebody said earlier, I think Denham
21 did, that we sometimes work in silos. And for
22 those who haven't heard me share the story, one of

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1 my mates used to say, "Those are cylindrical
2 centers of excellence, and we all our cylindrical
3 of excellence is the dominant one."
4 Advanced illness forces families and
5 individuals to become their own care managers. Our
6 blog this week out of Curadux is actually on
7 healthcare coaching. The paper, Dr. Beamer is a
8 researcher at Mayo and just published a paper on
9 Healthcare Coaching at the Mayo Clinic.
10 I practiced there for seven years. They
11 used to pride themselves on navigating anybody
12 through the system. There were general internists
13 that were the coordinating docs. If Mayo is
14 starting to coach individuals to be their own care
15 managers, the system is just about tipped.
16 Powerful incentives, mainly revenue,
17 top-line revenue dominates the unique values and
18 goals and individuals. Futility and suffering
19 rapidly increase. I can tell you that suffering is
20 real in an ICU, but it's not all physical
21 suffering. There's a lot of emotional suffering at
22 that. But this is not my words. This is Mate and

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1 Compton-Phillips.
2 So with that, I thank you all for listening.
3 And at this point, my illness was a gift, and I see
4 it in that fashion.
5 (Applause.)
6 DR. WARD: David, we'll hold questions till
7 we do the panels.
8 Now, I think we've had the patient
9 perspective, and now I think Dale will talk about
10 how do we measure that patient perspective.
11 Anecdotally is important, stories are important,
12 but the broader perspective of multiple stories are
13 also important.
14 Dale?
15 Presentation - Dale Needham
16 DR. NEEDHAM: A very hard act to follow, so
17 I'll try my best. This is a case study not
18 directly applicable to sedation, but hopefully
19 there's some generalizable concepts. The work that
20 I'm going to talk about was funded by an NHLBI R24
21 grant. That's a grant mechanism to create research
22 infrastructure rather than to do original research.

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1 With that grant, we're looking at creating
2 outcome measures that should be used in evaluating
3 the post-discharge outcomes of ICU survivors. We
4 also were interested in how to retain these
5 survivors in longitudinal research, so
6 state-of-the-art cohort retention, and then
7 statistical methods because these data are hard and
8 complex, and Elizabeth Colantuoni will talk about
9 some of that separately.
10 So what I'm going to focus on is one aspect
11 of Aim 1, and I'm going to try to go through these
12 points. I'm going to start with a scoping review
13 to tell us the size of the nature of the problem
14 that we're trying to address.
15 Within critical care, as you can see from
16 the figure, there's a growing number of studies
17 evaluating survivorship experience. You see the
18 figure with the graphs going up. So we're very
19 much interested in this, but out of the 425 papers
20 that have been published on this topic, we're all
21 measuring different outcomes.
22 Quality of life seems to be a pretty popular

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1 outcome; 65 percent of the 425 studies evaluated
2 that, but only 6 percent of studies actually
3 evaluated physical functioning through an in-person
4 assessment of patients. So large variability.
5 There's sort of no standardization in how we think
6 about the survivorship experience.
7 This makes it very challenging for us to
8 have comparable and consistent comparisons and
9 representation of survivorship experience, and I
10 think it really reflects that we don't know what's
11 important, what our patient important outcomes.
12 We're all sort of just measuring different things,
13 but are there a core set of minimum things that we
14 should always be measuring if we want to understand
15 survivorship? So that's a key question.
16 The next question is how the heck are we
17 going to measure these outcomes? Across 425
18 papers, there were 250 different measurement
19 instruments. Within post traumatic stress
20 disorder, for example, there are 70 papers that
21 evaluated it. They use a whole host of different
22 measures. This is like if we're going to measure

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1 temperature and somebody's going to use Celsius and
2 somebody's going to use Fahrenheit and 10 other
3 instruments with no crosswalks between them. We
4 really can't bring the field forward if we're going
5 to continue this.
6 Also, there's a big chance that important
7 outcomes will simply get missed when we don't have
8 a consistent minimum approach. It's difficult to
9 compare results and to meta-analyze. These are our
10 big issues, so the scoping review helps us
11 understand the nature of this problem.
12 Now I'm going to talk about one approach to
13 addressing these core sets and a number of
14 subpoints, so a little bit of jargon. A core
15 outcome -- and this isn't my idea. This is
16 something that's happening across all fields of
17 healthcare that lots of people are interested in
18 what are called core outcome sets. A core outcome
19 is a concept, health-related condition, or aspect
20 of health that always must be measured within a
21 field, so it's what you should measure.
22 A core outcome measures how we're going to

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1 measure it, so how should we measure it. So the
2 what and the how, those are two different questions
3 but related. Then the core outcome sets that
4 minimum set of outcomes that all of us agree to
5 measure as a minimum within a specific field of
6 study, and a core outcome measurement sets the
7 minimum collection of measurement instruments.
8 Importantly, this doesn't restrict
9 investigators from measuring a hundred other things
10 if you want. This is supposed to be a small,
11 feasible minimum set that we all agree to do.
12 Within critical care, this work that we did in our
13 grant is not telling researchers that everybody has
14 to measure patient outcomes after the ICU. Lots of
15 people got sort of upset about this. This is just
16 saying if you choose to do this, if this is
17 relevant to you, would you consider measuring this
18 minimum set of core outcomes with these measurement
19 instruments? That's sort of where this is trying
20 to address things.
21 To do this, we're going to need to
22 understand a few things. We're going to need to

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1 understand, first of all, what are patient
2 important outcomes, how we might measure them, and
3 how we might make decisions. I want people in
4 critical care to stop saying we don't understand
5 patient important outcomes. I'm going to present
6 you a series of arguments to tell you that I think
7 we do.
8 I'm going to go through each of these points
9 and start with a qualitative research study that
10 our group did sampling patients from across the
11 U.S. We wanted to understand this experience of
12 acute respiratory failure survivorship. We had
13 48 survivors recruited from 35 hospitals. They're
14 followed up around 9 months after follow-up,
15 starting with open-ended questions, and then
16 probing after the open-ended questions using the
17 PROMIS framework, that I'll talk about a little bit
18 later, to make sure that nothing seemed to have
19 been overlooked.
20 These are some of the experiences that
21 survivors reported to us in their qualitative work.
22 A 34-year-old man a year later said, "I have the

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1 tendency to forget a little bit more. My brain's a
2 little bit more scattered," so thinking about
3 cognition; a 67-year-old male at 6 months talking
4 about mood, "I'm a useless person and basically a
5 parasite. I have this emptiness inside. You
6 wonder why I should even wake up," then a 63-year-
7 old woman at 6 months -- or 9 months, still having
8 difficulty with swallowing and talking about how
9 she needs to relearn how to swallow her food so she
10 didn't choke. This is just a little bit of
11 examples.
12 The key findings to synthesize in a slide is
13 that patients' experiences seem to fall within
14 these categories, having physical impairments,
15 problems with mobility, pulmonary symptoms,
16 stamina, having mental health symptoms that we
17 thought fell into depression, anxiety, and concerns
18 around getting sick again; and then social health,
19 which really hasn't been looked at so much in the
20 empirical literature, but changes in employment,
21 and changes in being able to do your valued
22 activities.

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1 That's the first bit. I'm going to go
2 through each of the bullet points. The paper that
3 I keep showing at the bottom of this slide
4 synthesizes everything that I've just said in a
5 single paper for people that are interested and
6 don't want to look up all the individual papers.
7 It's free, full text.
8 Our qualitative work was just a one person's
9 study. We then did a systematic review of all the
10 published qualitative studies that had been done.
11 There are 21 studies at this time, and the key
12 findings from these studies looked at to synthesize
13 for physical function, mental health, and social
14 health; and then also, some patients, as we've just
15 heard, having a positive experience after their
16 critical illness, describing gratitude, changes in
17 outlook, this being a gift having been critically
18 ill. So again, something that's not captured so
19 much in empirical research.
20 To triangulate our one qualitative work with
21 everybody else's qualitative work, there seemed to
22 be consistent signals around patients having

<p style="text-align: right;">Page 141</p> <p>1 impairment across a lot of different domains, that 2 some survivors had a positive impact, and that 3 social health was important such as return to work 4 but not often captured in quantitative studies. 5 Then we want to take a different angle to 6 understand patient important experiences. We 7 wanted to understand these measurement instruments 8 that we commonly use, are they capturing what 9 patients think are important experiences. Here we 10 had a unique opportunity. We'd done that 11 qualitative study, and those same ARDS survivors 12 happened in a separate study to have had standard 13 patient-reported outcome measurement instruments 14 performed. 15 What we did is we independently looked at 16 these qualitative findings and tried to 17 characterize what some of the themes were from 18 those, and then compared these patient-reported 19 outcomes in those with and without symptoms that 20 were self-described in the qualitative research. 21 Patients may have described something that 22 sounded like mobility impairment when two</p>	<p style="text-align: right;">Page 143</p> <p>1 objective performance-based measures of cognition. 2 Common measures that are used and actually 3 happened to be part of the core outcome measurement 4 set seemed to reflect patients' experiences of 5 mobility, anxiety, depression, and PTSD, but when 6 patients are reporting cognition, they're reporting 7 something different than what we pick up with 8 objective cognitive testing. 9 So I think we need to think very carefully 10 about that. Patients may have objective problems 11 on cognitive testing, but not actually have any 12 insight into that, and vice versa. 13 Now we're going to move and think about what 14 clinicians perceive. Here we have two independent 15 Delphi consensus projects. These were sort of test 16 runs for our big Delphi at the end. Here we took 17 an international audience in the United States. We 18 had a hundred clinicians that responded to a poll, 19 and 44 of them were able to come to an in-person 20 meeting for a second round of voting. And after we 21 finished that, this exact same Delphi project was 22 completed in Australia, mainly with PTs, but the</p>
<p style="text-align: right;">Page 142</p> <p>1 independent people looked at the qualitative 2 research. And we said for example, those that that 3 qualitatively described a mobility impairment, how 4 did their objective scores or their 5 patient-reported scores look differently? We did 6 the same with mental health and cognition. 7 For example, those patients that endorsed 8 having problems with mobility had much worse scores 9 when it came to two different measures of physical 10 functioning, the SF-36 physical component Score, 11 the EQ-5D mobility score. Those seemed to capture 12 the patient's experience. 13 Again, patients that qualitatively described 14 what independent people thought were anxiety or 15 depressive symptoms also had worse scores on 16 objective measures, HADS anxiety score, HADS 17 depression score, and ISR score for PTSD. So those 18 measurement instruments, again, seemed to have 19 captured the patient experience. But then when it 20 came to cognition, interestingly, patients 21 endorsing memory impairment compared to those who 22 didn't had virtually identical median scores across</p>	<p style="text-align: right;">Page 144</p> <p>1 same project, a completely different audience, at a 2 different time, but done in the same way, so we 3 could look at comparisons between two sites. 4 What we have offered up to these clinicians 5 were what we could think of as 19 different 6 domains. We've spent a lot of time thinking about 7 what are going to be outcome domains that might be 8 relevant for the patient experience during ICU 9 survivorship, and we used lots of different ways to 10 populate those 19 domains. 11 We used this NIH-PROMIS framework, which is 12 a comprehensive measurement framework for 13 patient-reported outcomes. It's a whole system 14 that the NIH has had millions and millions of 15 dollars into. You can see some of the domains that 16 they talk about there and then here. So we used 17 that to populate these 19 domains. 18 We also used the SCCM's post-intensive care 19 syndrome framework to, again, get more things for 20 those domains that clinicians voted on, and then we 21 used the WHO's ICF. So we had lots of different 22 ways that we triangulated to get 19 different</p>

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1 domains to ask about.

2 This compares the American-based Delphi work

3 with the Australian based. Importantly, there were

4 signals across two different continents, two

5 different populations, that these clinicians'

6 perceptions were that research studies should

7 always be measuring survival, physical function,

8 cognition, and health-related quality of life. We

9 ask patients in a whole bunch of different ways.

10 We now ask clinicians in a whole bunch of different

11 ways to figure out these core outcomes.

12 Then finally, I'm going to talk to you about

13 a survey that we did. We had 279 respondents. We

14 had about 80 survivors from across the United

15 States of ARDS and acute respiratory failure. We

16 had 80 family members and 55 pairs of patients and

17 families from across the U.S., and then we had 121

18 clinical researchers in this field from around the

19 world, predominantly from Europe, some from North

20 America, and Australia.

21 We all asked them the same question. We

22 gave them those exact same 19 domains, and we asked

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1 them, should these be measured as a minimum

2 measurement in every single ICU survivorship study?

3 Interestingly, the patients and family members

4 thought 18 of the 19 outcomes are really important

5 and should always be measured, so these have a lot

6 of face validity with them.

7 Of course the researchers recognized that

8 that probably wasn't feasible in terms of response

9 burden, and universally researchers, except for

10 survival, thought all of the outcomes were a little

11 less important than patients and families. But if

12 we triangulate and say what did they both agree on,

13 they both agreed on physical function, cognition,

14 mental health, and return to work or prior valued

15 activities.

16 So this is a whole program of research with

17 lots of different lenses to figure out what seemed

18 to be important outcomes.

19 To triangulate across every single study

20 that's been done, then, over several years, it

21 seems like important outcomes are survival,

22 physical function, cognition, mental health, return

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1 to work, and quality of life, across a whole series

2 of different kinds of studies and different

3 perspectives.

4 So we've maybe got some thoughts around

5 that, but we're also going to need to think how are

6 we going to measure these if we're doing

7 quantitative, empirical research? We actually did

8 another systematic review, and we found that there

9 are only 20 studies ever published in critical care

10 that looked at the measurement of any instrument

11 for ICU survivors.

12 There's a dearth of data, and most of the

13 studies using COSMIN reporting weren't high-quality

14 studies or high-quality reporting. That spurned us

15 because we had this grant from the NIH that allowed

16 us to do at least a number of other psychometric

17 studies, really aimed to help populate and provide

18 data for the upcoming Delphi across a number of

19 mental health fields and physical fields. We at

20 least gave some more data to inform the field, and

21 probably maybe almost doubled the number of studies

22 that had been published ever before.

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1 All of that's leading up to an international

2 Delphi consensus process. All of that is just the

3 prelude for the main thing. For people that don't

4 know what this Delphi process is, it's a way of

5 achieving consensus among experts when there is no

6 empirical data or inadequate empirical data. We're

7 just trying to get expert opinions and expert

8 consensus.

9 To do this, we have to have a panel of

10 informed experts, which we strongly believe needed

11 to be patients and family members, as I'll talk

12 about. Everybody in the panel needs to remain

13 anonymous. The panel members didn't know who else

14 was on the panel because we don't want one person

15 to influence another person. What makes that

16 different than maybe this meeting is the loudest

17 voice or the most influential person has the same

18 say in a Delphi as everybody else. We feed back

19 iteratively results of the Delphi after rounds, and

20 people can reconsider their results if they want,

21 but it's all anonymized, and then we have an a

22 priori criteria for what consensus is.

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1 What this figure shows is, first of all,
2 who's going to be on this panel. We used a lot of
3 different things to figure out who might be on the
4 panel. The way we finalized it is about half of
5 the panel -- there is I think 77 members -- half of
6 them were clinical researchers who were our target
7 audience, but a quarter of them were patients and
8 family members. A quarter of them were clinicians,
9 and then a few were U.S. funding bodies.

10 We defined consensus such that one of those
11 minority groups, patients and families or
12 clinicians, could totally veto us reaching
13 consensus. Even a portion of those family members
14 thought that we're out to lunch, that we could not
15 reach consensus. So they were about a quarter each
16 and strongly empowered.

17 Because we used the InFACT umbrella
18 organization, we had an official representative
19 from every InFACT member group around the world.
20 That means that the Asian critical care trials
21 group, the African group, the Latin American group,
22 the Greek group, whatever; every single

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1 organization provided a representative to give us
2 some international coverage in terms of clinical
3 researchers.

4 We also recognized that not everybody's part
5 of a clinical trials group, so we also had some key
6 leaders in outcomes research, and we randomly
7 sampled corresponding authors from that database
8 from the scoping review. We had federal U.S.
9 funding bodies. And then we had patients and
10 caregivers from Canada, Australia, the United
11 States, and the UK.

12 We also had official representatives of
13 critical care nursing, critical care medicine, and
14 critical care PT from the same four continents. In
15 the U.S., we also had international critical care
16 groups, an official representative from the SCCM,
17 CHEST, ATS, et cetera.

18 Those were who were part of this Delphi
19 panel. We then presented to them outcomes. I gave
20 all this stuff, but then we went to the panel with
21 all that information I just presented and said,
22 okay, here are 19 different outcomes. Are there

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1 any missing?

2 So they suggested 8 others, but as it turned
3 out, none of those 8 others made it into the
4 consensus. And we asked them to vote using all the
5 data that I've just presented to you on what they
6 thought were the core minimum set of outcomes that
7 should always be measured, and they voted without
8 thinking about any measurement properties of an
9 instrument.

10 There might've been an outcome that had no
11 instrument because the focus was what are the
12 important outcomes? There may not be an
13 instrument; there may not be a valid month. Let's
14 just talk about what's important as an instrument.
15 Then, there are 2 rounds of Delphi for that around
16 core outcomes, and we're so fortunate to have 97
17 and 99 percent response rates across the 2 rounds
18 for the core outcomes, even with patients and
19 caregivers.

20 We went on and did three more Delphi rounds
21 to look at the measurement instruments, and what we
22 did there was we presented to them 38 measurement

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1 instruments. The panel then suggested, well,
2 there's 37 additional ones that they thought we
3 should think about, so they got put into the mix
4 for voting.

5 Every single one of those measurement
6 instruments were summarized in a standardized way
7 that we hoped were understandable to patients and
8 caregivers as well. They often had videos showing
9 how you do a 6-minute walk test, how long it takes,
10 what's involved, what's the cost, and what are the
11 psychometrics of the instrument.

12 Here for these 3 rounds of voting, we asked
13 them to specifically look at feasibility, cost,
14 measurement instrument, measurement properties, et
15 cetera, and we had 91 to 97 percent response rates
16 across the 3 rounds there.

17 How did this all turn out after this 5 years
18 of work? The Delphi panel agreed on these
19 8 outcomes as outcomes that should be measured in
20 every single critical care survivorship study:
21 survivor; health-related survival; health-related
22 quality of life; mental health; pain; pulmonary

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1 function; muscle and/or nerve function; physical
2 function; and cognition.
3 How do we measure these? That was the last
4 3 rounds of the Delphi. For survival, we didn't
5 ask groups; we just suggested that you measure a
6 date and a location of death rather than dead or
7 alive at 90 days. No; you measure the exact date
8 of death so you could do survival analysis if you
9 want.
10 Health-related quality of life, they agreed
11 on the EQ-5D measurement, which is small and easy.
12 For those that want more detail, they agreed on the
13 SF-36. They reached consensus; two different
14 measures for mental health, hospital anxiety and
15 depression scale, and impact of events scale
16 revised that specifically measures PTSD.
17 For pain, their consensus was don't have a
18 new pain instrument; use the EQ-5D pain measure.
19 On the bottom row, they reached consensus that
20 there is no feasible way to measure pulmonary
21 function. They didn't think surveys were
22 appropriate, and they didn't think that we could

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1 mandate spirometry for instance so that every study
2 had to include spirometry. We all know that that
3 really isn't so feasible. So the consensus was
4 there is no appropriate way to measure it.
5 For physical function and muscle or nerve
6 function, I read every single comment from every
7 single participant, and there's this big tension
8 between people wanting to do performance-based
9 measures. So you have to have the patient in
10 person, and you measure their strength physically,
11 and you have them do a walk test. People thought
12 that was the best way to do it but felt that it
13 wasn't going to be feasible, and we shouldn't make
14 that a mandatory minimum measurement.
15 So there was no consensus, but if people are
16 able to do in-person testing, the greatest
17 consensus around standard manual muscle strength
18 testing, grip strength testing, and the 6-minute
19 walk test, but the group didn't feel that those
20 should be made mandatory because they wouldn't be
21 feasible in large-scale studies.
22 Then for cognition, there is data showing

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1 that in our population of acute respiratory failure
2 survivors, the mini mental status is very poor
3 measurement characteristics, so there's no
4 consensus reached. The greatest interest was in
5 the instrument called the Montreal Cognitive
6 Assessment scale, which has had very little
7 valuation and didn't reach consensus because
8 there's not a lot of data. There's a little bit of
9 preliminary data that's come out that shows us that
10 it may have some challenges.
11 To put this in an easy to understand way,
12 the Delphi panel agreed on measuring using these
13 three instruments: EQ-5D, HADS, and ISR. This
14 would be 42 questions, take 12 minutes in ICU
15 survivors, and cost about a \$1.50 per assessment.
16 If people want to add on cognition, which we didn't
17 reach consensus, it could add the MoCA BLIND, take
18 a little bit longer, go on to deep dive and quality
19 of life that could add in the SF-36, which would
20 increase the cost, and the time, and the questions.
21 If they want the Cadillac version, then they could
22 do all of those at a cost of around \$3 and about 26

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1 minutes of time. All can be done by phone.
2 It can be done in 15 different languages.
3 All of these instruments happen to be available in
4 15 different languages. There are lots of other
5 research agenda that I won't get into for the sake
6 of time, but there's lots of other things. We
7 recognize this as a very early start. There's a
8 whole years and years of research to make things
9 better.
10 We also are actively seeking input from
11 research participants, once they've gone through
12 the core outcomes set, what did they think of the
13 experience, and the same from the research staff.
14 You just administered this small battery; how do
15 you think it went?
16 This is the article that I talked about, the
17 full-text article. We've got lots of information
18 at our website if you're actually interested in
19 this kind of research. And importantly, that
20 website, if you're interested in measurement, this
21 website has lots and lots of different measures,
22 these standardized instrument cards.

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1 I get emailed most days of the week with,
 2 "Dale, how might you measure this? I'm interested
 3 in doing a study of ICU survivors. I want to
 4 measure cognition. How might I do this?" This
 5 website gives all sorts of guidance on that. And
 6 if you want to do your own core outcome measurement
 7 set in Delphi, this gives resources.
 8 If you're doing these longitudinal studies,
 9 how the heck do we keep patients in these studies?
 10 Again, there's lots of free tools. We've got a
 11 database with more than 600 ideas for cohort
 12 retention strategies based on unpublished studies.
 13 We've got lots of tools that are free. This is all
 14 funded by the NIH, free, everyone can use. We've
 15 got checklists how to search for patients that have
 16 become lost to follow-up, and then we've got lots
 17 of statistical things that have been published that
 18 Elizabeth will talk about a little bit later.
 19 So lots of things out there. Hopefully this
 20 is -- really, it's a case study. I know this isn't
 21 directly related to sedation, but gives one way of
 22 incorporating patients and families, one way of

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1 or that of our patients, enough, and some of your
 2 work has.
 3 So we know that it happens often. We hear
 4 stories of how burdensome it is. Is there anyone
 5 who's linked the two to reflect our earlier
 6 discussion about societal costs and the argument
 7 that this may be a financially interesting
 8 dimension to pursue. Do you know that?
 9 DR. NEEDHAM: I can't think of a lot
 10 of -- there's other smart people around, and Mona
 11 in the back, too, to chime in. I can't think of
 12 any rigorous empirical papers that have shown
 13 those. I think many of us who see these patients
 14 routinely, in clinical
 15 or research studies, know that they're
 16 intrinsically linked. We know the person that
 17 doesn't survive --
 18 DR. SKROBIK: So Margaret's shown it, for
 19 ARDS survivors, but you've got much larger
 20 non-ARDS --
 21 DR. NEEDHAM: Yes. But the issue was around
 22 quantifying in dollars; I can't think of it. We've

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1 thinking about consensus, and one way of trying to
 2 think about measurements. So hopefully that helps
 3 inform things a little bit. Thanks.
 4 (Applause.)
 5 Q&A and Panel Discussion
 6 DR. WARD: We'll take some questions and add
 7 Ingrid to the panel.
 8 DR. SKROBIK: Dale, thank you a very nice
 9 summary of a complex topic. Do you know if there
 10 is a relationship between all of the elements that
 11 you captured and societal impact and cost?
 12 DR. NEEDHAM: Yoanna, is the question, if
 13 somebody has problems in mental health, is there an
 14 association between that and societal impact?
 15 DR. SKROBIK: If I could take issue with
 16 mental health as a term, I think psychological
 17 wellbeing might be -- sorry for the -- because
 18 you're traumatized beyond belief, and then you
 19 recover, right? I don't think it's a mental health
 20 issue. It doesn't make you schizophrenic. But I
 21 think -- sorry for the -- I think we as physicians
 22 don't talk about psychological wellbeing, our own

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1 published a couple of papers looking at return to
 2 work, both from a national sample and a
 3 Baltimore-based sample, and we actually put the
 4 economic valued lost income. We worked with a
 5 labor economist to try to put dollar signs on that.
 6 DR. SKROBIK: But do you have a grading of
 7 the HADS that say in relationship to whether you do
 8 go back to work? I think that's the --
 9 DR. NEEDHAM: We have a graduate student in
 10 Seattle, University of Washington, who's looking at
 11 return to work in these kind of factors, using our
 12 data. But other people -- am I missing the study
 13 that people can think of?
 14 DR. FLOOD: It's an important aspect. I
 15 just want to jump in, Denny [ph]. I'm Pamela
 16 Flood. I know many of you personally. Denny asked
 17 me to give you kind of a quick summary of -- I'm
 18 here as a patient, of my experience as a patient.
 19 I became ill around the same time as David
 20 did, and I was working. Mervyn was my boss at
 21 UCSF. I was the director of OB anesthesia and had
 22 a background in preclinical and clinical research.

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1 I'd been a plenary lecturer in Hong Kong the night
2 before, and like an idiot, flew back, and I was on
3 call the next night.
4 I felt awful. I thought I had a sinus
5 infection. But nonetheless, I showed up to call as
6 good anesthesiologists do, but I was vomiting
7 uncontrollably in the sink, and my very wise
8 colleague said, "Sorry. You can't take call if you
9 can't stop vomiting."
10 (Laughter.)
11 DR. FLOOD: So brought me down to the ER
12 where I was vomiting and had a small fever. They
13 thought I had some sort of virus; maybe SARS
14 because I had been in China, so they kept me aside
15 from everyone else, and then shipped me over to
16 Mount Zion, which is the less acute care hospital.
17 But I had a severe headache, and a stiff neck, and
18 a fever. And my husband showed up and insisted
19 that they do an LP, which they did, and I had no
20 cells but very, very high protein.
21 So the long and the short of it is I had an
22 autoimmune encephalitis. I was intubated for about

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1 a week. I have some memory of being lightly and
2 deeply sedated with propofol. I have an amazing
3 memory of my extubation on dex, and I have to say,
4 Mervyn, it's a great molecule; I love it.
5 I remember very, very clearly, very specific
6 details. I remember Mervyn coming by. I remember
7 Ted Eger [ph] coming by. I remember Larry Saidman
8 coming by. I remember wondering if Mervyn was mad
9 because I had missed some calls.
10 (Laughter.)
11 DR. FLOOD: I remember feeling my chest go
12 up and down and thinking, "Wow! That's so
13 interesting. I'm on positive pressure
14 ventilation." I remember I had some amnesia. I
15 have a master's degree in neuroscience, and I
16 remember, even intubated, thinking, "Wow! I have
17 plastic hippocampal amnesia." It's really very
18 short-term memory loss. But I didn't care. I did
19 not care at all. None of this was worrisome to me
20 at all. I found it intellectually fascinating, but
21 I did not care.
22 My experience, I was never -- well, I guess

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1 I told my husband -- they told my husband I might
2 die, but as soon as I woke up, I knew I wasn't
3 going to die. So perhaps my husband should be here
4 to give you a family perspective because, frankly,
5 I had my own struggles coming back to work and
6 recovering. But I think he has PTSD, and I think
7 that's an important consideration. So just a quick
8 summary to put my being here in context.
9 Mervyn?
10 DR. MAZE: Yes?
11 DR. FLOOD: By the way, were you mad at me
12 for missing call?
13 (Laughter.)
14 DR. MAZE: No.
15 I have a question for Ingrid, and this
16 follows on something I mentioned early to a couple
17 of people, which is that you guys have done such a
18 good job with these guidelines assessing the
19 evidence, that you'll be taken over by machines
20 pretty quickly, i.e., machine learning will do this
21 for you or do this for subsequent generations quite
22 well. But I worry about the patient qualitative

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1 aspect of it, where the evidence and measuring the
2 quality of the evidence is going to be so
3 challenging, yet so important, and something
4 machines will not be able to do.
5 So I'd like to get your perspective of
6 whether the qualitative behavioral aspects of the
7 work that you're doing, will it achieve a level at
8 which we now look at RCTs and meta-analyses, and so
9 forth?
10 DR. EGEROD: Thank you for that question. I
11 was very happy to be invited here because I have
12 felt for the last 20 years, as a qualitative
13 researcher that I'm a nurse and that very few
14 physicians would ever read something written by a
15 nurse. So I think it's tremendous that you're even
16 asking the question because I've experienced that
17 some doctors say, well that's interesting, but it's
18 overwhelming that there is very little interest in
19 the kind of research, asking the patients how they
20 do -- if they want to have that kind of research,
21 they want someone else like an anthropologist or
22 some real scientists to do it.

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1 So anyway, I'm very happy that there is
2 concern about that. I definitely feel that it
3 should reach status, maybe not equivalent to RCTs,
4 depending on what is your measurement. I'm very
5 aware that basically survival is number one, and
6 you don't learn about survival necessarily from
7 qualitative research, but I think it is so
8 important.

9 Also, I feel that your whole study, Dale,
10 shows that, yes, you can do these big triangulated
11 studies where you do get something generalizable
12 from a qualitative research, but it might not
13 always be the goal. I think the human reaction is
14 so individual that you always have to have remember
15 somewhere in there that there is something that
16 cannot be generalized and that has to be seen and
17 understood in context.

18 So I think the two things should always go
19 hand in hand. They're important in different ways,
20 but they're definitely important to understanding
21 why we want to survive.

22 DR. BROWN: If I could just weigh in, I

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1 think Ingrid has said it very well. It's both/and.
2 We need the narrative pieces in here, but we need
3 the algorithm to know where to fit a narrative in.
4 But if there's anything I wished the health care
5 system would do right now is put my values and
6 Goals as a unique human being in the chart. You
7 can't find it. You cannot find my values and goals
8 in an electronic health record of Epic or any of
9 the other commonly used ones. I'm just like
10 everybody here, and you're just like I am, and
11 we're very clearly not.

12 DR. FLOOD: I don't know how you would put
13 your values and goals until an electronic health
14 record.

15 DR. BROWN: You'd actually ask a question.
16 You'd ask a question, and you wouldn't have a
17 billing document serve as your clinical record,
18 which is what our electronic health records are,
19 billing documents. I will now muzzle myself
20 because I have some passion about that.

21 DR. FLOOD: Mona Hopkins at the back.

22 DR. HOPKINS: I want to go back to Yoanna's

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1 comment about the link between our outcomes and
2 social outcomes, employment and funding. We don't
3 have a lot in ICU. We have some hints there are
4 interrelationships across these domains. But we
5 shouldn't ignore the huge literature in traumatic
6 brain injury that shows cognitive impairment is
7 directly related to return to work and your
8 financial status.

9 We shouldn't ignore the work and caregivers,
10 and how that impacts family values, and we have
11 some of that in the ICU and impacts their financial
12 income. And we shouldn't ignore the work that
13 comes out of our veterans and other people with
14 PTSD, showing that that directly affects their
15 ability to return to work and affects their
16 financial outcomes.

17 DR. FLOOD: Steve?

18 DR. SHAFER: In terms of looking at the
19 long-term outcomes, a lot of it is clearly based on
20 reaching people by phone and by following up. I'd
21 just like to ask you if that's becoming
22 increasingly difficult. This is sort of a nuts and

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1 bolts question, but I watched Pamela, who's doing
2 some phone outcome studies, curse at the number of
3 people who won't answer their phone because it's
4 going to be another spam call. And it seems that
5 that's actually really consequential in trying to
6 pursue this.

7 DR. NEEDHAM: So you're right. This is Dale
8 Needham; a couple of methodologic things. With our
9 studies -- and Mona Hopkins was a principal
10 investigator with me on a lot of the work I
11 presented -- we would have 2 call centers, for
12 example, in Utah and in Baltimore, for phone, and
13 then we would have a subset of the entire research
14 network where we do in-person assessments as well.

15 I think they're both complementary and
16 they're both necessary, but in-person assessments
17 aren't feasible to do across a thousand patients
18 with our current funding budgets. They're
19 feasible. It's just people don't have enough
20 money.

21 DR. NEEDHAM: Then how do you get people to
22 answer the phone?

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1 DR. SHAFER: So that's actually why, when I
2 created this grant almost, whatever, 8 years ago or
3 something, I insisted that aim around cohort
4 retention methods. Peer reviewers weren't keen on
5 it, but having done so much of this, I knew it was
6 absolutely critical.
7 So we have lots and lots of different
8 approaches to doing it. It takes an awful lot of
9 work. For example, one of the key things is
10 collecting contact information at the beginning of
11 the study and making sure the contact information
12 actually works.
13 We've got a study going on right now. We
14 were given 3 numbers for a patient in Nashville.
15 Two of the 3 numbers didn't work, then we were down
16 to a single lifeline to connect to that patient.
17 Two of the numbers didn't work to start with at all
18 because the patient had memory problems, and when
19 they provided them to the research staff, they gave
20 them wrong numbers.
21 So there are a number of best practices.
22 And in the studies that Mona and I've done that

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1 have enrolled more than a thousand patients from 48
2 hospitals across the country, we've had cohort
3 retention rates of 97 percent at 6 and 12-month
4 follow-up. So it is possible, but it takes time
5 and persistence.
6 JP Kress was talking about it last night
7 with follow-up work that they're doing in Chicago,
8 and in-person follow-up work in disadvantaged
9 communities that there are safety issues, and
10 challenges, and things as well. But it is possible
11 when we treat it like a science. We also design
12 research strategies and budgets for doing this and
13 hire the right kind of people.
14 The staff that do in-patient ICU studies are
15 often not the same kind of staff that should be
16 doing follow-up. They just don't have the mind-
17 set, and it's just something that most of them find
18 uncomfortable, which is why we found that
19 centralized call centers with specially trained
20 staff often are a much more successful approach.
21 DR. FLOOD: I've already downloaded your
22 deadlines and cohort retention.

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1 Tony?
2 DR. ABSALOM: Tony Absalom from the
3 Netherlands. A chap in the Netherlands has
4 developed an app that allows patients to do
5 longitudinal, quality-of-life assessments. It
6 sounds attractive to me, but I'd be interested in
7 your opinion because for myself, I worry which
8 patients would be the ones that would respond and
9 how many would. How many would respond to an
10 email? How many would even look at email?
11 DR. NEEDHAM: I think it's very challenging.
12 I think there's a huge selection bias. I think
13 that our patients -- as JP and I were talking about
14 last night, some of our patients that are the
15 hardest to contact often fall into two categories.
16 Some of them are completely great, back to work;
17 "Why are you bothering me? I'm fine." And they
18 don't even appreciate that the vast majority of
19 survivors are not fine. They don't recognize
20 they're an outlier, and they're busy, and they're
21 back to their normal life.
22 The others are patients that have an awful

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1 lot of challenges. We've had patients say things
2 to us like, "I just couldn't pick up the phone. I
3 felt so down in the dumps that I just couldn't."
4 But we are persistent, and then say, "Thanks for
5 not giving up on me." After we've done our 50th
6 phone call, rather than saying this to us, cursing
7 at us, they say thanks for not giving up on me, or
8 I knew it was important because you didn't stop
9 calling. When we get trained in our social
10 interactions, we believe that somebody is going to
11 curse at us, right? But in fact that almost never
12 happens, and it's the exact opposite.
13 So there's a huge selection bias around
14 that. For each patient, we do need to take an
15 approach that will work. Some are email responses
16 and some use apps. In our experience, most don't
17 use any of those things, and we found phone is the
18 best way to -- and then you've got an idea of how
19 much time and effort people are putting into the
20 answers and are they understanding it. You're
21 having a human connection. So we found that much
22 more successful than an app, or email, or trying to

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1 mail a questionnaire out to people.
2 DR. FLOOD: Yoanna?
3 DR. SKROBIK: I just wanted to ask all of
4 you what you thought of the value, the therapeutic
5 value, of the narrative in follow-up studies and
6 how to capture that. I was surprised when I did
7 the Towards RECOVER study with Margaret Herridge in
8 Canada, that patients were grateful for the
9 capacity to tell the story. And I
10 learned -- because, like most people, I knew
11 everything at 30 -- that if you tell the story in
12 your own words, that's part of the journey back.
13 I'm curious about people talk about the
14 burden, and in the Canadian critical care trials
15 group that I belong to with Lisa and others, the
16 nurses always worry about burdening patients with
17 follow-up studies, whereas my observation is that
18 some of them don't care, don't mind, but there's a
19 spectrum. Who are we harming, who are we
20 burdening, and are there any that we're helping in
21 those evaluations? I welcome your thoughts.
22 DR. EGEROD: I think one problem we have

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1 with a lot of the kind of narrative responses and
2 other interventions we do to try to help the
3 patients, like ICU diaries and other kinds of
4 follow-up, is that we often measure it on SF-36 to
5 get the quality of life, and they always show
6 nothing. It's very distressing, that we know
7 there's something out there. We know there are
8 some values out there. We know it's good to tell
9 your story, but we can't find the instrument that
10 shows the value.
11 DR. FLOOD: There are a couple of hands.
12 DR. BALAS: I think to follow up on that
13 question -- Michele Balas -- I'm wondering is it
14 safe, Dale, to assume that the core outcome
15 measures that you're suggesting for the long-term
16 follow-up, would those same measures be applicable
17 to use, like the pre-ICU, before ICU. I wonder if
18 we have that core set of measures because that's
19 obviously one of the challenges that we have. How
20 do you know this is different from their baseline?
21 DR. NEEDHAM: Yes, and that's a very tough
22 issue. We didn't tackle it at all, so I don't know

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1 what the answer is. I can give you an opinion.
2 Sometimes we try retrospective recall using the
3 same -- a couple of the psychological instruments,
4 you can't use that, but the SF-36, you can say
5 think back to before the onset of the illness that
6 brought you in the hospital and score it.
7 We have some results that show that proxy
8 and patient results are quite different, so we
9 generally rely on patient rather than proxy. And
10 we've got some results that showed dramatic
11 differences that seem to have face validity, but of
12 course it's tainted by recall bias, and your
13 current state may influence how you see the past.
14 But I think that's sort of a starting point,
15 but I think it is a really big problem and issue.
16 I think there are some innovative studies happening
17 where there are ongoing large-scale prospective
18 studies -- Lauren Ferrante is one of many people
19 doing these -- where they're just prospective
20 studies and things are measured. And some of the
21 patients happen to end up in the ICU, and therefore
22 you have a truly valid prospective. But that takes

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1 large-scale studies. You need to enroll an awful
2 lot of patients to get a few that go into the ICU.
3 DR. BALAS: Then I guess the question also
4 comes up with the validity and reliability of the
5 recommended core outcome measures in terms of a
6 patient that has known or preexisting cognitive
7 impairment. So now you have patients that have
8 cognitive impairment, and are the anxiety and the
9 depression tools valid and reliable to use with
10 someone with cognitive impairment? We always get
11 this by reviewers, and I don't know how to answer
12 it.
13 DR. NEEDHAM: Yes, exactly. I know that
14 there are no data, at least based on our systematic
15 review, in ICU survivors around that. I guess
16 whether they're preexisting, and then certainly
17 many patients have post-ICU cognitive impairment,
18 it becomes a judgment around are the answers
19 consistent, and it becomes sort of judgment, which
20 stresses the importance of training the people who
21 are doing that, having lots of contact with Mona
22 and I working together -- Tim will chime in, in a

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1 second -- when Mona and I talk together, if there
 2 are things that we're not sure about, we'll have a
 3 conversation as PIs and say what do you think of
 4 this?
 5 Tim?
 6 DR. GIRARD: Tim Girard. I actually didn't
 7 have a comment but a question. I feel like it
 8 probably will sound like a loaded question, but
 9 it's not, and this is for Dale and Mona and anyone
 10 else. You've alluded several times to the lack of
 11 psychometric data on many of these measurements in
 12 this population. Can you tell us -- and when I
 13 hear that, I feel like you're implying that it
 14 needs to be done and that the measurement qualities
 15 may be different.
 16 Can you talk about why that would be? When
 17 I think about that, I'm not sure that they would or
 18 they wouldn't. Mona just got through saying we've
 19 got all this data from other populations about
 20 various aspects of what we're discussing.
 21 DR. NEEDHAM: I think a classic one -- and
 22 Mona can chime in; she's more expert than me -- is

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1 the Mini-Mental Status Exam is the world's most
 2 validated, most used screening question and seems
 3 to work well in lots and lots of populations. We
 4 then administered it in ARDS survivors against a
 5 reference standard cognitive testing and found that
 6 the performance characteristics were very poor.
 7 That's one example.
 8 Other examples would be -- and why I like
 9 that mixed-method study that we did, that looked at
 10 the measurement instruments, patient-reported
 11 outcomes versus qualitative, is some people, as
 12 Ingrid said, feel like the instrument itself isn't
 13 capturing what's really important.
 14 Mona, do you have more?
 15 DR. HOPKINS: Yes. When we look at the
 16 MMSE, these were developed for elderly patients to
 17 identify dementia. And if you look at the ICU
 18 outcome studies, with one or two exceptions, the
 19 mean age in those studies is 52, which does not
 20 anywhere near meet the criteria of elderly.
 21 Certainly, most of the people who are 52 that are
 22 healthy and have no other disorders don't have

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1 cognitive impairments.
 2 So one of the problems is we're taking a
 3 geriatric measure designed to detect a degenerative
 4 disease and applying it in an ICU population. So
 5 the Mini-Mental Status may be uniquely different,
 6 where something like measuring depression doesn't
 7 seem to have those differences as much across
 8 populations.
 9 So on some measures, I think it works better
 10 than others, so I think it's important to get
 11 data -- and Joe Bianvenilla [ph] has done a lot of
 12 the [indiscernible] Conley mental health through
 13 psychological wellbeing, although anybody that
 14 designed those measurements wouldn't call it
 15 psychological wellbeing -- and look at these
 16 instruments in specific populations because you
 17 can't just pull something like the Mini-Mental
 18 Status design for a specific purpose. And in other
 19 populations where they've been used, they've done
 20 these validation studies as well.
 21 DR. NEEDHAM: For people who are critical
 22 researchers, can we embed a study within a study?

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1 So you're already going to be using these
 2 instruments. Can you find a way to embed a
 3 reference standard or something? And that's what
 4 we did. We had a psychological, semi-structured
 5 diagnostic interview for PTSD embedded into another
 6 study, so we had sort of a psychiatric diagnosis of
 7 PTSD in a subset of patients while we're using this
 8 screening instruments.
 9 So can we build those things in, partnering
 10 with our colleagues who are experts, and say, hey,
 11 we've got an ongoing study; could you contribute to
 12 it and do this so that we learn? And we're doing
 13 that now with HADS, a depression screening
 14 instrument and a semi-structured diagnostic
 15 interview for depression, for instance.
 16 DR. FLOOD: David, I know you had a comment,
 17 and then a question from Richard.
 18 DR. BROWN: I'll make it very brief. Yoanna
 19 had asked a question about narrative, and another
 20 personal experience. I think I wrote about my
 21 illness a lot. I think that was very helpful, but
 22 I can tell you, having watched my wife who I think

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1 still has PTSD because she thought she was going to
2 have to take me to dialysis for the rest of my
3 life, she finally, 6 years after the event, wrote
4 about it. And I can tell you, it was quite
5 liberating to her to get her feelings out about it.
6 So I think there's some healing that goes on
7 in those narrative descriptions.
8 DR. FLOOD: Richard?
9 DR. RIKER: Yes. A question for David and
10 Pam. You both implied a little bit the difference
11 in the sedation quality between dexmedetomidine and
12 propofol in a manner that I don't think we would
13 ever capture with a RASS score or time to
14 extubation. I wonder if you can embellish your
15 descriptions a little bit, or in physicians, how
16 would we capture this? What is it and how would we
17 capture it?
18 DR. FLOOD: Well, propofol, of course, it
19 depends how deeply sedated you are. While I was
20 deeply sedated, I have no memory at all. While I
21 was lightly sedated, it wasn't that it was
22 unpleasant, but I was very aware, for instance, of

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1 time now, and I was very aware that I was not
2 sleeping. I appeared to be sleeping, and no one
3 could tell that I wasn't sleeping, but I was not,
4 and I wished I could go to sleep. In fact, I felt
5 fatigued.
6 Then on dexmedetomidine, I felt that my mind
7 was much clearer, and in fact I was even aware in
8 which ways my mind was not normal and not clear.
9 So I much preferred that feeling. In some
10 settings, a patient might prefer to be unconscious.
11 Something truly awful might be happening to them,
12 and they might have 5 million tubes coming out of
13 them, and that might be a period that would be
14 better to forget.
15 FEMALE VOICE: It depends on the person.
16 DR. FLOOD: Yes, it very much depends on the
17 person.
18 DR. EGEROD: We have a non-sedation regime
19 at one of our Danish hospitals, and we invited one
20 of the patients there to tell her story. She
21 happened to be a nurse from the same department, so
22 she also knew both sides.

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1 Her message was, being non-sedated is the
2 worst thing she's ever tried, and that kind of went
3 against everything we were working for. But we
4 have to listen to all these perspectives. But it
5 is difficult when you get a lot of patients that
6 say it was good to be awake, it was good to
7 interact with the staff, and then you have some
8 that say it was just horrible. Then what do you
9 do?
10 DR. FLOOD: Well, did this individual have
11 pain? Because I think there's a huge
12 differentiator. I did not have a condition that
13 caused pain.
14 DR. BROWN: Part of mine was I was too
15 hemodynamically unstable to have much propofol.
16 And when I was really hemodynamically unstable,
17 they didn't use dex either; it was just native.
18 But the part that Pam talked about, it took me
19 2 months to sleep more than about 20 minutes after
20 recovery, and that was probably one of the single
21 things that was troublesome as far as the fatigue
22 and starting to feel cognitively intact.

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1 DR. WARD: Last question.
2 DR. FLOOD: Denny, do you want to have the
3 last word? I think we're getting to the end.
4 DR. WARD: I don't want to delay lunch, but
5 to bring us back to the sedation in the meeting,
6 Dale talked about a lot of validated, from many
7 directions, outcome measures, but he started off
8 with saying, well, these are optional. If you want
9 to do this, these are the things that you can use.
10 Is there a strong enough correlation between
11 what goes on in the ICU as far as sedation that
12 will provide a measurable signal in these outcome
13 measures that you've talked about; that we should
14 move beyond saying, well, if you want to measure
15 some outcome measures, here's some good ones you
16 can measure. And say if you are investigating
17 sedation in the ICU, you should be, must be,
18 measuring these outcomes because there is a signal
19 there that is measurable, either qualitatively or
20 quantitatively.
21 DR. NEEDHAM: I'm going to say yes, but I
22 should share the voice with Pratik and/or Tim. I

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1 absolutely think this is so important. Our
2 patients have a legacy of problems from their
3 critical illness. Some of it they bring in, some
4 of it's their comorbidity, but some of it is
5 related to what we're doing.
6 DR. NEEDHAM: There's so much that goes on
7 in the ICU, and sedation is a small -- analgesia is
8 a small piece of it. Is there a detectable signal
9 in these measurements given everything else that
10 goes on in the ICU, or are we just going to pick up
11 noise and we're not going to be able to
12 differentiate propofol versus dexmedetomidine
13 versus something new coming along in these?
14 DR. FLOOD: Pratik?
15 DR. PANDHARIPANDE: So going back to the
16 guidelines, when we are creating the guidelines and
17 creating the priority list as far as outcomes and
18 as a result of which we have a lot of the
19 conditional recommendation and low evidence, all
20 the outcomes that were deemed important align very
21 similar to the outcomes which were in the core
22 outcome group; not the set of instruments but the

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1 basic teams of cognitive impairment, mental
2 illness, et cetera.
3 So that's one point. I feel that there is a
4 lot of similarity between what was identified as a
5 priority area in not a formalized Delphi method,
6 but a prioritized scoring that the experts and
7 patients did in the PADIS guideline.
8 So that was one point. I feel that there is
9 a fair amount of similarity, and there should be
10 little reason why we have to go far away from some
11 of the things that Dale presented.
12 The other thing is, looking at Dale's
13 outcomes, which are related with acute respiratory
14 failure, if you look at one of the strongest
15 indication, at this point at least, that people
16 tend to use, they all seem to be linked. The
17 majority of patients in the ICU who are
18 mechanically ventilated are sedated, and they are
19 mainly in the ICU for respiratory failure.
20 So I think they're all, again, hand in hand
21 with that regard, that these are all related, so
22 there should be very little reason I think for

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1 having very different outcomes versus what was
2 presented by Dale.
3 DR. WARD: We'll go to lunch. We need to be
4 back here at 1 o'clock.
5 DR. FLOOD: Comment?
6 MALE VOICE: I'm sorry to interrupt. I just
7 wanted to extend a real thanks to Dr. Brown and
8 Flood for sharing these very personal stories. I
9 think to the extent that we can incorporate these
10 kinds of really deeply personal patient
11 perspectives into our research activities, we can
12 try to approach this aspiration we had as medical
13 students to be the kinds of doctors that are taking
14 care of real people. Those stories were really
15 thought-provoking, and I just want to thank you for
16 sharing them.
17 (Applause.)
18 DR. WARD: Back at 1 o'clock.
19 (Whereupon, at 12:07 p.m., a lunch recess
20 was taken.)
21
22

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1 AFTERNOON SESSION
2 (1:06 p.m.)
3 DR. WARD: I've asked Rich to -- there have
4 been a lot of great studies out there already done,
5 and there are some lessons that we can learn
6 different than the lessons from PADIS this morning,
7 but lessons really in the methodology on the great
8 studies that have been the foundation for
9 recommendation; and then Marti [ph] from the FDA,
10 who can help us a little bit with the FDA
11 perspective on the stuff we're doing, because some
12 of this does end up on the desk of the FDA.
13 As Bob talked about, one of the initial
14 ideas at the FDA head to start ACTTION was how can
15 we improve the quality of the clinical trials that
16 are coming to us that we have to look at to make
17 the approval or disapproval for a new drug or
18 indication for that. So this is all about
19 improving the quality of clinical trials. Then
20 we'll have a panel to kind of put this together and
21 talk about the current controversies and unmet
22 needs.

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1 Rich, if you'll start us off.
2 Presentation - Richard Riker
3 DR. RIKER: Sure. Thanks, Denham.
4 Well, I've got the unenviable task of taking
5 us from lunch, so hopefully I can try to keep you
6 awake. It's a little bit daunting to give this
7 talk. We all have very different perspectives, and
8 there are some things that we're going to agree to
9 disagree on, but I think we all carry a lot of
10 evidence that it guides our decision making and
11 also our study design approach.
12 What I'm going to try to do is to summarize
13 not so much what the results were but maybe some
14 things on the second or third level that may have
15 confounded or potentially confounded some of our
16 outcomes or our ability to interpret some of the
17 studies.
18 So I'm going to go through some of the older
19 studies and some of the more recent ones, tell them
20 what you're going to tell them, tell them, and then
21 tell them what you told them kind of thing. The
22 control group is critical. Targeted level of

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1 sedation is important. Sedative versus other drug
2 therapy, timing is everything, and then in the
3 anticipation of the FDA holding the microphone
4 next, I want to ask some provocative questions.
5 This is an old summary systemic review by
6 Ostermann. The thing I want to have you look at,
7 it's hard to read, but about the fifth or sixth
8 column is mean percent time at sedation target
9 level. If you follow that down through the rows,
10 you can see that every study has some of that
11 information. But if you look further to the right,
12 time to extubation, length of ventilation, ICU
13 length of stay, the majority of the studies don't
14 have that.
15 So if we think back 15 or 20 years, the
16 standard primary outcome for sedation studies was
17 how often are you at that target level of sedation.
18 If we look at some of the more recent studies, I
19 think Pratik in their MENDS study was really one of
20 the first to look at something more meaningful
21 perhaps. So they looked at 12-day delirium-free,
22 coma-free outcome. In SEDCOM, we kind of fell back

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1 to the percent time and target. MIDEX and PRODEX,
2 the combined dexmedetomidine versus midazolam or
3 propofol studies, looked at percent time and target
4 but had a noninferiority design. Then Yahya in his
5 SPICE study took the real leap and looked at 90-day
6 all-cause mortality.
7 So we've seen a wide range of primary
8 outcomes that have been targeted for these sedation
9 studies, and I think it prompts a fair discussion
10 about what should the primary outcome be as we move
11 forward. So I want to back up now to one of the
12 real pivotal studies. It's a little bit daunting
13 to stand here and tell JP what he learned in his
14 study, but I'll do my best.
15 This was really a groundbreaking study that
16 randomized patients to either daily interruption or
17 standard sedation, and also randomized to midazolam
18 or propofol starting 48 hours after enrollment.
19 The target sedation level, which is Ramsay 3 or 4,
20 and in the group that was in the intervention arm,
21 midazolam and propofol and morphine were
22 interrupted daily. The patients were awake

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1 following 3 to 4 instructions or became agitated.
2 If they did become restless or agitated and
3 sedation needed to be restarted, it was started at
4 half the previous rate.
5 I go through that in agonizing detail
6 because many follow-up studies use this same
7 approach, so I'll refer back to JP's study as the
8 methodology for some of the other studies that
9 we're going to talk about.
10 As you all know, daily interruption prompted
11 a dramatic reduction in duration of ventilation,
12 median ICU length of stay, and the need for
13 diagnostic testing. One of the important things
14 for this study now looking back is that if you look
15 at what percent of the days on study patients were
16 awake, in the intervention group, that was
17 85 percent of the day. But in the control group,
18 it was 9 percent. That means that 91 percent of
19 the days on study, the control group was never
20 awake. That's an important control group aspect
21 that we need to keep in mind when we look at these
22 outcomes.

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1 Interestingly, the drug doses were
2 dramatically lower, intervention group with the
3 daily wake up compared to the control group for
4 midazolam, but there was no difference in drug
5 doses between propofol, maybe reflecting to some
6 degree the duration of effect that we see with
7 those two drugs.
8 Now contrast that study, where the
9 conclusion was clearly daily sedation interrupted
10 improves outcomes, to a more recent study that used
11 the exact same type of intervention. The study
12 drug was interrupted. Drugs were not controlled.
13 The main difference in the study was that the
14 targeted level of sedation was much lighter.
15 Instead of a Ramsay of 3 or 4, it was a SAS of 3 or
16 4 or a RASS of minus 3 to 0, but the interruption
17 protocol was exactly the same.
18 As you can see, the outcome here is the
19 number of patients or the proportion who are
20 extubated, and you can see those curves overlap.
21 The sedation scores, the mean scores were exactly
22 the same in both arms of the study. There was no

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1 time to extubation difference, no difference in any
2 of the other outcomes, but there was a difference
3 in the amount of doses of drug that were given and
4 the number of boluses that were given, and the
5 workload for nurses was greater.
6 The conclusion from this exact type of study
7 was the opposite; sedation interruption doesn't
8 make a difference. In fact, it makes it more drug
9 doses, more work for the nurses, and more bolus
10 doses. So how do we reconcile those two things;
11 same intervention to different conclusions? It's
12 the control group. We need to really be thoughtful
13 about designing a study and incorporating that
14 control group. Is it the standard of care? How do
15 we really want that comparison to look?
16 We know that there are a lot of studies out
17 there in critical care where the control group
18 difference made a big difference for the study.
19 For partial liquid ventilation, remember the
20 control group did much better than expected. For
21 early goal-directed therapy, the control group did
22 much worse than any other study of sepsis. So

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1 incorporating those kinds of concepts as we design
2 these studies I think is important.
3 I think another component we need to be
4 thoughtful about is the level of sedation. This is
5 Pratik's wonderful study, MENDS study, where they
6 randomized patients to either lorazepam or
7 dexmedetomidine; allowed bedside clinicians to
8 determine the level of sedation as was the standard
9 of care at that time; and then post-study, grouped
10 them into deep with a RASS of minus 3, 4, or 5
11 versus light, and found that the dexmedetomidine
12 patients had more days free of coma and delirium or
13 just of coma, but there were no differences in
14 ventilator-free days, ICU length of stay, and
15 almost but not quite 28-day mortality.
16 This is just the median and IQR bar graphs
17 for the coma-free days, delirium-free days, or
18 both. One of the findings of this study, which was
19 different than the prior phase 3 and other dex
20 studies that had been published up to that time,
21 was that the dexmedetomidine group actually got a
22 lot more fentanyl than did the control group. Many

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1 of the prior studies had suggested that
2 dexmedetomidine was actually a fentanyl sparing
3 type of intervention.
4 Pratik and his colleagues did probably one
5 of the best graphs I've ever seen -- oh, how did
6 that get in there? I'm missing a slide here; oh,
7 it's here -- one of the best graphs I've seen,
8 where they looked at the light sedation group, RASS
9 of minus 2 to 1, and then on the bottom half, it's
10 the deeper sedation group.
11 This compares the fentanyl doses in the two
12 arms. It's a little bit hard to see, but the round
13 dots to the left of each number study, day 1, 2, 3,
14 4, 5, are the dex patients and their fentanyl dose.
15 The one to the right in triangles are the lorazepam
16 patients and their fentanyl doses. And if you look
17 at the bars that represent the median across the
18 top there, they're very similar for the light
19 sedation group, whereas for the deep sedation
20 group, you can see a dramatic difference in that
21 the dexmedetomidine patients were getting much more
22 fentanyl.

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1 I think the interpretation you guys had was
2 that it was primarily -- because it's hard to get
3 patients on dexmedetomidine
4 deeply sedated, and the fentanyl was being used not
5 so much as an analgesic but to try to get them into
6 that target level of sedation.
7 Is that fair?
8 DR. PANDHARIPANDE: I think a little bit of
9 both.
10 DR. RIKER: Yeah. I think the take-home
11 here is that although the study was randomizing for
12 two different medications, the range of sedation
13 targets may have affected the dosing of some other
14 medications.
15 So let me go back here because I think I got
16 things a little bit out of sequence. Within the
17 SEDCOM study here, one of the things to take note
18 of is the stuff in blue. There we didn't let the
19 bedside clinicians identify the level of sedation.
20 We said it's going to be a light level of sedation
21 in both arms of the study, so a RASS of minus 2 to
22 plus 1.

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1 When we look at that, those patients were at
2 that level of sedation to the same degree in both
3 arms of the study. So because this was our primary
4 outcome, it was a negative study. We didn't have a
5 higher degree of compliance or time and target
6 sedation in one arm or the other. It was ideally
7 the same in both.
8 It turns out that that was probably one of
9 the best things that could've happened because then
10 any future differences in outcomes -- time on the
11 ventilator, incidence of delirium, any of those
12 kinds of things -- could not be blamed on a deeper
13 level of sedation, more coma in one arm than
14 another. In fact, because they were sedated to the
15 same degree in both arms, any of the outcome
16 differences would better be explained by the drug
17 itself or some other factor that we didn't take
18 into account.
19 So if we look at this, and with that same
20 level of sedation in both arms, the dexmedetomidine
21 group get extubated about 2 days faster and they
22 had some other outcome benefits as well. So we

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1 went through that already.
2 I want to talk about another trial where
3 maybe it wasn't so much sedation; it may have been
4 other things. And that's the study we all know
5 well, the Strom No Sedation protocol. Remember
6 there, patients were randomized to either standard
7 propofol or midazolam versus no sedation.
8 The no sedation group had some resources
9 that are quite uncommon in the U.S. They had 1 to
10 1 nursing. If the patient was not calm or
11 comfortable with that, they could have a bedside
12 sitter in addition. They could receive as much
13 morphine as needed. They could receive as much
14 haloperidol as needed.
15 If they were still restless or agitated,
16 they could get continuous propofol for 6 hours and
17 get that up to 3 times. And if that happened, if
18 they needed that 3 times, they would go on
19 continuous infusion propofol. About 20 percent of
20 the patients in the intervention group actually
21 ended up back on continuous sedation.
22 I think that's an important take-home for

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1 this model. They may have traded sedation for
2 human resources to keep those patients calm and
3 other medications, besides the sedative, to keep
4 those patients calm. The outcomes were quite
5 striking, more ventilator-free days, shorter ICU
6 hospital length of stay, and almost a mortality
7 benefit.
8 Interestingly, I think this was not ideal
9 from my standpoint. They excluded 27 patients who
10 either died or were extubated in the first 2 days.
11 Those are kind of important outcomes. I wish they
12 had left those patients in. The whole
13 intention-to-treat analysis is critical, but why
14 did some of the patients get extubated and why did
15 some of the patients die? I think those are two
16 outcomes we don't want to exclude patients for.
17 Yahya I think in his series of SPICE studies
18 has shown us that timing is critical, the timing of
19 sedation when we look at what kind of sedation
20 we're giving and when in the ICU stay are we
21 talking about. Almost all of the studies that I
22 talk about up to this point have been done with

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1 enrollment starting somewhere in the 24, 48, maybe
 2 even 72-hour time frame after being intubated.
 3 SPICE looked very early at these patients.
 4 Data started within 4 hours and really looked at
 5 during that first 48 hours in the ICU, a time that
 6 most of the other studies had ignored or not
 7 enrolled, was deep sedation a significant problem?
 8 They treated deep sedation as a continuous
 9 variable, the number of deep sedation events you
 10 had, and showed that time to extubation, time to
 11 delirium, time to hospital death, and 180 day
 12 mortality were affected by that incidence of
 13 sedation.
 14 This is a very similar analogous study done
 15 in a very different population of patients, which
 16 basically showed the same thing. If we look at the
 17 bar graph in the lower left here, the black bars
 18 are the first 48 hours. You can see there's really
 19 a trend to the right where many more patients are
 20 deeply sedated in that first 48 hours. The gray
 21 bars are the rest of their ICU stay, and you can
 22 see there a greater shift towards a RASS of zero

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1 where those patients are awake.
 2 I think Yahya really showed us that
 3 targeting a specific level of sedation after 48 or
 4 72 hours may be missing a critical interval in
 5 those patients' care, so I think we'll have time to
 6 talk about that.
 7 There was another study that was designed
 8 very differently but also looked at that early time
 9 frame. This is Gerald Chanques study where they
 10 took a group of surgical patients, primarily
 11 abdominal surgery, coming to the ICU and randomized
 12 them within 2 to 4 hours of arrival in the ICU to
 13 either standard care with sedation, which turned
 14 out to be light sedation, versus immediate
 15 interruption of their sedation.
 16 When they interrupted sedation, they used a
 17 protocol very similar to the one that JP had
 18 designed and that Geeda Macha [ph] had used in the
 19 sleep study, where they only restarted the sedation
 20 if the patients were restless or uncomfortable. If
 21 they needed that, they could get on continuous
 22 sedation for 6 hours. If that happened more than

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1 twice in a 24-hour period, they left them on
 2 continuous sedation till the next day, and then
 3 they started over again.
 4 That interruption was associated with a
 5 dramatic reduction in time to extubation, 8 hours
 6 in the interruption group versus 50 hours in the
 7 standard care group, a dramatic reduction in the
 8 incidence of coma and a reduction in the incidence
 9 of delirium as well. So I think this early time
 10 frame in the ICU is something that we need to be
 11 cognizant of as we move forward and design these
 12 studies.
 13 I think we could draw some possible
 14 conclusions from these findings. Number one would
 15 be that the control group is critical to our
 16 understanding about the impact of intervention and
 17 we really need to look carefully at that standard
 18 care, or alternative drug, or whatever we want to
 19 design.
 20 I think a second important take-home may be
 21 that the targeted level of sedation may alter those
 22 outcomes in that in this day and age, light

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1 sedation is probably the standard for many ICU
 2 patients.
 3 The concept of deep sedation in the ICU and
 4 who needs it is an area we've got very little
 5 evidence to guide us. I think we all have our
 6 biases about who we want to keep deeply sedated and
 7 why, but the evidence supporting that is not very
 8 great and probably is another area we need to do
 9 more investigating in, not so much with RCTs
 10 perhaps, but with other design approaches.
 11 The third point would be that the protocol
 12 must prevent or monitor bailout medications to
 13 avoid confounding our conclusions and perhaps even
 14 our outcomes. Then lastly, timing is everything.
 15 That first 48 hours is pretty critical.
 16 So I want to finish up, and I don't know if
 17 we're going to do questions now or do that after.
 18 DR. WARD: We will bring up the panel.
 19 DR. RIKER: Yeah. A couple of provocative
 20 questions, and I target these to each of us in the
 21 audience and also to the FDA who will be coming up
 22 next. One would be can we take placebo-controlled

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1 ICU sedation studies off the table? This is a
2 standard, embraced, religious almost approach to
3 study design that doesn't work in the ICU. It's so
4 cumbersome to try to do a placebo-controlled
5 sedation study. It has its own problems. It's
6 nowhere close to the standard of care we provide.
7 So if we're going to include a
8 placebo-controlled group, I think there are many
9 issues with it we need to consider. And I would
10 pitch -- again, I'm being a bit provocative here,
11 not necessarily telling you what I think. I would
12 propose that we take that off the table.
13 Are we beyond time in target sedation zone
14 as the primary outcome? I think we probably are.
15 I think that's no longer a reasonable primary
16 outcome. It's not all that important. It's an
17 important secondary outcome. We need to know how
18 compliant people were with the various sedation
19 strategies, but by itself as a primary outcome, I
20 don't think we're there.
21 This one is maybe a little bit more
22 controversial. Is mortality too high a bar for a

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1 sedation study in the ICU? I would pitch that it
2 is, that if we have a negative study with mortality
3 as the outcome, there may be many, many more
4 meaningful outcomes that we could consider
5 advantageous to us as clinicians, to patients and
6 their families, that we lose if that's our primary
7 outcome. I don't know what the other alternative
8 right one is, but I would pitch to you that maybe
9 mortality is too high a bar.
10 This is another controversial one. Does ICU
11 sedation really impact late outcomes? Our patients
12 are so complicated with sepsis and renal failure
13 and a bunch of comorbidities that they come in
14 with, and various complications that are occurring
15 during their ICU stay that might or might not be
16 related to sedation.
17 How much of poor long-term outcome, poor
18 functional status can we blame on sedation? Some?
19 All? None? I don't know the answer to that, but I
20 think it's worth asking the question.
21 I think to challenge the FDA a bit, is
22 resource utilization meaningful? I've heard them

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1 say at this meeting in the past that they don't
2 view it as a meaningful outcome. I think it is a
3 meaningful outcome to us as clinicians. I think it
4 probably is to patients and families.
5 So if we can get patients off the ventilator
6 or have greater ventilator-free days, similar for
7 ICU length of stay, discharge to home or rehab
8 versus death or skilled nursing facilities, those
9 are maybe more functional types of outcomes;
10 looking at short-term functional outcomes. Then as
11 we talked about this morning, the great range of
12 patient-focused outcomes and priorities that we
13 need to consider probably need to be included
14 there.
15 I'll stop there. Thank you.
16 (Applause.)
17 DR. WARD: The perspectives from when all
18 this stuff ends up on your desk.
19 DR. SKROBIK: Can I just ask a clarification
20 question, Rich? When you pleaded for no studies
21 where the control group gets placebo, you didn't
22 mean that every patient in every trial should get a

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1 sedative, did you?
2 DR. RIKER: Riker. I did not mean that, but
3 to use a placebo for an arm of critically ill
4 patients for sedation, I think --
5 DR. SKROBIK: So not make it available is
6 what you meant.
7 DR. RIKER: I would not design a study where
8 placebo was part of the design.
9 DR. SKROBIK: Where one arm was unable to
10 get a pharmacological intervention.
11 DR. RIKER: Correct.
12 DR. SKROBIK: Because the way you presented
13 it, I had some -- it wasn't clear to me whether you
14 meant that each should necessarily get a
15 pharmacological intervention.
16 DR. RIKER: No. If a patient doesn't need a
17 pharmacologic agent, I don't think they should get
18 one.
19 DR. SKROBIK: And that can be part of what
20 you consider a no-placebo group.
21 DR. RIKER: Yes.
22 DR. SKROBIK: Thanks for clarifying.

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1 Presentation - Martha Van Clief
 2 DR. VAN CLIEF: Well,, it's an honor to be
 3 here.
 4 I found the conversation and the presentations very
 5 challenging to me on an intellectual basis. It's
 6 an incredible group of people, so thank you for
 7 letting me come here today. I'm an
 8 anesthesiologist by training. I don't have a huge
 9 ICU background, and it's been a while since I was
 10 in training. I'm here to give you a regulatory
 11 perspective, and I hope that I can add something to
 12 this conversation.
 13 This is my disclosure statement that's
 14 required. This presentation reflects the views of
 15 myself and should not be construed as representing
 16 the views and policies of the FDA.
 17 Just as a brief outline of what we're going
 18 to discuss today, I want to start off with some
 19 regulatory concepts, and then we'll move into
 20 talking a little bit more about defining the
 21 effect. After that, we'll talk a little bit about
 22 measuring the effect, and then we'll finish up with

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1 some requirements for marketing approval.
 2 What does the FDA regulate? Obviously, you
 3 know that we regulate drugs. In addition, we
 4 regulate medical gases, which is kind of an
 5 interesting segment that we control, and also
 6 devices.
 7 This is actually a timeline. I thought it
 8 was an interesting timeline because it gives you a
 9 perspective from the late 1960s to roughly around
 10 2000 as to what drugs were approved that are used
 11 for sedation. A lot of these are used for sedation
 12 off label. The only drugs that are on label for
 13 ICU sedation include the propofol, the midazolam,
 14 and the dexmedetomidine, which are highlighted in
 15 red.
 16 Obviously, since 2000, we're almost two
 17 decades later and we're still -- we haven't come up
 18 with any new options. We would love to see some
 19 new drugs come out to address the ICU sedation
 20 challenge as well as just sedation in general.
 21 Among the compressed medical gases, there
 22 are gases called the designated medical gases, and

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1 these gases include the list there that you can
 2 see. The interesting thing is that nitrous oxide
 3 is the only agent with properties that might be
 4 useful for sedation, however, it's typically used
 5 for short-term procedural sedation, and that's an
 6 off-label use of that drug.
 7 As an anesthesiologist, I was amazed when I
 8 first arrived at the FDA and started learning about
 9 these medical gases, that inhalational anesthetics
 10 are not medical gases; they're actually drugs. I
 11 thought that was a unique perspective.
 12 With respect to devices, the FDA also clears
 13 devices for uses, and these devices would
 14 potentially provide an objective measure of brain
 15 function that might be helpful in the setting of
 16 ICU sedation. An example is the BIS monitor, which
 17 was cleared in 1996, primarily for use in sedation.
 18 It's been around for quite a while, and it's been
 19 studied in several different settings. I did find
 20 one publication in 2018 that looked like in
 21 patients with severe traumatic brain injury, that
 22 the BIS had some benefits over the RASS.

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1 When we look at the FDA, the indications
 2 that have been used that incorporate the concept of
 3 sedation include the sedation, anxiolysis, and
 4 amnesia during therapeutic and diagnostic
 5 procedures, and that's the procedural sedation
 6 that's already been addressed through this
 7 organization, and also the sedation of intubated
 8 mechanically-ventilated patients for treatment in
 9 the ICU setting.
 10 Let's skip this slide because you guys
 11 already know that. So I'm going to go on now and
 12 talk about defining the effect. This is a slide
 13 from probably -- most of you have seen this. It's
 14 the sedation continuum. It's like what we were
 15 taught as anesthesiologists about sedating patients
 16 for therapeutic or diagnostic procedures. Of
 17 interest, it's a pretty simplistic looking diagram.
 18 It's like, okay, it make sense, but again, how do
 19 you define minimal, moderate, or deep?
 20 The FDA has never really even evaluated a
 21 medication for minimum, moderate, or deep. And as
 22 you mentioned before, a lot of these agents came

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1 out of anesthesia that were then used in the ICU.
2 That's another, I think -- I think there was some
3 bias early on because they were using this type of
4 approach.
5 Thank you, Denham. I know that I'm using
6 the slide you used earlier, but I found this slide
7 incredibly fascinating and a bit overwhelming.
8 What I did want to point out from this, which I
9 thought was very interesting, is that this author
10 described this triad of pain, agitation, and
11 delirium as the ICU triad. He also made analogies
12 to the anesthesia triad. So I liked that aspect,
13 and I thought it was worthwhile to kind of think
14 about that in terms of how to manage ICU sedation.
15 The goal of the anesthesia triad was to
16 develop a balanced anesthetic. We were taught to
17 basically always think of amnesia, analgesia, and
18 muscle relaxation when we were planning an
19 anesthetic for a patient. There are lots of
20 different ways to achieve those things, but you
21 want to have each element to actually provide a
22 balanced anesthetic.

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1 I had a colleague -- this was quite a while
2 after I was out of training -- who decided to do a
3 short-term case with just remifentanyl in a young
4 guy, and the anesthetic -- the vital signs were
5 perfect, however, the patient remembered
6 everything. So that was a good lesson in making
7 sure you have everything covered.
8 The ICU triad that was mentioned in this
9 paper includes the pain, agitation, and delirium
10 with the goal of a coordinated approach. I know
11 we're not really talking much about delirium, that
12 that's not a high priority, but I felt like it was
13 worth putting into this -- just for the concept of
14 the triad.
15 Pain is typically opioids, however, if a
16 patient has neuropathic pain, you may be adding in
17 different medications to help address that.
18 Regional anesthesia is actually becoming quite a
19 prominent option for pain management. Every since
20 ultrasound-guided regional anesthesia came about,
21 we've been putting a local anesthetic in the
22 [indiscernible] plane we can find. So it may have

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1 a greater role in the ICU setting.
2 Agitation is really a normal brain in an
3 abnormal situation, and that's where we've been
4 using dex and propofol mostly. The delirium
5 becomes a little bit more complicated because
6 there's an underlying pathology of the brain. The
7 problem with that of course is that there are risk
8 factors associated with some of the drugs that we
9 normally would give for sedation. Fortunately, dex
10 has probably the lowest prevalence of delirium
11 associated with it, but it's not without its own
12 problems.
13 We're going to talk a little bit now about
14 measuring the effect, and I think some of these
15 were already mentioned, but I'm just going to go
16 through them quickly. Challenges to ICU sedation
17 sedation trials would be what will be the
18 comparator. As was mentioned in the previous
19 lecture, we're talking about will the comparator
20 actually be the current practice since the
21 combination drugs are usually what are utilized.
22 How will the patients be randomized? Will

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1 they be already on a sedation regimen or will it be
2 something newly initiated?
3 How will you create standardization and
4 protocols? This I think is kind of tricky because
5 you want to standardize as much as possible, but
6 you have to give people a certain level of
7 flexibility because everybody has their own bias or
8 own comfort level I should say with certain
9 medications. How do you deal with
10 discontinuations? Also, some of what's been
11 obviously a very important part of the discussion
12 today is how to measure long-term patient outcomes.
13 Trial design, superiority has always been
14 kind of the gold standard for the FDA because it's
15 easier to interpret. But there are some other
16 options. Besides just the placebo-controlled
17 trial, you could use a placebo in an add-on trial
18 and you could also use an active control.
19 It seems like noninferiority trials are
20 becoming more prominent; at least I've seen more of
21 these lately. I know you guys probably already
22 know what a noninferiority trial is, but the point

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1 is that the new treatment may have similar efficacy
2 as a standard drug, however, it may offer some
3 additional advantages such as fewer side effects
4 and easier to administer.
5 Desirable attributes of an endpoint that we
6 look for are the endpoint should be clinically
7 meaningful. Does it give us a direct measure of
8 how the patient feels, functions, or survives?
9 Does it provides clinically relevant and convincing
10 evidence directly related to the trials primary
11 objective?
12 Is it reliable, which means consistent and
13 reproducible? Is it sensitive, which allows you to
14 detect changes in the treatment effect? Is it
15 readily measurable and does it reflect accepted
16 norms and standards in the field? The endpoint
17 should be carefully defined in the protocol with
18 its rationale just to make sure that you're really
19 measuring what you're planning on measuring.
20 What are the considerations when defining an
21 outcome measure? These are also known as clinical
22 outcome assessments, and we want to know is the COA

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1 appropriate for a clinical trial intended for drug
2 development? Is there an appropriate target
3 population? Can it identify signs and symptoms
4 that would constitute a clinically meaningful
5 benefit in the target population if improved? And
6 will it allow you to establish the magnitude of
7 change in the score that will provide convincing
8 evidence of a clear benefit?
9 One thing I've learned a lot at the FDA is
10 statistical significance and clinically meaningful
11 or not the same thing, and we are much more
12 interested in seeing case reports that show us
13 really a clinically meaningful benefit.
14 I went back and looked at our previous
15 marketing approvals. It was pretty slim.
16 Midazolam was approved in 1985. Diprivan, again,
17 was initially approved in '89 primarily for
18 anesthesia, but then it was approved in 1993 for
19 ICU sedation. Precedex was our most recent
20 approval, which was 1999.
21 Of interest, the assessment tools for the
22 most recent approvals, Diprivan and Precedex, they

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1 used the Ramsay scale. However, as you are well
2 aware, there are limitations to these drugs.
3 Propofol has accumulation as well as the risk of
4 PRIS. Dex can cause tachyphylaxis and adrenal
5 suppression, and midazolam also has a problem with
6 accumulation, and it may be a risk factor for
7 delirium, so we're really in need of some new
8 drugs.
9 I wanted to talk a little bit about the
10 Precedex trial to give you an idea of how this was
11 approved. Sedative properties of Precedex were
12 evaluated into adequate and well-controlled trials.
13 It was dexmedetomidine compared to a placebo
14 control, and they evaluated the manner of rescue
15 medication required to achieve a Ramsay sedation
16 scale of greater than or equal to 3. One of the
17 trials they used midazolam for rescue; the other,
18 they used propofol. The duration of the trial was
19 24 hours.
20 We think that probably 24 hours is too short
21 of a time; 48 would probably be more appropriate.
22 Obviously, I'll talk a little bit more about the

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1 Ramsay scale on the next slide.
2 What was interesting to me, when I looked at
3 this Ramsay scale and what their criteria was,
4 which was great than 3, I thought, wow, that's like
5 a broad swath of sedation. That could be anywhere
6 on that spectrum, and it didn't seem to be very
7 patient driven.
8 The other thing to determine was the fact
9 that level 6 is comatose like we discussed, so
10 really, what value is that, unless you need a
11 patient absolutely still and unresponsive.
12 Fortunately, the scales have improved. As some of
13 the studies that were previously discussed, there's
14 a lot more granularity in this scale for two
15 reasons. One, the Ramsay scale just has one number
16 for agitation, whereas this gives you greater
17 options for determining agitation. In addition, I
18 like the fact that there are levels that respond to
19 verbal stimulation, and then those that need a
20 heavier level of sedation.
21 So I think that this obviously is a more
22 effective tool, but I'm not going -- I think that

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1 I'm not going to say that this is the effective
2 tool. It's just a newer tool than the Ramsay, so
3 obviously it was designed to give more information.
4 I'm not going to talk about this very much
5 because you all know about all these assessment
6 tools, and I've just created not a comprehensive
7 list but just an example of the tools that are
8 currently available.
9 Now, we'll talk a little bit about the
10 requirements for marketing approval, and I want to
11 talk about the CDER Clinical Outcome Assessment
12 Qualification program to finish up. Marketing
13 approval typically involves these elements, a
14 robust clinical program; adequate and
15 well-controlled trials, and typically it's two
16 trials; to provide independent substantiation of
17 the results. However, if it's not a new molecular
18 entity, we may be okay with a single trial if it's
19 a repurposed drug. We would just need a rationale
20 for that, but what's going to be your clinical
21 outcome assessment and is qualified?
22 Qualified, we'll talk about in just a

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1 minute. If you do create a unique scale, that's
2 fine, but you might want to consider getting it
3 qualified through the program that I'll discuss in
4 a minute. You'll need an adequate safety database,
5 and this again will depend on whether it's a well
6 known drug that we are familiar with or if it's a
7 new molecular entity that we have to get more
8 information on.
9 I'm going to talk a little bit now about the
10 Clinical Outcome Assessment Qualification program.
11 This is actually the website where you would go to
12 get some information about this program. There is
13 even an email address there that you can
14 communicate with people at the FDA.
15 I know this writing is rather small, but
16 this tells you a little bit more about what the
17 program does. It manages the qualification
18 process, it works directly with the requesters, and
19 it encourages collaboration and multidisciplinary
20 interactions.
21 Just to know, the COA qualification is
22 basically a regulatory conclusion that whatever

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1 assessment tool you're putting forth, that it
2 actually has psychometric features that we're
3 looking for. This particular program, like I said,
4 we're willing to let you design your own, but if
5 it's not qualified, then it may take a little bit
6 more work for us to agree with your study.
7 That's all I have today. Thank you.
8 (Applause.)
9 Q&A and Panel Discussion
10 DR. WARD: I suspect there are going to be
11 lots of questions, so I'd like to get a group up
12 here on the panel who have had some experience of
13 putting clinical trials together.
14 DR. SKROBIK: I have a question for Dr. Van
15 Clief. I am heartened that an institution like the
16 FDA would care about patients and their
17 experiences. Do you ever invite people to -- in
18 critical care, one of the challenges we've had over
19 the years in doing trials is that ethics committees
20 will often view ICU patients as being extremely
21 vulnerable, and therefore forbid doing any kind of
22 research rather than ask a question of these most

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1 vulnerable people. We've really been effective,
2 across Canada anyway, in militating for having at
3 least an ICU person come and pitch why it's so
4 important.
5 Is there a process for that kind of
6 clarification at the FDA? I mean it, because here
7 you are. You adjudicate the fate of things that
8 are game changers for people who want to implement
9 whatever. I'm curious what your outside input is,
10 if any.
11 DR. VAN CLIEF: Well, we evaluate studies
12 that come in sometimes before -- they're called IND
13 exemptions, so investigators take advantage of that
14 approach. If they have a supportive IRB that feels
15 like it's a safe study and we evaluate and we agree
16 that it's something that we don't need to do under
17 an IND, then that may be one pathway.
18 But the other pathway I think that more
19 addresses your concern is if you submit your
20 protocol under an IND, we have an opportunity to
21 give feedback and see how we can work with you to
22 maybe make that protocol safe enough to go forward.

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1 DR. SKROBIK: I apologize. I wasn't clear
2 enough because I talked about to things.
3 DR. VAN CLIEF: Okay.
4 DR. SKROBIK: When you decide whether you're
5 going to approve a molecule for use, you have an
6 inside panel of experts like you and there are
7 rules that you can go by.
8 DR. VAN CLIEF: Yes.
9 DR. SKROBIK: Do you ask anybody from the
10 outside?
11 DR. VAN CLIEF: Yes, we do. We have -- I'll
12 let my boss answer.
13 (Laughter.)
14 DR. ROCA: Hello. I'm Rigo Roca. I'm from
15 the FDA and the deputy division director in the
16 review division. So to answer your question, yes,
17 definitely. Particularly, if we have questions
18 about a new product, we're trying to figure out
19 what it means, we definitely, as was being
20 described, go through the development program with
21 the sponsor and all that. But at the very end, we
22 also have the opportunity for advisory committees.

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1 Within the advisory committee, we have a panel of
2 experts, but there's also a patient representatives
3 there.
4 There's also a section in the open public
5 hearing where patients can come up and share their
6 experiences, so what's important for them. The
7 panel takes all that into consideration. The
8 panel, the advisory committee members, then give us
9 their thoughts and recommendations, and we
10 assimilate the patient's information, the patient
11 representative on the panel, as well as the
12 committee.
13 So we definitely do that. But then there's
14 also something else that we do, and recently, that
15 you may or may not have heard is patient-focused
16 meetings. These are actually listening sessions.
17 We've had a couple. Most recently there was one
18 for opioid-use disorder, which was interesting to
19 find out what is important for a person who's
20 suffered from opioid-use disorder. And as you can
21 suspect, sometimes it's different than what we
22 thought was important.

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1 DR. SKROBIK: I belong to an opioid-abuse
2 community. That's why I'm smiling because the
3 patients say things that are completely different.
4 DR. ROCA: Exactly. There was also another
5 one several years back regarding -- I believe it
6 was debilitating neuromuscular disease, and we
7 felt -- well, it was in a different dimension, but
8 the FDA felt that what we needed to do was have a
9 certain degree of mobility, and I think one of them
10 was the ability to walk a certain distance. Out of
11 that meeting, what came out was that patients were
12 happy if their sibling or the family member was
13 able to just simply sit up. That was considered to
14 be something important.
15 So we do have those patient-focused
16 meetings, and we do use them to learn as to what it
17 is that's important for the patient. As you were
18 alluding to, sometimes it's different than we
19 thought.
20 DR. SKROBIK: Thank you.
21 MALE VOICE: Gilles, I think you're
22 moderating.

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1 MALE VOICE: Gilles or Doug.
2 DR. COURSIN: Well, I think someone with a
3 bow tie looks very professorial.
4 (Laughter.)
5 DR. COURSIN: I will defer to his kind
6 judgment.
7 DR. FRASER: You'll notice there are
8 lobsters here. That's no coincidence since I come
9 from Maine.
10 Today we've had I think a wonderful series
11 of presentations about the guidelines that we've
12 presented and the primary data that were formed as
13 a part of the guidelines, or actually the
14 guidelines were formed from the primary data.
15 We've looked at the methodology, and we've also
16 looked at the outcomes and the metrics that were
17 involved in getting those outcomes.
18 What I would like to open up with in this
19 particular session is where do we go from here?
20 What do we need to know in order to further the
21 science?
22 DR. SKROBIK: Just like that?

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1 DR. WARD: A question for Marti. I just
2 went on your website and looked at your COAs, at
3 least the PDF file that's up there. There aren't
4 any for any sedation. There's some for pain, which
5 is just a numerical rating scale or a visual analog
6 scale, but there's none that would apply to the
7 things we've been talking about through ICU
8 sedation.

9 Is it worthwhile to get some of these scales
10 that we've been talking about qualified? Should
11 the Ramsay scale be a COA, and is that worthwhile
12 to help future clinical trials to have that done?

13 DR. ROCA: I'm being told to say yes, but
14 actually the answer is yes. I think there are a
15 lot of advantages of having a qualified. As the
16 slide mentioned, it is a multidisciplinary team
17 that comes in and addresses it from all different
18 aspects. We have ongoing discussions with whoever
19 it is that is proposing to have a particular tool
20 or scale qualified.

21 So there is that ability, and then the nice
22 thing about it afterwards is that if a tool is

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1 qualified, as you are indicating, then it's
2 actually something that we have already looked
3 through and vetted as being a tool that could
4 potentially be used in different kinds of clinical
5 trials. Obviously, as the last sentence in there,
6 it depends that it's been qualified for a
7 particular use and a particular population, et
8 cetera, as most tools are, but still it would be
9 something that would be useful.

10 Now, the other thing that was mentioned was
11 that if you have a tool and you haven't gone
12 through the qualification process, you could
13 potentially still use it. We would use the same
14 multidisciplinary team to do that and assess it,
15 but then it's a little bit more within the review
16 time clock, and therefore we may not be able to
17 have as much interaction.

18 Furthermore, it's already a done deal, and
19 there's a possibility that at the end of that
20 assessment, at the end of the review clock, we may
21 end up concluding that it probably was not a tool
22 that could have generated the data that they felt

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1 it was generating. But that doesn't mean that you
2 can't use it; it's just that it might end up not
3 being as positive an outcome as you would have had
4 otherwise.

5 DR. MAZE: Can I ask a more structural
6 question or rather a foundational question? When
7 you have a scale like the RASS scale, which
8 obviously, as you said, is more granular, are the
9 biological foundations, neurobiologic foundations,
10 for those elements in the scale different?

11 In other words, when you're producing
12 sedation, you possibly need some different neural
13 pathways involved versus producing agitation, yet
14 you've got them in a continuum. Is there any
15 benefit in having a scale that is actually
16 continuous with respect to the neurobiologic
17 pathways that are involved?

18 DR. VAN CLIEF: That would be interesting to
19 entertain as a scale. I use that scale just as an
20 example of where we've come from the Ramsay to that
21 level. But I do think that whatever scale is
22 selected, you just really want to make sure it's

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1 going to measure what you're interested in looking
2 at and studying. I think the scale you're
3 describing might be difficult to develop, but it
4 would be very good to have.

5 DR. MAZE: I was kind of surprised at the
6 acronym PAD and PADIS, that sedation isn't
7 mentioned there, but agitation is mentioned there,
8 as if they are the same thing. I know Yoanna is
9 going to say --

10 DR. SKROBIK: I was going to say the amount
11 of discussion around the acronym was subjective,
12 more energy than I would ever want to admit. We
13 didn't have Dr. Dworkin around --

14 (Laughter)

15 DR. SKROBIK: -- for cued acronyms, so this
16 was the compromise that had to do with branding
17 with the similarity of the PAD. But just briefly
18 to speak to the point of the sedation scale and its
19 validation, the FDA metrics don't reflect the
20 previous guidelines effort, where we actually went
21 through all the psychometric elements of all of the
22 scales.

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1 What I am curious about is whether this
2 would be an opportunity because you were saying you
3 invite people to come and testify. Here we all are
4 talking about sedatives in the ICU. Would this be
5 an opportunity, without neglecting what we don't
6 know, to say, well, here's what we know; would you
7 like to integrate it just now; the things that we
8 have brought forward and that we have discussed and
9 agreed on? I think that might be one.

10 DR. ROCA: One of the things about a meeting
11 like this is that my role here is actually to
12 listen, and my role would be to help facilitate the
13 discussion, particularly if you have a question
14 regarding the process of how do we do things, what
15 do we need, and that I think might help the
16 discussion. But with respect to a decision, yeah,
17 this is what we need and this is what we should do,
18 I don't think I can do that.

19 There are particular reasons for that.
20 Number one, this is not really an all encompassing
21 audience, so therefore it would not be appropriate
22 for me to indicate what would be regulatorily

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1 appropriate or not. That would be one thing. The
2 other thing, too, it would be definitely drug
3 dependent, population dependent, and indication
4 dependent. There are so many variables.

5 DR. SKROBIK: You're talking about the
6 scales.

7 DR. ROCA: Definitely, scales as well. It
8 depends on what the company is proposing to have
9 their drug do. And they come to us, and they have
10 often asked us which scale we should use, and as
11 you can suspect, we really don't have one that we
12 can say, yes, this is the one you should use
13 because it really depends on what it is that
14 they're trying to have their product demonstrate
15 its efficacy for.

16 So we usually tell a company that they can
17 choose whatever scale they want, but they're going
18 to have to be able to provide supporting
19 information as to what that scale, or two, is the
20 most appropriate one for the patient population,
21 the indication, the drug, and all of those things.
22 We would take that into our review process, and

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1 then at the end, if we still have questions, we go
2 to the advisory committee. Therefore, the ability
3 for me to say anything regarding whether a
4 particular scale is more appropriate than another
5 in this setting would be very difficult.

6 DR. SHAFER: Mervyn -- Steve Shafer -- I
7 want to directly address your question. The idea
8 is, is there a neurobiology that you can tap into
9 here. By suggesting that there isn't with a
10 comparison to three different drugs, sedation with
11 propofol, and sedation with dex, and sedation with
12 ketamine, what would be very different experiences
13 from the patient perspective, most people find
14 propofol somewhat pleasant to actually experience.
15 Dex seems to be neutral. A lot of people seem to
16 find ketamine somewhat dysphoric at really high
17 doses.

18 They might look the same on the scale here,
19 but from the patient's perspective, because the
20 neurobiology is so different, I don't think you're
21 going to find a scale that you would put them all
22 on. In some ways, you'll have different scales.

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1 One is are you clinically achieving the effect that
2 you want from what you can measure in the ICU, and
3 that would be something like a RASS scale perhaps.

4 The other is then a more patient-centered
5 thing; what was the sedation experience like? And
6 as we heard from the earlier presentations from
7 Dave and Pamela, that can be quite different with
8 different drugs, and that would perhaps be an
9 orthogonal scale that might be captured as well.

10 DR. FRASER: In order to get to that point,
11 I think what you'd have to do is allow for
12 wakefulness so that you can gain some feedback from
13 your patient. And that is what I think is the next
14 step in terms of the sedation scales. They really
15 don't evaluate wakefulness, and they don't gather
16 data or feedback specifically from patients.

17 So I would ask this group at some point in
18 time, if there's appetite for revision of RASS or
19 revision of SAS, to include a wakefulness algorithm
20 such as what JP Kress actually developed in the New
21 England Journal of Medicine.

22 DR. SHAFER: You don't need a different

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1 scale on access. This is an orthogonal access to
2 assess something quite different.
3 DR. FRASER: Right. So you could use RASS
4 and then supplement it with wakefulness.
5 DR. EGAN: Talmage Egan. It seems that one
6 of the problems with these sedation scales that
7 have arisen for use in the ICU is that they don't
8 seem to have methodologically as rigorous a
9 foundation just in terms of how they were
10 validated. In the procedural sedation domain,
11 although it's got problems, the Modified Observers'
12 Assessment of Alertness and Sedation, the so-called
13 MOAS scale, has really sort of become the main one
14 used in clinical trials.
15 The reason is simple. There's quite a
16 rigorous methods paper that quantified the
17 inter-observer variability, and there are also some
18 training materials that are available -- this was
19 alluded to earlier -- that one can use to train the
20 study personnel.
21 I've seen that there's some room for that
22 here. There are these various scales. They seem

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1 to be used because it's what other people have used
2 and there's lots of clinical experience with them.
3 But perhaps some quantification of the
4 inter-observer variability and some training
5 materials would be useful, especially as it relates
6 to quality controlling of the studies for
7 regulatory purposes.
8 DR. RIKER: There is data available for both
9 of the scales. The 2013 PAD guidelines highlighted
10 some of that, then there was a separate publication
11 that looked just at the psychometrics of the
12 sedation scale piece. There have been a number of
13 inter-rater reliability studies and some validation
14 studies. There are educational things out there.
15 So it may not be at the level of the MOAS scale,
16 but there certainly are things out there.
17 DR. EGAN: Experts in the area that do these
18 trials, are you guys satisfied with the overall
19 robustness of the scales? Are they missing some of
20 these attributes? What's the key piece that's
21 missing?
22 DR. RIKER: I'll give you my opinion. This

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1 is Riker again. I think Gilles put his finger
2 right on one of the issues, and that's what do they
3 really measure? If you open your eyes, but that's
4 all you do, what is that telling us? Are you
5 awake? Are you able to follow commands? Each of
6 the two scales that have been highlighted look at
7 different things to get to their endpoint.
8 I think one of the issues is in addition to
9 the complexity of reliability, is it really
10 measuring -- or can we both say the same thing, and
11 then validity, is it measuring what we think it is?
12 As trial designers, how do we use that information?
13 What are we targeting? How do we best apply that
14 level when and in what way? So it's kind of a
15 pharmacokinetic/pharmacodynamic kind of thing. We
16 can measure it, but then what do we do with that
17 information and what are we trying to do with that
18 information.
19 DR. COURSIN: Well, but there's wakefulness
20 and wakefulness. I mean, are you looking at
21 wakefulness with cognition? And if you're looking
22 for cognition, what level of cognition? I mean, we

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1 can give them a computer game, and can they flip
2 cards quickly and tell us they have 21? Can they
3 make executive decisions?
4 That again also morphs into what Steve's
5 referring to, which seems to be, I'm awake, but I'm
6 delirious, and that seems to have two factors I
7 want. Ultimately, in the ICU, we don't want you
8 jumping out of bed and hurting yourself. We don't
9 want you in bed if you don't have to be in bed.
10 And we don't want to be giving you something if you
11 don't need it.
12 Now, those are three simple statements, but
13 I'm not sure how to put them into a MOAS type
14 scale. Clearly, just tapping somebody's glabella
15 and having them blink was pretty simple; never
16 particularly well validated. That's Ramsay, which
17 had been the gold standard. I think the RASS and
18 SAS scores are a good stride beyond that, but I'm
19 not really quite sure either what we want by saying
20 wakefulness or whether we're necessarily going to
21 be able to quantify what we want.
22 DR. FRASER: JP?

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1 DR. KRESS: I think Doug spoke to the same
 2 question I was going to ask, is wakefulness a
 3 bivariate outcome or shades of gray? So I don't
 4 need to reiterate that.
 5 I actually have a question for Rich. You
 6 talked about the importance of the control group in
 7 your review, and I think it's really important. As
 8 we move forward, of course the competition with the
 9 control group continues to get tougher and tougher
 10 because we learned things. That's good.
 11 As we think about moving forward, should we
 12 think about control group as a regimented approach
 13 or some people talk about this so-called wild type
 14 where you just basically let the care providers do
 15 as they wish. I wonder if you have any thoughts
 16 about that.
 17 DR. RIKER: It's a great question, JP, and I
 18 think the idea of pragmatic trials or adaptive
 19 trials, I hope we're going to talk about that later
 20 on in the meeting. I think it looks like we will
 21 be. But the old intervention control, RCT, power
 22 sample calculation, I think we're really bumping up

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1 into the limits of that for our population.
 2 You look at the complexity of our patients,
 3 the varying populations we have, and I think it
 4 makes it really hard to -- the concept that a
 5 general ICU patient is interchangeable with another
 6 general ICU patient, I don't think that works as
 7 well anymore. So splitting, lumping, which is the
 8 right approach? It's pretty darn complex, but I
 9 think you're right on target that we have to ask
 10 that question. I don't know what the right answer
 11 is, but I think we have to ask that question.
 12 I want to say one other thing. Wakefulness
 13 may mean different things depending on how we want
 14 to use that information. In other words, if we
 15 want to see is our patient awake enough to tell us
 16 how much pain they're having, or is the patient
 17 awake enough to do a delirium assessment, that
 18 might be a different kind of wakefulness assessment
 19 than if I keep my patient above a certain level of
 20 non-wakefulness, do I reduce their long-term
 21 outcome problems? So different issues may need
 22 different levels of wakefulness and potentially

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1 different assessments of wakefulness.
 2 Tim, excuse me, and then Pam. Tim, you had
 3 a comment?
 4 DR. GIRARD: This is Tim Girard. I agree
 5 with what Rich just said. Just to take that
 6 thought even further, I feel like one area that we
 7 have a gap is the relationship between all of the
 8 various ways that we're describing, looking at
 9 wakefulness or consciousness and the various
 10 outcomes that we and patients care about.
 11 For example, I think, Gilles, you're
 12 referring to the process that JP used in his early
 13 [indiscernible] sedation trial following commands.
 14 There's definitely a lot of value in being able to
 15 follow a command. But for example, if your
 16 decision is whether or not to extubate a patient
 17 and if they're alert enough for that, I'm not aware
 18 of any data that suggest -- even though it's
 19 sometimes used at the bedside, I'm aware of no data
 20 that suggests that your ability to follow commands
 21 predicts your likelihood of passing and extubation.
 22 Alternatively, there may be other very

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1 important patient-centered outcomes that are
 2 related to your ability to follow commands.
 3 Certainly, a patient who is delirious often does
 4 not follow commands, and there are a lot of data
 5 suggesting that delirium is related to both short-
 6 and long-term outcomes.
 7 So the issue is quite complex, as we all
 8 said, and I doubt that there's a single, easily
 9 applied scale that's reliable that can capture all
 10 of this, the content of consciousness, the level of
 11 arousal. It's unlikely, in my opinion, that a
 12 single scale would do that.
 13 However, the two scales that are recommended
 14 by the SCCM guidelines -- and I was not on any of
 15 the guideline panels, so I don't have any, I don't
 16 think, bias in this respect. But both of those
 17 scales were very well validated. The reliability
 18 has been studied in numerous environments and in
 19 numerous studies, and it's been shown that both the
 20 SAS and the RASS are very reliable and that they
 21 are valid in terms of measuring the constructs that
 22 they were intended to measure against multiple

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1 other reference standards. So I think at least for
2 what those tools are supposed to do, which is
3 measure level of arousal, then they are valid in
4 that context.
5 DR. COURSIN: One thing from Pam as well is
6 the question of, okay, we want wakefulness. What
7 about restorative sleepfulness? I'd like you to
8 comment.
9 DR. FLOOD: I'll answer that second. Not to
10 make matters more complex, but I was going to speak
11 to cognition because I don't think anyone really
12 wants to play 21 in the ICU. Well, maybe if
13 they're intubated, it's something to do. But
14 there's pleasant cognition and unpleasant
15 cognition. There's being peacefully sedated and
16 being aware of your surroundings, and then there's
17 being frightened, and distressed, and so on and so
18 forth.
19 So you might think of that as being
20 described with the continuum of sedation versus
21 agitation, but that's only the behavioral
22 manifestation. You might not know what the -- it's

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1 very hard to know what the patient's feeling. I
2 think David and I both spoke to the feeling that
3 everybody thought we were asleep, but we weren't,
4 and we weren't able to sleep, and we were very
5 fatigued.
6 So getting to your question, the more and
7 more I know about the nature of sleep makes me
8 realize I know less and less about it. But getting
9 real sleep in an ICU setting, at least from what I
10 understand in terms of people who study sleep, this
11 is next to impossible. So I think a better
12 question is what can you do to do the best you can
13 with that and to limit fatigue.
14 DR. COURSIN: Denham?
15 DR. WARD: In your discussion, you get a
16 little bit on inclusion criteria and exclusion
17 criteria. Well, one -- let's see if I'm quoting
18 this right -- would be that the first 24 hours is
19 important to the outcomes. For most of the studies
20 that you looked at it and I've looked at, too,
21 that's usually not an inclusion criteria; usually
22 it's after 24 hours. So it would seem like one of

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1 the concepts that we're coming to is that patients
2 should be included much earlier into a sedation
3 study that is within the first 24 hours.
4 Are there other inclusion/exclusion criteria
5 that -- I reviewed a number of studies just to
6 educate myself, and one of the things that I rarely
7 saw was a history of drug or alcohol abuse as an
8 exclusion criteria, that is, is withdrawal going to
9 be complicating the other measurement of these
10 things? But most studies never mentioned
11 opioid-use disorder as a premorbid condition or
12 alcohol-use disorder as a premorbid condition.
13 What's your thinking about
14 inclusion/exclusion criteria?
15 DR. FRASER: The more we exclude to try to
16 provide homogeneity in our cohort, the less
17 generalizable that information is. Maybe efficacy,
18 effectiveness, there are a lot of issues that go
19 into what you're trying to accomplish with your
20 study.
21 I'm speaking way over my head here, and I
22 hope when Dan gives his presentation or our other

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1 future discussions about design, we'll get to this.
2 But we've heard of adaptive responsive kinds of
3 studies and platform design studies that may allow
4 us to recognize specific risk factors and emphasize
5 them or better understand the role they play.
6 Hopefully, as we move into the future, we
7 get away from this black and white intervention
8 control thing and more into design that allows us
9 to try to answer some of these questions, not by
10 excluding those patients but perhaps by including
11 them and building that into the design, so I don't
12 know.
13 DR. COURSIN: Sir, in the back?
14 DR. DWORKIN: Rich, my recollection is that
15 you and I first met at an FDA meeting on sedation
16 about half a dozen years ago -- it's a long time
17 ago -- that discussed both procedural and ICU
18 sedation. My recollection is that one of the
19 conclusions of that FDA-sponsored meeting -- this
20 was before ACTTION had anything to do with
21 sedation -- is that in the ICU setting, the target,
22 if you will, that patients would find most

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1 desirable is calm and comfortable.
2 So being from outside the field and sitting
3 here all day, I'm a little surprised that that
4 meeting six years ago ended up with calm and
5 comfort being objective of ICU sedation. I haven't
6 heard that so far today. I've heard a lot about
7 sedation and a lot about agitation, but nothing
8 about calm and comfort.
9 Is that a reasonable measure to think about
10 developing, ICU calm and comfort?
11 DR. RIKER: Yes. I think everybody in this
12 room is going to give you a little bit different
13 answer, but I think from my perspective, the
14 evidence, especially six years ago, that supports
15 that claim is quite thin. It's a thing that makes
16 sense. We know the evils of deep sedation; we try
17 to avoid those. We have a little understanding
18 about the evils of not enough sedation, and
19 probably for the majority of patients, we err more
20 on the side of too much sedation rather than not
21 enough sedation.
22 But I think we've heard even within our two

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1 patient representatives today how complex that
2 issue is and that there may be patients who are
3 awake and don't want to be that awake, or patients
4 that are calm but not cognitively intact enough to
5 be comfortable and want to be more awake, and our
6 ability to assess that and understand that is quite
7 limited right now.
8 So it's a great question, but I don't know
9 how much evidence there is supporting that concept.
10 DR. COURSIN: Dale, you had a comment?
11 DR. NEEDHAM: Just as a clinician, not sort
12 of an expert, I want to reflect back what I'm
13 hearing or my biases. I think that we've talked a
14 lot about sedation scales, but I think most people
15 agree that they're not patient-centered outcomes.
16 I think I've heard people say that we probably need
17 development of a patient experienced measurement,
18 which would be totally patient centered around the
19 type of sleep that would be complex to develop and
20 acquire time to develop, and think about, and
21 validate, and reliability.
22 But then we need to reflect on what is

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1 patient centered. And for FDA or other purposes,
2 are we okay with something that's health care
3 centered? There may be something that there's no
4 patient-centered impact, but it reduces our
5 mechanical ventilation duration length of stay.
6 Are those four accurate?
7 DR. RIKER: One of the things I really liked
8 about what you said is that patient-centered
9 assessment tool. And ideally, that would be a
10 real-time assessment tool as well, not a
11 retrospective how was your stay in the ICU, so that
12 we could respond to that answer.
13 DR. NEEDHAM: To give you an example, we've
14 got an R01 from NINR looking at laryngeal injury,
15 and in fact when patients are awake, we're asking
16 about symptoms related to potential laryngeal
17 injury. And we've had to take other instruments
18 and figure out how can you do it in a patient with
19 an endotracheal tube in order to try to understand
20 the symptoms that patients are feeling and whether
21 those symptoms are then relevant to a subsequent
22 outcome; so I think a little bit about a process

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1 there and how we may need something like that
2 perhaps to understand patient experience.
3 DR. COURSIN: Tim?
4 DR. GIRARD: Tim Girard. In theory, I agree
5 completely, Dale, but in practice, I think there's
6 a huge problem, which you, and I, and Elizabeth
7 have discussed extensively, which is that to
8 measure something like that in the setting that
9 we're discussing, you will have a huge amount of
10 missing data because there will be patients who
11 cannot respond at various times, and that missing
12 data may very likely be differential between
13 different treatment groups.
14 So I would agree that using a
15 patient-centered, real-time response would be a
16 helpful adjunct to understanding what the effects
17 of the different therapies that we're studying are,
18 but I would argue that it could not be a
19 stand-alone because you would end up with too much
20 missing data, and that that different data would be
21 differential.
22 DR. COURSIN: Michele?

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1 DR. BALAS: I'm going to have to agree with
2 that comment as well. I think it would be
3 wonderful to have such a measure, but we're doing a
4 small study right now, and we're just trying to
5 measure anxiety -- again, the reason people give
6 for giving sedation -- and we're missing it on over
7 85 percent of the patients because of their level
8 of arousal.
9 So to have a patient-centered outcome
10 report, the patient would have to have some level
11 of arousal, some level of consciousness, however we
12 define that part, just to measure these other
13 symptoms or to get their perspective. And what
14 we're finding in clinical practice and with our
15 work with the SCCM ICU Liberation outside of
16 clinical trials, patients aren't at that basic
17 level. Even though everybody's charting our goals,
18 0 to minus 2 right now, when you go in and you do
19 those direct observations, they're charted minus 1,
20 minus 2, and they're still deeply sedated. They're
21 still in a coma, most of them.
22 So there's a huge disconnect between I

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1 think -- the validity and reliability of our tool I
2 think is solid in terms of research, but I think
3 that inter-rater reliability again, even in
4 clinical trials, is kind of suboptimal, and
5 clinical practice, I'm going to argue it's pretty
6 nonexistent.
7 DR. COURSIN: Dale?
8 DR. NEEDHAM: I would agree with everything.
9 I think it couldn't be a primary outcome. It may
10 be something that allows us to get some insight
11 into that. I was talking earlier around meeting
12 for mixed methods study so we actually get a
13 qualitative experience, and I think it's maybe a
14 tiny bit like delirium, where there may be a group
15 of patients where we can't assess it and then
16 there's a group that we can, and then we need to
17 figure out what is the statistical method to look
18 at these two different -- like where one group of
19 patients can't even have it assessed, and that may
20 mean something in whether it's compensated, or a
21 two-part model, or I don't know what.
22 DR. COURSIN: John?

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1 MALE VOICE: I don't think it could ever be
2 a primary outcome because of that problem.
3 DR. DEVLIN: The other quick comment I
4 wanted to make was in our PAD guidelines, we,
5 obviously as everybody knows, found widely
6 divergent restraint use, highly prevalent in the
7 United States, very low in Europe. So I think that
8 kind of plays a role; and with that, the
9 nonpharmacologic things that could affect
10 agitation, I think being certainly rehabilitation
11 or mobility, and that whole interface that has
12 really nothing to do with what we're giving for a
13 sedative or could drive sedative use.
14 DR. COURSIN: Steve, you have a comment?
15 DR. SHAFER: It's a question actually. I'm
16 having a little bit of a challenge here. It's a
17 question for the entire panel. Let's say that I'm
18 a magician and I can actually produce a drug that
19 does anything you want. I'm trying to figure out
20 in terms of what we're talking about here, what
21 claim would you want that drug to be able to make
22 to actually give you a better patient-centered

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1 outcome for sedation?
2 A lot of ICU trials look at survival, which
3 is a great thing to look at when you're in the ICU,
4 and that's a wonderful thing. A lot of stuff in
5 the area of sedation looks at surrogate endpoints,
6 time to extubation, extubation-free days and things
7 like this, but those are surrogates.
8 What claim -- you've done all these clinical
9 trials, FDA, introduced dexmedetomidine. What
10 claim would a magical drug that I could give you
11 make that you would actually study and then take to
12 the agency, and the agency would say, yes, this is
13 a valid claim to make for a product?
14 DR. COURSIN: I'd like to be 25 again, I'd
15 like to know what I turn out, and I'd like to have
16 a full head of hair.
17 DR. SHAFER: You've got it.
18 (Laughter.)
19 DR. MAZE: In the dex trial, all we set out
20 to do was to show that it was a sedative in the ICU
21 patients by virtue of the reduction in risk of
22 medication. That's not a very good endpoint as we

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1 now know. It just demonstrated that this drug
2 falls into a particular class but didn't tell us
3 anything about the effectiveness versus other
4 drugs.
5 For example, the lack of that
6 placebo-controlled group -- rather, the use of a
7 placebo-controlled group with rescue medication was
8 what we used rather than a more comparative
9 effectiveness type of trial, comparing it against
10 perhaps midazolam or propofol at that time. So I
11 don't think we did a great job at defining the
12 endpoint. It wasn't my idea, so I can criticize
13 it.
14 DR. RIKER: I'll throw something out as a
15 straw man, and then everybody else can weigh in.
16 Maybe it allows you to be calm and responsive so
17 you can say I'm having pain, I want to be more
18 deeply sedated, there's an IV sticking in my left
19 hip that hurts a lot, and doesn't have adverse
20 effects like hemodynamic compromise, cognitive
21 impairment, doesn't make your platelets --
22 DR. COURSIN: But it's not fair -- all the

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1 classics; it's not fair --
2 DR. MAZE: It sounds great, but we had a
3 name for that. Remember, we called that cognitive
4 sedation.
5 DR. COURSIN: Yes.
6 DR. SHAFER: But then how do you get that to
7 become an FDA claim on a label?
8 DR. FRASER: You can measure the degree of
9 participation in care that influences outcomes like
10 early mobility for example. I think that's a
11 measurable metric.
12 DR. COURSIN: Avery, do you have a comment?
13 DR. TUNG: Taking a page from the anesthesia
14 playbook where most patients would prefer general
15 anesthesia if you gave them a choice -- and in
16 fact, we're finding in our hospital satisfaction
17 with general greater than satisfaction with
18 regional.
19 Here's a claim: allows deep sedation
20 without any of the length of stay, long intubation,
21 delirium, and outcome drawbacks of deep sedation.
22 There's a claim you could make.

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1 DR. RIKER: But do you think families would
2 buy into that? Would families want you to be in a
3 box for 3 days or 4 days, and not awake and not
4 responsive?
5 FEMALE VOICE: I'm not sure all patients
6 would want that either. I wouldn't.
7 DR. TUNG: If your entire ICU stay would
8 pass by and you wouldn't even know it was there,
9 then that might not be so bad. There have been
10 daily sedation interruption trials stopped because
11 the families didn't like them.
12 FEMALE VOICE: It depends on the stress.
13 DR. VAN CLIEF: I just want to make a
14 comment about the indication that goes into the
15 label. It really is a description of what the drug
16 does. And if you go beyond that and say, well, it
17 provides a deep level of sedation and x, Y and Z
18 happened, we won't necessarily accept that because
19 those are promotional claims, and we're not there
20 for promoting, but we want to describe what the
21 drug does.
22 DR. SHAFER That's what I'm sort of asking,

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1 for the outcome. What outcome that they can define
2 and you can falsify; it either happened or didn't
3 happen in the trial.
4 DR. VAN CLIEF: Right.
5 DR. COURSIN: Claudia, did you have
6 something?
7 DR. SPIES: Yes, I have several comments.
8 The point is I fully agree with what Timothy said
9 also about the scores and all those things. I
10 think that's validated, it's globally used, and I
11 think in many settings it's validated. That's the
12 first part.
13 The second part is I think it's not so easy
14 to say that the scores are really those that, at
15 the end, are the relevant thing because you
16 haven't -- if you aim a RASS score, that doesn't
17 mean you achieve it. This is one of the points.
18 Even if you try to achieve it, it's context
19 sensitive. That means all the nurses, all the
20 staff, 24-7 has to agree on that.
21 That means, also, if you have a sedation
22 procedure that's really adapted to awake,

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1 cooperative, calm, not anxious, whatever people, I
2 think if you're really take that serious, I think
3 you also have to do other things. That means other
4 groups need to be involved, like physiotherapy for
5 example. So if you don't use your muscles in the
6 first 3 to 4 days, you also lose muscle strength.
7 So it's a lot of composites that need to be
8 defined, and I think what we need is a protocol
9 violation of all studies. I think that's something
10 I will try to have in all of the studies, how many
11 protocol violations do you have due to all that
12 noise you have, and then you make a decision how
13 you can improve that. That's nothing that's bad
14 for the study. I think that's very good if you do
15 that.
16 I think I'm probably trying to convince my
17 colleagues to do it. It's not so easy, but I think
18 it's the way to be honest to the patients, and then
19 not to get reimbursed at the end for the outcome.
20 The outcome is a measurement. I think what's
21 better is if we really stick to that what we
22 believe in and what is evidence based, what we

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1 researched. Then at the end, if we really do that,
2 what we think we should do, and then at the end, we
3 measure an outcome, and then we see if the patients
4 really have these outcomes, and then we need to
5 change the studies.
6 But I think that's something -- the majority
7 of the studies, at least what I read from all IPEC
8 journals is that the point is that the protocol
9 violations are not given. I know from my studies
10 at least that it's not so easy to do it, and I can
11 tell you I'm fighting with that all the years, and
12 I need help for that.
13 DR. COURSIN: Yoanna?
14 DR. SKROBIK: I think there's a dichotomy in
15 what I'm hearing over the last several points that
16 were made between the wish to find one dichotomous
17 administration and the need to individualize, and
18 to individualize not only based on patient
19 preferences. I would consider being sedated deeply
20 a violation of my personal rights, and I know
21 50 percent of my patients would disagree with that.
22 How do you then choose one answer if the

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1 population's that different?
2 The technology assessment unit at McGill has
3 just gone through the exercise of asking the
4 question, what should determine what you consider
5 standard or the best, as decreed by the technology
6 assessment unit, but it also applies to drugs. And
7 they've come up with a very interesting model that
8 doesn't actually look at the evidence in specific
9 populations but integrates the contextual elements
10 that you talk about.
11 You have a donor in one institution that
12 wants you to study fear and anxiety. Well, maybe
13 you're going to add that to your questionnaire in
14 that institution because then it will be reliable
15 because you're going to have an extra \$19 million
16 to do it.
17 So with the adaptability, considering the
18 inter-individual variability between the patients
19 receiving the intervention, the carers giving it,
20 and the specific institution -- I can't get my head
21 around the dichotomy between the one model, what
22 would the FDA recommend, as if there were one

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1 model, and what I'm hearing about there being
2 many -- the personalized approach, whether for the
3 individual recipient or the individual place.
4 DR. COURSIN: Mervyn, you had a comment?
5 DR. MAZE: I actually have a new question if
6 you don't mind.
7 DR. COURSIN: All right.
8 DR. MAZE: We've spoken exclusively, really,
9 about symptom mitigation versus disease
10 modification. I presume in the ICU that is a
11 problem because you're dealing with a plethora of
12 diseases. But I would hazard a guess that
13 inflammation is consistently present in your ICU
14 patients, and I'd like to hear an ICU patient that
15 doesn't have that.
16 So to what extent are their attempts to
17 modify the disease in order to mitigate the
18 symptoms?
19 DR. COURSIN: Well, there's a huge trail of
20 tears of failed therapies that have attempted. And
21 one of the major problems was everyone was a single
22 magic bullet, anti-tumor necrosis factor;

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1 interleukin 1; complement this, complement that.
2 It also speaks to the fact we've had one drug in my
3 lifetime approved primarily for ICU use, and I'm
4 still waiting for the first therapy that we can
5 absolutely say was developed in the ICU that made a
6 bit of difference. But older, sicker people
7 survive in the ICU. We don't know why.
8 DR. MAZE: Right. I think my view of where
9 the immunology, inflammatory response field is
10 going is that this magic bullet, this
11 anti-inflammatory, whether it be anti-TNFL, or Cox
12 inhibitors, or whatever it is, that that approach
13 is in fact not the correct approach because it
14 interferes with some of the repair processes that
15 have to occur. And what's more, you often don't
16 know where the patient is in the inflammatory
17 response at any one time.
18 So I think the problems with that TNF-alpha
19 sepsis study could be that there was such a
20 heterogeneity of the patients at where they were in
21 their SIRS or non-SIRS. But the field now has gone
22 to inflammation resolution rather than

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1 anti-inflammatory, and that's a big difference
2 because what you're saying is we're going to
3 trigger a new response in the patient or we're
4 going to enhance the existing responses in the
5 patient's recovery from that inflammatory process.
6 DR. COURSIN: A lot of food for thought.
7 I'm getting a signal from the boss that we are at a
8 break time, and we will have to get to the question
9 I have about controls later. But thank you,
10 everyone.
11 (Applause.)
12 (Whereupon, at 2:37 p.m., a recess was
13 taken.)
14 DR. WARD: The last session, for lack of a
15 better term, will be kind of a deeper dive into the
16 clinical trial design, both for drugs but also for
17 protocols. That's why I wanted Leanne to
18 participate, because it's not just about trials for
19 new drugs. Protocols in the ICU are an important
20 part of improving care. It may not be something
21 that ends up at the FDA, but it is something that
22 is important to having a repertoire.

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1 We'll start out with Dan.
2 Presentation - Daniel Sessler
3 DR. SESSLER: My assignment was to talk
4 about protocol design or trial design. Of course
5 most of you do trials, so my challenge was to think
6 of something that wasn't completely obvious to
7 everyone in the room.
8 What I'd like to talk about is five major
9 trends in clinical trials. One of them is towards
10 large size, and this is a recognition that small
11 studies give fragile results that often prove to be
12 wrong. The second is towards composite outcomes
13 rather than having a single outcome, and there are
14 two reasons for this. One is that it reduces
15 sample size, and perhaps a better reason is that a
16 composite can better characterize the totality of
17 an intervention's effect.
18 Third is factorial design, which is an
19 efficient way to do studies and allows you
20 sometimes to do two or even three things at the
21 same time at very little additional cost. Then
22 adoptive designs, which are essentially ways to

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1 incorporate information that becomes available
2 during this study, either externally or from the
3 trial itself, into the trial design, and therefore
4 to make sure that the trial fully addresses all
5 available information rather than following a
6 protocol that might have been designed years ago.
7 Then finally, I want to talk a little bit about
8 novel trial designs that require altered or waived
9 consent.
10 Let's start with large trials. How big a
11 trial is really matters. I'm going to give you two
12 examples here. These are only slightly disguised
13 real studies. They were both published in the New
14 England Journal of Medicine granted 20 years apart,
15 and these were both studies of interventions to
16 reduce myocardial infarction after non-cardiac
17 surgery.
18 The first study had 200 patients. There was
19 one infarction in the treatment group, 9 in the
20 placebo group that gave a relative risk of 0.11,
21 and the p-value was 0.02. The second trial had
22 4,000 patients. There were 200 events in the

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1 treatment group; 250 events in the control group
 2 for a relative risk of 0.8. The p-value was
 3 exactly the same, 0.02.
 4 Now, which do you believe? Well, of course
 5 you believe the second one, and intuitively you
 6 think this makes more sense, first because everyone
 7 believes in the law of large numbers, but also keep
 8 in mind that a relative risk reduction of
 9 90 percent is biologically implausible. There's
 10 not conceivably any single intervention that
 11 reduces the risk of something as complicated as a
 12 heart attack by 90 percent. It's just an
 13 unbelievable result.
 14 The first result is fragile; the second is
 15 not. And what I mean by fragile is that if you add
 16 a couple of positive outcomes to the treatment to
 17 group, does it change anything? Well, in the first
 18 study, if you add 2 outcomes to the treatment
 19 group, the result is no longer statistically
 20 significant. You add to 2 outcomes to the second
 21 study, it doesn't change the p-value out to about
 22 the fifth decimal; it has no effect whatsoever. So

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1 the first one is fragile; the second is robust.
 2 Let me put this another way. Sticking with
 3 something like a heart attack, heart attacks after
 4 non-cardiac surgery in patients over 45 has
 5 something of a 10 percent incidence; they're
 6 surprisingly common. You don't know about this
 7 because they're mostly silent, but they happen.
 8 So let's consider an intervention that
 9 reduces the risk by 50 percent, reduces the risk by
 10 a factor of 2; the relative risk is 0.5 that's set
 11 here. This simply shows the 95 percent confidence
 12 intervals as a function of trial size. These are
 13 all statistically significant results.
 14 In the first lowest one, N equals 500. This
 15 is a statistically significant result. 500 is a
 16 large trial. I suspect there are not many people
 17 in this room who have done a 500-patient trial.
 18 Yet, the confidence intervals range from about
 19 0.25, which is a factor of 4 reduction -- this is
 20 biologically implausible -- to almost 1, which is
 21 no effect whatsoever.
 22 This trial while statistically significant

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1 has not provided a lot of guidance to clinicians.
 2 To shrink those confidence intervals to a range
 3 that gives clinicians good guidance, you need to
 4 increase sample size by a factor of 10. You need
 5 to go to N equals 5,000, and that's why trials of
 6 myocardial injury are 5 to 10,000 patients these
 7 days. So you need to have very large studies.
 8 Almost everyone believes that a p-value of
 9 0.05 means that there is a 95 percent chance of
 10 replicating the study. That is not at all what it
 11 means. What it means is that there is only a 5
 12 percent chance that by pure random motion, you've
 13 got the observed distribution of values. It
 14 doesn't directly tell you about replication.
 15 So let's talk about replication. Let's say
 16 we're testing a drug that is completely
 17 ineffective. This is essentially placebo versus
 18 another placebo. You expect to have no treatment
 19 effect. They're both placebos. I'm giving you
 20 that. The relative risk should be zero -- should
 21 be 1 or the treatment at absolute risk should be
 22 zero.

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1 So I'm giving you that, and then you go
 2 repeat the trial. But if you repeat the trial,
 3 you're not going to get exactly the same result
 4 each time. You're going to get things around a
 5 zero treatment effect but not exactly treatment
 6 effect. In fact, if you repeat this thousands of
 7 times, what you will get is a normal Gaussian
 8 distribution. It's going to look like that.
 9 Equal to 0.05 means that the distribution is
 10 in the most extreme, 2.5 percent on each end,
 11 because you don't know in which direction you're
 12 going to go.
 13 Now let's change the paradigm, so now I'm
 14 giving you an effective drug, you do a trial, and
 15 the p-value turns out to be 0.05. What does that
 16 tell us about replication? Well, if you start
 17 repeating this study, you will on average get the
 18 effect that you got the first time. That's now
 19 your best estimate of the treatment effect. But of
 20 course you won't exactly get that every time. You
 21 will again get a normal distribution around that.
 22 Okay. Well, let's look at that then. Half

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1 of the values will be more extreme, that is the
2 p-value will be smaller, and you will consider
3 those to be replications. But half the time, you
4 will have less extreme values and a larger p-value.
5 So a p-value of 0.05 means that you have a
6 50 percent chance of replicating the study. That
7 is a coin flip. That's not actually very helpful.
8 A reasonable question then is how extreme a
9 p-value do you need to actually have a 95 percent
10 chance of replicating the study? You get that
11 answer by sliding this bottom curve to the right
12 until only 5 percent is less than your original
13 observation. Then what you do is you take the peak
14 of that and you trace it back up to your original,
15 and you read off the p-value. It turns out to be p
16 is equal to 0.0003. It's really small.
17 So why on earth do we use a p-value of 0.05
18 as our criteria for significance? It's a mistake
19 of history. It came from a misunderstanding of
20 what p-values really mean. It never should have
21 been the p-value. The p-value probably should have
22 been 0.001, and if that were the p-value, it'd be a

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1 lot harder to get a positive result, it'd be a lot
2 harder to publish papers, and our literature would
3 not be crammed with rubbish the way it currently
4 is.
5 (Laughter.)
6 DR. SESSLER: Next, composite outcomes.
7 Composite outcome is any group of outcomes; for
8 example, a cardiac death, myocardial infarction,
9 nonfatal cardiac arrest. These are usually used
10 for dichotomous outcomes, and the reason people use
11 them is that it allows a smaller sample size. The
12 reason it allows a smaller sample size is that the
13 number of patients you need for a study with
14 dichotomous outcome depends mostly on the treatment
15 effect -- but that of course is beyond your
16 control -- and partially on the baseline incidence
17 of whenever you're looking at.
18 So if you have a composite outcome and
19 you're looking at lots of things, the incidence
20 goes up. The incidence of a composite is always
21 higher than the incidence of the components of a
22 composite.

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1 Now, that's not actually the best reason to
2 use a composite. The real reason to use a
3 composite is that it better characterizes some
4 intervention. Take for example a drug treatment
5 for diabetes. It doesn't really make sense to say
6 I'm going to do a study of an intervention for
7 diabetes, and I'm going to make blindness my
8 primary outcome and amputation secondary, and renal
9 disease tertiary.
10 These are all important outcomes, and
11 anybody who had diabetes would be interested in all
12 of them. This is a perfect example of when it
13 makes sense to have a composite of blindness,
14 amputation, renal disease, and heart attack, the
15 four major things maybe that diabetics worry about
16 because it characterizes the disease well.
17 Now, one thing you have to be careful of
18 with composite outcomes is heterogeneous results.
19 A perfect example of this was the original POISE
20 trial of beta blockers, which had a composite of
21 myocardial infarction, and stroke, and death.
22 Well, myocardial infarction went down with beta

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1 blockers, significantly; stroke went up. So the
2 two components of the composite were going in
3 opposite directions.
4 When you have that, you have an interaction
5 term, and it doesn't make any sense to average them
6 together. It doesn't make any sense at all to
7 average an increase in stroke with a decrease in
8 myocardial infarction. So when you have that, you
9 have to split it apart. And the trouble is that
10 most trials are not powered at that point because
11 one of the reasons you used the composite was to
12 reduce your power. So if you have heterogeneous
13 results, it's very likely that you'll end up with
14 an underpowered trial.
15 The most common way of dealing with a
16 composite is a so-called collapsed composite, which
17 is a fancy way of saying all are none; that is if
18 any one component is positive, one or more
19 components is positive, you say the composite is
20 positive. If you take that approach -- and it's by
21 far and away the most common approach -- then there
22 are two rules you have to worry about.

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1 The first is that the incidence of each
2 component has to be at least roughly comparable,
3 because if you have one component that, say, is 10
4 times as common as all the others combined,
5 effectively that becomes your outcome. That's all
6 you're looking at, so you can't do that. The
7 second thing is that the severity of the components
8 has to be roughly comparable. So it does not make
9 sense to have a composite of, say, sternal wound
10 infection, abdominal abscess, wound dehiscence, and
11 urinary tract infection.

12 You see this all the time. This has been
13 published lots and lots of times, but it makes no
14 sense. Urinary tract infections are 10 times as
15 common as the others, and they're about a hundred
16 times less serious. That essentially is saying a
17 urinary tract infection is the outcome, but that's
18 not what people care about, so that's a bad
19 composite.

20 Now, you don't have to use a collapsed
21 composite or an all or nothing composite. You can
22 evaluate the number of components that are

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1 positive. It's not a common approach but it's one
2 that you can use. A better approach, at least to
3 take care of different incidents, is to use
4 something called the average relative effect, which
5 was popularized by our statistician in Cleveland at
6 MASHA [ph], and that's a way of looking at the
7 average effect of each component independent of
8 incidence.

9 You can also weight the components. So if
10 you have some components that are far more serious
11 than others, you can essentially clinically weight
12 them and say, I'm going to conclude urinary tract
13 infections, but I'm going to count them as 100th of
14 a deep sternal wound infection because I don't
15 think it's very serious.

16 Third trend is towards factorial
17 randomization. Factorial studies are really
18 powerful because they allow you to evaluate two or
19 more outcomes with only slightly more effort and
20 patients than you would have for a single one. It
21 also allows you to evaluate the interactions
22 between different interventions.

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1 Suppose you're looking at two different
2 sedatives. You would like to know if each sedative
3 is effective, but suppose you show that each
4 sedative is affective? Any reasonable clinician
5 would turn around and say, "Okay, what about if I
6 combine them? Do I get better efficacy with less
7 toxicity?"

8 Well, let's say you did a 500-patient trial
9 of one sedative, and it shows efficacy and not too
10 much toxicity, then you do a 500-patient trial of
11 the second sedative; again, efficacy and not too
12 many complications. The clinician asks you, what
13 if I combine them? Do you have any information?

14 You have no information whatsoever because
15 these are separate trials, but suppose instead you
16 had done a factorial trial where patients were
17 randomized to the first sedative, the second
18 sedative, to the combination of the two sedatives,
19 or to nothing? Then you could evaluate
20 independently what each one does and what the
21 combination does. If you have enough patients, you
22 can evaluate the type of interaction; specifically,

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1 are the effects additive, are they synergistic, or
2 are they antagonistic?

3 Now, fair warning; you need a lot more
4 patients to evaluate the interaction term, about 4
5 times as many. But if you're just looking at the
6 marginal effects, that is a one drug, second drug,
7 and the two combined, you can do that with an
8 increase in sample size of only about 10 percent,
9 so it's very efficient, and we're seeing more and
10 more of these.

11 Let me just very quickly show you how this
12 works. The example is the POISE 2 trial. In this
13 trial, we randomized 10,000 patients to clonidine
14 or placebo and to aspirin or placebo. Now, suppose
15 you want to evaluate the clonidine effects. You
16 get to the end of the trial and say, okay, what did
17 clonidine do? Well, the most obvious thing would
18 be to evaluate clonidine plus placebo aspirin
19 versus placebo-placebo. These are drugs, patients
20 who only got clonidine or only got placebo.

21 The trouble with that is that you can only
22 use half of the patients, so this is 2500 patients

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1 in each group. But in fact there's absolutely
2 nothing wrong with looking at the clonidine plus
3 aspirin versus placebo plus aspirin. Aspirin drops
4 out of the equation here. It's like being over 60.
5 It just drops out of the equation. And by
6 definition, by the way it's randomized, you have
7 exactly the same number of people with aspirin in
8 each group. So in fact, you can do your analysis
9 across all clonidine patients and all placebo
10 patients, 5,000 of each.
11 Exactly the same thing applies for aspirin.
12 Again, the most logical thing would be to do
13 aspirin plus placebo, but there's absolutely
14 nothing wrong with doing aspirin plus clonidine or
15 aspirin and placebo, and that allows you then to
16 look at clonidine plus placebo -- aspirin with or
17 without clonidine versus placebo with or without
18 clonidine. You don't care about the clonidine; it
19 drops out. It's a baseline factor. So you can use
20 all 5,000 patients for your analysis.
21 The trial with the most factors that I know
22 of was Christian Apfel's study of PONV. In this

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1 trial, we actually had 6 different factors, but
2 I'll present just three of them here, the three
3 drug antiemetics.
4 This is an example of how you can study the
5 interactions. On the top, you have the amount of
6 nausea and vomiting with no intervention, and then
7 you have the effect of any one intervention, any
8 one antiemetic, and it turns out that they all
9 provide a 25 percent risk reduction. But then you
10 can go on and look at the combinations. You can
11 look at all three combinations of the antiemetics,
12 and again, we had almost exactly a 25 percent risk
13 reduction, and then you can look at all three, and
14 again, it's a 25 percent risk reduction from the
15 previous condition.
16 So large factorial randomized trials are
17 powerful, not only because you can look at multiple
18 things simultaneously without much increasing
19 sample size, but you can look at the interactions
20 and determine whether they are additive,
21 antagonistic, or synergistic.
22 DR. SHAFER: What was on the left?

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1 FEMALE VOICE: I was going to say, why
2 Marilyn Monroe?
3 DR. SESSLER: Oh, yeah. The risk factors
4 for nausea and vomiting are female gender, opioids,
5 nonsmoking, and a history of motion sickness.
6 (Laughter.)
7 MALE VOICE: She under-fits in that picture.
8 DR. SESSLER: Next up is adoptive designs.
9 Adoptive designs are relatively new, and there's
10 been a shift in thinking. Until fairly recently,
11 the thought was that you should design a protocol
12 and it was essentially written in stone. You
13 registered the protocol, and even if the trial took
14 9 years -- and I would hate to tell you how many of
15 our studies have taken 9 years -- you couldn't
16 change anything. You had keep everything exactly
17 the same.
18 There is now increasing recognition that
19 things happen during trials. Things could be
20 external, for example, other people publish
21 relevant work. Maybe somebody else publishes a
22 trial that's almost identical to yours, or it's

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1 similar to yours in a different population, and
2 they get some answers, and the answers might be
3 about efficacy, but they might be about toxicity
4 also, and it might be about toxicity in a specific
5 population.
6 Well, if you now know that a certain subset
7 of the population of your trial is especially
8 sensitive and especially likely to have
9 complication, it would be unethical to keep
10 enrolling them, so you have to make changes.
11 But similarly, suppose you know that a
12 certain subset is more likely to benefit? You
13 might well say, okay, I did start with something
14 different five years ago, but now I know more. Now
15 I'm going to change my trial to target a group that
16 seems to especially benefit from whatever
17 intervention I'm evaluating.
18 So you could alter the study population.
19 You could restrict enrollment, or perhaps broaden
20 enrollment, or somehow change the enrollment
21 criteria to enrich the population for efficacy and
22 reduce the risk of complications. You can also do

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1 things like adoptive randomization. You can change
2 the treatment ratio. You could give more people
3 the drug; fewer people placebo. But if you're
4 testing two different drugs, you also could say,
5 I'm going to focus on the drug that's looking best,
6 and it might be data for internal for your trial.
7 From an interim analysis, you can say, okay,
8 one of these treatments seems to be far better than
9 the other one. I'm going to play the winner, and
10 that might be just dropping one of them, but it
11 might also be saying I'm going 2 to 1 to 1,
12 randomization. So instead of having 1 to 1 to 1,
13 you might have 2 to 1 to 1 type of randomization.
14 An example of adoptive design that's common
15 in anesthesia is the Dixon up-and-down method for
16 determining volatile anesthetic potency. The way
17 those studies are done is that you start with some
18 essentially random dose. You give it to the first
19 patient, and at skin incision, you see whether the
20 patient moves or not. The movement is unconscious.
21 It doesn't hurt the patient, although it looks
22 spectacular. If the patient moves, then you

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1 increase the concentration. If the patient doesn't
2 move, you decrease the concentration.
3 So it doesn't matter whether you started too
4 high or too low, you very quickly move down to
5 about the average anesthetic potency and then you
6 start bouncing around there. This is classic
7 adoptive design, and it's been used in anesthesia
8 for a half century, but we're beginning to use it
9 in other contexts as well.
10 Another thing you might change is sample
11 size. When you start a trial, you do a sample size
12 estimate, and you use best available information in
13 estimating sample size. But the most important
14 contributor to sample size is treatment effect,
15 which of course you don't know because the whole
16 point of the study is to determine the treatment
17 effect.
18 Very often you're wrong, and mostly people
19 are overly optimistic about guessing what the
20 treatment effect is or they adjust the treatment
21 effect to get a sample size that they can do before
22 the end of their fellowship or what have you. The

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1 trouble is that biology doesn't care. Treatment
2 effect is whatever the treatment effect is going to
3 be, so it's not uncommon to get most of the way
4 through the trial, and it's absolutely obvious that
5 your trial is underpowered.
6 It is not really very logical to sort of
7 slavishly go ahead and say, okay, well I said I was
8 going to study 239 patients; that's what I'm going
9 to do. There's a certain logic in getting to 150
10 patients, picking what data you have, re-estimating
11 sample size, and saying I'm going to go to 325
12 patients, which is what I'm actually going to need
13 to make a reasonable conclusion.
14 Now, of course it has to be transparent and
15 you have to disclose this. Ideally, your protocol
16 would have this in the statistical plan. So right
17 from the beginning you would say we are going to do
18 interim analyses. We will re-estimate the sample
19 size as necessary and increase treatment effect,
20 and should be done somewhat independently from the
21 investigators. We always do this on a group
22 A/group B basis. We do it without knowing which

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1 group is which.
2 Then finally, you can change the drug or the
3 drug dose. It might be that you're halfway through
4 a trial and obviously you picked the wrong dose.
5 You're giving half as much of this drug as you
6 should, or you're getting complications and lots of
7 efficacy, and maybe you should use half the dose
8 that you started with; or maybe it's just the wrong
9 drug. The drug isn't working; pick something else.
10 That could be in the context of the same trial,
11 which would be sort of a platform type of design,
12 or you could kill that trial and start a new one.
13 Finally, novel designs. I think everybody
14 knows about cluster randomization and a randomized
15 step-wedge, which is a type of cluster design.
16 There's a new type of trial. The first one is
17 actually being done now, which is called opt-out in
18 the routine care design.
19 If there's a clear standard for routine
20 care, you can enroll those patients in a trial but
21 not actually get consent because you're not doing
22 anything different to those patients. They are

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1 getting routine care. You only get consent in
2 patients who are randomized to the experimental
3 treatment. The danger of course is that some won't
4 consent, and they may consent non-randomly and with
5 bias.

6 The final type of novel design, which I
7 think we developed, so I'm fond of this, is an
8 alternating cohort study. This is like a clustered
9 trial, except that the clusters instead of being
10 randomized in space are randomized in time. And
11 basically what you do is you do some treatment for
12 a period of time, like 2 weeks, and then you switch
13 to the alternate treatment, and then you switch
14 back again, and you keep doing this for, say, a
15 year.

16 Since there's no reason that patients would
17 be in any particular 2-week block, it is a
18 controlled trial; you're controlling the exposure.
19 Even though the exposure periods are not randomized
20 and certainly the individuals are not randomized,
21 it's a trial design that's easy to implement. It's
22 inexpensive. It allows you to enroll very large

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1 numbers of patients. We've done a bunch of these
2 now with thousands of patients. It costs almost
3 nothing, and they have a lot of the protections of
4 a randomized trial at a tiny fraction of the cost.

5 I'm going to skip the rest of this, so thank
6 you much.

7 (Applause.)

8 DR. WARD: We've been talking a lot about
9 drugs, but protocols are very important. So
10 Leanne's going to fill us in a little bit more on
11 design for protocols.

12 Presentation - Leanne Aitken

13 DR. AITKEN: Thank you.

14 Yes, so my thought is very much that we have
15 spent all this time talking about drugs, and
16 absolutely we need to find the right drugs, but we
17 need to look at how we're giving the drugs because
18 the best drug in world, if we're giving it in the
19 wrong way, we're not going to achieve the outcome
20 that we want to achieve.

21 Largely, what I was asked to do was to talk
22 about some of my experience in doing predominantly

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1 these Cochrane reviews, although I have done a
2 couple of studies in the same area, so I'm
3 obviously informed by that, and I'm informed by
4 some of the more recent work that I'm doing in
5 looking at some of this sedation as well, and I'll
6 bring that in later in the time.

7 Bearing in mind that the first of these
8 Cochrane reviews was done six or seven years ago,
9 so the protocol was written eight years ago. And I
10 look at it now and think I'd write it very
11 differently now to what we did back then. We just
12 did the revision, which was published last year.

13 My learning from that is that if you end up
14 in the situation where most of your studies are
15 individual patient randomized studies, and then
16 there's one cluster randomization trial that needs
17 to be included, run as far as you can. Don't hang
18 around or pay a statistician a large amount of
19 money because it becomes a nightmare when you've
20 got one cluster randomized study to go in the
21 review, which was the situation in this case.

22 When I'm talking about protocols directed

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1 sedation, what I'm talking about is where the
2 sedation has been ordered by a physician and is
3 implemented by nurses, pharmacists, or others.
4 That was our provision, but the reality is all of
5 the sedation protocols are implemented by nurses in
6 the review that we've included.

7 The protocol should contain information on
8 the sedative agent or agents to use, and when to
9 commence increase, decrease, or cease sedative
10 agents. It should be in some way based on patient
11 assessment, and it might include other
12 interventions such as daily sedation interruption.

13 It's similar to but distinct from a weaning
14 protocol, so there are other studies that look very
15 specifically at weaning protocols that are not
16 included in here. The likely mechanism for
17 improvement of a sedation protocol is simply
18 through reducing the individual variations, so
19 getting people to work more consistently towards a
20 target.

21 This is the bit that I now look at and
22 think, yes, I'd probably choose some different

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1 outcomes if we were starting afresh at this point,
 2 but these are the outcomes that we identified about
 3 eight years ago based on what was available in the
 4 literature at that point and where our thinking was
 5 at that point. So some of them are still not
 6 consistently in the literature, but this was the
 7 drain list at that point, where the primary
 8 outcomes were either duration of mechanical
 9 ventilation or mortality, either within the ICU or
 10 within the hospital.

11 The secondary outcomes -- and I've got no
 12 idea why that's appearing in both. Oh, no, that's
 13 length of stay, not mortality; sorry, I'm reading
 14 wrongly. The secondary outcomes were length of
 15 stay, total dose of sedation, adverse events within
 16 the ICU, incidence of delirium, incidence of
 17 tracheostomy, some post-hospital outcomes along the
 18 lines of memory, psychological, or cognitive
 19 function, and quality of life. And I'll talk just
 20 a little bit about how often we found those
 21 outcomes in the studies.

22 In the review that we published last year,

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1 we included four studies, and in those four studies
 2 were a total of just over 3,000 patients. The
 3 study that bumped up the numbers, because that's a
 4 fair size patient number for four studies, was the
 5 pediatric cluster randomized protocol study that
 6 Martha Curley led that was published about three
 7 years or so ago, so that is a big study sitting in
 8 the middle of this.

9 But you can see that all of the studies had
 10 measured duration of mechanical ventilation in some
 11 form, and I'll talk about that in a moment. Two of
 12 the studies had ICU mortality; three had hospital
 13 mortality. All of them had ICU length of stay;
 14 three of them had hospital length of stay. Two had
 15 self-extubation and one had reintubation. And
 16 obviously, they're getting at the same concept but
 17 are slightly different. And then one had
 18 tracheostomies in there.

19 When I said duration of mechanical
 20 ventilation, one of the challenges that we had to
 21 deal with was that in the various studies -- and
 22 there were only four, but duration of mechanical

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1 ventilation was defined either as duration of
 2 mechanical ventilation, or time to extubation, or
 3 ventilator-free days in the first 28 days, and that
 4 obviously created a huge problem for us.

5 Now, fortunately we were able to get from
 6 the authors some consistent data that we could then
 7 do a meta-analysis, but it wasn't necessarily the
 8 format that was published in the study in the first
 9 place. So I think we do need to think about what's
 10 the right version.

11 To this point in time, there's been no
 12 sedation protocols that have studied, that have
 13 looked at, total dose of sedation or any of the
 14 risks of that list that's there. Obviously, those
 15 outcomes have been measured in lots of other
 16 studies, but not many studies that's been comparing
 17 different versions of sedation protocols. It's
 18 worth reminding you that this is a Cochrane review,
 19 so it was only RCTs. There are some other
 20 observational studies that do have some of these in
 21 there but not much.

22 Total dose of sedation is an interesting one

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1 that I'm not sure I would put in there now, and I'm
 2 not sure it's of value. I think we need to think
 3 more carefully about that, and I've got some notes
 4 for the [indiscernible]. The other thing that I've
 5 said there is these four included studies were
 6 conducted or published back in 1999 and then more
 7 recently than that. The 1999 one was -- his name's
 8 just gone.

9 MALE VOICE: Brook.

10 DR. AITKEN: Brook. Thank you. I was going
 11 to say the wrong name. It was Brook, and that's a
 12 mid-nineties study when it was designed, so we have
 13 moved on quite some distance of time since then.

14 Now, as you can see -- and it doesn't matter
 15 that you can't see the detail particularly well,
 16 but what we've done there is just included a few
 17 different studies, the top three studies of
 18 individual patient randomized studies and then the
 19 fourth study is the cluster randomized study. But
 20 you can see with the individual study results that
 21 there really is quite a lot of variation between
 22 the studies in terms of some of them providing

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1 absolutely no benefit and if anything harm, whereas
2 other studies are a long way on the benefit side.
3 This was the original Brook study. Now,
4 particularly given my background is the one study
5 that does go on the harm side, is the study done by
6 Trace Bucknell in Australia, and we have a setting
7 that is very well known for having 1 to 1 nursing
8 at every bedside, having 70 to 80 percent of our
9 nursing staff with post-graduate qualifications in
10 critical care, probably a different environment to
11 the other three studies that are done in the North
12 American setting. So it raises the question a lot
13 about context, which I'll speak about in a moment;
14 so certainly inconsistent results across those
15 contexts.
16 Some of the factors that we think affect
17 this are things like what's the usual practice; how
18 much implementation was there of the intervention?
19 In other words, it's all very well and good that
20 we've set out what the intervention is meant to
21 consist of, but was that actually achieved. And as
22 I said, what were the staffing types and levels.

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1 This is where I've become conscious of the
2 lesson today that my use of language is probably
3 heavily influenced by the UK environment now,
4 rather than something that necessarily is used
5 internationally as language. But we've spent a lot
6 of time thinking about process measures or process
7 evaluation.
8 Earlier today, I mentioned that I'm a co-app
9 on an RCT for dexmedetomidine versus clonidine
10 versus usual care. My role in that is to lead the
11 work strain for process evaluation. So even in an
12 RCT of a drug, we have a whole work strain that's
13 looking at how are we implementing this drug, how
14 are we actually achieving what we think we're
15 achieving? I guess on reflection, I realized that
16 that's very UK oriented language in thinking about
17 process evaluation, but it's in essence how well
18 implemented was the intervention.
19 So I don't think of things like total dose
20 of sedation as being an outcome measure. I think
21 of it as being a process measure. I don't really
22 think of a percentage of time target sedation as

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1 being an outcome measure. I think of that as a
2 process measure now. So particularly for something
3 that is a behavioral intervention like the sedation
4 protocols are, I think it's vital that we have some
5 detail process measures about what the context is
6 and what the intervention fidelity is; in other
7 words, how well implemented was the intervention.
8 What was the dose of sedation that we
9 achieved? One of the things that we've noticed in
10 looking at some other work around depth of sedation
11 is that there's no agreement on how we should be
12 measuring depth of sedation. So is it the average
13 daily dose of various drugs? Is it what sedation
14 measure was achieved? Or is it some sort of
15 calculated measure? And there are a couple of
16 variations on sedation index that you can find.
17 I'm not sure at something like percentage of
18 time at sedation target because achieving a
19 sedation target of a RASS of minus 4/minus 5 versus
20 achieving a sedation target of zero to minus 1,
21 both of them are completely achieving the target
22 but very different sedation states. So I'm not

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1 sure it tells us much about the depth or the dose.
2 Certainly, talking about coverage or rate, how many
3 of our patients got the intervention that was
4 intended? Did we get to all of our patients, and
5 did we get to them in a timely manner?
6 Just recently, Lydia Emerson, she's about
7 two seconds of finishing her PhD, but she's
8 developed a model for process evaluation in
9 critical care studies, including RCTs of drugs, but
10 critical care studies more broadly. I know that's
11 a bit difficult to see from the size, but she's
12 talked about there being elements that you need to
13 look at during the baseline period of the study,
14 the exploration period, and then during the study.
15 And then to clarify at the end of the trial with
16 the thought being that these data will help us
17 better implement the study as we go, but perhaps
18 more importantly, help us to explain the results at
19 the end of the study.
20 The elements included in her model are
21 context, attitudes and perceptions, fidelity, dose,
22 reach, recruitment, and then level of

<p style="text-align: right;">Page 301</p> <p>1 implementation. In one of the recent ICU studies 2 that's just been finished in the UK, which was the 3 POPPI study, which was a nurse-delivered 4 psychological intervention within the ICU. 5 They applied this model to that, and on 6 first analysis, which is all that's available at 7 this stage, it looks like those sites that had a 8 higher level of implementation had more effective 9 benefit, even though the study as a whole didn't 10 find benefit on the straight RCT. So they're going 11 to do some more analysis to see if that measure of 12 implementation is valuable. We're applying it to 13 the A to B dexmedetomidine versus clonidine study 14 to see if that can help us there. So I raise that 15 as many of the elements that particularly in a 16 behavioral intervention like a sedation protocol I 17 think is absolutely essential. 18 My thoughts in moving forward -- I've 19 raised a lot of the questions as I've gone through, 20 but I think in thinking about the patient-centered 21 outcomes, that we need to be obviously thinking 22 those that are ICU focus but then those that are</p>	<p style="text-align: right;">Page 303</p> <p>1 is one of controversial statistical measures that 2 people use, particularly when you get to things 3 like composite outcomes. Hopefully, they're going 4 to enlighten us. 5 Presentation - Elizabeth Colantuoni 6 DR. COLANTUONI: I hope so. Do you guys 7 want to stretch, a 4 o'clock stretch before the 8 statistics talk? Highly recommended. Feel free to 9 stand while I'm talking. 10 I should just start by saying that sedation 11 trials is somewhat out of my wheelhouse. I've been 12 involved much more with long-term observational 13 studies and randomized trials within ARDS 14 populations, and now getting a little bit more into 15 trial setting within the context of delirium. 16 Leanne gave such a nice summary of the literature. 17 I was reading up into the published trials, so I'm 18 going to highlight some of the outcomes that she 19 just mentioned. 20 But here's just a schematic of the standard 21 design. Intubated and mechanically ventilated 22 patients are enrolled and randomized to receive one</p>
<p style="text-align: right;">Page 302</p> <p>1 hospital focused and those that are long term. And 2 in sedation studies, we're going to be thinking 3 across all of those. 4 My strong emphasis is that whatever outcomes 5 we have, we also need what I've referred to as 6 process measures to help us explain the variation 7 in outcomes that we get to at the end. That's 8 interesting that Lydia said in one of the 9 ventilation studies, where she was leading the 10 process evaluation, most of the co-apps on the 11 study couldn't work out what the process evaluation 12 was all about and couldn't really see the benefit 13 until they got to the end and got no difference in 14 the statistical analysis and said, "Oh, now we need 15 to look at the process evaluation" and work out 16 what was going on. So it wasn't quite the right 17 way around, but that's certainly what she's found 18 in getting to the point where those measures became 19 important. So I'll leave it there. 20 (Applause.) 21 DR. WARD: Before the panel and we get to 22 ask all the questions, my reading of the literature</p>	<p style="text-align: right;">Page 304</p> <p>1 of two pharmacologic agents representing sedatives 2 and then administered those drugs through 3 extubation, and typically followed through ICU 4 discharge and perhaps through hospital discharge, 5 at least accumulating length of stay. 6 The whole time that the patients, then in 7 the ICU and moving through hospital discharge, 8 death is a potential competing risk. In my reading 9 of the literature in these sedation trials, it 10 looks like death is 30-day mortality, ranging from 11 anywhere from 15 to 30 percent, so a pretty high 12 rate of mortality in these populations. 13 Identified endpoints from my quick 14 look -- and many of these just popped up on in the 15 prior presentation -- is that primary and secondary 16 endpoints are highly variable. They range from 17 proportion of time; reaching the sedation target 18 and goal; duration of mechanical ventilation; ICU 19 and hospital length of stay; and mortality and 20 delirium. But there's a lot of inconsistency even 21 in just primary endpoint definition across trials, 22 let alone a wide range of variation in secondary</p>

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1 endpoints.

2 Today I'm going to talk about how to

3 operationalize delirium as an endpoint within this

4 setting, so that will be the first part of the

5 talk. Secondly, in reviewing some of the protocols

6 and ongoing trials, you see some additional

7 duration of follow-up in the sedation trials, maybe

8 perhaps extending to 3 months or 6 months

9 post-randomization, where we're looking at longer

10 term mortality, but we're also starting to measure

11 functional outcomes similar to what Dale described

12 earlier today.

13 These could be measures of physical

14 function, either self-reported measures of physical

15 function or actual, like hand-grip

16 strength -- those sorts of things could be included

17 here -- mental illness or mental health measures,

18 and then quality of life.

19 So my talk is going to talk a little bit

20 about how we operationalize delirium as an endpoint

21 and the statistical challenges there, and then

22 separately I'm going to talk about the challenges

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1 in evaluating these longer term functional

2 outcomes, particularly within the context of this

3 competing risk of death.

4 I want to highlight here before I move on,

5 the competing risk of death is not just affecting

6 delirium and these longer term functional outcomes.

7 Our evaluation of duration of mechanical

8 ventilation, ICU, and hospital length of stay are

9 also endpoints for which mortality has to be

10 considered.

11 This paper that I'm highlighting here is a

12 paper from a bunch of colleagues at the School of

13 Public Health at Hopkins. It's just a nice review

14 of the differences in the statistical methodology

15 available to compare relative hazards versus

16 relative risks when there's a competing risk of

17 death. I find myself going back over and over

18 again to this manuscript to remind me of all the

19 definitions.

20 Delirium as an endpoint, up until a few

21 years ago, my primary exposure with delirium was

22 thinking about delirium as an exposure and

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1 correlating delirium with subsequent outcomes in

2 patients. Dale approached me a few years ago and

3 said I need you to write a statistical analysis

4 plan. The endpoint is delirium, and I had no idea

5 what to do with proposal. So we were evaluating an

6 ancillary study to the SAILS trial, which was a

7 multicenter randomized trial evaluating the use of

8 rosuvastatin versus placebo, looking at patient

9 mortality and duration of mechanical ventilation in

10 patients with sepsis-associated ARDS.

11 The data we had was an ancillary study, so

12 within a small number of sites. Delirium was

13 measured daily up to death, ICU discharge, or 28

14 days. Our goal was to try to operationalize

15 delirium as an endpoint, and then make a comparison

16 between delirium as an endpoint across the two

17 treatment groups.

18 I'm going to walk through my thinking around

19 developing this statistical analysis plan. We

20 utilized statistical approach that was different

21 than what was the predominant approach in the

22 literature at the time. Our paper appeared, the

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1 actual analysis appeared in Lancet Respiratory

2 Medicine in 2016, in January, and then there was a

3 subsequent series of commentaries, for which I

4 responded to one where I just had a highlight of

5 some of the statistical challenges.

6 Delirium, as many of you in this room are

7 experts in delirium, so talk correct me where I get

8 off course. But this is a state that's in constant

9 flux of change. Your delirium outcome can change

10 over the course of hours or days. Here I have

11 hypothetical patient. Time zero is enrollment,

12 randomization, and then we're following the patient

13 for 28 days. The zeros and 1's above the time

14 scale are just indicators of when the patient was

15 evaluated and whether they were observed to be in a

16 delirious state versus not.

17 I highlight here at the bottom that this

18 kind of change over time also applies to

19 sedation -- that's most interesting to most of you

20 in the audience -- with the potential for maybe

21 greater variation and more rapid changes over time.

22 Second, delirium occurs along a continuum of

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1 severity, and you cannot assess delirium when a
2 patient is severely impaired. When a patient is
3 comatose, we're not able to do a delirium
4 assessment. For this particular patient, we see
5 the first 2 days, the patient is comatose and
6 unable to be assessed for delirium. Once the
7 patient is not in a comatose state anymore, we have
8 0-1 indicators for their delirium state, so that's
9 a challenge.

10 Third, delirium evaluation is often stopped
11 when patients are transferred out of the ICU, so
12 stepping down from the ICU to the hospital ward,
13 but delirium may persist. Some of the data that we
14 have available when patients are evaluated during
15 the last day of their ICU stay, anywhere from 15 to
16 about 50 percent of the patients are positive for
17 delirium at that time. So how do we treat delirium
18 as an endpoint where we're only observing it, a
19 half of it or a potential small portion of the
20 delirium process? And lastly, death, death is a
21 common occurrence in these ICU studies. The whole
22 delirium process is truncated once the patient

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1 dies.

2 The approach that had been taken in the
3 literature and continues to be used as calculation
4 of delirium-free days to X days. This statistic or
5 composite is based on ventilator-free days to X
6 days variable that's used commonly in studies of
7 mechanical ventilation. This composite endpoint is
8 composed by assigning zero to patients that die
9 prior to day X. Among survivors through day X, you
10 count up the number of days where the patient is
11 off the ventilator; take that composite variable,
12 and you compare it across treatment groups
13 typically using a rank-based test and/or present
14 prespecified quantiles.

15 Over the years since this was proposed in
16 2002 by David Schoenfeld and others, there have
17 been a lot of publications trying to identify and
18 just bring to attention that there are some
19 challenges with using this endpoint. Recently, a
20 French group from Inserm last year published
21 another paper on some of the drawbacks to using
22 this as an endpoint.

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1 How has this endpoint been translated into
2 sedation trials? Well, first thing is how do we
3 define X. Just in my reading of sedation trial
4 literature, there's quite a bit of variation in how
5 we're defining X. It's 7 days, 12 days, 28 days.
6 Ideally, you want X to be specified such that the
7 vast majority of the patients would either have
8 died or have been extubated prior to your time
9 point. That would be a target to try and figure
10 out how to set X.

11 How do you deal with coma days? You can
12 change the endpoint from delirium-free days, to X
13 days, to coma and delirium-free days to include
14 coma within the continuum of the delirium process.
15 I'm sure there would be a heated argument here
16 about whether that's part of the process or not.
17 In the ABC trial, they counted days of CAM-ICU
18 positive but when non-comatose. So there are
19 alternative ways to treat coma.

20 In death, do we set delirium-free days to
21 zero if a patient dies? In the protocol for the
22 SPICE 3 trial I was reading, they're counting the

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1 days free of delirium prior to death as part of the
2 composite, so there is another twist to the
3 variable definition. But universally, most when
4 we're defining this as an endpoint, almost everyone
5 assumes that once the patient leaves the ICU that
6 they're delirium free.

7 As an alternative approach, we're going to
8 suggest that you can directly model both the
9 delirium and the competing event process by using a
10 joint model sometimes referred to as a shared
11 frailty model in statistics. In the first model,
12 you would build a survival model for being positive
13 or absent of delirium on any given day. This is
14 like a recurrent event survival model. The second
15 model is a survival model for your competing
16 events, ICU discharge or death.

17 The two models are linked by a random effect
18 or what's referred to as a frailty term in the
19 survival analysis literature. The frailty term
20 appears in the first model as a way that we can
21 link the repeated daily observations of delirium
22 within a person over time, and then that frailty

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1 term appears in the second model as a way to link
2 the risk of delirium with the risk of the competing
3 event.
4 How we apply these models is that we allow
5 the coma days to be days for which the patients
6 were not at risk of delirium. Within the recurrent
7 event model 1 there, patients were only in the
8 denominator of that survival analysis when they
9 were comatose free. The treatment effect is
10 estimated by having a main term for treatment, and
11 the recurrent event survival model in that term can
12 be interpreted as on any non-comatose day in the
13 ICU, the relative hazard of delirium comparing the
14 treatment to the control group.
15 How all these analyses played out in the
16 SAILS trial ended up not mattering, really, how we
17 evaluated the endpoints, so we compared ever and
18 never delirious across the treatment groups, days
19 alive without delirium and coma where essentially
20 the number of days were identical -- the median
21 number of days were identical across the two arms,
22 and from the joint model, we estimated a hazard

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1 ratio of 1.4, but our confidence interval's quite
2 wide. Here we would say on any non-comatose day in
3 the ICU, the hazard of delirium is 14 percent
4 greater for patients receiving rosuvastatin
5 compared to placebo.
6 There are many challenges within this
7 setting. If you're going to go with a composite
8 endpoint approach, there needs to be a consistent
9 definition applied across the trials, both with the
10 duration of follow-up, how you're going to account
11 for death and coma in the ICU discharge.
12 If you're taking the joint modeling
13 approach, there are limitations here as well. In
14 the current implementation, the joint modeling
15 approach only allows for a single model, a single
16 competing risk, whereas we really have the
17 competing risk of discharge and death, which are
18 two separate processes and have two different
19 relationships with delirium. So patients who have
20 a higher risk of delirium are at higher risk of
21 death, and patients with lower risk of delirium
22 have higher risk of ICU discharge.

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1 There could be alternatives to both of these
2 approaches that we haven't thought of. One thing
3 that I didn't talk about along the way is the
4 complications introduced by missing data, so missed
5 delirium assessments on any given day add another
6 layer of challenge.
7 I just started an NIA funded R01 that is
8 specifically looking at delirium as an endpoint
9 within preventative and therapeutic delirium RCTs.
10 I'm going to be doing some systematic reviews of
11 the methodology applied across delirium trials and
12 then also a series of extensive simulation studies
13 and try to identify where these endpoints can work
14 and where they can't. Then there includes a whole
15 aim for statistical methods development, so try to
16 improve the joint model by allowing for separate
17 models for the competing events, and hopefully make
18 some good recommendations for use of these
19 approaches.
20 Now I'm going to shift from thinking about
21 delirium to talking about the functional outcomes.
22 When I mean functional outcomes, I'm thinking of

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1 something that's not defined as a survival
2 endpoint, something that you evaluate the patient
3 and you get a measure of their physical function or
4 their quality of life; so something that's a scaled
5 or quantitative variable.
6 Everything I'm going to discuss here you can
7 find in this BMJ paper. This was with Tim and Dale
8 as co-authors. This was a culmination of the third
9 aim of the R24 that Dale described earlier today.
10 I'm going to have a little bit of mind games at
11 4:30 in the afternoon. I'm going to introduce this
12 idea of potential outcomes to the group just as a
13 way for us to organize our thinking around how we
14 can identify the causal effect or identify a
15 treatment effect.
16 First, I want you to imagine you're in a
17 setting. Your goal is to evaluate 90-day cognitive
18 function in patients, and there's no mortality.
19 There are two interventions, an intervention and a
20 control. Under the potential outcomes framework,
21 you're imagining, or we organize our thinking to
22 say, that any given patient would have a measure of

<p style="text-align: right;">Page 317</p> <p>1 cognitive function if they had received the 2 intervention. Similarly, they would have a measure 3 of cognitive function if they had received the 4 control. 5 The individual causal effect is the 6 difference, then, between those two potential 7 outcomes of cognitive function, one under 8 intervention and control, and the marginal or the 9 average treatment effect is the average of all 10 those individual causal effects over the population 11 of interest. 12 How does this change when we have mortality 13 as a complicating factor? Now I'm going to 14 imagine, first, that I have potential mortality 15 experiences in each two groups, so I'm going to 16 imagine that I can know the time of death in days 17 and an indicator of whether a patient survived to 18 90 days both under the intervention and the control 19 arm. 20 In addition to knowing this information, 21 then I can also start to categorize people into 22 their potential survival experiences. Always</p>	<p style="text-align: right;">Page 319</p> <p>1 only get to see 90-day cognitive function for the 2 always survivors and the mortality benefitters. 3 Similarly, I only get to observe 90-day cognition 4 under always survivors or specials. The only group 5 of patients for which I can identify or even define 6 an individual causal effect is the always 7 survivors. 8 In the statistics literature, the survivor 9 average causal effect, which is also known as the 10 SACE, is the average of these individual causal 11 effects but only among the very specialized subset 12 of the population, and the specialized subset is 13 those who would survive regardless of what 14 intervention they received. You immediately think 15 that there are some problems here because in 16 practice, we don't get to observe those states; we 17 only get to observe one. So in the end when we're 18 analyzing the data, we don't know who's an always 19 survivor or not. 20 There are ways in which we can estimate the 21 SACE by making additional assumptions. We can get 22 an upper and lower bound for the survivor average</p>
<p style="text-align: right;">Page 318</p> <p>1 survivors would be a subset of patients that would 2 survive to 90 days regardless of the treatment they 3 received. These are likely the most resilient 4 patients in the trial. Mortality benefitters would 5 be those that would survive under intervention but 6 would experience death by 90 days if they received 7 control, so these would be less resilient patients. 8 The always diers, these would be our pretty 9 severe patients. These are patients that would 10 experience mortality regardless of the treatment 11 they received. And then there's this category 12 called the specials. These would be patients that 13 might die under the intervention but survive under 14 the control group, and I'll talk a little bit more 15 about these in a couple of slides. 16 Now we can think about when we actually get 17 to observe cognitive function at 90 days based on 18 these potential outcomes. I only have cognitive 19 function declined if a patient would survive to 90 20 days. Once you die, the cognitive functions no 21 longer are evaluable. 22 Here now I see that under intervention, I</p>	<p style="text-align: right;">Page 320</p> <p>1 causal effect if we're willing to assume there are 2 no specials, so that there would be no one who 3 would survive under control but die under the 4 intervention. If you want to get a point estimate 5 for this causal effect, you have to make 6 additional, more restrictive assumptions, and none 7 of the assumptions are verifiable by any observed 8 data that you have in the trial. 9 In practice, that survivor average causal 10 effect is very rarely reported in the literature. 11 What's more often reported is just the survivors 12 only analysis. There you should just take all the 13 survivors data, take the average of your cognitive 14 function measure under intervention, and compare 15 that to the average under your survivors in the 16 control arm. 17 The only time in which the survivors only 18 analysis reduces to an actual estimate of a causal 19 effect is when the mortality is not different 20 across the treatment groups. So if there's no 21 mortality difference across the groups, there's no 22 mortality benefitters or specials, so the survivors</p>

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1 only analysis reduces to the actual causal effect.
 2 The problem with the survivors only analysis
 3 is if there is a mortality benefit for the
 4 intervention, then you basically have a mixed bag
 5 of patients. Your survivors under intervention are
 6 always survivors and mortality benefitters whom
 7 could be inherently quite different from one
 8 another, and that can introduce a bias.
 9 Both of these approaches are what would be
 10 referred to as conditional methods because they
 11 condition on a particular subset of the patient
 12 population in order to make a treatment comparison.
 13 They suffer from a disadvantage in terms of
 14 evaluating randomized trials that they don't
 15 satisfy the intention-to-treat principle.
 16 There are other advantages and disadvantages of
 17 them, but that's kind of a primary one.
 18 What could we do as an alternative to these
 19 approaches where we might be able to utilize all
 20 the patients that were randomized? One approach is
 21 to utilize a composite endpoint. Most of the
 22 composite endpoint approaches require that we've

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1 ranked the patients in terms of severity. One
 2 example is a proposal by Lachin in 1999 that
 3 utilizes a ranking of patients that incorporates
 4 the timing of death, not just an indicator of when
 5 patients die, and then information about the scale
 6 of interest or the functional outcome.
 7 Let's imagine that we all agree that earlier
 8 death is worse than later death, and remember,
 9 these are longer term outcomes, so it might make
 10 sense for us to be willing to compare survival
 11 3 months post-randomization is worse than survival
 12 180 days post-randomization. Also among survivors,
 13 poor functional outcomes are worse than good
 14 functional outcome.
 15 Then we define a new variable -- I'm just
 16 calling it W -- which would be equal to the time of
 17 death for those who died prior to the time of
 18 interest, 90 days, and then is equal to the
 19 functional outcome plus some constant just to allow
 20 us to differentiate times of death from the
 21 functional endpoint.
 22 So now we have this composite variable,

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1 which is just a variable that's happening on
 2 continuum with higher values indicating better
 3 function. It doesn't make sense here to compare
 4 the means across the treatment arms in this
 5 composite; it would be better to compare the
 6 distribution of a composite endpoint like this, so
 7 you could do like a rank-sum test or you could
 8 compete various quantiles from the distribution of
 9 this composite.
 10 Just as an example, I just made these
 11 numbers up, if you targeted the median of this
 12 composite endpoint, you could compare the
 13 interventions like this. So you could say under
 14 the intervention, 50 percent of the patients
 15 receiving the intervention survived to 90 days with
 16 cognitive function scores that were less than 30,
 17 compared to under the control group, 50 percent of
 18 the patients had experienced death by 50 days.
 19 This is a useful metric as a way to rank
 20 experiences across the two intervention arms.
 21 In terms of recommendations, when mortality
 22 is involved, there's no real solution that doesn't

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1 have a disadvantage. The approach that you choose
 2 is going to depend on the assumptions that you're
 3 willing to make within the context of the problem.
 4 There are a couple of recommendations I
 5 would make. If it's biologically unlikely that the
 6 intervention is going to impact mortality, then
 7 you're safe with the survivors only analysis. The
 8 survivors of the intervention to a particular time
 9 will represent a random sample of the original
 10 randomized patients, so you should be fine.
 11 When mortality is a primary endpoint, as it
 12 is in many of the trials that we do in critical
 13 illness, you're hypothesizing that there is a
 14 difference, so you should build into your
 15 statistical approaches the potential that there is
 16 a difference.
 17 You should have some step-down approach or
 18 specification that any analyses of functional
 19 outcomes would consider mortality, so by using the
 20 composite endpoint approach and/or one of the
 21 causal inferential approach the SACE.
 22 Here, this is the two parts of the talk that

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1 are most familiar to me, and then here are some
2 other observations I made while I was reading
3 through the sedation trial literature. It looks
4 like there's limited use of group sequential
5 designs within this setting. I found one trial,
6 the NONSEDA trial that performed a single interim
7 analysis after 350 patients were recruited. Choice
8 to use a group sequential design depends on a lot
9 of things, but mainly on your projected rate of
10 recruitment and the duration of follow-up.

11 There also was no mention of utilizing
12 baseline covariate adjustment. If you're
13 collecting baseline variables that are prognostic
14 for your outcome of interest, you can include those
15 variables in your analysis to improve precision and
16 to estimate your average treatment effect, so get
17 this in power. There's a whole host of adaptive
18 enrichment designs, which were alluded to in the
19 prior talk, and then other novel designs.

20 One of which that came to mind today in our
21 discussion particularly around how patients are
22 changing rapidly over time, there are these micro

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1 randomization trials that are developed by Susan
2 Murphy at Harvard beyond my scope, because it
3 requires a lot of interesting optimization
4 problems.

5 The idea is that patients our originally
6 randomized to a treatment. If the patient responds
7 to that treatment, they remain on the treatment,
8 but if the patient doesn't, then they're
9 re-randomized again to other different conditions.

10 Then that happens sequentially in time until the
11 patient ends up in an optimal treatment category.

12 Along the way of those micro randomized
13 designs, there's constant assessment of the
14 patients. So when the patient is identified to not
15 be performing well under the current randomized
16 treatment, you can do the randomization again to
17 move the patient into a more optimal condition.

18 There's also POP [ph] trials and pragmatic trials
19 that have been used in other critical illness
20 settings that might work in this setting as well,
21 so that's all I have.

22 (Applause.)

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1 Q&A and Panel Discussion

2 DR. WARD: Before I have a couple of other
3 people to join us, [inaudible - off mic] to get a
4 deeper dive into how we should be designing those
5 clinical trials.

6 DR. SHAFER: I'm going to be moderating this
7 session, and I want to start off by just repeating
8 something that Dr. Colantuoni said a second ago.
9 Everybody stand up and stretch.

10 It turns out that -- we were talking about
11 patient-centered outcomes. I'm actually in a
12 category that hasn't been discussed so far. You've
13 heard from my wife, Pamela Flood. I'm an ICU
14 survivor-survivor --

15 (Laughter.)

16 DR. SHAFER: -- and when Pamela was
17 hospitalized at UCSF, I spent literally every night
18 sleeping there by her side. And then when she
19 needed to have the care advanced to intubation and
20 sedation, I quite fortunately advocated for this,
21 and you won't be surprised to know that I advocated
22 that she get propofol.

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1 She was on that for a couple of days, and
2 then Mervyn Maze, the chair, said, "You know, what
3 do you think about dex?" So Mervyn had a strong
4 role in the suggestion that we move to dex, which
5 of course since it was Mervyn's suggestion, we did.

6 And I want to share that as an ICU
7 survivor-survivor, it was very consequential
8 because it was when I knew that she was going to
9 make it.

10 She had been unresponsive on the propofol
11 for about 3 days. We went to dex for about
12 8 hours, and Mervyn and Marty Bogetz came into the
13 room. Pamela has been completely unresponsive this
14 whole time -- and she knows what I'm going to say
15 here -- and I said to her, "Pamela, two stud
16 muffins have just walked into the room, Mervyn and
17 Marty."

18 DR. FLOOD: Hoping it would wake me up.

19 DR. SHAFER: And Pamela goes [gestures], and
20 that's when I knew she'd be coming back. But as a
21 survivor and a survivor-survivor, it does continue
22 to affect us. And one of the ways that I'm

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1 conscious of every day is that I have to take care
2 of my -- I've never had to take care of somebody
3 like that before. And I have to take care of
4 myself so that I can take care of my wife. It
5 changes one's perspective on these things.
6 We've had a wonderful discussion here, and
7 I'd like to open this up for questions and thoughts
8 about clinical trial design and some of the ways of
9 moving this field forward.
10 DR. RIKER: Riker. Yahya, you haven't had a
11 chance to really tell us much about what you've
12 learned in your SPICE series of studies and what
13 you would do today if you were designing SPICE 3.
14 I'm eager to hear your thoughts as far as RCTs
15 versus other alternatives or where you are.
16 DR. SHEHABI: Thanks, Rich. I will start by
17 what Steven just alluded to about Pamela being
18 unresponsive for 2 days, and then suddenly becoming
19 awake and doing this [gestures]. I think this is
20 really a part that will end very early in the SPICE
21 program, that the first 2-3 days of the acute phase
22 of critical illness is very different to the days

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1 from day 3, day 4, and onwards. You are kind of
2 like in the eye of the storm in the first 2 days,
3 and then the storm will pass, and you're now
4 cleaning up.
5 I think clinical trials ought to accommodate
6 for that, and perhaps we need clinical trials that
7 tackle the early part of critical illness where
8 it's very hot, very dynamic, and everything's
9 happening, procedures, imaging, dialysis, to go to
10 theatre and come back; all that stuff is happening
11 and it's very different from when the dust has
12 settled and we're now in a recovery phase.
13 I think trials so far has ignored that first
14 2 or 3 days mainly for logistic reasons because we
15 could not consent people in time to get them into
16 these studies. The only way you could do it with
17 SPICE is to have a deferred consent where the
18 patient would be randomized, and then once their
19 legal surrogate becomes available or they wake up,
20 then they will consent to continue part as a
21 patient, or say, no, I don't like this. I want to
22 get out.

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1 So that's one point. The second point, I
2 think we had a paradigm that is essentially age
3 independent in our trials. It's quite clear from
4 what we've done within SPICE -- which we knew
5 before but we didn't really have to know what's the
6 impact of the trials -- is that the patient who's
7 75 years old is not like a patient who's 35 year
8 old. They're both adults but very different
9 adults. They have very pharmacokinetics, very
10 different pharmacodynamics. They're sensitive to
11 drugs differently. They have comorbidities.
12 They're different, but regardless of that, we
13 treated them both as the same patient.
14 I think we have to stratify going forward in
15 clinical trials by age because we are definitely
16 dealing with two different biological systems
17 between a younger adult and an older adult.
18 The third point, which we've also realize,
19 is that particularly early in the course of
20 critical illness, clinicians use a combination of
21 drugs. While we do go and study X versus Y, even
22 in the guideline we say we're going to look at

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1 whether propofol is better than dex or dex is
2 better than this. But in real life, clinicians use
3 a combination of things. At one stage, they use
4 propofol, then they move to dex, and then they add
5 some midazolam. They add morphine. They add
6 fentanyl.
7 That combination pharmacotherapy is what
8 happens in real practice. For trials' conclusions
9 and results to be generalizable, it needs to
10 accommodate for that combination of usage.
11 DR. SHAFER: Other comments?
12 DR. SPIES: Maybe one additional, I full
13 agree with Yahya. The point is I think one thing
14 is vulnerability, so many patients have
15 different -- so chronological age is difficult
16 because usually people can be very frail when they
17 go into that setting. For example, if they have
18 cancer, prolonged cancer, they are much more frail
19 to what we are doing. I think that's something
20 that needs to be also considered, the physiological
21 reserve of the patients.
22 DR. SHAFER: Anybody want to respond?

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1 DR. SHEHABI: If I could just add to your
2 comment, Claudia, I think when we do clinical
3 trials, having a large sample size would allow you
4 to have adequate power to look into those different
5 subgroups and make meaningful results from doing
6 that. I think earlier Rich was talking about
7 having mortality as a primary outcome. We use
8 primary outcome primarily to sample size studies
9 rather than find what it's going to show. We just
10 want to know whether it's going to show different
11 or not but primarily to sample size for a study.
12 I think if used mortality, for example, as a
13 primary outcome, your sample size is with a large
14 sample, but that allows you a lot about clinically
15 relevant outcomes with a lot of power and a lot of
16 precision.
17 DR. SESSLER: Absolutely I support large
18 trials. If you know in advance that you're
19 interested in a particular subgroup, consider
20 stratifying so that you end up with a good balance
21 across your groups of interest. It essentially
22 cost nothing. With electronic randomization, you

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1 can add lots of stratification, and it will give
2 you good balance for free.
3 DR. COLANTUONI: I agree.
4 DR. SHAFER: Talmage?
5 DR. EGAN: I don't want to derail the
6 discussion too far afield, but at some point I
7 think this is worth discussing, and I don't see
8 that there's another point in the agenda where it
9 has an obvious place to come up, and that is the
10 question of using target-controlled infusions as
11 part of the study design.
12 I think if we look at this very broadly,
13 these kinds of studies are both pharmacodynamic
14 studies and outcome trials, so on an hour-to-hour
15 basis, it's a pharmacodynamic study. You're trying
16 to make some assessments about where the depth of
17 sedation is. And then you've got the sort of
18 broader question of what the ultimate outcomes are,
19 which is obviously the more important endpoint.
20 But in any case, at least for the
21 pharmacodynamic part of this study, controlling the
22 kinetic aspects of the study is so that you don't

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1 have drug levels jumping all over the place, so
2 that you're giving the drug in a very precise way
3 where you're getting some approximation of a known
4 plasma level. And more importantly, you are
5 locking in a relatively steady state of the drug,
6 and I think improves the overall design to some
7 degree.
8 As you'll recall, Steve, you and I
9 collaborated on a trial that used TCI as part of
10 the study design. So I just wondered our panel
11 thinks and what some of the audience thinks about
12 how that might improve these trials.
13 DR. SHAFER: Let me just follow up on that.
14 Quite specifically, that was one of the
15 registration trials for propofol.
16 DR. EGAN: Right.
17 DR. SHAFER: So propofol registration for
18 the ICU was done using TCI, and without knowing
19 your doses and your concentrations -- which is one
20 of the other things TCI can do, is it can capture
21 what you've actually done as well as allow you to
22 target things, which otherwise is very hard to

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1 capture what drugs were used. You can take a trial
2 and say, hey, drug A works better than B, but A is
3 just 20 percent more propofol. You can't really
4 identify it without actually getting the kinetic
5 dynamic model involved in the outcome analysis.
6 Anybody want to comment on this?
7 DR. GIRARD: This is Tim Girard. I think
8 that's a great idea. I think probably we need even
9 back up further because the pharmacokinetics of
10 most of these drugs is poorly understood, if not
11 completely un-understood. That's not a real word,
12 is it?
13 (Laughter.)
14 DR. GIRARD: I think you get my point. Many
15 of these drugs have had very little, if not any
16 pharmacokinetic studies, in this population. Our
17 group has done some work looking at
18 pharmacokinetics and pharmacodynamics, and found
19 that actually plasma concentrations of many of
20 these drugs did not correlate well, or at all, with
21 the observed clinical response to the drugs.
22 DR. SHAFER: Mervyn, wasn't dex also done

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1 with TCI?
2 DR. MAZE: No, it wasn't done with TCI, but
3 we had very specific infusion criteria.
4 Dan?
5 DR. SESSLER: Dose really matters, and it's
6 something that we've a little bit ignored here.
7 Talmage and Steve could speak to this better than I
8 can, but we're often comparing two different drugs
9 at essentially random doses, but if you use
10 slightly different doses, you could get completely
11 different results. It's very easy to do a trial
12 with two drugs and conclude one is better than the
13 other. It's not actually better than the other,
14 you just didn't give enough of the alternate drug.
15 DR. SHEHABI: I think the TCI model is based
16 on computer modeling in relatively healthy
17 volunteers, and I think transferring that into the
18 critical care population I think is not a
19 straightforward phenomenon.
20 MALE VOICE: Where are we going to get the
21 devices as well? Because wouldn't they be
22 investigational? They're not approved in the U.S.

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1 DR. SHAFER: Interestingly, for AstraZeneca,
2 it was just part of the trial, and the whole thing
3 was approved. And it was ironic because the FDA
4 device division would say, "Oh, we can't do these,"
5 but CDER was quite happy to use the data from TCI
6 in approving propofol for ICU administration.
7 But let me just address that specific point
8 because I know what Talmage and I would both say to
9 that. That is, what TCI allows you to do is at
10 least hold a more or less steady concentration
11 around which one titrates. If you're just talking
12 about giving boluses and infusions and randomly
13 going up and down, you're assuming that the
14 infusion rate, in and of itself, is going to
15 instantaneously translate to what's going on in the
16 patient's brain. At least the target has got a
17 better shot at giving you something and holding it
18 steady so you can then make your adjustments.
19 DR. SESSLER: Even if you don't know the
20 absolute.
21 DR. SHAFER: Even if you don't know the
22 absolute, because you'll measure it.

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1 DR. SESSLER: You get more stability.
2 MALE VOICE: And you're looking at an acidic
3 end-stage renal disease population for which we
4 have no data as to what the pump is actually going
5 to have in the body and the multiple compartments.
6 DR. SHAFER: So what are you going to do;
7 just pick dose? That's going to be better?
8 MALE VOICE: Titrate to an end effect.
9 DR. SHAFER: And if you're going to titrate,
10 use TCI.
11 Other questions?
12 DR. BALAS: I have a question. I'm
13 wondering if anybody in the United States has been
14 successful at getting an IRB through with a
15 deferred consent.
16 MALE VOICE: With what?
17 DR. BALAS: Deferred. As Yahya was
18 saying -- is it true for the SPICE trials? They
19 enroll the patients, randomize, start the
20 intervention, and get consent later.
21 DR. GIRARD: Are you specifically asking
22 about sedation trials or any trial?

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1 DR. BALAS: Anything in the ICU.
2 DR. GIRARD: Yes, It's been done for
3 non-sedation related trials, yes.
4 MALE VOICE: I think it's been done in
5 emergency settings like seizures out in the field
6 and that sort of thing, but I think your point is
7 it's almost impossible.
8 MALE VOICE: I mean, there's an ethic model,
9 so I think that's with cardiac arrest and those
10 things. And there's a community consent, and there
11 there's a process. We've actually had three trials
12 that we've done, none of them sedation trials, but
13 we talked about doing it in a cardiac arrest model
14 with early antibiotic therapy and doing ethic for
15 that.
16 We didn't do the study because we didn't get
17 funded, but ethic is a pathway where you can
18 proceed. You try to get consent if you can. If
19 there's no family or no surrogate around you, you
20 enroll the patient if they haven't excluded
21 themselves in advance, and then when the family
22 arrives, you inform them and go from there. So

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1 there is a model.

2 MALE VOICE: There's a second thing you have

3 to do with those patients, is when they become at a

4 state where they can consent, you have to approach

5 them, and they can obviously withdraw at any stage.

6 DR. SESSLER: Cluster randomized trials

7 automatically have waived consent because you're

8 randomizing an entire facility to something or

9 something else, and they're used typically for

10 system-wide interventions.

11 Let's say electronic records. Electronic

12 records are not something you can turn on and off

13 on a patient basis, but if you want to assess the

14 effect, the only way to do it rigorously is either

15 cluster randomization where you have whole

16 facilities that start, or don't start, or a

17 step-wedge, which is similar to cluster. Neither

18 of those has individual patient consents.

19 We've also done half a dozen of these

20 alternating cohort studies, which are good for

21 comparative intervention studies, so when you're

22 comparing two perfectly reasonable standard

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1 clinical interventions that are done all the time.

2 For instance, isoflurane versus desflurane,

3 lactated ringers versus saline; two different title

4 volumes. These are examples of trials that we've

5 done with waived consent, so there certainly is a

6 precedent for doing some sorts of studies with an

7 altered or a waived consent.

8 DR. AITKEN: I've got a feeling that I

9 remember Martha Curley telling me that in her

10 cluster RCT, they could obviously allocate the

11 sites to the intervention, but they couldn't

12 collect any data in the intervention sites until

13 they had consent. I don't remember the details,

14 but I remember her having a real problem.

15 DR. SESSLER: It's certainly possible; it's

16 not the classical way to do a cluster --

17 DR. AITKEN: Yes, it seemed odd.

18 DR. SESSLER: -- because if you're doing

19 something like electronic records or an enhanced

20 recovery pathway, you can't really turn it on and

21 off.

22 DR. AITKEN: No. It seemed really odd, but

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1 it might be worth just checking.

2 DR. SESSLER: So the normal way to do is

3 just you do it.

4 DR. AITKEN: Yes.

5 DR. SESSLER: There are rules about waiving

6 consent. In Europe and in Australia, it's very

7 difficult. There's essentially no regulatory

8 pathway for doing it. In the United States, there

9 is a legal pathway for waived consent, and it

10 requires a number of things, which include minimal

11 risk, and the study can't be practical without

12 waived consent. Now what defines practical is open

13 to some dispute, but one of the things that is

14 considered part of the practicality decision is the

15 cost and difficulty of the trial.

16 DR. SHEHABI: Can I just make a comment

17 about the clustered randomized trials? We're

18 involved with two clustered randomized trials in

19 Australia. One is the MIT [ph], which is the

20 likely rapid response team, and doing the clustered

21 studies require a huge number of sites, a huge

22 number of -- I mean, each cluster essentially

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1 blocks one --

2 DR. SESSLER: N equals 1.

3 DR. SHAFER: It needs such a massive number

4 of patients involved to get to power.

5 The second thing I wanted to make a comment

6 about is the waived consent. There is a regulatory

7 process in Australia to do that. There is a

8 regulatory framework to do that. Essentially, it

9 varies from state to state, and it changes by

10 whatever the parliament thinks on the day.

11 In Victoria for example, if the two

12 interventions are considered within usual accepted

13 practice, then waived of consent or deferred

14 consent is acceptable. In New South Wales, the

15 same trial, which is FOSTER [ph], the same trial,

16 the guardianship board, which is like the body that

17 makes the law, said, "No, no, you can't do that."

18 And we said, "No, we disagree with you." We have

19 to take the guardianship board to the Supreme Court

20 to change their mind, and now they're changing the

21 law in New South Wales to say, yes, when things are

22 similar, yes, you can do a deferred consent.

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1 DR. SESSLER: All localities allow at least
2 deferred consent for emergencies, say out of
3 hospital cardiac arrest. That was actually on hold
4 for about a decade worldwide to everyone's
5 detriment. Now everyone allows that.
6 MALE VOICE: Not everyone. Sweden doesn't
7 do that.
8 DR. SESSLER: Okay.
9 MALE VOICE: Be careful when you travel to
10 Stockholm.
11 (Laughter.)
12 DR. ABSALOM: Tony Absalom. I was just
13 going to say there was this trial of adrenaline
14 during CPR in the UK, but they had to jump through
15 an awful lot of hoops to do that. They had to have
16 all these media campaigns to allow all exposed
17 possible people to notify that they wouldn't like
18 to be enrolled should they have a cardiac arrest.
19 MALE VOICE: Do you wear a bracelet?
20 MALE VOICE: Yes.
21 DR. DEVLIN: John Devlin. The one thing I
22 just want to bring up, too, is the extent to

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1 exclusion and inclusion, which a lot of things are
2 obvious, safety issues and confounders. But we end
3 up with studies that are sort of a leading
4 [indiscernible]. It's quite low. Maybe only
5 10 percent of the population is actually enrolled.
6 Any thoughts from the panel on -- I realize
7 I guess a pragmatic approach could be used to
8 eliminate some of that, but any thoughts on where
9 we're trying to always remove all those sources of
10 bias up front?
11 DR. SESSLER: It's an issue that all trials
12 face. One of the factors that influences sample
13 size is variability, and that's under your control,
14 unlike treatment effect, which is not under your
15 control. So you can reduce sample size by reducing
16 variability, and the way to reduce variability is
17 to have a fairly narrow homogeneous population.
18 The other thing is that if you're testing a
19 new drug or device, especially if this is funded by
20 people who have an interest in your drug and
21 device, they want to select patients who are most
22 likely to benefit and least likely to have

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1 complications. So that's why sponsored trials have
2 these very long lists of inclusion/exclusion
3 criteria, whereas investigator initiated trials
4 tend to be more reasonable.
5 Narrow enrollment criteria reduce
6 variability. It makes the trial results easier to
7 interpret, but it makes it harder to enroll and
8 less generalizable. So the broader you can make
9 them at the expense of variability and increased
10 sample size, you end up with a result that's more
11 useful.
12 DR. SHAFER: There are regulatory
13 implications, too. If I might ask how the FDA
14 views going narrow to get something that's very
15 precise. And you can say, well, gee, I can really
16 interpret this trial because it's very narrow
17 versus some label that's going to be used by 2
18 million people within a month of being approved.
19 DR. ROCA: This is Rigo Roca again. I think
20 those are both very valid points. As you noted, if
21 it has a very narrow enrollment, you're right; it's
22 easy to interpret. We get a better assessment of

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1 the treatment effect, the side effect profile of
2 the product and all that, but the ability to
3 generalize is limited.
4 So one of the other things that we are
5 certainly open to is that one trial would be
6 narrow, and then you could have another trial to
7 replicate the results but have that be, if you
8 wish, all comers, or a little wider, but you can
9 get a wider population that may be more
10 generalizable to the public. We're very much
11 willing to see that.
12 DR. SHAFER: Dr. Ward?
13 DR. WARD: Denham Ward. We've heard a lot
14 of things about outcomes. The amount of time at
15 sedation level is probably no longer an appropriate
16 primary outcome; we've kind of moved past that.
17 And now we've heard some things about composite
18 outcomes as a way to improve and get more power on
19 a clinical trial. What composite outcome should we
20 be using? If we're going to use a composite
21 outcome in a clinical trial for sedation, what is
22 it?

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1 DR. COLANTUONI: Never ask you statistician
2 that question.
3 (Laughter.)
4 DR. COLANTUONI: I'm just kidding. No, but
5 I'm not.
6 DR. SHEHABI: I think a composite outcome
7 may look like a solution, but it's really a very
8 imperfect solution. I think there is a lot of
9 issues with composite outcomes. We find that
10 public funders in Australia, for sample, they will
11 rank a trial that has a primary outcome as a
12 composite outcome of multiple things, and their
13 rank is brought down because of all the issues that
14 you've mentioned before and I've mentioned before.
15 So I'm not sure that we do need to invent a
16 composite outcome for sedation trials.
17 Probably to go further to what you said,
18 Dan, before, that a certified baseline, what we
19 chose to do with a spot [indiscernible], rather
20 than serve at baseline, is to have a better sample
21 size is to choose the subgroups at the median level
22 of what are you looking at, whether it's age, or

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1 Apache [ph], or whatever, and that would
2 immediately give you two halves of the groups,
3 distributed nicely between the groups.
4 DR. SESSLER: Composite outcomes are good
5 for rare dichotomous outcomes. Most of the
6 outcomes we're talking about here are not
7 dichotomous. Death is, but the others are not.
8 We're talking about mechanical ventilation, time in
9 the ICU, functional outcome; those are all
10 continuous outcome. They don't lend themselves to
11 composites very well.
12 DR. COLANTUONI: I think there's a
13 distinction between what Dan just said and the
14 approach to summarize an outcome that's dynamic
15 over time like ventilator-free days and
16 delirium-free days, that incorporates the
17 complicating factors of mortality, which is how I
18 was defining composite outcome versus the
19 difference between what Dan was defining as
20 composite outcome.
21 So you can create a composite that is a
22 delirium, but summarizing over a time course and

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1 potentially calling for competing risks is slightly
2 different in my thinking than saying we're going to
3 include mortality and some other adverse events
4 that we might see -- other binary adverse events
5 that we might see over the course.
6 DR. SESSLER: Well, I think it's good for
7 complications --
8 DR. COLANTUONI: Oh, yeah.
9 DR. SESSLER: -- because very often,
10 complications are rare. Your primary outcome is
11 how well does a drug sedate
12 somebody? Well, you're going to look at measures
13 of sedation for that primarily. But if you want to
14 know does this drug cause complications, now you're
15 suddenly looking at a wide variety of presumably
16 rare events, and many of these are dichotomous.
17 Composites are a really good way to look at the
18 complication. You're never going to be powered for
19 individual types of complications.
20 DR. SHAFER: Let me point out that Dr. Ward
21 just asked a question that was similar to the one I
22 asked, and looking at what we are here for, a

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1 patient-centered outcome. I think he sort of said
2 what is that patient-centered outcome, which I
3 tried to ask earlier, and I did not get an answer.
4 And you tried to ask it, and you just didn't get an
5 answer.
6 Let's try again. Both to the people on the
7 panel and people in the audience, what is a
8 measurable, triable, falsifiable,
9 patient-centered outcome?
10 DR. AITKEN: I'll start by saying it has to
11 be beyond hospital. I don't think that we can be
12 having a primary outcome that's only in hospital
13 would be my suggestion. But what it should be, I
14 think we could argue for various things.
15 DR. SHAFER: Like?
16 DR. AITKEN: Like, certainly mortality is
17 the obvious one, but I think more functional
18 measures like returning to work, or that's probably
19 the one that jumps out as an obvious one because
20 that incorporates a whole lot of other things in
21 there. You can't return to work if you don't have
22 reasonable, functional health, reasonable,

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1 psychological health; and reasonable cognitive
2 health.
3 DR. GIRARD: And we should
4 recognize -- actually, you just described it
5 beautifully -- return to work is a composite
6 outcome because all of those things have to be true
7 for you to return to work.
8 DR. AITKEN: That's the risk of it.
9 DR. FLOOD: The thing about return to work
10 is that many people in the ICU aren't working.
11 DR. AITKEN: Sorry. I should say return to
12 work or previous normal activity. Sorry. Yes, it
13 has to be a broader definition than that; you're
14 right.
15 DR. FLOOD: How about a quality-of-life
16 outcome?
17 DR. TANG: Sorry. Real quickly. There's a
18 work productivity, activity measure that -- it's
19 WPAI. I apologize. I'm just scrambling to
20 remember what the acronym stands for, but it does
21 measure essentially not only work but also activity
22 impairment that could be associated. So just a

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1 note that that's a regularly used one in the
2 quality-of-life space that's typically used.
3 DR. DEXTER: I was going to say from a point
4 of view, two separate issues. When it comes at
5 least to the retrospective analysis of data, I
6 found it to be quite challenging to do something,
7 whether it's work or functional activity, among
8 patients for which you don't have baseline
9 measures. Unless you are planning to be in the
10 ICU, at least when I try to analyze those data, I
11 tend to find very weak baseline measures. So it's
12 something to consider.
13 But I'd like to go back to address your
14 point about patient-centered outcome. Avery has
15 made the comment in terms of thinking about an
16 indication. The point that you brought up is to be
17 able to provide for those patients for whom the
18 goal is to provide a deep level of sedation to
19 prevent adverse events or something like that.
20 I think that actually there is something to
21 be said for that. When you think about analogies
22 in terms of endpoints of anesthesia trials, there

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1 are a large number of patients, large numbers of
2 procedures, where general anesthesia is not an
3 appropriate endpoint. You may use a drug for
4 different applications, but initially at least you
5 start with the subgroup of patients for whom you
6 think you want to do something.
7 The other thing about it is you can also ask
8 individual patients whether or not that would be an
9 appropriate choice and so forth. I think that that
10 is not an unreasonable approach. It's not going to
11 be that trying to provide a deep level of sedation
12 is appropriate for all patients; it's going to be a
13 minority of patients, but you can have a
14 patient-centered outcome for the subset of patients
15 for whom you want to be providing that.
16 MALE VOICE: So an individualized
17 patient-centered outcome.
18 DR. DEXTER: Well, that is how we would be
19 doing -- if this were not a question about ICU
20 patients, if this were a question about
21 satisfaction of patients after general anesthesia,
22 satisfaction with monitored anesthesia care, that

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1 is exactly how we would do it. You would ask the
2 patient, so to speak, or the surrogate for the
3 patient, what would that patient want given this
4 particular context. That would be the
5 patient-centered approach. And given the condition
6 on the idea that it's going to be general
7 anesthesia or deep so to speak, go forward in that
8 way.
9 DR. NEEDHAM: This is Dale Needham. I think
10 we're giving all our perspectives on
11 patient-centered outcomes, but what research has
12 been done to rigorously understand what are
13 patient-centered outcomes, I'm not aware of it with
14 respect to sedation. So I think until there
15 actually is research done doing that it's just kind
16 of everybody's opinion on that.
17 So I think there needs to be an agenda so
18 that people actually do that, and I think one
19 starting point that is great, as Leanne showed, is
20 these are the outcomes that have been used. That's
21 kind of like a scoping review kind of thing to
22 think about. Those are kind of candidate things.

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1 Then we need to be talking to patients.
2 Also, we need to think about maybe the most
3 important outcome is going to be a resource
4 utilization one, perhaps, in terms of shortening
5 duration, mechanical ventilation, length of stay at
6 hospital, that might be where the strongest signal
7 is between an intervention and an outcome, at least
8 based on my understanding of prior studies, and we
9 want to show that there are positive signals of
10 benefit in other things as well and no harm, and
11 that might be, at least from my naive perspective,
12 the best way to be thinking about it.
13 Do people want to argue the opposite?
14 DR. SHEHABI: I just wanted to add, I think
15 the context is quite important. And if you're
16 looking at a patient-centered outcome that looks at
17 function or outcome, for example, it's important to
18 go back to the inclusion/exclusion criteria that
19 Tim was talking about, where you would not include
20 in a sedation trial, for example, traumatic brain
21 injury patients, or patients who come with a green
22 beret, or patients who are going to be intubated

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1 for 6 months because of a neurological disease
2 because the outcome is going to be determined by
3 their underlying illness rather than by the
4 sedation that you're doing.
5 I think it's very important to marry the
6 patient's outcome we're looking at with the
7 population you're studying and pretty much like
8 what you mentioned about the seizure population,
9 the same for the ICU population. In our trial,
10 John, we've excluded anybody who had any
11 neurological problems whatsoever, whether they have
12 weakness or brain injury of any kind.
13 So we want them to be completely
14 neurologically intact on entering the study, and
15 for that that, the patient-centered outcomes that
16 we looked at were specific on things like -- in
17 addition to mortality, we looked at cognitive
18 function at 180 days, institution dependency at 180
19 days with basically societal resource utilization.
20 Then on top of that looked at their quality
21 of life at 180 days in terms of what are they able
22 to do, and because we knew that they entered

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1 intact, we could assess them at 6 months and say
2 this is where they were at this point in time.
3 DR. SHAFER: Leanne?
4 DR. AITKEN: I was just going to pick up on
5 Dale's comments. Certainly, I think the issue of
6 talking more to patients and asking them what they
7 want is absolutely essential. It still doesn't
8 tell us what every individual is going to want, but
9 that gives us a better sense.
10 My only hesitation in what you said about
11 resource utilization is I think we have to think
12 health system wide rather than just hospitals, so
13 I'd be hesitant in only looking at resource
14 utilization within the hospital because if we're
15 shifting sick or dependent patients outside the
16 hospital, then we're shifting resource utilization.
17 So I do think we have to think across the system.
18 DR. SHAFER: I'd like to pose a question to
19 Frank. Frank, you do a lot of work with economic
20 analysis, and basically why should somebody invest
21 in something? Why should they invest in a certain
22 kind of system? Why should they undertake a

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1 certain study?
2 Let's say that we come up with a
3 patient-centered outcome that everybody says this
4 is a great patient-centered outcome. This will
5 really improve the wellbeing, somehow measured, of
6 patients who are sedated in the ICU. Somebody's
7 got to invest in that. There's got to be some sort
8 of return. I mean, I agree that we do this for
9 noble reasons and for academic glory and things
10 like this, but these trials are big. Big trials
11 are expensive. Somebody's got to invest.
12 How would you put together economic argument
13 that whatever this great thing is that we're going
14 to measure should be studied, measured, and
15 improved? How does one go about making that
16 economic case?
17 DR. DEXTER: I don't think I can answer that
18 question per se.
19 DR. SHAFER: Can you answer a different one?
20 (Laughter.)
21 DR. DEXTER: Yeah.
22 DR. SHAFER: Let's suppose that you've got a

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1 company with a hypothetic gold product, and they're
 2 thinking about actually bringing product to market.
 3 Let's suppose that you've got the following option.
 4 One is you've got resource use in the hospital,
 5 ventilator days with adjustment or something like
 6 that.
 7 One of the challenges you have -- I'm sorry;
 8 it's a slightly long answer here. One of the
 9 challenges you have is that the dollar value
 10 associated with these resource uses will vary
 11 massively among organizations, and really this is a
 12 function of the variability in the workload within
 13 the organization.
 14 So that's why things like ventilator days, a
 15 few primary endpoints which are measurable, works
 16 totally adequately. If you've got tons of
 17 ventilator days, you have more costs. That is easy
 18 to understand. Also, there's a difference from a
 19 regulatory point of view, you can measure it and do
 20 the trial.
 21 In contrast, when you're thinking
 22 about -- let's take a couple of others -- long term

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1 from the point of view, something about the
 2 functional measure, quality recovery of the
 3 patient, or something like that, at least from the
 4 point of view of critical care and watching
 5 companies make these decisions, they freak out
 6 because you don't have the baseline measurements.
 7 You're not really randomizing patients where you
 8 have this and stuff like that.
 9 It seems very large sample sizes compared to
 10 the consumption or something like that. That seems
 11 to be something which you would do after you have
 12 the drug approved, then you might go ahead and do
 13 it; at least that's what I tend to hear.
 14 The costs are oftentimes the families and
 15 things like that. But again, the problem is going
 16 to be are they then going to be able to sell the
 17 drug and what is going to be the variability, and
 18 how are you going to actually randomize a patient,
 19 stratify based upon that? I think that the answer
 20 would be, typically, hospital resource use makes
 21 quite a bit of sense practically.
 22 DR. DEXTER: How about how about a post-use

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1 like looking at SNF facilities. They're long-term
 2 care after ICU, so try to avoid these very
 3 expensive outcomes that are measurable.
 4 DR. SHAFER: Yes, but I think that one of
 5 the things would be is that it's quite -- when I
 6 say straightforward, I don't mean like trivial; to
 7 be able to use a variety of different economic
 8 endpoints such as that, which is days in
 9 [indiscernible] care or after the hospital; days on
 10 the ventilator and things like that. Those things
 11 can be combined in terms of quantitatively and
 12 stuff like that.
 13 DR. MAZE: Steve, can I ask you a question
 14 about your question to Frank, that he changed the
 15 question up.
 16 DR. SHAFER: He really didn't.
 17 DR. MAZE: No, he didn't. In a situation
 18 where the patient is not directly responsible for
 19 the cost of the care, and there are many countries
 20 like that, what does it matter? Where's the
 21 patient centeredness about that?
 22 DR. SHAFER: About --

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1 DR. MAZE: -- about resource utilization?
 2 DR. SHAFER: That's why I'm asking the
 3 question.
 4 DR. DEXTER: I don't think it's patient. I
 5 going to take an extreme example. Like ventilator
 6 days, I don't see how that's patient centered at
 7 all. It completely escapes me how that would be
 8 patient centered, or maybe I'm totally missing
 9 something, and I apologize.
 10 MALE VOICE: You probably haven't been on a
 11 vent.
 12 (Crosstalk.)
 13 FEMALE VOICE: The risk of respiratory
 14 infection and death is directly tied to ventilator
 15 days.
 16 DR. AITKEN: But those say some patients
 17 describe quite vividly wanting to get the tube out,
 18 so there's that angle of it as well.
 19 DR. KRESS: But I think it's important, this
 20 concept of patient centered, I certainly think it
 21 sounds good. You have to be careful what you ask
 22 for, though, because you ask the patient, the

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1 patient doesn't necessarily understand what the
2 implications are. Put me in a coma for 4 days;
3 wake me when it's over. It sounds good except when
4 you actually come to realize what that entails.
5 So ventilator days isn't [inaudible - mic
6 face] patient-centered from one perspective, but
7 from another perspective, the longer you stay on
8 the ventilator, more likely you are to have
9 problems X, Y, and Z, that are going to affect you
10 down the road. So maybe that's just semantics, but
11 I would argue that ventilator days is very patient
12 centered if you look at what it means to the
13 patient down the road.
14 DR. SHAFER: So we're in our last two
15 minutes. Go ahead, Frank, but we're going to kind
16 of go quickly here.
17 DR. DEXTER: I think when I think from an
18 anesthesia point of view of patient centered, it is
19 in things that are -- all outcomes, death is very
20 bad for the patient. Pneumonia is bad for the
21 patient, but that's not what I think of. When I
22 think of patient-centered outcome as something like

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1 that, it's quality of life, quality of recovery,
2 those types of things.
3 FEMALE VOICE: But if you have pneumonia,
4 your recovery is going to be awful.
5 DR. SHAFER: Claudia?
6 DR. SPIES: I think the preference of some
7 not very valid structure established, and I think
8 what we did last year is try to inform the patients
9 much better. So the patient preferences need to be
10 in fact boxes at some point.
11 I think it's very difficult for patients to
12 understand what we tell them, and even as for us,
13 it's difficult at the end because we often give the
14 wrong information because we have not enough
15 knowledge. This is also a problem because we don't
16 always see the whole path.
17 So I think we need preference with processes
18 of structured interviews like in the shared
19 decision making processes, and then we can evaluate
20 if we have the right knowledge, all of us, think.
21 That's a major issue I have. So I think we need
22 global knowledge in that structured patient

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1 preference.
2 DR. SHAFER: We're down to 60 seconds. Bob,
3 you're next.
4 DR. DWORKIN: We were reminded this morning
5 that the FDA approves drugs, biologics, and devices
6 that improve the way patients feel, function, or
7 survive. At least to me, those all sound like
8 patient-centered outcomes: feels, functions,
9 survives. So I think as long as we're in that big
10 bucket, we're talking about patient-centered
11 outcomes, and also in line with how the FDA
12 regulates drugs, devices, and biologics.
13 DR. SHAFER: Anna?
14 DR. ZHAO-WONG: Thank you. I'm just trying
15 to think out of the box. When you ask the
16 question, economically, why should we do these
17 large expensive trials? Well, one thing to think
18 about is insurance, and insurance would pay those
19 ways, methods, and treatments that have better
20 patient outcomes.
21 DR. SHAFER: My insurance company doesn't
22 care, but maybe yours does.

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1 You had one comment.
2 DR. SHEHABI: I just wanted to make sure
3 that we don't really lose the baby with the bath
4 tub. As you sit there, the patient-centered
5 outcomes should improve the patient's survival,
6 function, and feeding.
7 For that reason, I think we must not just
8 focus on things that come outside the ICU because,
9 for example, delirium, when we know how much it
10 impacts patients, must really be an important
11 patient-centered outcome. We may argue about
12 ventilation, an extra day or an extra 6 hours, but
13 I think we need to be quite clear that delirium is
14 absolutely a patient-centered outcome.
15 DR. SHAFER: Dr. Ward, you get the last
16 word.
17 Adjournment
18 DR. WARD: A couple of things, housekeeping.
19 But just to comment, for example, the drug from my
20 generation, droperidol, is a great,
21 non-patient-centered drug. It works great as a
22 sedative, but if you ask a patient how they felt,

1 they felt horrible. So you address patient
2 centered by finding out how the patient actually
3 felt through it all.
4 Thank you all.
5 (Applause.)
6 (Whereupon, at 5:04 p.m., the meeting was
7 adjourned.)

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