

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

March 29, 2019

*A Matter of Record
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15	Friday, March 29, 2019	15	
16	8:00 a.m. to 2:38 p.m.	16	
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1	C O N T E N T S	1	PROCEEDINGS
2	AGENDA ITEM PAGE	2	(8:00 a.m.)
3	Defining and Measuring Light vs. Moderate	3	DR. WARD: It was really an exciting day
4	Sedation/Analgesia	4	yesterday with some controversies and some
5	Pratik Pandharipande, MD, MSCI 8	5	questions. We have a couple of talks this morning
6	Case Study: Approval of Dexmed for	6	before we get into really kind of the meat of the
7	ICU Sedation	7	meeting, and that is really to continue the
8	Mervyn Maze, MBChB 41	8	discussion on how you would design a clinical trial
9	Who Should Be Studied and How?	9	for ICU sedation. At the end of the meeting, I
10	Avery Tung, MD 65	10	will talk about some of the deliverables that we
11	Panel Discussion: Who Should Be	11	would like to have.
12	Studied and How? 71	12	I think one of the things to keep in mind
13	Moderator - Avery Tung	13	among the things we're talking about is -- Merv is
14	Panel Discussion: Evaluating Acute	14	going to talk about dexmedetomidine -- if a new dex
15	Use of ICU Sedation/Analgesia 124	15	that comes along, if a company's got the new dex,
16	Moderator - Yoanna Skrobik	16	what do they have to do to get it approved?
17	Panel Discussion: Acute, Subacute and	17	Probably the FDA is not going to say, well, if you
18	Chronic Outcomes after ICU Sedation 216	18	show that the quality of life improves 6 months
19	Moderator - Tim Girard	19	later and back to work, that's not going to get new
20		20	dex approved as an ICU sedation drug.
21		21	Those are all great things, and we should be
22		22	talking about them, and those are things we would

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1 like sedation in the ICU to accomplish, but
2 indications have to be a lot tighter connected to
3 the mechanism of action for the drug. The question
4 that I asked yesterday, and at dinner last night,
5 and I still haven't got an answer to -- I think it
6 was Rich who said we should move past a RASS score
7 minus 1 or 2 as the primary outcome. What is the
8 primary outcome?
9 If you have the new dex, and you have a
10 company that -- not to push the money too much,
11 with Steve, but if the money was there to get new
12 dex approved and you're the consultant, what would
13 you say the primary outcome should be for that
14 study?
15 DR. FLOOD: Why would a significantly
16 improved talk about quality of life at 6 months not
17 be an acceptable outcome?
18 DR. WARD: Could you use the microphone?
19 DR. FLOOD: Sure. Pamela Flood. Why would
20 an improved quality of life at 6 months not be an
21 acceptable outcome?
22 DR. WARD: Bob?

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1 DR. DWORKIN: There's no question it's an
2 acceptable outcome -- [inaudible - mic distortion],
3 and of course you'd want to know that, but it's a
4 basis for approving a drug. I don't see anyone
5 here from the FDA. I don't see Rigo or Marti [ph].
6 I think that if you want to approve a drug
7 with a label for sedation, when you do it for ICU,
8 [indiscernible - mic distortion] to talk about
9 quality of life 6 months later. If there was
10 someone from the FDA, I'm sure they could flush out
11 that answer a little better.
12 DR. FLOOD: I was assuming that it was
13 actually functional as an anesthetic, but it would
14 definitely show a benefit over other sedatives if
15 it was just as good acutely as a sedative but there
16 was a recovery benefit. No?
17 DR. WARD: As a primary endpoint, if the
18 labeling says it's a sedative, you've got to show
19 it's a sedative for that. It's not going to be
20 assumed that the regulatory agency level. I think
21 that's a question that we need. If we're going to
22 help people design clinical trials, we need to come

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1 up with some thoughts about what would be our
2 primary endpoint for that.
3 There's some housekeeping stuff. Sign in.
4 Silence your cell phones. Remember, you're being
5 audiotaped, and there's going to be no 18-minute
6 blanks in these tapes. You're all going to be
7 there for that. WiFi. Checkout is noon. You can
8 bring your luggage down here. Lunch is the same
9 place, and the usual transportation will be
10 available to go to the airport, or train station,
11 or wherever you're going afterwards.
12 This morning, before we have the first
13 panel, Pratik is going to talk about what I kind of
14 just talked about, is how do we define a major
15 light versus moderate sedation analgesia. Then I
16 want to finish up with the presentations. Dex is
17 the only drug that has been specifically approved
18 for ICU sedation, and Mervyn was one of the key
19 people in that ever since he came down to UCLA and
20 said, "I've got this drug. Would you like to do
21 some phase 1 trials with it?" And I said, "How
22 come you're not doing it first?" He said, "Well, I

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1 think we should do it in southern California
2 first," and really got dex through the whole
3 approval process. So I've asked Mervyn to talk
4 about the story for getting that drug approved.
5 Pratik?
6 Presentation - Pratik Pandharipande
7 DR. PANDHARIPANDE: Good morning. When I
8 initially had suggested this talk, I thought I was
9 going to do a recap of the literature, talking
10 about how light levels of sedation would be defined
11 in the literature. Then after yesterday's
12 discussion, realizing that a lot of people over
13 here are knowledgeable and have actually created
14 the literature that supports those definitions, as
15 well as the fact that we already got off to a
16 relatively robust discussion about what light level
17 versus deep level should be.
18 I thought I'd split this talk about
19 introducing the elements in the guidelines, how it
20 was defined there to give us a framework, and then
21 bring in some of the discussions we've already had
22 yesterday to try and use that as a springboard for

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1 discussion so that we're actually moving forward
2 and not just talking about what we've talked about
3 in the past.
4 For disclosure, I do have a research grant
5 from Hospira, now Pfizer, which makes
6 dexmedetomidine, and it's a collaborative effort
7 between the NIH for an RCT that we're doing on
8 propofol versus dexmedetomidine. The study drug is
9 provided by Pfizer. All other grant supports are
10 shown over there. NIH R01s are what form the bulk
11 of non-Vanderbilt [indiscernible] salary support.
12 As we think about light sedation, I think
13 it's important to realize what are the indications,
14 at least in the literature, for sedation use
15 because as we move away from using sedatives and
16 moving towards light sedatives, we need to remember
17 why we initially at least taught sedation is
18 required in some patients in the ICU. And while
19 it's true that all these indications no longer may
20 hold true, it's important to at least keep that in
21 mind. So perhaps we still feel it's important that
22 patients don't have anxiety in the ICU. Perhaps

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1 it's still important that patients in the ICU don't
2 remove their devices, their endotracheal tubes,
3 their central lines.
4 The question about whether it reduces
5 physiological stress response, in some patients it
6 may be important and we may want to consider that.
7 Patient ventilator synchrony seems to be a big one
8 that shows up in many articles regarding sedation
9 levels, and that may be something that we have to
10 think of. And I bring this up later on, whether
11 there is a temporal change in sedation levels that
12 one needs to consider. Is it one score at all
13 times in critical illness or do we also need to
14 think about how we define light sedation
15 differentially as the time and the elements of
16 critical illness results?
17 At least in the past, I think there's been a
18 fair amount of concern that we needed to have
19 patient sedated in the ICU so that they didn't
20 remember anything about their ICU stay. This is an
21 area that is debated. The question is whether we
22 have strong enough evidence now to say that that

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1 entire concept of deep sedation associated with
2 improved psychological outcomes, or the other way
3 around, being awake, not associated with
4 psychological, heavy debunked that complete
5 association.
6 So the question is whether we have large
7 enough studies, and most studies that I have at
8 least looked at are relatively small. They're post
9 doc analysis of other studies, so that's something
10 I think we need to keep in mind.
11 Deep sedation, we all know is associated
12 with worse outcomes, and I'm not going to belabor
13 this point. At least some of the studies that have
14 been looked at in the 2018 PADIS guidelines focused
15 on RCTs that have shown that having a lighter level
16 of sedation -- and we'll discuss about how those
17 were defined -- were associated with shorter time
18 on mechanical ventilation, shorter time in the ICU,
19 et cetera. The question is whether light versus
20 deep sedation makes an impact on mobility, and I
21 think most of us, anecdotally at least, know that
22 your comatose patients can't walk, so that may be

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1 something to obviously think about.
2 More recent data, at least starting with
3 associations, I don't think we have gotten to
4 causality over there; the associations of deep
5 levels of sedation and mortality, deep levels of
6 sedation or sedation levels higher than what should
7 be probably prescribed to delirium, and then the
8 question, again, about neuropsychological outcomes.
9 This is a study that I put up a couple of
10 years ago. And I was telling Mona that only
11 yesterday when I revised my reading of this study
12 that I realized that Mona Hopkins over here was the
13 senior author on this paper. This is ARDS
14 survivors looking at recall of the ICU state. I
15 think many of us years ago would see patients come
16 back to the ICU and say, do you remember anything
17 of the ICU state, and patients would say, "No, I
18 don't," and I would consider that a victory on my
19 part that I got you through the critical illness,
20 the worst period of your life. I managed to erase
21 all memories of that. What a great job I did. I
22 think many of us now would think that perhaps not

<p style="text-align: right;">Page 13</p> <p>1 so fast; maybe we were actually doing patients 2 harm. 3 In this study in particular, what they 4 looked at was in 70 ICU survivors after ARDS, 5 whether recall of the ICU stay was associated with 6 neuropsychological sequelae, cognitive impairment, 7 and other sequelae. What they showed was that at 8 discharge, 1 year or 2 years, if you look at the no 9 recall group in yellow, you had worse 10 neurocognitive sequelae than the group that had 11 recall. Other studies that Christina Jones, et 12 cetera, have done have shown that if you have 13 recall of ICU stay, as long as it's factual, even 14 if it's painful, you tend to do better. You 15 process it better than if you have delusional 16 memories of your ICU stay. So the context of what 17 kind of memory of the ICU stay, that's important as 18 well. 19 Let's switch gears a little bit to the 20 guideline recommendations of light versus modern 21 deep sedation. The 2013 guidelines did look at 22 this question, and the question that they</p>	<p style="text-align: right;">Page 15</p> <p>1 level of sedation with a positive 1B 2 recommendation; so strong recommendation based on 3 moderate level of data. 4 If you look at the 2018 guidelines, there 5 are some differences. We looked at the long-term 6 outcomes. We actually defined the way we look at 7 light versus deep sedation in these guidelines. 8 The question was does light sedation versus deep 9 sedation, regardless of the sedatives -- so the 10 sedative was not considered in this discussion at 11 all -- does it significantly impact outcomes? And 12 the outcomes based on the priority scoring will 13 focus on long-term outcomes, 90-day mortality, 14 cognitive impairment, PTSD, so not any of the 15 short-term outcomes, all 90 days and beyond. 16 The recommendations, and more importantly 17 even the gaps -- the recommendations were we 18 suggested light versus deep sedation. It's a 19 conditional recommendation, low quality of evidence 20 because there weren't many RCTs looking at 21 long-term outcomes. There were a few, but not too 22 many. And the evidence gap is I think what we need</p>
<p style="text-align: right;">Page 14</p> <p>1 specifically asked, with regards to the depth of 2 sedation, is should ICU patients be maintained at a 3 light level of sedation? It was an actionable 4 item. It was a graded recommendation. 5 What their recommendations were was 6 maintaining light levels of sedation is associated 7 with improved short-term outcomes. So that was the 8 focus of the question. The 2018 guidelines, as I 9 show you, focused on more of the long-term 10 outcomes. We did not want to revisit what was 11 already shown to be decent quality data, so 12 moderate quality data. These are B 13 recommendations; associated with a shorter time on 14 mechanical ventilation in ICU length of stay, that 15 there may be some importance with regards to 16 physiological stress response, and unclear about 17 the psychological dysfunction, and therefore we try 18 to look at it in the long term in the 2018 19 guidelines and still found that there was very 20 little evidence. 21 They recommended that sedative medications 22 be titrated to maintain a light rather than a deep</p>	<p style="text-align: right;">Page 16</p> <p>1 to focus on. 2 There was no consensus of definition of 3 light versus deep in the literature, so we utilized 4 certain definitions, which I'll get to in the next 5 slide. The relationship between changing sedation 6 level over time; is one time good enough? You have 7 to figure out a way to capture sedation over time, 8 over time in a day, over time in the ICU, et 9 cetera. How do you factor that in? 10 Then ultimately, those light levels of 11 sedation have to be associated with outcomes. When 12 we talk about let's target light levels of 13 sedation, we need to be able to show that those are 14 consistently associated with outcomes, especially 15 the long-term outcomes, and that's where the gaps 16 were. 17 Here's how the 2018 guidelines defined light 18 versus deep sedation for the purpose of the studies 19 that were chosen for the recommendation. We 20 utilized those studies where light versus deep 21 sedation was explicitly stated by the authors as 22 the criteria for randomization. They may have used</p>

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1 different definitions, but they clearly stated that
2 they wanted to study light versus deep sedation
3 a priori; that they measured it based on the
4 instruments that they said they were going to use
5 to measure; and they actually reported the levels
6 of sedation in the two groups as they have said
7 that they were going to report.

8 It described whether those targets were met
9 on time, so it wasn't just that we decided to do
10 light versus deep and never mention about that on
11 the backend. They clearly articulated what those
12 targets were that they actually achieved,
13 separation of groups, et cetera.

14 We did not consider any surrogate markers.
15 There were many studies which used plasma levels
16 and used those as surrogate markers of light versus
17 deep. That was not a consideration in these
18 guidelines. Then we specifically excluded studies
19 which looked at spontaneous awakening trials
20 because it was deemed by the group that was
21 evaluating it that those studies don't explicitly
22 target light versus deep. They get patients to

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1 light levels of sedation consistently at a single
2 point during the day, but there's no report of
3 consistent light versus deep separation over the
4 study a priori defined.

5 That's how the 2018 guidelines at least
6 articulated and showed that the few studies that we
7 were able to get for all of this, there was some
8 semblance of data supporting use of light versus
9 deep, even for the long-term outcomes specifically
10 dealing with some of the PTSD outcomes, et cetera,
11 tracheostomy outcomes.

12 The first part in this discussion of which
13 pools should be used, should we be using objective
14 tools, is a question that we need to address.
15 Should we be using objective? I say that these
16 sedation tools are relatively objective. There are
17 always subjective elements. In the RASS scale,
18 somebody has to look at you for 10 seconds or less
19 than 10 seconds. Not everyone sits with a timer in
20 the hand to measure those 10 seconds, so there's an
21 element of subjectiveness. Some of the other
22 scales talk about response to a loud voice. It's

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1 subjective. Some people talk softly; some people
2 talk loudly. Is there some element?
3 In general, there are some guidelines, so I
4 would say that they're relatively objective versus
5 moderate sedation, deep sedation, et cetera, but
6 there is some element of subjectivity in these
7 scales.

8 If you look at some of the scales that have
9 been used for the studies that were shown in the
10 2018 guidelines, again, I didn't know that John
11 Devlin had validated this scale. You learn new
12 things every day. The motor activity sedation
13 scale, even though it's not one right now part of
14 the psychometric scales that have been stated as
15 the top one or two, this was used in a lot of the
16 early work that Samuelson showed with PTSD related
17 outcomes.

18 What this scale looked at was the definition
19 of deep sedation versus light sedation, when you
20 look at red, every time I've drawn boxes, the deep
21 sedation will be in red and the light sedation will
22 be in the tranquil blue. Deep sedation shown as

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1 responsive to only noxious stimulus, or responsive
2 to touch, or name. Every time where the voice
3 element comes in some of these scales where they've
4 not separated verbal from physical, there's a
5 qualification that it's a loud voice.

6 It says over here, "Moves limbs when touched
7 or name is loudly spoken." So there's some element
8 over there that you can softly speak. If it's
9 loudly, then you fall into the deeper sedation
10 criteria. If it's a little bit of a lower volume
11 and they follow-up the match, and you get into the
12 lower category of the scale.

13 If you look at the sedation agitation scales
14 and looking again at some of the studies that
15 define light versus deep, deep was in the SAS
16 scores of 1 and 2. The lighter levels in many of
17 the studies that were evaluated were grouped as 3,
18 4, and 5. Again, similar themes where if you have
19 to either cause pain, or touch, or scream at
20 patients, you tended to be in the deeper category.
21 If you didn't need to do all that, you tended to be
22 in the lighter category as defined by these tools.

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1 The Richmond Agitation Sedation Scale,
2 again, another scale that is being utilized
3 frequently, the cutoff in the studies that we
4 looked was somewhere in that minus 3, 4, 5. So if
5 you were a negative 3, 4, 5, again, either minimal
6 eye contact with negative 3 to voice, or then
7 unresponsive to voice and only requiring physical
8 stimulus at minus 4 and minus 5 was shown as deep
9 in some of the studies with minus 2 all the way to
10 plus 1, and a little bit of restlessness still
11 being considered light level of sedation. These
12 are the definitions that are out there in the
13 literature with regards to defining how light level
14 was deemed by the authors at that time. Perhaps
15 there is some rationale for these cutoffs.

16 I'm going to switch a little bit to one of
17 Yahya's studies showing support for these
18 thresholds. We have other data there, but Yahya in
19 the SPICE study looked at deep sedation, shown as
20 4-hour epochs of sedation where they were minus 3,
21 minus 4, or minus 5 in one bucket. If you were
22 lighter than that, so fitting with that minus 2 and

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1 above looking at greater the episodes of minus 3 to
2 minus 5 or more epochs of those in a 4-hour period
3 looking at mortality, 250 patients in a number of
4 ICUs in Australia and New Zealand.

5 What they showed was that if you were a RASS
6 minus 3 to minus 5, up top over there, your
7 extubation time was increased -- Yahya walks in
8 just as I'm showing his study; good job,
9 Yahya -- delirium after 48 hours, and then more
10 importantly even mortality.

11 So using a threshold of minus 3 to minus 5,
12 it has been shown in RCTs to have some difference
13 with regards to light versus deep sedation, and
14 then even in observational studies showing that the
15 minus 3 to minus 5 is associated with outcomes.
16 Now, where you move that cutoff off, that's a part
17 that we just don't have additional data. We know
18 minus 3 to minus 5 is associated with worse
19 outcomes.

20 If you look at the ABC study that Tim and JP
21 Kress did, what they found was that in the group
22 that had the awakening and breathing link trial,

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1 the amount of benzos was significant reduced. So
2 in the group that had the usual care, which was
3 just the targeted sedation, not a linked approach
4 to SAT/SBT, you had an average 50 to 60 milligrams
5 of midazolam in the in the day. On the other hand,
6 if you were in the group that had the link approach
7 of awakening and breathing, you were in that 30 to
8 40 milligrams.

9 What we don't have published, this is a
10 slide from Tim's study looking at coma. Now we're
11 saying if you were a minus 4 to minus 5. So Yahya
12 looked at minus 3 to minus 5; Tim's looking at coma
13 minus 4, minus 5. You had more days of minus 4
14 minus 5 in the control group. You had fewer days
15 of minus 4, minus 5 in the intervention, so yellow
16 showing the control group, the protocol group shown
17 in red with less days of coma.

18 What this study showed was that if you had a
19 protocol regimen perhaps linked to the lower
20 benzodiazepine use and linked to the lower coma,
21 you had an improved outcome with regards to
22 survival. So Yahya's study is looking at minus 3

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1 to minus 5, and some studies looking at minus 4 to
2 minus 5.

3 You can see that you can try and figure out
4 where that cutoff is, and we don't know the optimal
5 cutoff, whether we analyze these same data and look
6 at a cutoff of minus 1 and above and figure out
7 whether that's where that threshold is. I think
8 those are studies that we need to do by changing
9 the threshold and seeing how these outcomes differ.

10 The other question, and John Devlin brought
11 this up, is are goals static or should they change
12 over time? As we define light versus deep
13 sedation, should it be acceptable -- and I'm not
14 saying it is, I'm just putting it out there -- that
15 in the early stages of critical illness when there
16 is significant range related to synchrony, if the
17 SPICE studies have shown that minus 3 to minus 5
18 early is associated with worse outcomes, perhaps
19 during that early phase, one might consider a minus
20 2 or minus 1 to be appropriate.

21 As you move to the next stage, 2 days later,
22 those ventilator patients with the synchrony

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1 changes. It's not as much. Then your definition
2 of light sedation moves to zero to minus 1. So
3 over a period of time should the definition of
4 light sedation change with regards to the fact that
5 critical illness is resolving or getting worse?
6 The third part, which was introduced over
7 here yesterday in conversation, and whether this
8 becomes an element as an outcome or it gets even
9 incorporated into some of the objective scales,
10 where we have a little bit of subjectivity added to
11 an objective scale, is whether we should be looking
12 at these elements. Is following commands an
13 important outcome? Perhaps it's a number, but
14 should we be going further? Is it ability to
15 follow commands?
16 In JP's study, it was defined as three out
17 of four objective actions. You had to open eyes to
18 voice. You had to track the investigator and
19 request. You had to squeeze hands on request or
20 stick out the tongue on request. So is that where
21 you should set the bar or is it just opening eyes
22 and making eye contact for 10 seconds? That's one

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1 area to think about.
2 Is ability to communicate important? When
3 you look at the PRODEX and MIDEX studies, looking
4 at propofol versus dex or midazolam versus dex,
5 some of the outcomes that were shown to be
6 beneficial were the ability to communicate. And
7 the ability to communicate is beyond just talking
8 to your team or your family. That's important.
9 We already heard yesterday, when Dr. Shafer
10 said the first thing that comes up was a big
11 element in him realizing that we're going to get
12 through this, and other patients have also
13 communicated that with us.
14 You can communicate with your medical team
15 and actually be a part of your management, being
16 able to discuss goals of care, et cetera, which
17 otherwise a surrogate has to do. You can
18 communicate your pain needs. Some of the studies
19 which have shown lighter levels of sedation have
20 also shown more in medication requirements, perhaps
21 because patients are now able to communicate that
22 I'm not comatose. I'm in pain. Give me some

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1 medications for that.
2 Ability to participate in mobilization, I
3 think that's another important outcome and whether
4 that should be considered as a stand-alone outcome.
5 Many of our survivors when we see them in clinics
6 or when we have them come back to Vanderbilt, they
7 note that the day they participated physically
8 themselves actively in mobilization was the day
9 that they felt that they were going to survive
10 because that was the first time in their life that
11 they actually had some control.
12 Everything else somebody else was doing.
13 When they had a bowel movement, somebody else was
14 cleaning them up. But if they were able to sit on
15 their own or stand up on their own, that was a very
16 big moment in their lives, and we'll see whether
17 other patients represent, that we have that same
18 thought. That is one thing that many of our ICU
19 survivors in our clinic say, "That was the first
20 time that I felt I'm going to survive and I can be
21 independent. I can do something that I have control
22 of. I decided to stand up or I decided to

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1 participate in physical therapy."
2 The other part is as we think about
3 long-term outcomes, having a patient not comatose
4 and interactive, apart from participating in
5 physical therapy, there may be benefits, ability to
6 participate in cognitive exercises. Is that
7 something we should be looking at?
8 Again, there are data to show that being
9 able to participate in some of these activities are
10 associated with improved outcomes. So going back
11 to JP and [indiscernible] study, looking at ability
12 to mobilize, even though sedation regimens in this
13 study have been reported that they were equal in
14 both groups, the ability to mobilize is associated
15 with improved outcomes.
16 If you're targeting a light level of
17 sedation, which ends up in having more mobility, we
18 have data which shows that that is associated with
19 long-term outcomes, so perhaps an outcome that we
20 should consider for our short-term benefits because
21 it has impact on our long-term outcomes.
22 The next part is this relationship between

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1 changing sedation over time. I think this is an
 2 area that we do need to think about. It's one
 3 thing to be able to get a static measure, did
 4 somebody communicate. And the question is how do
 5 you look at level of sedation over time?
 6 How do you summarize sedation over time?
 7 Looking at, again, the SPICE study and Yahya's
 8 observational study, looking at number of 4-hour
 9 epochs of light versus deep sedation, categorized
 10 as minus 3. Perhaps if we change that threshold,
 11 the same data set can probably be looked at, at
 12 minus 2, minus 1, and trying to figure out whether
 13 there's a difference in outcomes based on that.
 14 Is there a way that we have an area under
 15 the curve approach, the minimal time? How long do
 16 you need to be light? However you define it, is it
 17 one time a day? Do you have to be there for at
 18 least 4 hours? Is it half a day? I think that
 19 needs to be defined. So some way to try and get a
 20 burden of the area under the curve, and we'll have
 21 to figure out how that outcome can be defined. But
 22 that needs to be considered, the length of time

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1 that one is light per day.
 2 The [indiscernible] published the Sedation
 3 Index, looking at the number of negative RASS
 4 scores. You add them up. You divide with the
 5 number of evaluations, and that has an indication
 6 with mortality. Again, that's another way to
 7 summarize that. While it may not be a way to do it
 8 real time because you have to wait for evaluating
 9 that over time, it's something to at least think
 10 about, and perhaps every 12 hours you can
 11 re-evaluate the Sedation Index in the previous 12
 12 hours to try and optimize the regimen for the next
 13 day, so it is something to think about.
 14 Plasma levels, there have been some studies
 15 looking at it, not the greatest amount of
 16 correlation, at least with sedation levels based on
 17 some of the literature reading that I've done, but
 18 those are out there. Maybe we will get better at
 19 doing that. Maybe it will be faster. We can
 20 incorporate some of the changes that are going on
 21 in critical illness, but that's something out
 22 there.

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1 Then early work in objective sedation tools,
 2 EEG based, haven't really panned out with
 3 significant data, but at least they're out there,
 4 and in the future we probably need to get high
 5 fidelity instruments, and we may be able to assess
 6 light versus deep on that. I don't think we're
 7 there yet.
 8 Ultimately, we're going to have to figure
 9 out whatever we define, so there are various
 10 ways -- I talk about how you can define light
 11 sedation. Ultimately, that has to be associated
 12 with improved outcomes. That's one thing because
 13 on the other side of it, there's risk.
 14 So you have to make sure that whatever we
 15 decide as far as threshold, incorporating that time
 16 element, it has to be evaluated for short and
 17 long-term outcomes and then balanced against the
 18 perceived risk because, still, those
 19 self-extubations, those device removals, anxiety,
 20 et cetera, and perhaps some unintended consequences
 21 that we don't even know yet all have to be
 22 balanced.

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1 I'm going to end with that, and hopefully
 2 I'm on time. Thank you.
 3 (Applause.)
 4 DR. WARD: We can take some time for some
 5 questions now because we don't have a specific
 6 panel. I have a question. How do you incorporate
 7 sleep and the need for sleep into your sedation
 8 assessment every 4 hours? You wake somebody up?
 9 Is a sedation assessment different at 2 o'clock in
 10 the morning than it would be at 2 o'clock in the
 11 afternoon? Because there is a diurnal rhythm that
 12 still takes place in the ICU, I assume.
 13 DR. PANDHARIPANDE: I think incorporation of
 14 sleep in some ways is important. The question is
 15 how. I really don't know the answer because adding
 16 24-hour polysomnography is not a very easy option,
 17 practically, I mean. It can be done in the
 18 research setting. Whether some of the newer
 19 devices are going to be able to show you EEG
 20 patterns without doing full polysomnography, I
 21 think those are things that have to be considered.
 22 So I think at this point with at least the

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1 definition of light versus deep sedation, I'm not
2 sure how you can incorporate sleep in it as well.
3 As we discussed yesterday, it would be great to
4 incorporate pain in it as well and incorporate
5 sleep in it as well. But all of these agents are
6 not necessarily sleep promoting all the time.
7 There are some data showing that perhaps
8 dexmedetomidine is associated with better sleep
9 outcomes.
10 Yoanna and John have done the nocturnal dex
11 study, which showed those benefits. On the other
12 hand, many of the other studies have all been done
13 in normal human volunteers. So we don't really
14 know whether we have the best drug. It does
15 improve non-REM sleep but reduces REM sleep. The
16 whole REM cycling, et cetera, none of these agents
17 actually do that.
18 Michele and then -- lots of questions.
19 DR. BALAS: I'd like to start by saying, God
20 bless the souls of the people who developed these
21 tools and did the psychometric testing, something I
22 swore I'd never do. I've been using these for over

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1 a decade.
2 I think it's interesting. If you could flip
3 your slides back to whatever sedation scale you
4 want.
5 DR. PANDHARIPANDE: Will you load my slides
6 back up, please?
7 DR. BALAS: Oh, sorry. Anyway, I never
8 considered this before, but the definition of
9 agitation just popped out at me. Once again,
10 bringing up the point about what we're trying to
11 measure and the need for conceptual clarity, it's
12 interesting to see how all of the different tools
13 define the agitation.
14 Let's start with the first one.
15 DR. PANDHARIPANDE: Which one do you want to
16 start with?
17 DR. BALAS: Whatever one is first.
18 DR. PANDHARIPANDE: John's going to answer
19 the question since he validated the tool.
20 DR. BALAS: No external stimulation required
21 to stimulate movement. Why is that bad? Why would
22 that be considered agitation? Attempting to sit

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1 up, why would that be bad? So you need both of
2 them. So if the patient's just awake moving around
3 by himself trying to sit up, that would be
4 considered part of agitation. I would consider
5 that maybe part of normal behavior.
6 I could understand not consistently
7 following commands, but then if you flip to the
8 next one --
9 DR. PANDHARIPANDE: The next scale or
10 next --
11 DR. BALAS: I think the next -- it's either
12 the next scale or the following scale. There's
13 something even about physical restraints. I've
14 never noticed this before; requires physical
15 restraints.
16 We know from the literature that almost
17 everybody in American ICUs is restrained. Right?
18 So that would necessarily -- I guess if you're
19 falling the scale --
20 DR. PANDHARIPANDE: Good points.
21 DR. BALAS: And it's the same one -- there's
22 something else with the next one. So I think my

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1 challenge is -- I think if we were to improve these
2 slides, I think one of the things that we should
3 look at is maybe those plus ones, the higher
4 scales.
5 DR. SKROBIK: They've never been validated,
6 right? That's the problem with them.
7 DR. BALAS: But the tools have.
8 DR. SKROBIK: No. If you look at the amount
9 of validation on the original studies, you go back
10 to the original studies, 95 percent of the
11 evaluations were at zero or lower, or whatever the
12 equivalent was.
13 DR. BALAS: So you mix them up?
14 DR. SKROBIK: I am saying -- that was what I
15 was about to say, but sorry to be jumping in, is
16 that the positive ones have never been validated.
17 I think to your point -- so thank you for bringing
18 it up --
19 DR. BALAS: Isn't that the exact same
20 problem now; people are quoting with my
21 [indiscernible] ICU study, that they didn't have
22 enough agitated people in the study?

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1 DR. SKROBIK: Well, no nurse is going to
2 agree to that.
3 DR. BALAS: But it's not documented, and we
4 found that --
5 DR. SKROBIK: You can't validate something
6 that you don't want to happen.
7 DR. PANDHARIPANDE: This is meant to be an
8 open discussion. There's no panel, and I'm not
9 supposed to be answering.
10 (Laughter.)
11 DR. PANDHARIPANDE: This is exactly how it
12 should be. I think Yahya had a question, and then
13 Ingrid.
14 DR. SHEHABI: I'm sorry I was late. I
15 thought the session started at 8:30, so I was
16 taking my time. My apology for that.
17 You talk about a new level of saying
18 wakefulness and communicating. What's wrong with
19 the RASS of zero? It says you are calm, you are
20 comfortable, and you're communicating. Why do we
21 need to find some other measure to say they're
22 awake and they're doing all that? I think a RASS

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1 of zero is like all of us right here now, so why do
2 we need one thing else?
3 DR. PANDHARIPANDE: I think it's completely
4 reasonable if you can target a RASS of zero and
5 have that as your definition of light levels. The
6 question is, from a pragmatic standpoint, whether
7 it's possible to get all your ICU patients targeted
8 at a RASS of zero, and whether there is any big
9 difference between a RASS of zero and a RASS of
10 minus 1. We just don't know the answer.
11 So from a pragmatic standpoint of actually
12 getting these things implemented, perhaps having
13 that information, saying if you target zero to
14 minus 1, your likelihood of outcomes is going to be
15 much better than any other level, or maybe it's
16 just zero, or it's zero to plus 1. I think that's
17 sort of where -- it's the balance.
18 Yes. If all patients in the ICU are alert
19 and calm all the time, then we won't have to sit
20 and target anything. But I think the goal is what
21 is the tightest level that we can be at, which is
22 pragmatic, but at the same time associated with the

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1 best possible outcomes for our patient.
2 DR. SHEHABI: I think the sedation index
3 that you referred to, the reason for doing that is
4 primarily because not many people would agitate, so
5 they are all in the negatives. So when you use
6 this index, it's quite clear that the largest
7 possible is better, and there isn't a minus 1
8 or -- the largest possible for that clinical
9 scenario is always better. If they need to be
10 sedated deeper for synchrony or any other reason,
11 then that needs to be done for the shortest
12 possible time until things are controlled better.
13 The other point I wanted to make is to talk
14 about the ability to do cognitive exercise. It
15 depends what sort of cognitive exercise you want
16 them to do. We had a small pilot within the SPICE
17 study where we tried to get people to -- battery of
18 assessment, and that was impossible. There are
19 people who are more competent and completely
20 perfect. They just could not do it. It's very
21 hard.
22 So I think you need to look at what sort of

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1 cognitive activity you want them to do. If you're
2 going to ask them to count the week days backwards
3 or do some mathematics, that's easy. But anything
4 more than that becomes just very difficult.
5 DR. PANDHARIPANDE: Nathan Brummel did the
6 ACT-ICU study where we did cognitive exercises. So
7 this is not testing but exercises in patients, just
8 like physical exercises, and many of the patients
9 by day 2 were able to do reorientation exercises,
10 were able to try and attempt Suduko and things like
11 that.
12 So it's possible, and all you're doing is
13 exercising them. You're not testing whether they
14 actually did the entire thing. And it's very
15 similar to physical therapy. You're trying to push
16 the boundary. It's not that first day everyone's
17 going to be able to run, but on the other hand,
18 you're just trying to push them. And if they pass
19 one thing, get them to the next level.
20 So I think one can as the levels of sedation
21 decrease, and if truly any of your patients are at
22 RASS zero, and we can get to that stage, I think

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1 many patients will be able to participate.
2 DR. WARD: I think we can continue the
3 discussion particularly in a couple panels that are
4 coming up. I think it will set the stage for the
5 discussion -- actually, all three of the panels.
6 Mervyn, you're the one that actually
7 accomplished this. You got a drug approved for ICU
8 sedation.
9 Presentation - Mervyn Maze
10 DR. MAZE: Well, you said this should be a
11 personal talk. There's no I in this because there
12 are lots of we's.
13 Thank you, and thank you very much for
14 inviting me. I really appreciate this. It's a
15 talk that I've never given before, so I hope I can
16 get through this okay. I do have a potential
17 conflict of interest. I would stress potential
18 because although I'm listed as the patent holder,
19 I'm certainly not the discover of this molecule.
20 It was synthesized long before I came along, but I
21 did find a certain property that it hadn't, and
22 that's why there's a patent in my name, together

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1 with Mika Scheinin.
2 Stanford then reassigned its rights to the
3 patent back to the company that synthesized the
4 molecule, a company called Farnos. Stanford
5 received \$50,000 a year for five years, which I
6 thought was a princely sum at the time, especially
7 since they gave it all to me in these \$50,000
8 dollops.
9 Thereafter, I was a consultant to Abbott,
10 who then took over the development of
11 dexmedetomidine through the phase 3 trial. I also
12 received some grants from them to understand the
13 mechanism of action. I've had no support for the
14 last 10 years, and I have had no royalties on this
15 \$1 billion a year drug. I think that sale was
16 probably the worst sale since the sale of Manhattan
17 Island.
18 (Laughter.)
19 DR. MAZE: So the background. There are now
20 870 RCTs published dexmedetomidine. They cover a
21 wide array of patient populations and indications
22 and so forth. But it is quite astounding how much

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1 work has been done with dexmedetomidine since its
2 inception. But how did it all begin? What was the
3 genesis of this? So I'm going to take a few
4 minutes to describe how this happened, and I've got
5 to be sure that I don't overstep my time.
6 How did this happen? I'm working through
7 the VA hospital, having just come back from a
8 sabbatical in Europe, where I saw with my own eyes,
9 at a pharmaceutical company, a dog being put to
10 sleep with an alpha 2 agonist; and I mean just
11 flopped off and lay prone, wilted and then lay
12 prone, and woke up in about 15-20 minutes later. I
13 said, hmm, that's really quite strange because I
14 was working alpha 2 agonists to try and see how
15 much can we reduce the amount of anesthetic in the
16 presence of an alpha 2 agonist indicative of
17 perhaps its anesthetic or sedative effects.
18 When I came back to the VA hospital and
19 walking through the grounds of the VA hospital, I
20 came across a psychiatrist that I knew, and he
21 asked me how my sabbatical was. I told him was
22 great. I was looking for a compound to further the

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1 alpha 2 studies. He said, "I've just had a guy do
2 a sabbatical with me who left this white powder
3 with me. And obviously, it's going to be used for
4 my studies, but it's doing nothing to what I'm
5 interested in," which was dopamine release. This
6 is the psychiatrist talking, John Schananski [ph].
7 He said, "Do you need it for your studies?" So I
8 said, "Yeah. I'll try it."
9 So we did some initial studies and showed it
10 was a sedative and tracked it with an anesthetic.
11 The one day that it really dawned on me that there
12 was something different about this drug was when
13 you do you a max [ph] study, for those who are not
14 anesthesiologists, what you're doing is you're
15 decreasing the dose of anesthetic and see how much
16 of a reduction of anesthetic you can get while the
17 reagent, in this case a dog, was not responding to
18 tail clamp.
19 After about 2 hours of withdrawing the
20 volatile anesthetic, the dog was still out, and I
21 thought that the technician had somehow cooked us,
22 and the dog was not gone. I went to the library.

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1 This is before PubMed, by the way, where you could
2 download things from the internet. I went to the
3 library, found the dose of yohimbine. We had some
4 yohimbine in the lab because it was doing all right
5 by A studies for plasma levels using yohimbine, and
6 he gave the drug, and the dog jumped off this
7 table. I heard him. He dropped the phone, in
8 fact, while he was speaking to me, and all I heard
9 was, "Oh shit," oh this, oh, that.

10 (Laughter.)

11 What had happened is the dog just lift off
12 the table with endotracheal tube in, PA catheter
13 in, A-line in, and was running around this dog lab,
14 that I shared with Steve Shafer. So it was a
15 remarkable event, and that's when we realized that
16 there was something important there.

17 The next thing -- well, it wasn't really the
18 next thing, but the next remarkable thing was the
19 first-time-in-man studies done initially down at
20 UCLA, as you heard, Denny and a colleague of ours,
21 Byron Blouer [ph], who now is deceased. Those were
22 really important studies. I have to take my hat

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1 off to people who do first-time-in-man studies.
2 Steve Shafer is another one who did
3 first-time-in-man studies with dexmedetomidine.

4 I'll tell you a story about what happened to
5 one of our subjects. In the old days, you could,
6 without permission, get your residents to be trial
7 subjects. You could volunteer them, in other
8 words --

9 (Laughter.)

10 DR. MAZE: -- for a small sum of money. It
11 could not be a coercive sum of money, but we were
12 allowed to do that. So again, A-line, PA catheter,
13 a Doppler to measure blood flow, the works, and
14 high-density EEG. We were doing PK/PD modeling
15 studies under Steve Shafer's auspices, and it was
16 my duty to be there that one Saturday morning when
17 we had this one trial subject.

18 Everything was going great. We had reached
19 the peak concentration. We were now coming down.
20 This was like 2 hours after the peak, fast asleep.
21 All of a sudden, I look up at the screen, and it's
22 completely blank. This patient has had a asystole,

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1 and essentially a sinus arrest. So there's an
2 entire screen that's blank, so that's about 11 and
3 a half seconds.

4 I said to the person with me, "Let's give
5 the glycopyrrolate through the PA catheter." I was
6 very specific about getting it into the patient
7 through the PA catheter in order to give an
8 antivagal stimulus. Sure enough, the heart rate
9 came back and everything was fine thereafter. But
10 we had to report this to the volunteer when he was
11 okay in the PACU.

12 I said, "Well, we had an event while we were
13 monitoring," and he said, "Yeah. You know, I
14 remember you saying give the glycopyrrolate through
15 the PA catheter." And I said, "You remember that?"
16 And they said, "Absolutely." And this is the time
17 that we were flatlined, and the EEG looked like an
18 ITIL [ph] episode, and there was this person
19 telling me that he remembers the event.

20 Steve?

21 DR. SHAFER: I can also add he also
22 described -- he's an anesthesia resident. He also

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1 described hearing his heart rate slow down, and
2 kind of going, "Oh, shit."

3 (Laughter.)

4 DR. MAZE: So as Steve said, he completed
5 his residency. He's now on the faculty at one of
6 our esteemed institutions. And I think it really
7 does prove the point, we didn't have a Doppler
8 monitor on and there was no cerebral blood flow.
9 It does prove the point that you can go through an
10 anesthesia residency at Stanford without any
11 cerebral blood flow.

12 (Laughter.)

13 DR. MAZE: We obviously had uncovered this
14 quite serious adverse event, bradycardia. In this
15 case it was sinus arrest, and obviously that
16 figured into what we subsequently did.

17 The big problem for this drug was it had so
18 many different effects, which one would be the
19 indication. Alpha-2 adrenergic receptors are
20 widely distributed, so the fact that it has a
21 multitude of action is interesting, and many of the
22 actions are actually useful in many settings.

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1 Listed here are some of the actions that we had
2 demonstrated in some preclinical studies and also
3 in clinical studies.

4 We were left with, well, what do you do with
5 a drug that has so many different actions? At this
6 point, Abbott had been sitting on this drug for 10
7 years. If they did not market the drug by the 12th
8 year, then they would lose their marketing rights
9 to dexmedetomidine. So they called in a
10 consultant, Romeo Bachand, a Texan who looked like
11 he just came out of Sopranos. He was a
12 hard-driving person who took no hostages and
13 decided that this was going to be an ICU sedation
14 drug, not a premedication drug, which is what
15 everybody else was angling for.

16 The way he arrived at this was, one, he
17 could do the study quickly. That was very
18 important for him and the company. And the second
19 was that we were worried about the SAEs, and if
20 there were SAEs, they had to occur in a monitored
21 setting where people could respond immediately. So
22 if you gave it as a premed, there would be a period

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1 of time where nobody was watching you and you could
2 have a sinus arrest at that stage.

3 So he was very pragmatic about this. We had
4 these pre-IND meetings with the FDA, and they
5 accepted dex for studying ICU sedation with no
6 comparator study needed. That becomes very
7 important. No comparator was needed. So this is a
8 discussion with the FDA, and they accepted an
9 endpoint that said reduce need for supplemental
10 sedatives, was all you had to do to demonstrate
11 efficacy. That was the efficacy of its sedative
12 effect in this patient population.

13 So that was the indication. The trial
14 design, you heard there were two pivotal trials
15 with either the rescue medication with midazolam or
16 with propofol, but exactly the same trial, and we
17 were looking for the difference in rescue sedative
18 use. There was secondary objectives, obviously
19 including safety.

20 Another important one was the use of
21 morphine, but the dosing of morphine was
22 problematic because we weren't giving it to a scale

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1 or anything like that. It was autonomic signs and
2 the nurses' decision. This was a very unusual drug
3 for the nursing staff because here were these
4 patients who seemingly were moving around, and in
5 their experience, a patient moving around the ICU
6 was not calm and cooperative. This was a patient
7 that you had to give more drug to. So it was
8 difficult to learn how to use this drug at the
9 nursing level because it was such an unusual drug.

10 We did do some nurse assessment
11 evaluations. The nurses assessed the patients, and
12 I'll show you how that was done. It was a very
13 poor study to look at the patient experience. In
14 fact, no meaningful data were collected to reflect
15 on this, so I cannot show you any important data
16 that relate to that.

17 Again, the way it was designed is you had a
18 surgical patient who was intubated for a minimum of
19 6 hours post-operatively, and was then extubated
20 and followed in the post-extubation phase for a
21 minimum of 6 hours. The entire period of infusion
22 of dexmedetomidine could not be greater than 24

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1 hours; could not be greater than 24 hours. The
2 patients were then followed up for a further
3 24 hours, so the entire period of observation of
4 these patients was 48 hours; that's it. Obviously,
5 we now know that was completely -- well, you
6 wouldn't want to do it that way.

7 Again. We could use either propofol morphine
8 or midazolam morphine, and they were two separate
9 trials. The patients were elective surgical
10 patients. You heard about the mechanical
11 ventilation requirements. The exclusion criteria,
12 the important one was no neurosurgery, no CNS
13 trauma. These are the exclusions.

14 The drug was to be started within 1 hour of
15 ICU admission to try and prevent any contamination
16 from other sedatives before the patient was started
17 on the study drugs. If they need a drug before the
18 study drug could be given, they had sedation with
19 these doses of midazolam or propofol, depending on
20 which study they were in.

21 While they received the drug infusion, they
22 were assessed for a minimum of 6 hours of

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1 mechanical ventilation and at least 6 hours
2 post-extubation while they received the infusion.
3 The drugs were titrated, as you heard, Ramsay of 3
4 or higher or 2 or higher in the post-extubation
5 phase. There was a loading dose, then there was an
6 infusion dose, which could go up or down. But the
7 maximum that you could use was 0.7 micrograms per
8 kilogram per hour, which is pretty much what is now
9 recommended.

10 The supplementation was with either
11 midazolam or propofol in this particular way, and
12 supplemental analgesia was done with 2 milligrams
13 of boluses of morphine given according to the
14 nurses' ability to communicate with the patient,
15 find out if they and/or autonomic signs, either.

16 So statistically, we required 150 patients
17 in each group, so essentially there are 4 groups.
18 There are 2 dexmedetomidine groups and 2 control
19 groups for each of midazolam and propofol. We
20 needed no fewer than 600 patients although 800
21 patients were enrolled, thinking that 90 percent of
22 the patients would be evaluable. It turns out that

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1 more were. We were working on the basis that we
2 had 35 percent reduction in the use of supplemental
3 sedatives in setting of dexmedetomidine. For
4 example, you'd go from 70 milligrams per kilogram
5 to 20 milligrams per kilogram. That was the
6 expectation, so it's quite a big difference.

7 Here is how the data were handled. The
8 important statistical analysis was the chi square
9 for the proportion of patients in each supplemental
10 category. Again, I'll show you those data. There
11 was also Kaplan-Meier curves to look at weaning
12 duration and time to extubation, and the total dose
13 of morphine administered during the drug
14 administration, during the study drug
15 administration, and of course the adverse affects.

16 I'll just show you quickly the results from
17 propofol as a supplement. Most of the patients
18 were male. Many of them had CABG surgery. CABG
19 surgery really lent itself to the study because
20 you'd have something akin to an 18-hour
21 post-surgical intubation, so that was a perfect
22 study population.

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1 Ramsay score you heard was used. It was
2 achieved. In dex, you can see the scores that were
3 achieved during study infusion versus the placebo.
4 During mechanical ventilation -- actually, I'll
5 show it to you on a different slide. And the
6 morphine requirements are there but halved
7 [indiscernible] during the study involving
8 propofol.

9 Here are the data for the reduction in the
10 amount of supplemental drug needed. In this case,
11 how much more propofol was needed in the total dose
12 during mechanical ventilation was this in the dex
13 group, and that was the control. So essentially, a
14 7-fold reduction. We were looking for a 65 percent
15 reduction. This was a 700 percent reduction in the
16 dose of sedative. During the study drug
17 administration, it quantified to a rate of
18 5 milligrams per hour for the dex group and
19 39 milligrams per hour for the control group. As I
20 said, similar data were obtained for midazolam.

21 Quickly, the nursing assessment, I'd like
22 to -- Michele, can you comment on this scale? I'm

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1 not that familiar with it.

2 DR. BALAS: I've never seen it before.

3 DR. MAZE: Okay. It was something that
4 was -- it was one of the secondary objectives.
5 They didn't seem to be any -- it wasn't worse in
6 the dex group, at least numerically, but it really
7 didn't yield meaningful data. The time to weaning
8 was slightly shorter with dex not meaningfully so,
9 63 minutes versus 30 minutes, and the total time to
10 extubation was a little shorter with
11 dexmedetomidine, again, but not statistically
12 significantly different.

13 As far as the AEs, of course, we knew that
14 there would be hypotension. Of course, we knew
15 there would be bradycardia. But interestingly,
16 there were fewer bouts of hypertension in the dex
17 group, so there were statistically less
18 hypertensive episodes, so it's more hypotensive
19 episodes and more bradycardic episodes. Otherwise,
20 no SAEs were uncovered during this.

21 Just to show you the time of change, this is
22 systolic blood pressure of a 48-hour study period.

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1 And you can see you get a 10 to 20-point drop in
2 blood pressure. This is the mean changes for the
3 entire population, and then it rapidly comes back
4 after the infusion stopped. Similarly, for the
5 heart rate, you see a drop from about 10 beats per
6 minute.
7 This is important, that the oxy sats [ph]
8 were no different in between the control and dex
9 group. Denny had already shown that the
10 hypercarbic ventro [ph] response to dexmedetomidine
11 was unchanged. Essentially, it didn't have any of
12 the properties of, say, an opiate.
13 Now, I'm just going to show you one or two
14 slides from the midazolam study. And I want to
15 point out that 60 percent of the patients had no
16 supplementation at all; zero. Now, that's
17 important because one criticism of the way that the
18 trial was done could be that all you're doing is
19 changing the pharmacokinetics of existing sedatives
20 and they become longer acting. Therefore, you're
21 not dealing with a sedative; you're dealing with a
22 drug that changes metabolism. In fact, that can't

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1 be the case because these patients had no drug at
2 all, and that was significantly different between
3 the two groups. Morphine was different between the
4 two groups in the midazolam study.
5 Now, this is something that I didn't see
6 used much at all anymore. It's called the critical
7 flicker fusion test. Do people remember this?
8 Okay. This is how much change you have in the rate
9 at which the light flickers before you say the
10 light is continuous, and it was significantly
11 better improved with dexmedetomidine. They were
12 more --
13 DR. SKROBIK: Could you clarify that for
14 those of us who have not heard of it?
15 DR. MAZE: Sorry?
16 DR. SKROBIK: What light flickers? I'm
17 sorry.
18 DR. MAZE: There's a light -- the patient
19 sees a light, and they're supposed to indicate when
20 it is that they see this light as a continuous
21 light versus a flickering light, the cutoff. So
22 the patient responds and says, "I now see this as

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1 continuous." In the dex group, they saw it as
2 continuous at a higher frequency.
3 DR. SKROBIK: The light was indeed
4 continuous.
5 DR. MAZE: Pardon me?
6 DR. SKROBIK: The light was continuous.
7 DR. MAZE: I didn't hear the --
8 DR. SKROBIK: The light was continuous.
9 DR. WARD: You start with a slow flicker,
10 and you get the flicker going faster, and faster,
11 and faster, and faster, to where at some point you
12 can't tell that it's flickering anymore.
13 DR. SKROBIK: Thank you.
14 DR. COURSIN: Either that or you start
15 seizing.
16 (Laughter.)
17 DR. SKROBIK: Thank you.
18 DR. MAZE: I just put this up here because
19 this is the message that came from the FDA, or came
20 to Abbott to those who were involved in the trial.
21 This was obviously good news. This happened, by
22 the way, that the entire enrollment of the study

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1 population occurred over 12 weeks. In the summer
2 of 1998, the data was submitted to the FDA and
3 approved by February '99. That was remarkable how
4 quickly this study was done.
5 MALE VOICE: Joan Tambling [ph]?
6 DR. MAZE: What's that?
7 MALE VOICE: Joan Tambling.
8 DR. MAZE: Yes. Oh, you remember this
9 person.
10 DR. NEEDHAM: It was 800 patients recruited
11 in 12 weeks? This is Dale Needham.
12 DR. MAZE: Correct. All of them -- well,
13 not all of them, but like 95 percent in European
14 trial centers and just a few from Canada; none in
15 North America, for an FDA-approved study.
16 DR. NEEDHAM: Roughly how many study sites?
17 DR. MAZE: Somewhere close to 20. It wasn't
18 remarkable, but there was some sites that did a lot
19 of patients. There are places that did more, some
20 way close to 10 percent of all patients came from a
21 single site.
22 MALE VOICE: Remarkable.

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1 FEMALE VOICE: How much were they paid for a
2 patient?
3 DR. MAZE: I don't recall.
4 FEMALE VOICE: Best guess.
5 DR. MAZE: This is Romeo Bachand.
6 FEMALE VOICE: I wonder what he's doing now.
7 DR. MAZE: He's retired now, but he's
8 somewhere in Texas. He must be the shortest man in
9 Texas. But he was pretty powerful in this trial.
10 So this led to this, which is the first -- I
11 tied this up. This was the first iteration of
12 MENDS. I visited with Pratik and Wes [ph], and
13 this is where MENDS was born when I -- I think
14 that's correct, right? Had you decided to do MENDS
15 before I came to visit you?
16 DR. PANDHARIPANDE: We decided to do MENDS
17 before, but you forced us to make it into a
18 randomized [inaudible].
19 DR. MAZE: I just want to point out the
20 problem with the regulatory agencies. The FDA,
21 they were hand in hand with the FDA every step,
22 lots of discussions with the FDA; no discussions at

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1 all with the EMEA. The EMEA, there was no protocol
2 discussions with them. We went through all the
3 competent authorities in Europe.
4 When we came to the EMEA afterwards, with
5 European patient data, what they said is, no, the
6 data do not support the claim. Their principal
7 objection was there was no comparator, and you
8 cannot introduce a drug into the marketplace in
9 Europe without demonstrating that it's at least
10 noninferior to drugs that are currently used in the
11 ICU.
12 In fact, here's another statement. They
13 said they didn't care what sparing effect it was.
14 It didn't matter to them. It didn't seem like
15 there was any benefit in clinical outcomes. Again,
16 no direct comparison to reference therapy, and they
17 were really worried about the side effects, which
18 are, essentially -- of course there are adverse
19 events, but they're expected based upon the
20 pharmacology of the drug. You expect this to
21 happen each and every time because of how the drug
22 works, but they were really worried about this.

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1 This never got approved through the EMEA on
2 the basis of the data that I just showed you. An
3 entire new trial, two new trials had to be done by
4 Takala, and these were published in JAMA, the MIDEX
5 trial and the PRODEX trial, that then resulted in
6 approval of dexmedetomidine in Europe.
7 So I'm going to stop there, and I'll take
8 questions if I have time.
9 DR. WARD: A couple questions.
10 DR. MAZE: Okay. Thank you.
11 DR. WARD: I had a bradycardia, too, but we
12 didn't have to give any glycopyrrolate.
13 DR. MAZE: Right. Talmage, you were a
14 subject, too, weren't you?
15 DR. EGAN: I was just going to say that I'm
16 probably the only person in the room that was
17 actually a subject. As a resident, I was a subject
18 in the kinetic study that the two of you were
19 doing, Steve and Mervyn. I was a subject one day,
20 and then a few days later, I was the supervising
21 fellow of another resident subject.
22 (Laughter.)

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1 DR. MAZE: See one, do one.
2 (Laughter.)
3 MALE VOICE: Be one; be one.
4 DR. MAZE: Be one, do one. Okay.
5 Our worse days are over, by the way. You
6 can't do this again.
7 DR. WARD: Thank you.
8 DR. MAZE: Thank you.
9 (Applause.)
10 DR. WARD: We're going to move on
11 [inaudible - off mic] -- arbitrary division on the
12 three panels. I don't necessarily expect that we
13 will do these exactly, so I won't limit the
14 comments to these panels. But I kind of divided up
15 with the first one, who should studied and how,
16 some of the indications of study design.
17 The second one that Yoanna is going to do
18 after break will be a little bit more on the acute,
19 how should we measure sedation and the other events
20 that take place. And then finally, the third panel
21 that Tim will moderate the longer term outcomes.
22 Thank you.

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1 Presentation - Avery Tung
 2 DR. TUNG: Good morning. I'm going to
 3 disclose in advance that I signed up for this in
 4 part so I could sit in the back of the room and
 5 listen to real experts talk about sedation. I have
 6 not been disappointed at that. It's been
 7 tremendously informative as I sit here. And I'm
 8 going to continue to listen because the goal of
 9 this panel is not for me to talk but for you to
 10 talk.
 11 I'm also going to disclose an
 12 anesthesiologist bias, which is that, generally
 13 speaking, we anesthesiologists believe the magician
 14 is more important than the wand, so drug focus
 15 studies are likely to, in expert hands, lead only
 16 modest effects, if ever.
 17 I added the critical care section of A&A,
 18 and we pushed this one through in mid 2016 and
 19 published it in print in 2017. Dr. Jerath is a
 20 huge fan of inhaled anesthetics for ICU sedation.
 21 She has subsequently published
 22 randomized-controlled trials supporting that. So

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1 our job here was to push back the bias she had in
 2 her paper, discuss issues with light versus deep
 3 sedation and interruption.
 4 You can see the kind of outcomes that she
 5 listed as secondary outcomes. This was the first
 6 one. I also do think that there's a huge need for
 7 outcomes that matter because if one were to publish
 8 a new drug study in 2019, I imagine that one would
 9 have a paper that looked roughly like this; these
 10 are your outcomes and this is your primary outcome,
 11 and any effect that you see as swamped by
 12 heterogeneity. So anything that's really
 13 interesting, you say, well, look at that. Time to
 14 obey verbal commands, but it's not significant
 15 because there's so much variability between
 16 studies.
 17 I also wanted to put in a plea for the
 18 practicing intensivist, that really when the rubber
 19 meets the road, it's a lot more than propofol
 20 versus dex, or interruption versus not. It's very,
 21 very complicated stuff, and patients that are
 22 easiest to sedate are easy, and those that are hard

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1 are hard.
 2 I'm just going to take 4 minutes to recount
 3 the four different vignettes that I came up to in
 4 my head while listening to what was going on
 5 yesterday. This is what happens in our ICU, this
 6 gabapentin, lidoderm, melatonin triad. This pops
 7 up everywhere I look. Everybody's on gabapentin,
 8 and we are only now in our OR realizing the
 9 sedative effects of gabapentin because sometimes
 10 our patients, after their ERA protocols, don't wake
 11 up because they all get their 900 of gabapentin
 12 before they get surgery.
 13 In this case you ask, why is this patient on
 14 so much stuff, and they describe the incremental
 15 adding of drugs when stuff that you use doesn't
 16 work. The question not really for me is whether
 17 dex or propofol is better, but how do I optimize
 18 this patient? What do I do to get this patient
 19 out? And my instinct, if a lung transplant, is to
 20 take off the stuff and wake them up; otherwise,
 21 they'll never get out of there. But is that
 22 patient centered or not?

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1 Here's another thing that happens often, and
 2 as the former SOCCA president, I see this
 3 everywhere I go, and that is that the neuro ICU
 4 people extubate patients with zero mental status,
 5 and the cardiac people don't dare do that because
 6 those patients will never fly. It's sort of an
 7 interesting difference.
 8 Here's an example of what happens when I
 9 wander into the neuro ICU and they extubate someone
 10 who had no mental status, and you say, "Really?"
 11 And they say, "Yeah, but usually it works pretty
 12 good." And you say, "Okay. Let me re-intubate
 13 them." So it sets up a whole bunch of questions as
 14 to whether time to extubation, the primary outcome
 15 in the Jerath trial I just showed you is relevant
 16 or not. Another question, which we're going to get
 17 to in design -- I have 12 design questions that the
 18 committee here is supposed to make recommendations
 19 on -- is whether ICU heterogeneity is an issue or
 20 not when you're designing trials.
 21 You come back to your ICU and your
 22 residents -- and this is why you have to keep

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1 reading as an intensivist because residents just
 2 ask stuff that you have to know the answer to.
 3 This is, "Well, should we use Tylenol?" because
 4 everybody knows that Tylenol reduces delirium. And
 5 it's so recent that if you don't keep up with your
 6 reading, you might say, "What Tylenol? I never
 7 heard of that." But in fact, here's a 2 by 2
 8 factorial trial with 120 patients, so that means 30
 9 patients in a group finding less delirium with the
 10 use of IV Tylenol in patients sedated with either
 11 dexmedetomidine or propofol, so what am I supposed
 12 to do with that? I mean, is this -- what? What?
 13 What?
 14 I searched this entire article for the words
 15 "hypo" or "hyperactive," and I did not see anything
 16 like that. One thing for the outcomes person is
 17 whether the world needs a hyper or hypo ratio for
 18 every single delirium trial so we understand that
 19 we're not just taking hyperactive patients and
 20 fixing their pain.
 21 Finally, what is a patient-centered outcome?
 22 This is the last vignette. It occurred to me, as

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1 listening to what patients experienced in ICU, and
 2 this patient, severe mitral annular calcification,
 3 and the patient has the dreaded complication of
 4 AV groove disruption, which is almost impossible to
 5 fix.
 6 Luckily, or not luckily, he was on ECMO, so
 7 he was able to wake up afterwards. And on the
 8 take-back, the realization is we simply cannot fix
 9 his heart. There is no exit from ECMO, and the
 10 question is do you wake him up and tell him he's
 11 going to die or do you just turn off the ECMO while
 12 he's still asleep, and what is patient-centered
 13 outcome there?
 14 In this brave heart contrast between freedom
 15 and mercy, the question is while there may be those
 16 who argue for freedom, there might also be those
 17 who would prefer mercy. So that's a good question
 18 here as to what a patient-centered outcome should
 19 be.
 20 This panel that is supposed to last an
 21 hour -- and I think I've chewed out 4 or 5 minutes
 22 of that -- is to identify, where possible, group

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1 recommendations regarding the conduct of clinical
 2 trials of ICU sedation, both for the new drug
 3 developer and I think for the practicing
 4 intensivist who wants to know what to do. It's not
 5 going to be measurement because that's panel 2, so
 6 anybody wanting to ask questions about
 7 patient-centered outcomes, or RASS, or SAS, or
 8 Ramsay, that is the next panel after the break.
 9 And anybody who wanted to talk about outcomes,
 10 including return to work 6-month recovery, that is
 11 panel 3.
 12 But instead we're going to talk about
 13 structural elements. We're going to talk about
 14 inclusion/exclusion criteria. I've got 12
 15 different specific questions, and then trial
 16 design, I brought in Dr. Coursin here to close the
 17 discussion if I cannot do it.
 18 DR. COURSIN: Comic relief.
 19 Panel Discussion
 20 DR. TUNG: Dr. Coursin is here to close it
 21 out. So we're going to go with structural, and the
 22 first question is -- and I've used this sort of

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1 language at the end in red here to frame what a
 2 paper might say. The first question for the -- and
 3 I'm just going to invite commentary now -- is
 4 whether there can be consensus on multi- versus
 5 single-center trials. For example, we could say,
 6 the paper could say, this committee could say that
 7 committee recommends that trials with station be
 8 multicenter if possible.
 9 Agree? Disagree? Comment?
 10 DR. SKROBIK: Can I just -- I'm sorry. We
 11 were having a conversation with a little bit
 12 earlier outside. You're not defining the model of
 13 the trial. When it comes to sedation, I wondered
 14 whether observational trials could also be
 15 considered rather than RCT.
 16 DR. TUNG: That is a good question. I left
 17 off everything except the randomized-controlled
 18 trial thinking that you couldn't really get FDA --
 19 DR. SKROBIK: I just would argue --
 20 DR. TUNG: -- that's a good question.
 21 DR. SKROBIK: that with large enough bodies
 22 of data, you can actually arrive at conclusions

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1 without having an RCT. And I think that if you're
 2 looking at depth of sedation, which is what we were
 3 talking about the first part of the morning, and if
 4 you had compelling data to say people at this level
 5 over cohorts of thousands, how would you then
 6 justify moving forward with an RCT?
 7 That would be my only comment.
 8 DR. TUNG: I will comment that this whole
 9 thing is not being scribed by me but being scribed
 10 by the people recording in the back. I guess the
 11 actionable thing is that the committee suggests
 12 that trial designs other than randomized-controlled
 13 trials is possible as strategies for investigating
 14 ICU sedation.
 15 DR. DEVLIN: This is John Devlin. The other
 16 thing is maybe the importance if it's a new
 17 molecule of a pilot study, really looking at some
 18 of the key things with feasibility, looking at
 19 safety signals, validation of tools, or outcomes,
 20 or some of those other things that could really
 21 guide maybe a multicenter study. I know that's not
 22 quite answering your question, but if we're just

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1 going from single versus multi, there could be some
 2 gaps and mistakes made.
 3 DR. SESSLER: The general rule is to do
 4 single-center studies if you can. It's more
 5 homogeneous, you have better control over things,
 6 and it's a lot less expensive and a lot faster to
 7 do a single-center study. There are advantages to
 8 multicenter studies. Obviously there are some
 9 where you need more patients than you can get at a
 10 single center, but you pay a penalty in terms of
 11 variability.
 12 So you're adding patients, but you're adding
 13 variability, and that actually increases the number
 14 of patients that you need. Generalizability is
 15 increased in a multicenter study, but still, at
 16 least for an initial study, go with a single center
 17 if you can.
 18 DR. TUNG: I know Dr. Pandharipande has done
 19 a multicenter sedation trial, and thus dealt with
 20 all the complications that that entails.
 21 Would you recommend that the committee
 22 recommend single or multicenter for trials studying

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1 ICU sedation?
 2 DR. PANDHARIPANDE: I again feel that for
 3 FDA approval, I think it's going to be important to
 4 have a more generalizable population as a start for
 5 a phase 2 study, perhaps, using a single-center
 6 model to try and get all the kinks worked out, but
 7 then moving on to a larger scale, phase 4, trying
 8 to see whether it's generalizable in the larger
 9 scale, not just in the research setting. I think
 10 it's important to get it as a multisite study.
 11 DR. SESSLER: The FDA does usually require
 12 at least a few centers.
 13 DR. SKROBIK: I was going to say I
 14 am -- best answer to that.
 15 MALE VOICE: I think there are multiple --
 16 DR. SESSLER: Rigoberto, do you want to
 17 comment?
 18 DR. ROCA: Sorry to interrupt. This is Rico
 19 Roca. Yes, I agree with the comments that are
 20 being said, in particular with respect to the fact
 21 that perhaps early on, a single-center study will
 22 give you more control and all that, but as far as

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1 regulatory approval, we do want to see the ability
 2 to extrapolate to a more generalized population.
 3 I also noted his comment that the magician
 4 is more important than the wand, so from that
 5 standpoint, we're going to get a lot more magicians
 6 that we can see how this drug performs and
 7 different things.
 8 MALE VOICE: And my only comment was I think
 9 in passing you mentioned phase 4. I think you
 10 meant phase 3.
 11 DR. PANDHARIPANDE: Phase 3. Sorry.
 12 DR. ROCA: Phase 4 will be after approval.
 13 DR. TUNG: Dr. Shehabi?
 14 DR. SHEHABI: I think for testing grounds,
 15 single-center studies are effective [inaudible -
 16 mic fade] -- single-center studies that came with
 17 major claims end up being completely wrong.
 18 MALE VOICE: Your microphone is not on.
 19 DR. SHEHABI: Well, I think it's the clicker
 20 thing' it's not me.
 21 (Laughter.)
 22 DR. SHEHABI: I think for things that will

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1 change practice and also, as I hear from an FDA
 2 perspective, they need to see more than just
 3 something done in a single center for regulatory
 4 approval. So I think there is a place for single
 5 center as testing grounds, but it has to be
 6 followed by multicenter for generalizability and
 7 extended validity.

8 DR. TUNG: So the phrasing would be the
 9 committee recognized then multicenter trials are
 10 required for FDA approval, but that studies should
 11 begin in single center constructs to identify
 12 aspects of drug delivery that are --

13 DR. RIKER: Or may begin rather than should
 14 begin.

15 DR. SESSLER: I would still say start with a
 16 single-center study, so your phase 2 study.

17 (Crosstalk.)

18 DR. COURSIN: Essentially, that's what
 19 you're saying, and then moving I think to a more
 20 generalizable. And clearly, what I'm hearing from
 21 people in the audience is the incredible diversity
 22 between our patient populations in the U.S. and our

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1 approaches to them, whether it's with the
 2 restraints, monitoring, or interventions.

3 DR. SKROBIK: This is Yoanna Skrobik.
 4 There's a tradition among Canadian critical care
 5 trials group now to do pilots that are more than in
 6 one center because of the logistics of recruiting
 7 patients. So we will seldom -- so if we want to
 8 assess sample size, or affect, or whatever we're
 9 trying to figure out, especially for a new molecule
 10 or some novel approach, what will often happen is
 11 that the pilot won't allow you to then plan the
 12 larger study because recruitment rates are so
 13 different.

14 In contrast to what's been said a little
 15 earlier by Dr. Sessler and others, we actually
 16 fostered and promoted the idea of having five
 17 centers that will recruit 20 patients each if we're
 18 planning a multicenter trial. So I think both can
 19 be argued and some of it has to do with the
 20 logistics of your analysis of the patients and some
 21 has to do with the on-the-ground train of
 22 recruitment. John and I had very different

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1 recruitment rates for our last sedation trial and
 2 our two sites, and we could spend an hour telling
 3 you the story.

4 DR. TUNG: Panharipande?

5 DR. PANDHARIPANDE: I think what you also
 6 have to factor in is the funding mechanisms. So as
 7 we realize more recent NIH guidelines for some of
 8 the clinical trials, many of them are coming up as
 9 phased single-site studies for pilot, which they're
 10 still considered \$500,000 or less, but pilot phase
 11 2 studies, single site, and then the bigger R01s.
 12 I think looking at who the investigators are who
 13 are going to be doing the work, that may also have
 14 to be factored in, in the design.

15 DR. TUNG: Okay. I think we have enough to
 16 get started. The next question, does the committee
 17 have suggestions or recommendations with respect to
 18 ICU diversity? I will say that as SOCCA president,
 19 one challenge we're facing with anesthesia
 20 intensivist recertification is that you work in a
 21 neuro ICU for 10 years and you have to re-cert, you
 22 have a different knowledge base than if you work in

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1 a CT ICU. In fact the far left, or right, is
 2 advocating that CT ICU be its own fellowship
 3 separate from all the other ICU fellowships. So
 4 we've got a splitting rather than a coming together
 5 of ICU management.

6 Does the community have recommendations as
 7 to whether the ICU should only be limited to a
 8 certain type with respect to sedation trials?

9 DR. RIKER: Riker. In the last guidelines,
 10 we went back and looked at comparative sedative
 11 drug trials, propofol and midazolam primarily, and
 12 broke out cardiothoracic surgery since it's such a
 13 different type and duration of sedation, and I
 14 think neuro is a whole different world. So I don't
 15 think you can throw everything in the same pot.
 16 Potentially, a more homogeneous general ICU,
 17 non-cardiothoracic, non-neuro makes some sense.

18 DR. COURSIN: And I think it's going to
 19 represent the bulk of critical care in the U.S.
 20 anyhow, in that most community hospitals are going
 21 to have a medical surgical type of unit, and they
 22 may even take care of their cardiac patients within

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1 that, and they may or may not have a neurosciences
2 unit.
3 DR. TUNG: We just became a trauma center,
4 and our trauma ICU is full of wildly outlandish
5 sedation practices, ketamine drips, dexmedetomidine
6 drips, ketamine and dexmedetomidine, propofol, you
7 name it, extubated patients. It doesn't matter.
8 DR. SKROBIK: Can I add to that you could
9 also make the politically incorrect suggestion that
10 it be stratified by type of hospital and patient
11 population because if you look at Hannah Wunsch's
12 work, looking at alcohol withdrawal, one of the
13 more important factors is what socioeconomic
14 population your hospital services.
15 So if you're in a county hospital in a town
16 in an area where there is a lot of recreational
17 drug use, the withdrawal syndromes are very
18 different. So your sedation practices are
19 necessarily going to reflect that unless those
20 people are excluded.
21 DR. TUNG: I think the committee is
22 suggesting that cardiac and neuro be carved out of

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1 any trial so that the heterogeneity doesn't swamp
2 any signal, and that may be stratified on patient
3 type and hospital.
4 DR. WARD: But listening to the group -- and
5 I'm not an intensivist, but a trauma patient versus
6 a community-acquired pneumonia patient is going to
7 have very different analgesic requirements;
8 somebody who's got a reason to have pain versus
9 somebody who is having pain because they're in the
10 ICU.
11 Is there a difference there between a trauma
12 ICU versus a medical ICU that's dealing with more
13 ARDS?
14 DR. COURSIN: Well, I think you're going to
15 find in the U.S. that academic centers for the most
16 part are going to do these studies, and academic
17 centers are going to reflect the silo and
18 increasing specialization of critical care and
19 trauma. The problem I have -- Yoanna, I appreciate
20 your fine suggestion, but what kind of end are you
21 going to need to do these studies to be able to
22 stratify them I think is one of the challenges I

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1 would see. Most community hospitals are not going
2 to see level 1 trauma, and level 2 and level 3
3 trauma are two very different entities.
4 DR. TUNG: Dr. Shehabi?
5 DR. SHEHABI: I think there is like a
6 rationale for departing [indiscernible] the
7 patients in terms of homogeneity or heterogeneity,
8 you would say, into a medical type part for your
9 patients and then the surgical part, which you
10 could include trauma, neuro, and cardiothoracic in
11 an in-depth part.
12 I agree with you that if you're going to
13 certify by [indiscernible], the more certification
14 you do, you're just going to go much, much, much
15 more. I think if you stick to medical, regardless
16 of where they are, that would include the
17 generalizability, whatever you would find. So
18 whether they're in a community hospital or an
19 academic center, if you apply the intervention, in
20 that population you should see the same result.
21 So I think medical and surgical have their
22 trauma, and neuro and cardiac under that is

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1 probably the best way forward.
2 DR. TUNG: Dr. Sessler?
3 DR. SESSLER: Well, all trials stratify by
4 site, and then the general rule is that you should
5 also stratify by things that you think will affect
6 the outcome. So within a site, you might well
7 stratify by type of ICU or type of patient, trauma
8 versus not, for example.
9 DR. TUNG: The committee recommends, then,
10 that outcomes of trials of ICU sedation be
11 stratified by type of ICU and maybe even by site as
12 well.
13 DR. SESSLER: Stratification always helps.
14 It doesn't increase sample size; it reduces the
15 risk of ending up by pure bad luck within
16 homogeneous groups. There's just no reason not to
17 stratify for pretty much everything you can think
18 of.
19 DR. COURSIN: But Pratik, would you comment
20 on what it was like to enroll in MENDS, both
21 centers and centers with the ability to actively
22 enroll, and thirdly, centers actively enrolled that

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1 could afford to do it?
2 DR. PANDHARIPANDE: It's definitely a
3 challenge. Even though you've gone through -- we
4 used to go through pretty rigorous -- what we
5 thought were rigorous evaluations of centers to
6 make sure that everyone had the systems in place to
7 be able to do a randomized-controlled trial; the
8 staff, the investigation, pharmacy, et cetera. But
9 things change over time, and those problems I think
10 are challenges to do multisite studies.
11 I think to come up with a recommendation, I
12 think it's still important that those need to be
13 put into place. So it's challenging. I'm not
14 going to say that it's easy. Tim with MIND-USA, we
15 had 17 sites, and perhaps you can add to that. I'm
16 going to put you on the spot. Sorry. I put you on
17 the spot. Sorry.
18 DR. SESSLER: The issue is not
19 stratification; it's inclusion. It's do you want
20 to broaden the population to include various
21 populations.
22 DR. PANDHARIPANDE: Yes.

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1 DR. SESSLER: Including them gives you
2 better generalizability, and it adds variability,
3 and it adds sample size to the study.
4 DR. TUNG: Unless the generalizability is
5 swamped by different ICU natures, so that if my CT
6 ICU and his CT ICU,
7 there may be a signal there that's just taken out
8 by all those M-ICUs [ph] we include.
9 DR. BALAS: I was just going to give my NIH
10 comments that I frequently receive on my grants.
11 The last one that got a great score but didn't get
12 funded was because we wanted to include medical and
13 surgical ICU patients together, and the reviewers
14 strongly believed because pain was whatever
15 outcomes, those two groups be separated; even
16 though we told them that we had enough sample size
17 to stratify by diagnostic category. And that's
18 happened on two separate applications so far.
19 DR. SESSLER: Let's be clear on the
20 terminology. Stratify is not the same as a
21 subanalysis. Stratification is how you randomize
22 patients. A subanalysis is how you divide the

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1 population afterwards for analysis purposes.
2 Stratification does not increase sample size.
3 Predefining subgroups in your population does
4 increase the sample size because you need to have
5 enough for each analysis.
6 DR. TUNG: Dr. Shehabi?
7 DR. SHEHABI: I just want to make a comment
8 about the selections. The pharma companies, they
9 always get you to do detailed site feasibility data
10 before they accept a site as one of the sites
11 they're going to run. We've done similar, but less
12 detail, feasibility of the sites that we included
13 in the SPICE study. So they have to show whether
14 they have used the drug before, what are their
15 [indiscernible], whether they used RASS, whether
16 they've done CAM.
17 So we ask them a lot of questions before we
18 say, yes, you're eligible; you can be within the
19 site. I think that's important in site selections;
20 otherwise, you end up with people, really, who have
21 no infrastructure to conduct the trials you want to
22 do.

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1 DR. TUNG: This last point here, we're going
2 to move on to this last point, which actually came
3 up in discussion yesterday. I would normally think
4 that the ICU diversity is so why that you have to
5 be very narrow. But then, Tim said, "Well, if
6 we're narrow, we don't have enough people," and
7 it's not generalizable.
8 Does the committee feel like making any
9 additional comments on the inclusion criteria to be
10 as broad as possible, as narrow as possible, or you
11 have to just go with the nature of the people you
12 have?
13 DR. RIKER: Riker. I think the biggest
14 criteria is going to be the components of the drug
15 that might be confounded by whatever's going on, or
16 the metabolism of the drug, or whatever else is
17 going on. So I don't know that we can really weigh
18 in very much there, aside from saying keep it as
19 inclusive as possible without compromising your
20 interpretability of the study.
21 DR. DEVLIN: One thing I've run into with
22 sedation studies is you interface with the clinical

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1 team, so there are these anticipated things that
2 might happen. Does an attending anticipate the
3 patient is going to be mechanically ventilated for
4 another 24 or to 48 hours? Are they anticipating
5 that the patient is so unstable that they might die
6 the next day?
7 Obviously, if there were a drug here, that's
8 another whole discussion. It's funny how when I
9 observe and have these discussions, how often the
10 clinical team might not always get the accurate
11 answer, and I realize they don't have all the data.
12 And then looking back, we probably could have
13 enrolled the patient, and they would have been an
14 evaluable patient.
15 So it's a tricky domain to evaluate, but I
16 think there could be a bias here of
17 putting -- there could be some patients who could
18 go into the study that we don't because of the way
19 these inclusions/exclusions are written.
20 DR. COURSIN: That was John Devlin.
21 DR. NEEDHAM: Dale Needham. I don't have an
22 answer, but I have a question. We've talked about

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1 patients with alcohol or substance abuse and
2 whether they should be in or not. I don't know if
3 this is the appropriate section to discuss it, but
4 I think it's a pretty important thing for the paper
5 to comment on.
6 DR. TUNG: So the committee would identify
7 aspects of patients that are relevant to
8 inclusion/exclusion.
9 Dr. Spies?
10 DR. SPIES: First, I would like to speak to
11 the stratification because, otherwise, you have it
12 too narrow and it takes too long to do the studies.
13 In addition, you don't get approval for your drug.
14 For this situation, I think it's too narrow.
15 The second point is, I think you talk a lot
16 about patients. You don't talk about your staff.
17 The staff is the major issue. So compared to that,
18 what you have for the patients variability, you
19 have much more with the behavior of your medical
20 staff. So I think before you do the inclusion, I
21 think I would include to have the staff trained and
22 that there is a visit before, a peer review that

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1 you really check that the staff assessment and
2 assessment by you is not differing too much.
3 The third point I think is appropriate is
4 also to say that if you want to include patients, I
5 think it's much more important also to include the
6 organization and the system that it's based in. I
7 think a lot of the trouble comes because you don't
8 get your team data, a source data, into your
9 medical records. This is a lot of validity of the
10 data you're missing.
11 So I think there's a lot of data warehouse
12 problems we have within the different ICUs and the
13 different centers, and that's something I should
14 really check because it's not only the patient;
15 it's us and the hospital that's much more
16 influencing the studies.
17 DR. TUNG: Dr Egan, and then we have to move
18 on.
19 DR. EGAN: Just a quick comment about a very
20 practically oriented consideration. We have to
21 remember that the goals of the pharmaceutical
22 company, which is what drives the drug across the

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1 finish line, and the goals of the clinical
2 community are quite different as it relates to the
3 kinds of studies one would want to do.
4 What the pharmaceutical company wants is to
5 get the drug approved, and they're quite happy and
6 satisfied with a relatively limited label; that is,
7 in terms of the inclusion criteria, they'd be happy
8 to have a very specific -- a defined patient
9 population and a relatively narrow label because
10 that's the easiest way to get the drug across the
11 finish line, and then the clinical community can
12 begin using the drug off label and define the rest
13 of the usage patterns after the drug is approved.
14 So I think that's a very important thing to
15 remember, that having relatively limited inclusion
16 criteria is perfectly fine for the company. In
17 fact, they'd probably prefer that in some respects
18 because all they want to do is get the drug across
19 the finish line, and then let the clinical
20 community decide how it's going to be used off
21 label.
22 DR. TUNG: We're trying to frame

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1 recommendations that we can make to investigators.
2 Dr. Spies?
3 DR. SPIES: I think I will directly comment
4 on that. The point is, at least for European
5 countries, it's necessary that you check for the
6 use. And if you don't have the use proven, you
7 don't get it reimbursed. So for any company who
8 wants to have a drug reimbursed, it's absolutely
9 necessary to prove the use. And if it's too
10 narrow, you can't use it because you don't get it
11 in your system. And that's for all European
12 countries, except maybe UK because --
13 (Laughter.)
14 DR. EGAN: Again, if you look at a case of
15 dexmedetomidine, for example, now dex eventually
16 did get the label of max sedation, but that was
17 many, many years after it had been used quite
18 broadly for that indication, at least in the United
19 States.
20 If you look at the example of the Sedasys
21 technology, which Steve and I were the chief
22 consultants for the development of Sedasys, they

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1 had a pretty narrow label actually. It was for a
2 very subset of patients, relatively healthy
3 patients, to undergo GI endoscopy procedures.
4 Their anticipation of course was that the system
5 was going to be used much more broadly after it was
6 approved for that narrow label. So at least in the
7 U.S., I think companies quite commonly assume that
8 there's going to be a much broader off-label use.
9 DR. TUNG: I will stay there are case
10 reports of asystole with dex and hearts trans on
11 patients. So among the heart transplant community,
12 that's not a very good drug.
13 I want to move on. I heard Dr. Shehabi
14 mention age as a potential issue in
15 inclusion/exclusion in clinical trial sedation
16 because patients who are younger are different than
17 patients who are older. Does the committee want to
18 make any comment on whether age should be more
19 tightly controlled than it maybe is now?
20 DR. SKROBIK: How about frailty instead?
21 DR. TUNG: How about frailty?
22 DR. SKROBIK: So cognitive frailty is poorly

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1 measured by all the frailty metrics used. This is
2 Yoanna Skrobik.
3 DR. TUNG: Identify pre-operative --
4 DR. SKROBIK: So when I think of sedative
5 use in the vulnerable population, vulnerability
6 means frailty. It means poor outcomes. It means
7 poor cognitive outcomes, et cetera. The frailty
8 metrics we use are primarily focused on physical
9 function and capture the cognitive frailty and the
10 social network frailty less well, and people are
11 starting to develop alternatives that haven't been
12 validated in the critical care setting. But I
13 would argue for sedation specifically, that would
14 be an important consideration.
15 DR. SPIES: What about introducing as a
16 useful measurement in our pre-medication clinic?
17 We oversee now more than 5,000 patients. The point
18 is we use the Fried, plus we use the Mini-Cog, plus
19 we use some social things. The point is 50 percent
20 of the patients who are frail and have cognitive
21 impairment, not by a DSM code but by Mini-Cog,
22 these have 50 percent of the complications.

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1 It's very relevant what you are saying. The
2 point is you don't get the answer from the
3 relatives and from the patients if you're not
4 taking the test because the patients sometimes
5 really think they are cognitive. They think they
6 can move, step upwards and downwards, and it's not
7 true if you really check for that.
8 So if you're asking only, it's complicated.
9 That's why I think if patients are admitted by an
10 emergency, sometimes it's not so easily seen.
11 DR. SKROBIK: I think that's better than not
12 asking, though.
13 (Crosstalk.)
14 DR. TUNG: -- are important issues, but that
15 also they be difficult for pre-enrollment.
16 Dr. Shehabi?
17 DR. SHEHABI: Without discounting the
18 frailty relevance and importance in this context, I
19 think when it comes to sedation and age, it's
20 really related to the change in pharmacodynamics
21 and pharmacokinetics in these people because
22 there's definitely a different context and dynamic

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1 between a younger adult and older adult. And
2 that's why I think the age needs to be taken in
3 consideration when we design clinical trials for
4 sedation.
5 DR. TUNG: I heard Dr. Riker mention time to
6 sedation is a potentially relevant issue in trials
7 of ICU sedation. Do you care to flesh that out?
8 DR. RIKER: Sure. I think Yahya really is
9 the one who taught us this information about how
10 important those first 2 or 3 days in the ICU may be
11 as far as long-term outcomes. Clearly, that's also
12 going to be a challenge regarding consent if we're
13 doing a randomized trial with a new drug. So that
14 may mandate an ethic approach or depending on the
15 country we're doing the study, and deferred
16 consent.
17 But I think it's an area that there may be
18 ways to incorporate study design to address that
19 early time frame. Even if we can't enroll patients
20 in that time frame, perhaps we could, after consent
21 is obtained and the patient's enrolled, go back and
22 get that data. I don't know. It's a complex area

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1 but one that, prior to Yahya's data, I think we
2 accepted with blinders on, and now I think we
3 understand better how important that early phase
4 is.
5 DR. TUNG: I imagine the question is if
6 you're going to do a trial on a new drug, that you
7 must analyze in part by time to sedation and where
8 you are in the course of critical -- is that
9 roughly the sense of what we're talking? Does the
10 committee agree?
11 DR. WARD: Just to comment, in reviewing the
12 papers that I did before this meeting, there was a
13 lot of variability in time to enrollment, and most
14 were after 24 or even 48 hours, with some sort of
15 hand waving about what kind of drugs they got
16 before they enrolled in the trial.
17 So I think this is one of our important
18 recommendations because it is to me a change in
19 what the current literature seems to have.
20 DR. TUNG: JP has a comment in the back.
21 DR. KRESS: I think these are important
22 endpoints. Be careful in terms of what you choose

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1 as your primary versus your secondary. Time to
2 sedation, to use layman's terms, is a kind of a
3 soft endpoint. It's interesting and it's
4 important, but if you targeted your study as that
5 as your primary outcome, I suspect you'd probably
6 miss the boat because it's not going to be the big
7 ticket item.
8 But I think they're important pieces.
9 Nowadays, the way these trials, they are more rigid
10 than they used to be. When you submit a proposal
11 through clinicaltrials.gov, for example, you can
12 only pick one primary outcome. It's kind of a rule
13 that's rigid. So I wouldn't put this as primary,
14 but certainly secondary.
15 DR. RIKER: Riker. I agree a hundred
16 percent. I think Elizabeth had a nice description
17 yesterday, uh, in her presentation, calling it a
18 process variable. Perhaps the time and target
19 sedation or the time to sedation, those are process
20 but not necessarily meaningful outcomes for what's
21 going to happen.
22 DR. WARD: I may have missed on interpreting

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1 that comment. I was not thinking of it as time to
2 achieve sedation, but the time in which the study
3 was initiated.
4 MALE VOICE: Yes.
5 DR. WARD: I think the time to achieve
6 sedation clearly is not an accepted outcome, as a
7 primary outcome.
8 DR. TUNG: One quick comment, and then we
9 have to move on. Yes?
10 DR. AITKEN: Leanne Aitken. I do think we
11 need to make a recommendation that we need to make
12 the time to intervention as early as possible,
13 bearing in mind all the ethical considerations.
14 And I think we should make that quite definite in
15 there, and whether that's 24 or 48 hours. But we
16 can't be thinking that sedation studies can start
17 72 hours later.
18 DR. COURSIN: One of the limitations I see
19 there -- I work, as many of you do, in a tertiary
20 coronary care facility, and I often see patients 2
21 or 3 days into their course who've had a mish-mash
22 of therapies, and then they show up on my doorstep.

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1 I may enroll them within 24 hours, but they're not
2 the same as the de novo pneumococcal sepsis that's
3 agitated and whatnot that I want to get under
4 control.
5 DR. AITKEN: But maybe they don't belong in
6 the study. Yes, we still have to manage them, but
7 they maybe don't belong in the study.
8 DR. COURSIN: I understand that. I think it
9 just makes -- again, in the world that most of us
10 live in here, it's an increasing challenge to get
11 patients enrolled and complete a timely study.
12 DR. TUNG: Okay. In this next bullet, what
13 I've done is reach far and wide into the delirium
14 literature to pull out everybody's delirium risk
15 prediction model. And the weirdest risk predictor
16 of co-factors in those models -- and I've come up
17 with this list of -- and the question is whether
18 the committee believes that if delirium is going to
19 be an outcome of your sedation trial, you must
20 match patients in the control and intervention
21 groups on these factors. You need to know the A1C,
22 for example, to match in the delirium trial.

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1 Isn't that why you're randomizing? I'm
2 confused as to why you would match in a
3 randomized-controlled trial.
4 Dr. Girard?
5 DR. GIRARD: I'd say you need to know the
6 number, and you need to be able to report the
7 number.
8 DR. TUNG: So tracking it --
9 DR. GIRARD: Tracking it.
10 DR. TUNG: -- not necessarily matching that
11 at enrollment.
12 DR. SKROBIK: I don't think you should go
13 there, myself. In all of the prediction
14 models -- there are several, and you've reviewed
15 them, and John and I have applied some of them in
16 our study data, and I think that it is a slippery
17 slope because a lot of different models will use
18 different metrics, and none have used all of them.
19 When the Dutch did theirs and applied it to
20 populations outside of their -- John, maybe you can
21 comment on this because you've worked on it with
22 them. But when pre-deliric is applied to other

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1 populations than theirs, it doesn't predict as
2 well. So is it useful, really? And then you could
3 really go crazy and say, and what is delirium? But
4 I'm not going to --
5 DR. TUNG: You could go crazy, even
6 delirious.
7 So the committee does not have a set of
8 patient characteristics that we must know about
9 when we --
10 DR. WARD: We should know, but not
11 necessarily -- from what Dan just said, they may be
12 things that you'd want to put --
13 DR. TUNG: But do you need to --
14 DR. WARD: -- you'd want to put in table 1.
15 DR. TUNG: Anyone see it for table 1?
16 That's the question.
17 DR. SESSLER: The matching is largely taken
18 care of by randomization in a sufficient and large
19 trial. And if you're worried about it, stratify
20 your randomization; that takes care of that. A
21 different issue is should you write down stuff?
22 The answer is of course. You should write down

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1 everything you think is conceivably relevant and
2 put it into table 1.
3 MALE VOICE: If things are not --
4 DR. SESSLER: The current approach is to use
5 absolute standardized differences, not p-values in
6 table 1. Then you set some rules if the absolute
7 standard difference is more than 0.1 or 0.2. You
8 include that in a multivariable analysis, and you
9 put that into your statistical plan ahead of time.
10 DR. TUNG: Does the committee have a
11 recommendation on this question here?
12 DR. RIKER: Riker. I think it depends if
13 you're talking about a new drug to market or an
14 improvement in our sedation approach in the ICU.
15 The second of course can be pragmatic. The former,
16 I don't know the answer to.
17 DR. SESSLER: I couldn't agree more. This
18 highly context-dependent, but a new chemical entity
19 is going to be tightly controlled. It's not going
20 to be a pragmatic trial. Something that's already
21 approved, for example, could well be done in a
22 pragmatic trial, which is less expensive, that

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1 enrolls faster, and tends to include a broader
2 population. It would be more generalizable.
3 So I don't think you can answer this in a
4 general fashion. It's going to be dependent on the
5 trial and the drug and mistake.
6 DR. TUNG: Can they be adaptive?
7 DR. SESSLER: Of course.
8 DR. TUNG: Should they be adaptive?
9 DR. SESSLER: Of course.
10 MALE VOICE: Will they be adaptive?
11 MALE VOICE: With they be adaptive?
12 DR. RIKER: There's a large and growing body
13 of literature refuting the role of RCTs in ICU
14 studies because the primary effect is
15 underestimated so often in the design of the study.
16 The results are negative. People don't know what
17 to do with that information and strongly
18 recommending alternative designs. I think as we,
19 as we move into adaptive responsive platform type
20 designs, we may get more return on our investment
21 and get much more meaningful information.
22 DR. SESSLER: I couldn't agree more. So

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1 many studies have overoptimistic sample size
2 estimates, and they tend to be estimated based on
3 time or budget or wishful thinking. You end up
4 with a p-value 0.09, which is uninterpretable.
5 That's statistical never-never land. You can't say
6 that there's no effect because the point estimate
7 suggests that there actually is a clinically
8 important effect. You can't say that it's
9 statistically significant.
10 It's the one place you really don't want to
11 end up at the end of a clinical trial. You can
12 avoid that by putting interim analyses in and
13 putting in your protocol that you will re-estimate
14 sample size as necessary, as strongly recommended.
15 DR. COLANTUONI: This is Elizabeth
16 Colantuoni. I just wanted, since we have an FDA
17 representative, maybe getting the FDA's
18 perspective. I agree with everything that's just
19 been said, but it would be nice to also have
20 confirmation from the FDA and if they have
21 preferences in terms of strength of evidence or
22 preferences in terms of what sorts of adaptive

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1 trials they're open to.
2 DR. ROCA: Well, they're certainly open to
3 adaptive trial designs. They have come into the
4 discussions the last four or five years of so.
5 Some divisions do them more than others. For
6 example, hematology/oncology does a lot of them, a
7 lot more than we do. So they do have a role.
8 I think one of the things would be, what
9 you're describing, is whatever strategy you're
10 going to be using, it really needs to be stated a
11 priori as opposed to on the fly, so we would be
12 looking at it. We do have statistical input,
13 multidisciplinary input as the adaptive design
14 comes in.
15 So it would be something we would consider.
16 We would want to have discussions, but it is
17 something.
18 DR. TUNG: Dr. Maze?
19 DR. MAZE: I could just add to that we're
20 dealing with a different division from anesthesia
21 with DCRP, and Dr. Temple has put out a lot of
22 literature on the subject. I'm strongly

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1 recommending, in this post-cardiac arrest syndrome
2 trial, that we do a -- we did adaptive design. And
3 we may still do it because we haven't completed our
4 SAP yet. So at the time that the SAP is finalized,
5 it may be that we will do an adaptive for the very
6 reason that Dan has stipulated. In fact, Dan is
7 head of DSMB, so he would be in a position to plan
8 that.
9 (Laughter.)
10 DR. TUNG: Does the committee recommend a
11 composite outcome, single primary outcome, or does
12 the committee have no comment on this question?
13 DR. NEEDHAM: This is Dale Needham. I fear
14 that we don't yet know what the outcome should be,
15 but it's the end of the discussion yesterday, so
16 I'd say we have no comment yet.
17 DR. WARD: After Yoanna's panel, we'll
18 have --
19 DR. SKROBIK: I was just going to say that I
20 think a lot of the subsections through are going to
21 be informed or over the next two groups, where I
22 look forward to all of your comments because I

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1 think some of the sub-items, if you will, have to
2 do with the process.
3 I've heard a lot of the local culture, the
4 local availability of technology, the electric
5 records versus not, I think you're allowed items
6 that can talk to the content. So even in the
7 question that you just asked, which we aren't
8 answering, we can also say why we're not. And I
9 think that's important, so thanks for the
10 expert [indiscernible].
11 DR. TUNG: I'm going to push forward to the
12 next one, which is I heard yesterday a discussion
13 of how a placebo-controlled trial is hard to do in
14 sedation for obvious reasons. Does the committee
15 want to recommend a single standard against which,
16 say, a new drug should be compared to?
17 DR. RIKER: I'll throw something out there.
18 Riker. I think, as we learn from the MENDS trial
19 and the complexity if you've got a wide range of
20 acceptable sedation and how you have to supplement
21 perhaps with other agents to get to your deeper
22 levels, I would recommend that we recommend not

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1 having light and deep sedation, however we're going
2 to define light, and that there may be different
3 standards for those two approaches. In other
4 words, based on the last PADIS guidelines and the
5 previous PAD guidelines, light sedation, the
6 standard may well be dexmedetomidine or propofol,
7 and for deeper sedation would probably be propofol.
8 So I'll throw that out there for comment;
9 not necessarily that it's the right answer.
10 DR. TUNG: Dr. Shehabi?
11 DR. SHEHABI: I think the comparator is
12 very, very important. I think in terms of usual
13 practice used as a comparator, you can do that, but
14 I think it has to be stipulated that the sedation
15 level, whatever that is, should be comparable in
16 both groups. I think that's fundamental because
17 we've seen trials that sedation targets were not
18 comparable, and you don't know whether that is the
19 effect of the intervention or the different
20 sedation. So I think that's a fundamental part of
21 the comparator.
22 Whether it's usual practice or controlled

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1 usual [indiscernible] practice, that really depends
2 on whether you believe the interventions used are
3 already considered standard practice. And if they
4 are, then yes, you can use usual practice as a
5 comparator. But if they're not, then you need to
6 have a control to do your practice.
7 DR. TUNG: Do we think there's some
8 comparator that's not only depth but also
9 potentially drug?
10 Dr. Egan?
11 DR. EGAN: Just a quick reminder about an
12 important point we discussed yesterday, and that is
13 that dose matters. I think that the depth of
14 sedation is a function more of the dose than it is
15 the drug, assuming that most of the sedatives that
16 we talk about are at least capable of approaching a
17 near deep sedation state. Certainly, propofol has
18 a more maximal effect than dexmedetomidine does,
19 but you've got to control for the dose. The level
20 of sedation, again, I think is more a function of
21 the dose than it is the drug that's chosen. So
22 that is an important consideration in terms of the

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1 comparator.
2 DR. TUNG: Dr. Kress?
3 DR. KRESS: I think Pratik touched on it in
4 his talk this morning with regard to this light
5 versus deep. The one thing I don't think we have
6 good literature on is, is there a difference
7 between light, where the patient comes up from the
8 depths of being under water for a bit of time so
9 that you know they're in there, but then the rest
10 of their 23 hours, they spend under the water, or
11 is that compared to a situation where they're alert
12 for longer periods of time?
13 You could do that study reasonably easily
14 using some kind of an area under the curve
15 analysis. And I'm not sure which is better or even
16 if they're the same. If I spend 23 hours sedated
17 but 1 hour awake following instructions, is that
18 fundamentally different? It is, but in terms of
19 outcomes, then if I spend most of my time able to
20 follow instructions and interact, certainly with
21 dexmedetomidine, the chance to get that latter goal
22 is much better I think. But I don't think

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1 anybody's looked at that.
2 So this light -- I don't know which of those
3 two I would categorize as better, light, but
4 lighter, Coors Light; I don't know.
5 (Laughter.)
6 DR. KRESS: They're not the same. One has
7 corn syrup, and one doesn't.
8 DR. TUNG: Dr. Girard?
9 DR. GIRARD: This is Tim Girard. It seems
10 like to me to
11 answer this question depends on what you think the
12 potential added benefit of the drug you're studying
13 is. These drugs that we currently use in study,
14 and certainly some drug, new molecule that we don't
15 yet know about, they're not all proposed to work
16 the same way. They're not all supposed to have the
17 same benefit.
18 If there's a new drug, for example, that we
19 think is going to uniquely affect sleep in a way
20 that no other sedating agent does, and you might
21 propose that dexmedetomidine is that. but let's say
22 a new drug, then maybe you would study that against

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1 placebo because there's not currently a drug that
2 we believe reliably induces restorative sleep, at
3 least that we know of based on existing randomized
4 trials in ICU patients.
5 Alternatively, if we think that the drug is
6 just going to do the same thing but maybe with a
7 better safety profile or better accuracy than, yes,
8 compared to a propofol standard. But I don't think
9 we can answer this question unless you know exactly
10 what it is you're studying.
11 DR. TUNG: I imagine if you compare it to
12 Valium, for example, you'd have a benefit no matter
13 what drug you used.
14 Okay. So the committee recognizes that
15 there may be issues, including depth of sedation,
16 including drug types for certain specific targeted
17 outcomes.
18 DR. COURSIN: Along those lines, since most
19 ICU drugs come from someplace else, are folks aware
20 of drugs in development in the psychotropic or
21 sleep world that might pay readily applicable to
22 our mission? Talmage?

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1 DR. EGAN: I think the biggest player on
2 this stage right now in the anesthesia world,
3 certainly as in the sedative [inaudible - mic
4 fades] not a category, is remimazolam, which is
5 esterase metabolized benzodiazepine. It will have
6 a pharmacokinetic profile akin to what you see with
7 remifentanyl, or at least an approximation of that
8 but with a pharmacodynamic profile that is
9 benzodiazepine like.
10 DR. COURSIN: But are you aware of anybody
11 in the psychotropic world that's looking for
12 anxiolytics, looking for disordered sleep, since
13 part of that world is driven by the psychiatrist?
14 People in obstructive sleep apnea research, aren't
15 they looking at any potential modulators that we
16 might want to glom on to? Because they're looking
17 at markets that are gigantic, and who's gonna come
18 into our market for our very niche short-term
19 utilization is one question I think that we have to
20 ask ourselves.
21 DR. EGAN: The only one I'm aware of is an
22 orexin related compound that is being developed by

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1 Takeda Pharmaceuticals in Japan, so there's some
2 activity in that domain as well.
3 Just to quickly tie up the remimazolam
4 point, it's being developed for the sedation
5 market; that is the procedural sedation market, but
6 it could potentially have some application in the
7 ICU at some point.
8 DR. TUNG: We are out of time, so I'm going
9 to defer to the moderator of whether we should get
10 through these three or not get through these three.
11 DR. WARD: We should go through these, and
12 we can delay the break.
13 DR. COURSIN: We'd like yes/no answers,
14 please.
15 MALE VOICE: Periscope depth, JP, needs to
16 pop up yes/no.
17 DR. TUNG: This first question has so many
18 different dimensions on it. I don't know how you
19 connect that one at all. Does anybody have any
20 suggestions as to how the committee should respond?
21 DR. SKROBIK: My suggestion is that you
22 email this to committee members, and get thoughts,

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1 and collate them because I think --
2 DR. WARD: I would propose a Delphi
3 afterwards [inaudible - off mic] and wrap this up.
4 To me, those are kind of table 1 things. Right?
5 You can't necessary control it, but you've got to
6 measure it; record it.
7 DR. TUNG: The second bullet was brought up
8 yesterday in discussion.
9 DR. ABSALOM: I think how strongly you make
10 the case for target-controlled infusions would
11 depend on the pharmacokinetics of the drug. So if
12 it's a drug that quickly reaches a steady state of
13 infusion like remifentanyl, it's not such a strong
14 case, but for other drugs which causes an infusion
15 and you have a slowly rising blood concentration,
16 there that would be a stronger argument.
17 DR. WARD: You need to design your study
18 knowing the PK of the drug. You need to have the
19 pharmacokinetics to design the design.
20 DR. TUNG: I guess then there might be drugs
21 in which the committee will say you should use a
22 TCI.

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1 DR. SKROBIK: What's a TCI?
2 DR. TUNG: Targeted control.
3 MALE VOICE: But you're going to need to get
4 the data on what those kinetics are.
5 DR. TUNG: Well, I think it was JP in one of
6 his commentary said that sometimes there's not
7 enough phase 1 and phase 2 data to help us really
8 design the phase 3 trial, and I think --
9 DR. SKROBIK: But question 1 and question 2
10 are actually linked. So if you're co-administering
11 fentanyl and midazolam, there's your
12 pharmacokinetic questions, so you can summarize in
13 what you just said.
14 DR. TUNG: Finally, the last question, for
15 those you can turn off protocols -- it's hard to
16 turn off and on protocols, so maybe you should just
17 turn it all on for one month, and then switch, and
18 then block randomize.
19 Is that a better way to do these kinds of
20 trials?
21 DR. GIRARD: Can you clarify what you mean
22 by block randomization? When I read that question,

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1 I was thinking you either block, which is yes every
2 day, but what you just described sounds different.
3 So can you clarify?
4 DR. TUNG: I guess maybe you randomize over
5 time. So for one month you'd do it one way and the
6 other month you do it a different way, to get
7 around the problem of protocols being switched on
8 and off. That's what I meant. Sorry.
9 MALE VOICE: You mean an alternating cohort.
10 DR. TUNG: Yes.
11 MALE VOICE: That's different from block
12 randomization.
13 DR. AITKEN: Leanne Aitken. No, because the
14 biggest problem in implementing most of these
15 sedation studies is actually to get the clinicians
16 to do it, and if you're changing every month,
17 you'll never get proper practice.
18 DR. KRESS: Just so I understand for the
19 biostatistician trending people in the room, and
20 maybe you touched on this, Tim, but to me, block
21 randomization means it's a randomized trial and the
22 groups, there are two or it could be more, and

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1 usually it's variable blocks. So there's a group
2 of 6, and 4 might be in one group and 2 in the
3 next, and then they start over.
4 The reason for that block randomization is
5 to ensure that you don't by happenstance hit a big
6 mail distribution at the end of the day, but I
7 think what you're touching on, Avery, is should we
8 alternate what we do based upon the calendar. Is
9 that right?
10 DR. TUNG: That was my vision for this
11 question --
12 DR. KRESS: So that --
13 (Crosstalk.)
14 DR. KRESS: Then you could conceivably do
15 that without consent, I suppose, if the IRBs felt
16 that the two interventions were -- there was
17 equipoise, you could argue that this is just the
18 way we do it for the next 3 months, and then you
19 could at least make an argument. I'm not sure you
20 would succeed depending on your IRB.
21 DR. SKROBIK: It wouldn't fly; we tried.
22 DR. KRESS: But to say we're going to do it

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1 this way, and we're not randomizing, so it's done
2 without consent. I suppose you could make that
3 argument.
4 DR. GIRARD: It has been done without
5 consent, not in sedation, and maybe it wouldn't
6 work in sedation. I'm not convinced that it would.
7 But for other interventions, clearly this has been
8 done. The two big -- crystalloid versus
9 imbalanced --
10 MALE VOICE: Salt trials.
11 DR. GIRARD: -- like salts,
12 REB [indiscernible], they did this. They didn't
13 call it the alternating cohort; they called it a
14 cluster randomized trial with crossover.
15 DR. TUNG: Cluster. That's the word I
16 wanted.
17 DR. GIRARD: Right. One group would cross
18 over to be the alternate strategy on a given month.
19 DR. SESSLER: It would be perfectly
20 reasonable for comparative effectiveness study.
21 Just suppose you want to compare propofol and
22 dexmedetomidine. Both are commonly used drugs. It

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1 would be perfectly reasonable to use one drug for a
2 month, and then you switch over and use the other
3 drug for a month, and you keep switching back and
4 forth. You'd have to have waived consent, but if
5 you had that, you can enroll a huge number of
6 patients relatively inexpensively.
7 DR. WARD: It may be more difficult if
8 you've got a new molecule in the picture.
9 DR. SESSLER: You probably could not get
10 waived consent for a new molecule. It's not
11 designed for that.
12 DR. WARD: Let's take 25-minute break and
13 get back here at 10:35.
14 (Whereupon, at 10:11 a.m., a recess was
15 taken.)
16 DR. WARD: Well, we think about what are the
17 indications for a sedation trial. We did inclusion
18 and exclusion criteria, so it was a little bit in
19 that one because the indication is the need for
20 sedation because these are clinical trials for
21 sedation. So we may need to do a little bit about
22 more what the indications are.

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1 The second clarification -- and this always
2 come up in this kind of meeting. It came up a lot
3 in SCEPTER II, where we were talking about safety
4 and the issue of a QI database is not a
5 particularly good database to base your information
6 about safety on. It's kind of the magician versus
7 wand issue.
8 If you're studying the wand -- if you've got
9 a new molecule you want to study, you want to study
10 the wand. You don't want to study how the magician
11 uses the wand. I may be pulling this analogy a
12 little bit too far. There's still kind of a Harry
13 Potter fan that's still a reasonable analogy for
14 it.
15 A phase 4 trial, a more pragmatic trial, is
16 where you want to get a bunch of magicians out
17 there using the wand and see if everybody manages
18 to use it the same way. This maybe covers a little
19 bit of both types of trials, but one type of trial
20 we're very interested in, of course, as Bob keeps
21 calling it, new dex. If new dex is coming along,
22 the new wand, we're going to talk about how would

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1 you design the trial for the registration. And
2 that's different than some of the other kinds of
3 things that we've been talking about that are
4 valuable, phase 4 or NIH-funded kind of trials, and
5 will add great information to it.
6 So I don't want to eliminate talking about
7 either kind, but I think we need to remember
8 there's kind of a different way that you would
9 design a trial if it's new dex versus you've got a
10 way to give propofol differently than we've been
11 giving it and you want to compare it to a
12 comparator.
13 Yoanna, you've got group 2.
14 DR. SKROBIK: Thank you.
15 DR. WARD: Thank you.
16 Panel Discussion
17 DR. SKROBIK: I was going to invite you all
18 to sit down in a circle around the room because I
19 think that what I would really like to ask are
20 questions based on this mandate that we have. I've
21 heard a lot of discussion over the last day and
22 this morning that I found fascinating, and I also

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1 think, to your point, Denham, that we are actually
2 discussing different kinds of trial models.
3 Lisa, help me, please, because we were
4 talking about -- what Lisa pointed out is that
5 there's the new drug, the new molecule, and what
6 are you going to compare it to and how are you
7 going to do that? Then there's the comparator
8 trial between two different kinds of molecules that
9 already exist.
10 What was the third category? Lisa, help me.
11 DR. BURRY: Sorry. As a pharmacist, I felt
12 very much we were trying to put all different kinds
13 of pills in the same container, and I had anxiety
14 about doing that.
15 (Laughter.)
16 DR. BURRY: They needed to sedate me, yes.
17 There were trials that I would have very specific
18 design ideas about if it was a brand new drug
19 coming to market and what I would expect, and I
20 expect, as already have been indicated, the
21 labeling would be rather narrow to start with and
22 then expand over time. Then am I comparing two

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1 different molecules that are already available, and
2 I need to think about the operating characteristics
3 of that molecule so I'm not unfairly biasing one
4 particular arm or another. Then am I going to take
5 the same molecule and compare it with different
6 methods of administration to tie in and accommodate
7 for poor pharmacokinetics or things that are less
8 than ideal to make the drug operate at a better
9 standard.
10 So I felt there were different types of
11 studies we were trying to address within the same
12 questions. Although the questions were valid, I
13 felt the answers would be very different depending
14 on what we were trying to achieve.
15 DR. SKROBIK: The last category I think
16 is -- the last item -- so I'm bringing up these
17 points even though they're not on this list because
18 as we're moving forward to answer, how to best
19 et cetera, that answer may vary based on the type
20 of trial that we're suggesting it for.
21 The last comment that I had to make -- and
22 perhaps Dr. Roca [indiscernible] can comment on

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1 this. But my sense is that the FDA, just like
2 Health Canada, if they're approving a new molecule,
3 you have to choose which comparator you're going to
4 choose it for. Dr. Maze was talking about it this
5 morning. Sedation was what dexmedetomidine was
6 chosen for when in fact it has analgesic
7 properties. So you have to pick one category and
8 how does that play into how you decide to structure
9 the trial or these questions.
10 So with that, I'd like to open the
11 discussion to the measurement of the level of
12 sedation. What I have here is a list of suggested
13 metrics, including the RASS and other sedation
14 level measurements. Some of them are actually not
15 only not validated but have been shown to not be
16 useful, like the Ramsay and the Glasgow, which were
17 ubiquitously used 20 years ago and no longer are
18 because of the dissemination of other sedation
19 scales.
20 There are other elements that are patient
21 population specific. Pain evaluations in the neuro
22 ICU population have been studied by Senengee [ph],

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1 and now who's in Montreal but also by others, but
2 they're population specific answers to some of
3 those questions.
4 What I would like before we address the
5 scale issue is to talk about process, and I've
6 heard -- Leanne, I didn't say a number of things
7 that really spoke to me about how things happen at
8 the bedside. All of these nice Cartesian, in the
9 OR, anesthesia comments, where you are the magician
10 and you're holding the wand in front of one
11 recipient of whatever that wand contains, don't
12 necessarily apply to the behavior at the bedside in
13 ICUs.
14 So I'd like to hear Leanne, and I'd like to
15 hear Michele, and I would like to hear Claudia,
16 because they're all of the dimensions of cultural
17 and behavioral bedside application that I think we
18 have not highlighted sufficiently, and this is an
19 opportunity to do that.
20 Take it away, girls. Come on.
21 DR. AITKEN: Leanne Aitken. I guess it
22 depends on the specific questions, but --

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1 DR. SKROBIK: So we're at point 1 --
2 DR. AITKEN: Okay.
3 DR. SKROBIK: -- and how are you measuring
4 it.
5 DR. AITKEN: The biggest challenge is
6 inter-rater reliability of anyone using the scales,
7 how do you get 100, or 200, or 300 predominantly
8 nurses assessing patients in the same way? And if
9 that's one of our either process measures, or
10 interim outcomes, or target that we're delivering
11 our sedation drug to, then we do need to get some
12 consistency in it, and I think we need to put some
13 thought into it.
14 DR. SKROBIK: Do you think that that should
15 be part of what we look at in the methodology of
16 sedation trials?
17 DR. AITKEN: I think it should be. It's
18 part of the intervention.
19 DR. SKROBIK: And should be perhaps
20 considered a marker of quality?
21 DR. AITKEN: Should be a marker of whether
22 we have achieved the intervention --

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1 DR. SKROBIK: Okay.
2 DR. AITKEN: -- because most of the time
3 we're going to be delivering the sedation to
4 achieve some sort of endpoint, to achieve a target
5 sedation score, or whatever. And if you've got
6 problems in setting that target sedation score,
7 then you've got problems in how much sedative's
8 being given.
9 DR. SKROBIK: So people have argued that for
10 behavioral change, if you understand why people are
11 not doing something, then you can implement
12 different approaches for specific environments and
13 achieve homogeneity in best target across sites. I
14 wondered how that would fit into --
15 DR. BALAS: Yoanna?
16 DR. SKROBIK: Yes?
17 DR. BALAS: I think this comes down to our
18 discussion regarding the purpose of the trial. I
19 personally feel as if it's a clinical trial looking
20 at safety and effectiveness, the RASS and the SAS
21 measurements will need to be measured differently
22 then reliance on bedside nurses. My personal

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1 opinion is that for a safety and effectiveness or
2 safety and efficacy trial, that there needs to be
3 standardized personnel doing the assessments, and
4 there also needs to be rigorous fidelity monitoring
5 of the people.
6 For safety and effectiveness trials, my
7 belief is I do not think we can go by EMR records
8 or by nursing assessment. If you're doing more of
9 an effectiveness trial, or a discrimination, or a
10 hybrid trial, I think that's where these questions
11 come in, in terms of how we're going to extract
12 that data and make sure that the bedside nurses are
13 doing it correctly.
14 Does that make sense?
15 DR. SKROBIK: It does.
16 DR. AITKEN: The challenge is the enormous
17 resource required to do that.
18 DR. BALAS: Yes.
19 DR. SKROBIK: Claudia?
20 DR. SPIES: Well, from a point of training,
21 I think it's very important that people know what
22 we are doing, the staff and the patients and the

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1 relatives. I think this is a major point. So the
2 question is how we can achieve that. I'm not sure
3 if we can achieve that if only registered nurses
4 will do that in the settings that they are study
5 nurses, and then at the end, the study nurses are
6 only there from regular day hours.
7 So I think that will not work. To my
8 impression, we need to train the staff and require
9 more and more peer reviews before we start the
10 study. There is so much variability between the
11 ICUs, and some ICUs still think like 20 years ago,
12 and the patients are over-sedated. They haven't
13 taken the cultural change.
14 In our ICU, no patient gets sedation if
15 that's not required. So also, we need to check
16 when sedation is required, and that means to
17 titrate the drugs. This is also from a
18 pharmacological point of view. This is not so easy
19 to titrate it.
20 Also, to keep the patients and the relatives
21 at that level means you have to train the relatives
22 to not make them anxious and keep them confident.

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1 There are a lot of things you need to train, and we
2 do that by blended learning concepts. We have that
3 available for all German ICUs because it's --
4 DR. SKROBIK: But it's in German, right?
5 DR. SPIES: That's why I think other people
6 need to do it. I think also it's not English
7 itself. It needs to be adapted to the culture. So
8 I think it's very important that we speak like we
9 usually speak to our families, to our staff, and I
10 think that needs to be reflected. That's at least
11 my point.
12 DR. SKROBIK: Pamela?
13 DR. FLOOD: I have a comment both based on
14 my observations as a patient and also on my
15 observations as a clinician. one is that I think
16 the variability is partially due to the burden on
17 the clinical nurse because I think in some
18 settings, they have a lot more burden of clinical
19 care. They may have two patients rather than one
20 patient. They have enormous documenting
21 responsibilities just based on clinical care.
22 So when you throw another documenting

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1 responsibility on them, on the basis of this study,
2 they're not really very interested, and you get the
3 issue that you mentioned, that every blood
4 pressure's the same and every sedation score is the
5 same because they just can't live up to the burden
6 because their clinical care is too much. In that
7 case, in the best of all possible worlds, it would
8 be better to have a more consistent study nurse or
9 study personnel taking those, but of course money
10 isn't everywhere.
11 DR. SKROBIK: I think there's nice data
12 showing that sedation levels actually rise with
13 burden. There's lots of literature on that.
14 To speak to the point of the
15 assessments. -- and I'll give you, Steve, in just a
16 second -- Mona was saying earlier to me -- I'll
17 find it -- that once you've trained somebody, that
18 that doesn't mean that you could assume that they
19 stay trained.
20 DR. SPIES: No, that's wrong.
21 DR. SKROBIK: Let her answer.
22 DR. HOPKINS: So I can talk? I can tell you

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1 in the ALPA [ph] study, Dale organized training
2 sessions. Before the study rolled out, people had
3 to come and practice and reach a certain level on
4 each assessment, both for RASS and CAM, and for all
5 the ICU outcomes assessments we did. There was
6 marked variability, and then when we would come
7 back a year later to recertify, most of us failed
8 in something, and we had to retrain and recertify
9 to that level.
10 So I don't think it's quite the case that
11 it's true, and in doing RASS and CAM, the
12 variability, if we couldn't get a study RASS and
13 CAM done, we would take the nursing RASS and CAM,
14 and those were, often if we did them at the same
15 time, markedly different. So I think there is an
16 importance to training and keep training, and
17 making sure -- maybe Dale wants to add any other
18 comments.
19 DR. NEEDHAM: I think we presumed that the
20 letters after somebody's name is associated with
21 their competence. There was a faculty member who
22 repeatedly didn't pass the QA and was very upset

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1 because this faculty member said, "Oh, I've done
2 these things in animal models" and whatever, some
3 of these things. I was like, "Oh. Sorry." That
4 was Dale Needham.
5 DR. SKROBIK: Claudia had a comment, and
6 Steve had a comment.
7 DR. SHAFER: All these scales involved at
8 the deep end, it's physical stimulation, something
9 noxious that the person responds to. Talmage and I
10 shared the experience with the development of
11 Sedasys, where the pivotal trial was a 1000-patient
12 trial, and the device was intended to put patients
13 in the area of moderate sedation, but trapezius
14 squeeze and response to trapezius squeeze was used
15 to define unarousable patients.
16 There were 5 patients in that trial who
17 failed to respond to trapezius squeeze. All were
18 assessed by the same nurse, and the same nurse had
19 administered a trapezius squeeze, and this was a
20 very somewhat -- a nurse who would not be expected
21 to be particularly aggressive in this maneuver.
22 The FDA interpreted that by saying this device puts

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1 people into general anesthesia, and that delayed
2 the approval of the product by 4 years, those 5
3 patients.
4 We pointed out repeatedly to the FDA, that 2
5 minutes later those patients were awake and
6 talkative, and you can't be awake and talkative
7 2 minutes after general anesthesia, and it was just
8 a weak trapezius squeeze.
9 I mentioned this because much better things
10 for noxious stimulation is electrical stimulation
11 that can be readily reproduced and is not dependent
12 on the strength and aggressive nature of the person
13 doing the tests. So the noxious stimulation really
14 has to be standardized because you may have people
15 saying, "They're unarousable on the RASS scale," or
16 they're a minus 5 when in fact nobody really tried.
17 DR. SKROBIK: I'm a little worried that you
18 would be describing the noxious stimuli and that
19 the patients would be that sedated, but that's a
20 very personal response.
21 DR. SHAFER: But they really weren't; that's
22 the problem.

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1 DR. SKROBIK: So in the sedative
2 assessments, we talked about scales to measure a
3 pharmacological agent administration. One of the
4 points that Ingrid raised a little earlier was what
5 do you do with patients when you're trying to
6 decide whether to give them a sedative at all? I
7 don't know if you wanted to speak to that.
8 DR. EGEROD: Yes. I just want to comment on
9 the other problem of consistency. I was a part of
10 the large Euro pain study with thousands and
11 thousands of patients, and there was actually very
12 good consistency in using the pain and discomfort
13 scoring instrument.
14 So I think that it's important to have some
15 kind of a research nurse in place, but that person
16 of course isn't there all the time, but that person
17 is responsible to see to it that the others are
18 doing what they're supposed to do, and that usually
19 does work pretty well.
20 So that was that. About the sedation, we've
21 been discussing light sedation, but we haven't been
22 discussing no sedation. I did a study in Denmark

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1 where on a single day, I asked every single ICU how
2 many patients they had and how much they had
3 sedated the patients. There were very few patients
4 that had been sedated. And I asked them if they'd
5 done the wake up, and of course they hadn't because
6 they were awake.
7 So I think that that is very cultural, and I
8 think more European countries are doing very close
9 to no sedation, so I think we should think about
10 that.
11 We were talking about light sedation this
12 morning, and some of the interviews I've had with
13 patients is that they would rather have no sedation
14 than light sedation because light sedation can be
15 uncomfortable to some patients because it takes
16 away their sense of control. Some of the patients
17 have described fighting sedation. So on top of all
18 their other ailments, they're fighting sedation.
19 So somehow, some patients would rather not be
20 sedated.
21 If they're not sedated, communication is
22 easier. One of my PhD studies did a year of

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1 observation in ICU, and what she saw was -- we
2 don't use restraints, we've never used restraints,
3 so we're not so concerned about patients pulling
4 things. But what she saw was that if the patient
5 was bothered by the tube that was pressing some
6 place in the mouth, the patient could adjust his
7 own tube.
8 What we see more and more is that we trust
9 the patients because they're awake, we're
10 communicating with them, and little discomforts can
11 be very difficult to describe that -- where is the
12 tube pressing or something -- they can do some of
13 the adjustments themselves. So I just think we
14 should also open this discussion to how we can work
15 much more with awake patients and communicate with
16 the awake patients.
17 DR. SKROBIK: Michele, did you have another
18 comment? No?
19 So does that speak to some of the no
20 sedation points, Claudia?
21 DR. SPIES: I fully agree with Ingrid. We
22 have the same experience. We don't sedate all the

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1 patients except if they are agitated on the levels,
2 and we titrate it, so it's no continuous, except
3 the half-life because it's required for that. But
4 the point is, in most of the cases, the half-life
5 is too long, so we don't need any IV infusions.
6 DR. WARD: Ward. I think it speaks to our
7 control group, and the control group could very
8 well be no sedation would be an acceptable control
9 group. But remember, the discussion is about if
10 you have a new molecule that you want to have the
11 registration be sedation, obviously a discussion
12 about, well, if you don't need sedation, safety
13 outcomes become the important piece, because if
14 your control group is no sedation and you've got a
15 new molecule that your indication is sedation, and
16 now you find that the, pick one, delirium occurs
17 more commonly with this new molecule, that has a
18 worse safety profile than no sedation.
19 You don't necessarily need to have an active
20 comparator. If the practice is no sedation, then
21 that's a fine control group. But you need to still
22 look at the safety outcomes for both your control

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1 group and your new molecule group.
2 DR. SKROBIK: But if we're discussing -- I'm
3 sorry, Claudia, to be cutting you off. But
4 regardless of whether we're testing a new molecule
5 or comparing two, what we're talking about is
6 delivering, as needed, sedatives in two groups that
7 then should be triggered by the same threshold.
8 My question is, do you think that the RASS
9 and the other methods that have been validated are
10 actually good threshold metrics to begin the
11 sedation? Because what they've been used for and
12 validated for is comparison of drug effect, but
13 nobody's actually said, to Ingrid's point, this is
14 when you might consider starting.
15 I remember reviewing a lot of the -- well,
16 not a lot. I reviewed some the earlier sedation
17 papers. Agitation is actually very poorly defined.
18 Sitting up in bed and moving, I agree with Michele,
19 is not -- and one of the reasons that I think the
20 RASS has become so popular is that everybody can
21 agree on what 10 seconds means. My sense of what
22 agitation is, is very different than what somebody

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1 else's sense of agitation is.
2 The minus whatever by subjective criteria, I
3 think that's where you find your highest
4 inter-rater reliability metrics. So do you think
5 that a threshold for administering sedation is
6 something that we should be thinking about and
7 proposing? And if so, what should that threshold
8 be?
9 I haven't heard you describe what the
10 Israeli practices are like. I was curious whether
11 you had any comments and thoughts on whether that
12 would be something that you might --
13 DR. GOZAL: David Gozal from Jerusalem.
14 [Indiscernible - mic distortion] American practice.
15 There are not much difference between the North
16 American practice and Israeli one. I agree the
17 biggest problem must be, first of all, education
18 and practice and training, and the second one, like
19 Pamela said, burden on the nurse and staff. I
20 think all over the world, nurse staffing is a big
21 problem and of course a problem of money.
22 DR. SKROBIK: So the reliability of bedside

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1 monitoring, you should either consider a validation
2 day to day with an expert or a supervising research
3 nurse -- did I get that -- for the measurements of
4 sedation?
5 What about sedation administration triggers?
6 Any thoughts on that, Pratik?
7 DR. PANDHARIPANDE: I don't think it can be
8 the lone trigger because it has to be in the
9 context of whether someone's on the ventilator, et
10 cetera. I would say greater than a RASS plus 2, or
11 RASS plus 2 above, one might consider in the
12 context of other things going on. It comes back to
13 what is our indication for sedation.
14 Just talking to what Ingrid pointed out, in
15 the morning, the discussion on light was the deep
16 sedation for the PADIS guidelines. It was in the
17 context of those who have indications for sedation.
18 Every patient doesn't need to be lightly sedated
19 because there are many patients who don't need to
20 be. But in the context of the group that has an
21 indication and whether that indication is
22 ventilator patient dyssynchrony or that indication

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1 is perhaps dangerous agitation while on the
2 endotracheal tube and with devices, I think that's
3 where the discussion needs to be focused. So you
4 could have some thresholds but in the context of
5 other parts as well, not individually one thing.
6 DR. SKROBIK: So that's perhaps a good segue
7 into the next part.
8 DR. WARD: Just a quick question. Are we
9 sort of agreeing how best to base the level of
10 sedation is RASS?
11 DR. SKROBIK: No. I think we're saying that
12 whatever the measurement is, -- this is a personal
13 thought. I think the Ramsay and the Glasgow don't
14 necessarily belong here, but using a validated
15 scale, I don't think it matters the one that you
16 use. The problem is with the metric with the
17 bedside. With a lot of the comments I've written
18 down, it's all of the caveats about how to improve
19 that methodologically and make sure it's consistent
20 within a trial so that it improves the trial's
21 quality.
22 Yahya?

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1 DR. SHEHABI: What about the frequency of
2 the measurements?
3 DR. SKROBIK: Ah, great point. Thoughts?
4 DR. SHEHABI: I think that's really
5 important because the more frequent it's done, the
6 more comfortable the bedside nurse becomes with
7 using the tool. In terms of within a context of a
8 trial, there has to be a research support staff who
9 checks that on a daily basis that people are doing
10 what they're supposed to do. And the more
11 frequently you do it, the more it reflects the time
12 deeply sedated or lightly sedated.
13 DR. SKROBIK: In your units, is it done
14 every shift, every 4 hours, every hour? How does
15 it work? And do you have thoughts on whether there
16 should be a standard?
17 DR. SHEHABI: We've mandated every 4 hours
18 on this part, so we picked up the 4-hour records,
19 but most units move to an hourly RASS. So it
20 became on their flow chart, they do a RASS with the
21 blood pressure and heart rate and urine output on
22 every patient.

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1 DR. RIKER: Both within our unit and as part
2 of SEDCOM, it was every 4 hours but before and 15
3 minutes after any change in dose. So if patient
4 gets restless, or has pain, or is agitated, you'd
5 document before you give the drug, then you give
6 the drug, then you document a response to that, or
7 if you change the infusion rate if it's a
8 continuous infusion medication.
9 DR. SKROBIK: What about the segue to the
10 next part, which is this patient and the family
11 perspective?
12 DR. WARD: I want to switch back a little
13 bit more on how best to measure sedation, because
14 there is a paper out there that did psychometric
15 comparison on sedation assessments. In fact, I
16 think your name is on that paper, I believe. And
17 it said that both --
18 DR. RIKER: It's a Robinson paper?
19 DR. WARD: RASS had a --
20 DR. SKROBIK: Can I just say it was
21 Richard's fault, okay?
22 (Laughter.)

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1 DR. WARD: RASS had very good and the
2 sedation agitation scale was very good. I didn't
3 put all of them down here.
4 DR. SKROBIK: But there's other data
5 suggesting that the Ramsay is not and that the
6 Glasgow is not.
7 DR. WARD: Well, Ramsay was not. Ramsay was
8 only medium.
9 DR. SKROBIK: That's it. So it's not just
10 our work, there are others.
11 DR. WARD: Yes. Would this group
12 recommend -- one of the things we did in the other
13 sector is we said not necessarily have to use it,
14 but we did recommend using the OAAS as a major for
15 procedural sedation, having reviewed all the other
16 sedation scales, including some of these, not many
17 of them, because there is a difference between
18 procedural sedation measurement and ICU sedation.
19 So is this group going to say that the RASS
20 is the one we recommend?
21 DR. SKROBIK: This is what we said in the
22 guidelines, right? So we recommended in the

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1 guidelines using a validated scale, and we
2 recommended the RASS and the SAS because we had in
3 the past. But we also didn't want to preclude
4 somebody coming up with a new scale that you then
5 couldn't use for whatever, direct comparison, if it
6 had been subsequently validated.
7 DR. WARD: There's a difference between the
8 clinical guidelines that you are promulgating and a
9 paper coming out of this group, which will serve as
10 a resource for people designing clinical trials for
11 maybe a new molecular entity or some other
12 combination. And I would think, and what I'm
13 hearing, is that the recommendation would be the
14 RASS.
15 DR. SKROBIK: Tim, do you have a comment?
16 DR. GIRARD: This is Tim Girard. I'm not
17 sure we can justify there being a difference
18 between the clinical recommendation and what's done
19 in the research study precisely because of the
20 approach that Rich just described, which I think is
21 the right approach, which is if the drug is
22 titrated, then the sedation level prior to

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1 titration and after should be documented.
2 Well, who's going to do that at 3AM? Is
3 anybody here proposing that we do large clinical
4 trials where research staff are at the bedside 24
5 hours a day? I cannot imagine that we would be
6 able to do that. So if that's not possible -- and
7 I welcome anyone to tell us that it is -- then the
8 alternative is to do what has been recommended in a
9 clinical setting.
10 DR. SKROBIK: So I think we're recommending
11 a middle path for the purpose of trials because of
12 the variability and the unreliability, variability
13 within institutions and between institutions, and
14 the unreliability of the patient record alone.
15 What we're suggesting -- I think what I heard -- is
16 that in a trial context, the reliability of the
17 sedation measurement be fostered and the
18 inter-rater reliability documented by the research
19 cheerleader team, regardless of the format, but for
20 the validation of the content if the results that
21 you're getting --
22 DR. GIRARD: I agree with that, but it can

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1 only be done if the clinical nurse --
2 DR. SKROBIK: And your point --
3 DR. GIRARD: is using the tool that's
4 already been validated in the clinical setting.
5 DR. SKROBIK: So I think that when you do
6 research studies -- my personal belief is that when
7 you do studies across multiple sites, you actually
8 disseminate knowledge on how to do clinical
9 practice in a way that isn't incorporated in the QA
10 initiatives.
11 So I think there's a benefit to that, but I
12 also think there's a practical dimension of not
13 being able to rely on just the -- and I agree with
14 you that it should only be validated scales, except
15 let's say it's the RASS or the SAS, then there's a
16 new scale that comes out in two years and there's
17 no guideline, I wouldn't want it to be limited by
18 that. That was my only thought.
19 Rich, you were going to say something.
20 DR. RIKER: I was just going to say the
21 other thing is we heard yesterday about qualifying
22 outcome measures or variables, and I don't think

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1 either SAS or RASS right now are qualified by the
2 FDA, so that may be another thing for us to kind of
3 consider. That may be an improvement.
4 DR. SKROBIK: One of the points that was
5 raised yesterday is that the electronic medical
6 record, which is a device, is not, right? The FDA
7 doesn't approve the medical records, does it?
8 DR. SPIES: It depends. It depends. If you
9 have open source and it's integrated, it's
10 accepted, I think.
11 DR. SKROBIK: No, no. So they don't
12 validate the -- as a technology, electronic medical
13 records are not part of what the FDA looks at,
14 right?
15 DR. SPIES: I think we had a study where we
16 could.
17 DR. ROCA: This is Rico Roca. I'm afraid I
18 can't answer that because I think that what you're
19 describing would probably be in the Center for
20 Devices, and I'm not sure where their purview is.
21 So I don't know whether electronic records would be
22 one of the things that they would look at.

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1 DR. WARD: I guess a question, but Rich
2 brought up, no, none of the sedation scales are
3 part of the validating. Is that something that
4 would be worthwhile for the ICU community to do,
5 would be to get -- and it's not a simple
6 process -- it through the FDA.
7 Bob, you've got some experience with pain
8 scales.
9 DR. DWORKIN: ACTTION is, at one point or
10 another, in the process of qualifying for different
11 novel measures, a new measure of pain intensity for
12 pain clinical trials, a measure based on
13 accelerometry of physical activity also for pain
14 trials, and then potentially a measure of
15 parasthesias and dysesthesias for peripheral
16 neuropathy and a measure of craving for addiction
17 clinical trials.
18 So we've got some experience doing this. I
19 guess the thing to say about it is it's a
20 substantial commitment and it doesn't happen
21 overnight. The FDA sets a rigorous bar for the
22 qualification of novel clinical outcome

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1 assessments. But sitting here for the last day and
2 a half and listening, I think it would be a
3 fascinating enterprise to develop and qualify a
4 sedation measure, challenging but fascinating. But
5 it is a substantial commitment, and you need
6 someone who's going to spearhead the effort and
7 devote considerable time to it.
8 DR. SKROBIK: John?
9 DR. DEVLIN: Just really quick, SCCM through
10 its ICU Liberation effort is finalizing working
11 with Epic and [indiscernible] and some of the
12 things to put all the metrics in for ADAF, which of
13 course is delirium scores, pain scores, and
14 sedation scores. So it's not answering the
15 question, but there is a lot of work trying to do
16 this, but I don't know if that's for a research
17 setting.
18 DR. SKROBIK: In my nominal reluctance,
19 other than taking off names on the list that are
20 there now, that are known to not be validated and
21 has to do with things like the evolving delirium
22 metrics, for instance, where people are starting to

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1 measure delirium not just with a tool that's a
2 screening tool, but with a severity 7-item score,
3 that I think has a lot of promise.
4 So I think if you say validated, then based
5 on the guidelines, I think that that would be
6 sufficient, but I'm a little bit biased towards the
7 work that we did in the guidelines context.
8 I'd like to take this opportunity to move
9 us onto the next topic because I don't
10 have -- certainly I can't pretend to even dream of
11 having Avery's speed, but I would like to get
12 through some of the bullet points.
13 Do you think that there are family and
14 patient dimensions to sedation administration?
15 I'll kick it off by saying I have been in the
16 clinical context of the patient's fine as far as
17 I'm, and it's the family member that's getting
18 agitated about that patient moving. Then of course
19 there's the prospective of communication while
20 you're being sedated that Ingrid mentioned, that
21 Pam has spoken of, and I think it's huge, and I
22 think it may be related to outcomes, which is what

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1 we'll be talking about in the next panel, but I
2 don't know how to capture that, so I welcome your
3 thoughts on both of those points.
4 When I said sometimes families get agitated
5 about the patient not being sedated enough, I saw a
6 few heads nod in the room.
7 DR. FLOOD: Pamela Flood. Well, I think the
8 patient's viewpoint, if you can communicate with
9 them, has to be primary. And I haven't heard
10 anybody say anything about asking the patient when
11 they appear agitated. If you can communicate with
12 them, if they're responsive, if they want more
13 sedation, saying to them, "You look uncomfortable.
14 Would you like something to help you relax?" that's
15 something we do with the patient very commonly. In
16 terms of the family member, if the patient can
17 communicate, then of course their view is primary.
18 If they can't communicate, then certainly the
19 family's opinion should be taken into account.
20 DR. SKROBIK: Other thoughts? Leanne?
21 DR. AITKEN: I just thought I'd mention
22 there was a priority setting exercise that was done

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1 with patients, family members, and clinicians in
2 the UK about four or five years ago, and I just
3 pulled up the results, and the second highest
4 ranked item for both patients and family members
5 and clinicians was how can we enhance patient
6 comfort during intensive care, i.e., minimize pain,
7 discomfort, agitation, and anxiety, and does this
8 improve patient outcome?
9 DR. SKROBIK: I know it's an important
10 topic, but in the context of studies, what I'm
11 hearing is that addressing whether the patient has
12 preference for lighter or deeper sedation may be
13 something that we might consider a metric to
14 request. So if you have -- let's see, I have
15 patients who are at minus 3. Is that because those
16 patients said to the nurse, "Yeah, bring it on.
17 Give me another bolus," and is that a justified
18 comment?
19 Lisa and Pratik have thoughts.
20 DR. BURRY: Lisa here. I just wonder if
21 that will influence consent for your trial, that
22 families and patients may have a particular desire.

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1 Some will want to be more sedated and not know
2 what's going on, and that will influence consent
3 into your trial. I just wanted to put that out
4 there.
5 DR. SKROBIK: I'm sorry. I have blonde
6 hair. Can you explain why?
7 DR. BURRY: If a family member wants their
8 patient to be awake -- I'm just thinking back to
9 when we originally enrolled for SLEEP [ph] --
10 DR. SKROBIK: For SLEEP, yes.
11 DR. BURRY: -- it was a struggle because
12 patients and families did not want to be awakened,
13 and that you are going to turn off my analgesia and
14 sedation and hurt my mother, or so on. And if I'm
15 in an awakened state, am I going to suffer and have
16 symptoms during that period? I think the issue of
17 light versus deep will have a lot of family and
18 contextual and culture issues that will influence
19 enrollment into your study. I just wanted to put
20 that out there.
21 DR. SKROBIK: I've never asked family
22 members whether they wanted their family member

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1 deeply sedated or not because I think that's a
2 reflection of their own discomfort, the family's
3 discomfort. But ever since we had our patient
4 representatives on our panel, I've asked patients
5 because I who have never wanted to nap in my life,
6 was astonished to discover that somebody
7 would want to be knocked out the way Avery was
8 suggesting that some people might prefer to, which
9 is inconceivable to me. And in my limited
10 observation over the last three or four years, it's
11 about 50/50 in the patient preferences that are
12 stated.
13 I don't know whether that should be in
14 incorporated because we're here for a
15 methodological recommendation. Should that be
16 included in what people describe in trial content
17 when it's adjusted to sedation? Is it ethical to
18 not ask the patient whether they would prefer to be
19 more -- or do you impose it on them because you
20 say, you know it's bad for you, so I'm going to
21 keep you awake.
22 Claudia and Tim have comments.

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1 DR. BALAS: If you have an intervention
2 that's known to cause harm, how ethical is it to
3 suggest or give the possibility that you're going
4 to give that intervention? To say the
5 patient -- would you do it with a catheter?
6 DR. SKROBIK: The huge majority of people
7 who administer sedatives do it with avuncular
8 intent. They believe they are providing relief.
9 They believe they're helping asynchrony.
10 Tim?
11 DR. GIRARD: Tim Girard. At the risk of
12 being provocative --
13 DR. SKROBIK: Let yourself go, Tim.
14 DR. GIRARD: -- we would not ask, unless it
15 was a family member, which is a unique
16 circumstance. In most cases, we would not ask the
17 family member, where do you want the tidal volume?
18 It looks like the patient -- or the patient for
19 that matter; we wouldn't ask them, "It looks like
20 you're feeling short of breath. Would you like for
21 me to alter your tidal volume?"
22 I understand that, yes, sedatives are

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1 treating symptoms, but they have other effects, and
2 that's very well established. So why is it that we
3 sedation as being just a treatment for symptoms
4 based on patient preferences rather than medical
5 treatment that has numerous potential effects?
6 So yes, we want treatment preferences to
7 guide therapy, but it's not the only consideration.
8 I feel like the conversation is going down this
9 path where we imply that it is the only
10 consideration. We go up to the room. We ask the
11 family do they want to be sedated or not, and then
12 we do that. I'm confused by that rationale.
13 DR. BURRY: That's not what I meant to
14 imply.
15 DR. GIRARD: And I wasn't speaking to what
16 you said, but there have been multiple other
17 comments --
18 DR. SKROBIK: So Tim, when I talk about
19 patient preferences, I think in my mind what that
20 means is either choosing to not sedate them at all
21 and keeping them at zero, and maybe horrors between
22 zero and plus 1, or leaving them at minus 1. So

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1 this is not a broad range, and I think that
2 Ingrid's point, which was the descriptors of the
3 patients who dislike light sedation because it
4 makes them lose their sense of agency, is a
5 provocative thought.
6 DR. GIRARD: And my comments were in
7 response to what Lisa described, where in a
8 clinical trial, the family members were saying we
9 want this and we want that.
10 DR. SKROBIK: No. And I've experienced the
11 same thing, and I've sweetly smiled. I agree with
12 you on that.
13 DR. BURRY: I think I should clarify, it was
14 the process of trying to get consent, not what they
15 wanted in the trial. But trying to get them to
16 consent to the trial, patients may have had
17 preferences. I don't want to -- "This sounds
18 great, Lisa, but I don't want to be randomized to
19 the arm that's going to have the interaction
20 because I don't want to be awake."
21 DR. SKROBIK: I don't want to suffer.
22 DR. BURRY: So I think it's the getting into

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1 the trial.
2 DR. SKROBIK: And I think the consent issue
3 is a separate, distinct part. We had this very
4 similar challenge with the dex trial when the
5 patient's families would say why are you going to
6 be giving a sleep drug when this patient's already
7 sedated? Like what's the point?
8 DR. BURRY: And to go back to Claudia's
9 point, once the patient was in the study, it
10 required tremendous education of not only the
11 bedside nurse, but actually the family. Now, we're
12 in the trial, and this is what's going to happen,
13 and if we are to do an awake, this is the level of
14 sedation in the trial. But we had to repeatedly
15 explain ourselves over and over as the shift
16 changed and the family members fluxed in and out of
17 the room, and it did require a lot of energy.
18 DR. SKROBIK: So there was pressure.
19 DR. BURRY: Tremendous pressure where I felt
20 like I needed a Tefler [sic] vest at times because
21 we were doing what people thought was unethical at
22 that time, even though it had already been

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1 published by JP.
2 DR. SKROBIK: Claudia?
3 DR. SPIES: I think that's very good what
4 was said. The point is I think it's very important
5 that we consider the patient's wishes, but I think
6 we have to inform the patients and the relatives as
7 structured. I think that's not what we do. We say
8 something, but that's nothing that comes up to the
9 mind of the relatives because they feel helpless,
10 and they don't listen to us so much.
11 So I think we need a structured element
12 where people can take that home and see fact boxes
13 or something like that, where they exactly know why
14 we do that. I agree with Pam's point that I think
15 at some point, when patients are agitated and you
16 structure the family to according what to do with
17 agitated patients, they can help the patients, and
18 then you don't need any drug.
19 I think at some point we should consider in
20 all of the studies that we should first go to
21 nonpharmacological, and then if that's not working,
22 then the next step should be to use a sedative. I

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1 think that's important because we don't -- well, to
2 my impression, I think if we don't learn and
3 educate our staff how to do nonpharmacological
4 intervention, all our drugs are senseless because
5 they are overdosed, and they are usually not doing
6 what they should do.
7 DR. SKROBIK: JP and then Pam?
8 DR. KRESS: I think what you're basically
9 outlining are two extremes. One of them is sort of
10 a paternalistic approach, which says I know better
11 than you do, so please just do as I say. I'm the
12 care provider and you aren't. And the other
13 extreme is sort of equal partnership where the
14 patient or the family gets equal say. Probably
15 either of those extremes is suboptimal.
16 We were talking, before when we were writing
17 the guidelines, about the patient's input. It's
18 certainly important, but I think it's important for
19 us to realize -- and I think Michele's touched on
20 this a little bit, the patient isn't as educated as
21 the care provider. That isn't meant to be a
22 derogatory statement, but it makes it really

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1 tricky.
2 The Kevlar vest experience, yeah. It's
3 just, because you walk into the arena, and I think
4 if you just simply say to the patient or the
5 family, "Here are the options. We'll do whatever
6 you think is best," that's foolish. On the other
7 hand, we walk in and say, "You do as I say, and you
8 don't have any say."
9 So I think there's an art to this, and the
10 consent process for these studies is often very
11 difficult, and it's very variable from place to
12 place, and probably country to country, too, just
13 because of social expectations and whatnot. I
14 think it's fascinating, but it makes these studies
15 tough to do.
16 DR. SKROBIK: I just want to ask one last
17 question before we move onto the next topic, and
18 I'll let you speak, Claudia. It won't be long. It
19 was Pratik who was speaking a little earlier about
20 using capacity to communicate as a metric for
21 sedation level that speaks to the patient family
22 perspective.

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1 I remember Pam mentioning how important it
2 was to be able to merge and make contact and how
3 crucial that was to a sense of wellbeing. This is
4 something that I've heard over and over from
5 various patients. I think maybe Ingrid could speak
6 to that. Would it be useful to have a metric in
7 future studies, particularly with the goal of
8 saying how are you going to measure outcomes like
9 PTSD or psychological fallout?
10 If the issue was that you couldn't make
11 contact when you were in the ICU and the family
12 member was lost, is there any interest in that
13 ability to make contact a metric? Does anybody
14 think that's a -- Ingrid?
15 DR. EGEROD: Yes. I think what we need is
16 more common sense in the situation because there
17 are so many factors. One important factor, of
18 course, is communication, and the other one is pain
19 medication. If they have been covered for their
20 pain and they are communicating, I think you can
21 get far. Also, some patients have been in ICU
22 before and might have an opinion from an earlier

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1 visit.
2 I'm not sure the family is always so
3 reliable because they might be trying to satisfy
4 their own concerns, but I think that common
5 sense -- I don't know where you put it in an
6 algorithm, but it needs to be in there somewhere.
7 DR. SKROBIK: I've got Claudia, Yahya, and
8 Denham, and I'll start with Claudia because you've
9 been waiting for the longest.
10 DR. SPIES: There are structured interviews
11 that can be done of both the patient and the family
12 in a chat session. The point is that it's not
13 paternalistic or you give the whole autonomy to the
14 patient and the relatives. If you can measure how
15 far patients want to be involved, that's a
16 structured interview. That's a short, structured
17 scale.
18 The second point is the patients and the
19 relatives can assess how you did that. You say
20 there's a decision to make. That's something you
21 need to say, and then the relatives and the patient
22 can say, "I came to that famous place. I want to

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1 be respected, but you make that decision." Then
2 that's fine, but you said to the patient that this
3 is a decision to be made.
4 The other thing is that patients can say,
5 okay, I want to take all responsibility; I decide.
6 And I think we don't measure that structured. We
7 do that now with a shared decision process in our
8 departments, and it's better to involve patients
9 and relatives. I think that's easily
10 implementable. However, it depends that the
11 patient and the family wants to be informed;
12 whatever they decide, they want to be informed.
13 That's the major issue.
14 DR. SKROBIK: Perfect. Thank you.
15 Pam?
16 DR. FLOOD: Well, again, clinically you're
17 getting back to the art, but in terms of a clinical
18 trial, how do you measure the art? It might be
19 something as simple as how integrated -- how much
20 is the patient and how much is the family able to
21 be usefully involved in their care because as a
22 clinician, if the patient says, "Get the tube out,

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1 get the tube out, get the tube out," but they have
2 no ventilation, then of course you're not going to
3 pull the tube out. If the family says the same
4 thing, of course you're not going to.
5 But it may be valuable to note whether or
6 not the patient and the family are able to
7 contribute to the care because there's so much
8 variability. If they don't even speak the language
9 and understand what you're talking about, and you
10 can barely communicate with them, they probably
11 can't add much.
12 DR. SKROBIK: Yahya, you were going to say
13 something?
14 DR. SHEHABI: I just wanted to make a
15 comment. Richard at dinner last night asked me
16 would I have changed the outcomes in a new SPICE
17 study. I think one of the things that I would
18 definitely change is to make the RASS target from
19 minus to plus 1, I would make it minus 1 to zero.
20 I think we found there's a big difference
21 between minus 2 and minus 1 in terms of patient
22 communication and also in terms of family

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1 interaction. We found that the nurse at the
2 bedside, once we said the patient is eligible,
3 we're going to go and randomize, they would say,
4 "Please, make him in this arm because this family
5 wants to communicate with the patient."
6 So I think there is a bit of that happening
7 between the bedside nurse and the family and the
8 patient. They know which one would like to be a
9 bit more zontum [ph] [indiscernible] and which one
10 likes to be a bit more awake, and tend to the
11 family, interact, and so forth. So I think there's
12 definitely a difference between that minus 2 level
13 and minus 1 level. I can communicate with someone
14 when it's minus 1 effectively, and so does the
15 family, but I cannot do that effectively with
16 someone at minus 2.
17 DR. SKROBIK: I think there's little time to
18 cover a topic as huge sleep in our discussion. I
19 think that the sleep group the guidelines was
20 probably one of our most novel and informative
21 panels because it's such a -- we assume that
22 sedatives are good for sleep. They taught us that

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1 not only are they bad for sleep, but we ended up
2 recommending that propofol not be used for sleep.
3 So begging the question of what you do with
4 your patient on propofol, what are you supposed to
5 do; turn it off at night? So I think that
6 there's -- but I think methodologically also, sleep
7 plays into agitation, recovery, and all of those
8 different elements of sedation trial outcomes, and
9 I would welcome the thoughts on how that could or
10 should be integrated.
11 Should sleep metrics be included in a
12 simplistic way? Obviously, you're not going to be
13 doing PSGs in every sedation trial, but should a
14 steep metric being incorporated in trials that
15 compare sedative molecules, for instance?
16 Dr. Maze?
17 DR. MAZE: Before that question is
18 addressed, can I just make the point that not only
19 is sleep important in delirium and other
20 consequences, but it also is very important for
21 inflammation, and all these patients how inflamed
22 in one way or another. I would say anything that

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1 you can do to improve sleep in the ICU, you should
2 try and do.
3 DR. SKROBIK: My thought on the topic was a
4 pragmatic one. I think that sleep is much more
5 influenced by the environment than anything else,
6 and it's a multimodal sort of thing. So the noise,
7 the combination -- and we've had these discussions
8 around the guideline panels where it's a question
9 of how much light, how much noise, how much
10 anxiety, this amalgam of things that contribute to
11 the sleeplessness that we know occur in ICU
12 patients.
13 In sedation trials, then, should we be
14 either, A, capturing quality of the self-reported
15 sleep in a simple metric to add that to the
16 comparator, or should we be looking at
17 environmental differences? When I listened to
18 Margaret Prezannie [ph] describe her ICU, if I were
19 ever going to go sleep in an ICU, which I wouldn't
20 want to, that's the one I would want to go to
21 because they actually dim the lights, turn off the
22 sounds, or in southern Brazil, where they give you

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1 a warm massage back rub, and give you warm milk if
2 you're not intubated
3 Thoughts on that, on that dimension of
4 sedation comparator?
5 DR. RIKER: I think as researchers and
6 clinicians, I think this is an area we want more
7 information about. But if we come back to the goal
8 of what we're trying to talk about, we're trying to
9 come up with a standard list of things that new
10 drug developers should provide, I don't know that
11 we -- I would suggest that sleep and probably
12 patient and family perspective are gaps that we
13 don't yet understand what the effect is, and
14 especially don't understand how best to measure it.
15 Ideally in the future, we would get that
16 information, but I don't think it's reasonable for
17 us to mandate that when a new dex comes down the
18 pipeline next year, that that's got to be part of
19 the data they provide because I don't think we
20 understand that yet.
21 DR. SKROBIK: So I'll try and imitate Avery
22 without much success, but would there be a panel

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1 consensus, or at least a coherent thought, that
2 these are indeed gaps that should be explored in
3 future studies? Yes, yes, yes; there's a lot of
4 head nodding.
5 DR. RIKER: But not necessarily as a
6 requirement for submission.
7 DR. SKROBIK: And that's not what I'm
8 saying. That's not what I'm saying.
9 Claudia, you were going to say something?
10 DR. SPIES: I think it's very important that
11 we consider to assess that because that's protocol
12 violation. Usually we have decibels of 60 to 80
13 during nighttime, even 100. So if you really
14 control for, you get to 40 to 60. This is even
15 high, but it's much better.
16 The second point, at least we should assess
17 noise. We should check if the alarms can go silent
18 during nighttime and can go outside so that the
19 supervision of the nurses is outside, so you have a
20 supervision room; something like the context where
21 we are living.
22 DR. SKROBIK: Are you saying that it's

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1 because it's an important confounder?
2 DR. SPIES: It's an important confounder,
3 and what we've seen also with our patients in the
4 new rooms we have -- so this is a new room, really,
5 that's giving us all these settings you require,
6 that you have better sleep, et cetera. I think
7 it's very important that we need less analgesics
8 for these patients. Analgesics are anticholinergic
9 usually because they are opiates. So it's
10 depending very much on the anticholinergic
11 activity, and this is also decreasing your sleep
12 level.
13 So there are a lot of things going on. We
14 should at least check for it.
15 DR. SKROBIK: So confounders should be
16 considered. Got it.
17 DR. SPIES: As a confounder, it's very
18 important. And in addition for the sleep
19 monitoring, I think polysomnography, it's not a
20 major issue to apply it. It's the major issue to
21 evaluate it. If they have data science people
22 using that, we can use it. But I think that's the

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1 major issue. We have to have somebody get that
2 analyzed because that's taking time.
3 Instead of polysomnography, what we are
4 using if that's not possible, we use actigraphy.
5 This is at least a measurement that's not perfect
6 but at least some idea what's going on. That's not
7 sleep, but that's at least a confounder that can be
8 measured.
9 DR. SKROBIK: I think we have some more
10 sleep thoughts.
11 DR. ABSALOM: Tony Absalom. I just wanted
12 to say it is very easy to measure the environmental
13 effects. We've done it in some studies, the
14 environmental, the lights and sound levels and so
15 on. I think it's less clear how much of an effect
16 that has. We've done some studies with volunteers
17 at sleeping at home, in an empty intensive care,
18 and in a busy intensive care, and actually they
19 slept quite well, although it was very noisy.
20 These were things that I think there's a lot
21 of assumptions about the effects of the
22 environment, but --

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1 DR. SKROBIK: There's some conflictual data,
2 too, right?
3 DR. ABSALOM: Sorry?
4 DR. SKROBIK: Some conflictual data, too.
5 DR. ABSALOM: That's a knowledge gap. In
6 terms of polysomnography, we've also done stuff for
7 that, and it's not that difficult to do. There's a
8 poor correlation with self-reported sleep in the
9 work that we've done. There's a Somnolyzer.
10 There's a product out there -- I don't know what
11 Claudia thinks about it -- that does the assessment
12 automatically, so it's not as difficult as a
13 neurophysiologist assessment of 24 hours.
14 DR. SKROBIK: Thank you for those points.
15 I think the sleep state, changing the
16 requirement for sedation, and the confounders for
17 the need for sedation like noise or other elements,
18 are things to consider but not -- my understanding
19 is it shouldn't be mandated as part of study design
20 if we're going to be looking at sedation trials.
21 DR. WARD: I wanted to be careful with the
22 use of the word "mandated."

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1 DR. SKROBIK: You're right.
2 DR. WARD: I think we're trying to come up
3 with a resource --
4 DR. SKROBIK: Suggested.
5 DR. WARD: -- to help people design trials.
6 DR. SKROBIK: Got it. Sorry about that. I
7 didn't mean it in a directive way.
8 I think we've gone on a fair bit about the
9 efficacy of both sedation and analgesia at some
10 length until now and have highlighted a number of
11 challenges in these two areas. So I'm not going to
12 go over it in more detail unless anyone wants to go
13 back to the topic. Yes? No? The topic of
14 analgesia and its metrics.
15 DR. DWORKIN: So maybe I missed it, but I
16 haven't heard an answer to Denham's question, I
17 think, that he began the morning with, is what
18 would be our recommendation, if someone was going
19 to be starting a clinical trial tomorrow, of a
20 novel approach to ICU sedation for a primary
21 efficacy endpoint? Or did I miss that?
22 (Laughter.)

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1 DR. SKROBIK: With regard to the pain
2 dimension, you mean?
3 DR. SEDATION: No, no, no. Sedation, the
4 sedation trial; what's our primary --
5 DR. WARD: I think what I heard outside of
6 Denham's presentation were a lot of answers that
7 said, well, it depends what you're doing because
8 there's a huge variability in the amount of trial
9 questions that people would propose. If you're
10 looking at let's say a psychological outcome focus
11 trial versus a mechanical ventilation duration
12 trial, a lot of points were made in a lot of -- did
13 I answer that?
14 DR. DWORKIN: Well, maybe I'm not
15 understanding; this is not my area. But it goes
16 back to the quip about new dex. So I've got new
17 dex, and I would like to do -- I've done some
18 phase 1 and phase 2 studies. I have a sense of the
19 dose, blah, blah, and now I want to do a
20 confirmatory phase 3 trial, establishing that new
21 dex has efficacy for sedation in the adult ICU.
22 What's my primary endpoint?

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1 Now, it could be I went to the men's room,
2 and I missed it, but I haven't heard one yet.
3 DR. SKROBIK: Tim and JP both have comments.
4 DR. GIRARD: I think a number of
5 conversations have occurred during the breaks and
6 meals, wherein it was suggested that you could have
7 a composite outcome that tracks the number of days
8 that a patient was alert, pain free, calm,
9 communicative, or cooperative, whatever sort
10 of -- it sounds complex, but I think it actually
11 just reflects what Yahya was saying, which is our
12 goal for the patients, and I think their goal as
13 well, is to get back to the state that they were in
14 prior to becoming acutely ill, and that would
15 include being alert and calm and pain free; the
16 faster, the better.
17 DR. SKROBIK: JP?
18 DR. KRESS: I'm just going to expand on that
19 a little bit. We didn't really hear much after
20 Dr. Tung, and when he gave his talk, he started by
21 showing an interesting idea, and is the use of the
22 volatile inhalational drugs. I sense we have two

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1 different groups in the room here, some who have
2 anesthesia background and some who have pulmonary
3 internal medicine background. But I was curious
4 what little people -- there is some literature out
5 on this, but not much.
6 So what about that as a novel approach?
7 What do people think: And if this is taking us way
8 off on a tangent, Yoanna, just tell me to shut up.
9 DR. SKROBIK: No, no. I think that some of
10 the studies that we are familiar with have to do
11 with very early anesthetic administration in the
12 first 24 to 48 hours of critical care in the
13 context of respiratory acute or respiratory
14 illness. And when you look at the data from those
15 studies, those patients are anesthetized
16 early -- so Papazian and others have shown
17 this -- and if you look at the amount of sedation
18 they require subsequent to that acute episode, it's
19 dramatically lower than what we administer over an
20 ICU admission in first 5 days.
21 I would like to open the discussion to
22 whether people think that inhaled anesthetics

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1 should be considered part of a
2 sedation regimen --
3 DR. KRESS: At least what we know about the
4 pharmacology of these drugs, at least some of the
5 more modern ones, the pharmacology is such that
6 there seems to be no accumulation at least in
7 animal studies over prolonged periods of time. So
8 you might potentially be able to have your cake and
9 eat it too. I don't know.
10 DR. COURSIN: Well, you have 3 agents, and
11 part of the historical aspect has been how do you
12 deliver them. Historically, if anybody remembers
13 the old 900 Servo series of ventilators made by
14 Siemens, they had a vaporizer built into them.
15 They had extremely high flow rates. They zipped
16 through volatile agents very quickly.
17 You're not really providing anesthesia with
18 these agents when you're using them in the ICU.
19 You're using them to provide sedation. You're
20 using low max somewhere in the neighborhood of 0.3
21 to 0.4 percent of a MAC. Patients tend to be calm.
22 The big limitation with them is going to be

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1 hemodynamic impact. At the low doses, you're not
2 likely to see them.
3 As far as the accumulation, one of the three
4 agents that are available in the U.S. is not
5 biometabolized at all, and that's desflurane. So
6 accumulation with desflurane would be a zero
7 problem. There are some issues with gas flow with
8 it, and there are some issues with it being a green
9 gas and creating a fair bit of carbon dioxide in
10 metabolic parameters. But if you just don't have
11 to take off a jet at our local Air Force base, we
12 probably could overcome that.
13 Sevo and isoflurane, all three of them are
14 good bronchodilators, which can be quite
15 advantageous. They can be extremely useful agents
16 at low doses in status asthmaticus. They can also
17 be extremely beneficial agents in occasional status
18 epilepticus.
19 The current kind -- AnaConDa I believe is
20 the name of the little vaporizer that's out on the
21 market. It would be a paradigm shift, and people
22 would be concerned regarding scavenging and whatnot

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1 with modern technology. I don't think that's a big
2 issue. I'm not aware of anybody who's routinely
3 trying to use it in the states.
4 DR. SKROBIK: I have Steve and Claudia.
5 DR. SHAFER: I'm an anesthesiologist, not an
6 intensivist, but these drugs are really associated
7 with substantial levels of agitation at low levels.
8 It's the stage 2 anesthesia. We see this on the
9 way down; we see this on the way back up. They do
10 accumulate substantially. If you run an anesthetic
11 for 24 hours to reattach a digit, you can be there
12 a very long period of time with any of the drugs
13 that we use unless you're running it right at a
14 level on the threshold between awake and asleep,
15 but there is substantial accumulation with these
16 drugs.
17 I'd be concerned about the agitation, and I
18 just would be curious whether or not this is seen.
19 You don't see agitation as people are going to
20 sleep with propofol or as people are going to sleep
21 with inhaled anesthetics.
22 DR. WARD: I'd like to just bring us back to

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1 the question that was asked. So here's the
2 discussion, but you can design it to look at an
3 anesthetic versus a drug, but that's really not
4 what we're trying to discuss here.
5 DR. SKROBIK: So whether we should consider
6 it isn't part of what you want to --
7 DR. WARD: It's just another drug. I mean,
8 it's another new dex. What clinical trial should
9 we use?
10 DR. SKROBIK: I am shocked by you saying
11 that, so I think it's important to --
12 DR. WARD: But I want to get back to Bob's
13 question. Again, is time at a RASS of zero or
14 minus 1 the effective outcome to measure
15 effectiveness?
16 DR. BALAS: Can I get back to Tim's point
17 and ask Dr. Sessler a question about the composite
18 outcomes? I think what you propose is very
19 interesting. Is anybody aware of a clinical trial
20 that combined the symptoms of pain, anxiety, level
21 of arousal and delirium together?
22 My question for you is you mentioned that

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1 they can't be too common of occurrence, so I
2 assumed that that would probably be a problem. But
3 if the goal is not to have a common occurrence, can
4 you do such a composite outcome?
5 DR. SESSLER: Sure. It's not a matter of
6 being common. It's that each component of the
7 composite has to have a relatively similar
8 incidence. So that seems like a reasonable
9 composite to me. You have to dichotomize these
10 inherently continuous outcomes, but that's a
11 reasonable thing to do.
12 DR. BALAS: So it has to be dichotomous.
13 DR. SESSLER: Let's say RASS should be in
14 this range --
15 DR. BALAS: Zero to minus 1.
16 DR. SESSLER: -- to make it dichotomous.
17 It's either in it or not. We actually had some
18 discussion last night at dinner about this. We
19 were saying that you could use the days that met a
20 composite of delirium, arousability, and pain, and
21 then you have a continuous or ordinal outcome
22 that's based on a dichotomous --

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1 DR. BALAS: Like a symptom burden index.
2 DR. SESSLER: Right.
3 DR. BALAS: Well, not every symptom, but the
4 common symptoms.
5 (Crosstalk.)
6 DR. SKROBIK: So delirium and coma is one
7 such example, that combination.
8 DR. SESSLER: It's actually a pretty
9 attractive outcome.
10 DR. RIKER: I think it's a great discussion,
11 but my concern with this is as you go to the other
12 extreme as far as incidence goes, you run into the
13 same problem as if you have very rare outcomes.
14 Cardiologists use this all the time because the
15 mortality with MI is 1 or 2 percent. So to avoid
16 having to enroll 20,000 people, they put the
17 composite together and then they can get by with
18 400 patients or whatever.
19 If we have an incidence of our composite
20 outcome that includes coma, delirium, and pain,
21 aren't we going to be having an incidence of
22 90 percent, and then we're fighting the other

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1 problem?
2 (Crosstalk.)
3 DR. GIRARD: Maybe earlier in the ICU stay,
4 but that's I why chose days rather than --
5 DR. BALAS: Did I hear incorrectly? Did you
6 say it's that the symptoms have to have similar
7 occurrence as opposed to being rare? Did I
8 misinterpret that?
9 DR. SESSLER: That's exactly correct.
10 DR. BALAS: So it doesn't really matter how
11 common they are as much as it means --
12 DR. SKROBIK: They have to all happen in the
13 same frequency.
14 DR. SESSLER: That's right. And the
15 incidence might be 90 percent for the first 2 days,
16 but if you look over 30 days, you see the number of
17 patients who were in a good stage for most of the
18 month, or their ICU stay over some other relevant
19 period.
20 DR. SKROBIK: Leanne?
21 DR. AITKEN: So if we used something like
22 that, and if on a day, a patient had one pain score

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1 that was above whatever your threshold was, and the
2 other 23 hours of the day, they were below it, does
3 that reflect what we want? Because 1 hour of pain
4 in 23 hours might not be -- it's not ideal, but it
5 may not be the thing that we're really wanting to
6 represent in that outcome.
7 DR. SESSLER: You can set it up any way you
8 want. It could be the average pain score, not the
9 highest pain score.
10 DR. SKROBIK: So this is the subject or
11 ongoing debate. We have 7 minutes left. I'm not
12 sure we're going to answer your question. It's not
13 that I'm not considering it, but I think one of the
14 items that is important to consider is the safety
15 of drugs, the pharmacology, the drug-drug
16 interactions, all of the points that we perhaps
17 don't -- that are very familiar to anesthesiologists but
18 perhaps not so familiar to the remainder of the ICU
19 community.
20 I wonder whether there are some of our
21 pharmacy experts in this room, so Gilles, Lisa, and
22 John, whether they could comment on whether safety

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1 measures could be expanded beyond excessive
2 sedation and what those should be if we look at
3 safety metrics during sedative administration.
4 DR. DEVLIN: I guess one really quick
5 comment, which was already brought up is
6 anticipated safety concerns for the pharmacology of
7 the drug versus unanticipated. Dex is
8 obviously -- Dr. Maze brought that up this morning.
9 So if we see bradycardia, I guess severe
10 bradycardia where there's an intervention or we
11 have to stop the drug, I think that plays a role.
12 DR. SKROBIK: I think so, but to speak to
13 that point, the accumulation of, say, midazolam
14 over time in the 60 percent of patients that have
15 renal failure in the ICU isn't considered a safety
16 feature in some of those older trials because it
17 just wasn't on the radar necessarily.
18 Others?
19 DR. SHAFER: I should just mention that
20 propofol has a significant safety concern for
21 propofol infusion syndrome.
22 DR. SKROBIK: It's one of the reasons I

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1 disagree with Rich on that point.
2 DR. SHAFER: But having said that, there are
3 reasons to think that that's a function of the
4 formulation of propofol, so there might be actually
5 a product that was propofol in a different
6 formulation because it looks like the specific
7 lipid emulsion composition actually can turn that
8 on and off. That would be a product that was just
9 a safety play.
10 DR. RIKER: Also dose and target level of
11 sedation. So we see it in the refractory status
12 epilepticus patients where they're getting 120 mics
13 per kilo per hour as opposed to 30 in our other
14 patients.
15 DR. SKROBIK: Thoughts? Gilles? Lisa?
16 DR. BURRY: I just want to comment that I
17 think in addition to drug adverse offense, that we
18 can anticipate and we'll have to measure if it's a
19 regulated trial for reporting purposes. Other
20 safety events are rarely standardized in the
21 trials, And having gone through several systematic
22 reviews, the reporting is all over the place, Even

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1 the definition or even if they report any adverse
2 events; not drug events, adverse events.
3 DR. SKROBIK: So would you consider sedative
4 withdrawal, benzo withdrawal as such an adverse
5 event?
6 DR. BURRY: I would potentially consider
7 drug withdrawal an adverse event if it's an
8 anticipated side effect of continuous exposure of
9 that drug.
10 DR. SKROBIK: So the risk factors for adults
11 are 48 hours of administration. So do you think
12 that that should be part of what is incorporated in
13 sedation trials?
14 DR. BURRY: I don't have an answer for that
15 because I don't even know how to assess for
16 withdrawal in an adult, in an ICU. So at this
17 point, there's no tool to even --
18 DR. SKROBIK: Or gaps.
19 DR. BURRY: -- there are more gaps. The
20 other point I wanted to comment on is if it's a
21 regulated trial and anticipating adverse side
22 effects or unanticipated side effects, having gone

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1 through and running a regulated trial for probably
2 the simplest molecule on the planet, melatonin, the
3 reporting for adverse events for new drugs or
4 off-label use is extremely difficult.
5 Deborah Cook has a great paper about
6 assessing adverse drug events in a critically ill
7 patient. We spent days battling with Health Canada
8 about the definition of adverse drug events because
9 you are often labeling something as a drug event,
10 which really has nothing to do with the drug at
11 all. And I think some of those things need to be
12 factored into regulatory trials, and reporting is
13 quite difficult
14 DR. SKROBIK: No. I've used that paper as
15 an argument.
16 DR. BURRY: We were successful with that
17 paper after many battles and advocates to move
18 forward.
19 DR. SKROBIK: The paper, for those of you
20 who don't know, is a paper that summarizes that
21 some of the things that are considered severe
22 events in fact are just standardized ICU stories,

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1 so dyspnea, hypertension, et cetera.
2 DR. ZHAO-WONG: In terms of what to report
3 on adverse events, we can always refer to the
4 International Council for Harmonization Standard.
5 They have definitions on what needs to be reported.
6 It doesn't have to be related to drug. If it
7 happens during a clinical trial, it needs to be
8 reported.
9 DR. FRASER: May I make one statement?
10 DR. SKROBIK: Yes.
11 DR. FRASER: I'd like to introduce the
12 concept of obesity and how it affects drug
13 deposition. Very often we have patients on 20
14 micrograms per kilogram per minute or propofol, and
15 that sounds like a low dose, except for if it's in
16 a 180-kilogram person, then all of a sudden the
17 absolute exposure of this drug is meaningful. So
18 any drug that is based on body weight without
19 consideration for obesity is actually missing the
20 boat.
21 DR. SKROBIK: Thank you.
22 DR. EGAN: A very good comment about that.

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1 This is something that perhaps our ICU colleagues
2 have not yet run across because it's relatively new
3 literature. Obviously whether the body weight
4 affects the disposition of the drug is a testable
5 hypothesis. This has been investigated for
6 propofol and also for remifentanyl by my lab. But
7 for propofol by a lab in the Netherlands, Tony is
8 one of the main investigators that have been,
9 involved.
10 The question now for propofol is really an
11 answered question. You now have a scientific
12 foundation in terms of adjusting the weight that
13 you would put in the pump as it relates to propofol
14 infusions. These are manuscripts by Eleveld, et
15 al. Tony is also a co-author. I think it would an
16 important thing to get into the ICU community
17 because you can avoid this problem of overdosing
18 these patients by putting in an adjusted weight.
19 DR. FRASER: Or consideration there for the
20 context-specific half-lives of these drugs or is
21 that just a short-term issue that you guys are
22 studying?

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1 DR. EGAN: Tony, do you want to comment on
2 that?
3 DR. ABSALOM: It's a complex issue, the
4 context-sensitive half-time, and the problem is
5 which weight you should use depends on the phase of
6 the infusion. In the beginning, the bolus is more
7 related to the lean mass and lays for maintenance
8 for the total mass. So it's a complex issue, and I
9 think we'd need hours or days.
10 DR. SESSLER: And it depends on the drug.
11 DR. ABSALOM: And the drug, but this is
12 propofol specific here, yes.
13 DR. SKROBIK: I think that is an issue,
14 though, that may apply to a number of other
15 sedative agents as well, the volume of
16 distribution, the amount, and time, and all of the
17 other factors. So those safety measures and those
18 safety considerations are very important to explore
19 in addition to things like extubation or excessive
20 sedation, which are the standards of care.
21 So I apologize, Dr. Ward, for not having
22 come up -- or Dr. Dworkin, for not having come up

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1 with, A, one answer, but I think what you've heard
2 is a smattering of various -- is there anybody who
3 would like to suggest one standard for sedative
4 delivery that you would consider to be clinically
5 meaningful?
6 DR. DWORKIN: How about we wait until people
7 get some food, and then do it after lunch?
8 DR. SKROBIK: Yes, which I will invite you
9 to do now. Thank you.
10 (Applause.)
11 (Whereupon, at 12:01 p.m., a lunch recess
12 was taken.)
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1 AFTERNOON SESSION
2 (1:01 p.m.)
3 DR. WARD: I will keep the trains running on
4 time here, so we will be through promptly at 3
5 o'clock. Nobody ever thanks a professor for
6 lecturing too long, so we'll make sure we'll stay
7 on time.
8 Can I have my first slide there. I do want
9 to usurp a little bit of Tim's time for the slide I
10 was planning on using in the next steps. I do want
11 to keep the conversation a little bit more about a
12 primary outcome because if we're going to have a
13 paper that's a resource for designing clinical
14 trials, and since we don't know what the primary
15 outcome is going to be, that paper is never going
16 to be accepted anywhere, and it's not going to be
17 particularly useful.
18 What's the best primary outcome? It's not
19 could we use as a primary outcome? I've got a
20 trial I'm designing today that I want to start ASAP
21 because I got new dex here, and I've got a drug
22 company that wants to fund it. What should I use

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1 as a primary outcome? Bob suggested that I lock
2 the doors and not let anybody leave.
3 My thoughts on this, going back to our
4 initial discussion from the IOM, is that treatment
5 should be effective, patient centered, and
6 efficient. Yes?
7 DR. EGEROD: I'm thinking, isn't it because
8 we haven't decided on the indication of sedation.
9 If we know why we're doing it, we should be getting
10 closer to the primary outcome.
11 DR. WARD: Okay. Well, what's the
12 indication for sedation?
13 DR. EGEROD: Well, that's one thing that we
14 haven't really discussed enough.
15 DR. COURSIN: Well, I will propose for
16 effectiveness is a RASS greater than zero could be
17 one of the indications for it. What do you need to
18 do if a patient is agitated and pulling their
19 endotracheal tube out? Is that an indication
20 for -- I don't think it's they're on mechanical
21 ventilation, therefore they need sedation is
22 necessarily going to be an indication.

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1 But let me defer that a little bit because I
2 think that's a little bit of a separate topic. If
3 we have an indication for a sedative, what's the
4 major of its effectiveness? I put a straw man up
5 there at a RASS of zero minus 1. That's what I've
6 been hearing from the group, and I've seen heads
7 shaking no, and I've seen heads shaking no.
8 I think don't want to usurp a lot of Tim's
9 time, but I think this is important. I think if we
10 want to have an outcome from this meeting that's
11 useful and publishable, effective is the first one
12 on the list. So we have to agree, if we can, on
13 what a measure of effectiveness is.
14 Steve?
15 DR. SHAFER: I assume by time, it's actually
16 a fraction, time at RASS versus time on drug.
17 DR. WARD: Area under the curve --
18 DR. SHAFER: It's got to be a ratio. It
19 can't just be time. The more longer in the ICU,
20 the more time you spend at the RASS score.
21 DR. WARD: Right.
22 DR. SHAFER: So it's fractional time at

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1 rest.
2 DR. WARD: Yes.
3 DR. AITKEN: Leanne. I don't think you can
4 have something like time at RASS because that's
5 just how well implemented was the intervention.
6 That's not how effective was the drug.
7 DR. WARD: But if I have a drug that doesn't
8 cause sedation, then it wouldn't achieve that.
9 DR. AITKEN: But you could achieve the same
10 outcome by giving 100 milligrams of the drug or
11 1 milligram of the drug. You still achieve that.
12 DR. WARD: It's not a dose-finding study.
13 That you should have been doing in a phase 1 and
14 phase 2 two trial.
15 DR. COURSIN: You seem to want to get an
16 objective, which makes a lot of sense. But my
17 sense is what we really want is much more
18 subjective. We want patients to be safe so it can
19 facilitate their care to recover or not recover.
20 Now, I don't know how you put that in a
21 graded scale that you can compare drug A to drug B,
22 but that interest is, in my mind, very directly,

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1 what's your indication, and there will be no
2 sedation.
3 DR. SKROBIK: I think also part of the
4 resistance to this answer is in having one primary
5 outcome be ranked as the best primary outcome for
6 sedative trials, whereas what I'm hearing now and I
7 think what I'm understanding is what you would like
8 is the identification of potential primary
9 outcomes, and they can be safety related. They can
10 be process related, and then that list can be made.
11 What I have heard from many members around
12 the table and earlier today is that there isn't one
13 item that all of us would agree is a good primary
14 outcome for any sedative trial. It depends what
15 you're looking for. Lisa was talking a little
16 earlier.
17 DR. WARD: Bob is coming out of his chair.
18 DR. DWORKIN: I want to clarify. If our
19 primary outcome is safety, that's fine, but that's
20 a different trial. That's a trial where the
21 primary outcome is a safety outcome. I think what
22 Denham is asking, and that says "effective," and it

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1 could say "efficacy," what is our primary efficacy
2 outcome if we're evaluating the efficacy of an
3 agent intended for ICU sedation?
4 So safety's a different question. If we're
5 doing a safety trial, it could be something totally
6 different.
7 DR. SKROBIK: Off line, and from all of our
8 patient representatives, and from qualitative work
9 that Ingrid has done and others, and Mona, the
10 answer to that is return to the best you can be. I
11 don't think it's a peri [ph] ICU metric globally,
12 if you want one global item that is the subject of
13 consensus, whereas the metric at the bedside is
14 problematic for all of the reasons that we've been
15 talking about, and everyone on that list is
16 problematic.
17 DR. DWORKIN: But maybe Yoanna and I should
18 take it outside, which is totally fine with me.
19 DR. SKROBIK: No, no, but that's important.
20 DR. DWORKIN: I think returning to the best
21 you can be from a patient perspective sounds
22 terrific, but I would challenge you have, do we

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1 have any measure of that that's even been used in a
2 single study? These measures are used in multiple
3 studies, conducted over the last 15 years, and at
4 least we know something about its performance
5 characteristics and its ability to show superiority
6 and noninferiority.

7 If you have an alternative measure that's
8 been used in a couple of trials that we should
9 consider, great but I think the important thing is
10 what -- we're not talking about developing a new
11 measure. That's a whole different conversation
12 that maybe we should have at the next SCEPTER
13 meeting. What we're talking about, and I think
14 Denham has said it clearly, is if we're starting a
15 clinical trial tomorrow of new dex and we want to
16 evaluate its efficacy, what's the best measure
17 currently available?

18 DR. SKROBIK: So let me argue back.

19 DR. DWORKIN: And then we'll take it
20 outside.

21 DR. SKROBIK: And then we'll take it
22 outside. I have heard Michele and Leanne

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1 highlight, and Tim and others, why we cannot even
2 rely on the measurement of the RASS at the bedside
3 even in an ideal context of a study. So regardless
4 of how well validated that metric is, how could you
5 possibly say, then, that should be your outcome?
6 Sorry, and that's the last thing I'll say.

7 DR. SHAFER: Two comments. One is I think
8 you're both right. As a pharmacological measure in
9 real time of is the drug working as a sedative,
10 that seems like a reasonable endpoint. Is the drug
11 actually doing what it's intended to do? But to
12 Yoanna's point, I don't think there's a value
13 statement around that. I can't put together a
14 value statement around that, that makes it worth
15 doing. I think the value statement is, is there
16 actually a benefit to the person after the fact?
17 Do they live? Do they get their life back in some
18 way? I can't put a value statement around the
19 statement that's up there.

20 I'd also like to just say that I think one
21 has to say that any study that's done is evaluating
22 the drug and the drug administration regimen at the

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1 same time, and it's very hard to separate and say
2 this drug is better or worse. It's this drug given
3 in the way that we did it in this trial.

4 DR. WARD: What's why the protocol is part
5 of -- the way you give the drug is part of the
6 protocol that you're coming up with a
7 recommendation, is this drug should be approved to
8 use in this manner.

9 DR. SHAFER: In this way, and the drug given
10 a different way may do better or worse than
11 something else.

12 DR. WARD: Yes, that's true.

13 Rich?

14 DR. RIKER: So I'm going to change my mind.
15 Denham asked me if you had a blood pressure
16 medication, how would you determine if it was an
17 effective antihypertensive? You would have to
18 monitor blood pressure and record those results.
19 Now inherent in that, if the drug caused acute
20 kidney injury in 80 percent of its subjects, that's
21 a key piece of the information we need but isn't
22 necessarily part of the efficacy assessment.

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1 I think all of us as passionate,
2 intelligent, committed ICU researchers in sedation
3 want more than time and target sedation level
4 because we understand all of these other things
5 that are so inherently challenging to us and our
6 patients. But we've got to cut down to a single
7 thing that best describes how did it work as a
8 sedative, unless we can come up with a composite.

9 DR. SKROBIK: So I agree with that point.
10 My only point is that to the -- and please forgive
11 me for what I'm about to say up front -- to the
12 very anesthesia traditional and sort of MD-dominant
13 traditional assumption that you give a drug, you
14 have an effect, and then you measure an outcome,
15 there are all of these multidisciplinary
16 participants who are telling us, uh-uh, it's
17 experienced physicians with clinical trial
18 experience behind them who are saying that's not
19 the way it works.

20 I think that if you're going to say applied,
21 yes, but applied that way and measured so that it
22 can be considered reliable, then I would accept it,

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1 because I think otherwise it negates -- it
2 simplifies what is in fact not a reflection of the
3 reality.
4 DR. WARD: Well, that's because there are
5 secondary outcomes that relate to these other
6 realities.
7 DR. SKROBIK: No. I'm not even going beyond
8 sedation. I'm describing the variability between
9 the way it's applied and variability in the way
10 it's interpreted. If you're going to say this is
11 the ideal world scenario, if you're recommending
12 something that's an ideal world scenario and the
13 real world doesn't have it 50 percent of the
14 time --
15 DR. WARD: Well, that's good clinical
16 practices for a clinical trial, which is different
17 than the way it's out in a phase 4 trial and
18 obviously being used by everybody out there. If
19 you're conducting your randomized-controlled trial
20 as a function with GCP, that very might give you a
21 different answer.
22 DR. SKROBIK: I didn't think we were here

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1 just for the phase 3's, but thanks for clarifying.
2 DR. WARD: Claudia and then Pratik.
3 DR. SPIES: The first part, I have a quality
4 assurance guideline for the whole hospitals
5 involving all disciplines and all from different
6 specialties. We agree on zero minus 1, but I have
7 one point I think I would like to make also. I
8 think it's time and talk.
9 So during the stay, the ICU stay, your
10 target may change, and even the drug is then -- you
11 don't have that primary outcome fulfilled if you
12 keep it that tight. So the question is if it's
13 zero and minus 1, I think if the target is
14 different, I think it needs to be acute. Why? If
15 there's a reason to do it that way -- for example,
16 for proning a patient or something like that,
17 sometimes you cannot keep zero minus 1. That's the
18 point.
19 DR. WARD: I agree with that.
20 DR. SPIES: So maybe we say time and target
21 and say, okay, the standard is zero minus 1, and if
22 there's an additional target to be mentioned, that

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1 has to be done before, not afterwards.
2 DR. WARD: As long as your clinical trial
3 prespecifies the reasons that you're changing the
4 target, you should be able to change the target,
5 but that shouldn't be as you go along in the trial.
6 It should be for certain conditions, you change the
7 target to minus 2.
8 DR. SPIES: Yes, but it's one patient, and
9 then it's decreasing the fragmented time, the
10 fractional time during the period, it's decreasing.
11 If you really delete that out of here, you have a
12 shorter period. I think if you come to the real
13 world and people do it different, I think that's
14 something we can consider because if we say it's
15 targeted to some level, and that needs to be
16 performed by the physician beforehand, the
17 physician has to achieve that.
18 Also, I think it's important because in some
19 patients you may target it lower for a certain
20 period, and this is also effective if you do that
21 that way. So I think if you have an argument why
22 you do it and you target it that way, it can be

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1 compared, and it can be, to my impression, also be
2 included as a primary outcome for the study. It
3 doesn't need to be --
4 DR. WARD: Pratik?
5 DR. PANDHARIPANDE: I'm sort of repeating it
6 now, but I think the time to time to target seems
7 the most effective, an effectiveness outcome. Now
8 what that target is over a period of time, that
9 will be an educational mission if 5 years from now,
10 we know that minus 1 is where it needs to be. But
11 from a new drug coming on, the ability that if you
12 want it to be a minus 1, we can get there. If it
13 needs to be a minus 3, we can get there, patients
14 and situations change.
15 I think all of that as a start, it's great.
16 I'm thinking about the composite outcomes. We had
17 this discussion over dinner yesterday and the
18 thought that it would be so great if there's a pain
19 element that can be added in. I think
20 unfortunately it becomes unfair because if you're
21 trying to look at the effectiveness of a sedative
22 regimen and then trying to put in an element that

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1 it really doesn't impact it, it's differential.
2 Then you have to selectively choose or try and
3 market a drug which has sedative and analgesic
4 properties because otherwise it will never hit the
5 other composited points of primary pain.
6 Then one last point is why target is
7 important, target sedation, the question is what is
8 going to be the target. And we've learned this
9 from some of our studies, is that having the
10 ordered target in the chart is very different than
11 what the bedside nurses are using as their target
12 in their head that they're titrating.
13 So effectiveness is probably closely related
14 to what the bedside nurses are actually targeting
15 it. If they want this patient to be minus 3, the
16 automate might say minus 1. The drug will not be
17 effective because nobody's been titrating it to
18 that. So the thought of having both those elements
19 in what is your target probably needs to be
20 considered.
21 DR. WARD: Tim, I think you're on.
22 DR. COLANTUONI: This is Elizabeth

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1 Colantuoni. Can I ask one more question before we
2 leave this part? How do you envision incorporating
3 mortality into this endpoint? If someone was
4 randomized and alive for 4 days and then
5 experienced death, would you incorporate the time
6 at the target RASS up until mortality, or are all
7 patient deaths ranked worse than the scale?
8 It's just a question that -- we have to
9 think about the complication of mortality within
10 this framework.
11 DR. WARD: I'm not the statistician, but
12 you're absolutely correct. That's got to be part
13 of how you measure this time at RASS.
14 DR. DWORKIN: I've got to answer for
15 Elizabeth.
16 Elizabeth, we're going to ask you to help us
17 write that section of the paper.
18 (Laughter.)
19 DR. DWORKIN: Okay?
20 DR. COLANTUONI: Sure.
21 DR. DWORKIN: Thank you.
22 DR. SHAFER: Actually, can I just as one

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1 question --
2 (Crosstalk.)
3 DR. SHAFER: You're assuming that otherwise
4 mortality is the same, because as a safety
5 endpoint, if one group increases mortality, nothing
6 else matters.
7 DR. COLANTUONI: But that's a challenge. So
8 if there is differential mortality and you exclude
9 it, then the treatment evaluation is no longer a
10 randomized trial. If you're only computing this
11 endpoint among survivors and there is
12 differential mortality across the treatment arms,
13 then the randomization doesn't hold anymore.
14 DR. SHAFER: But in thinking about your
15 question, I can't imagine there's a clinical trial
16 that would favor something which actually increased
17 mortality.
18 DR. COLANTUONI: Yes, I agree. I'm just
19 putting it out there as part of the discussion.
20 DR. SESSLER: It often is not significant.
21 It often is this small change. It's not
22 statistically significant [inaudible - off mic].

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1 DR. SHAFER: That's why I asked the
2 question. We're assuming that there's no
3 statistically significant difference in mortality.
4 DR. SESSLER: Right.
5 DR. COLANTUONI: Right, but in a couple of
6 the sedation trials that I read, there was like a
7 7 percent difference in absolute mortality, which
8 wasn't significant. I don't know this content area
9 very much, but that seemed big to me. I'm just
10 throwing it out there as a point that we need to
11 consider an emphasize. If you're going to make a
12 recommendation that this would be an endpoint, we
13 have to think of all the potential complicating
14 features of it.
15 Panel Discussion
16 DR. GIRARD: Which is a good segue into the
17 last topic.
18 Denham asked me to moderate the session on
19 acute, subacute, and chronic outcomes after ICU
20 sedation, and I asked Mona and Dale if they would
21 join me on the stage -- I guess this is a
22 stage -- because they have done so much work in

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1 this area. Obviously, like the other two sessions
2 today, we want this to be an open discussion. I
3 don't really think I have to encourage that.
4 (Laughter.)
5 DR. GIRARD: I get the sense that it just
6 happens naturally. Actually, as I thought about
7 this topic, I think we've actually covered, either
8 intentionally or unintentionally, a lot of ground
9 regarding acute outcomes. So I'm intending that we
10 mostly focus subacute or chronic, or what we would
11 call long-term outcomes, although I'm guessing that
12 there will be some conversation about shorter term
13 outcomes as well.
14 On that note, I wanted to just quickly throw
15 out this list and ask if there are thoughts that
16 haven't already been covered, and I'm intending
17 that we'll move quickly past this question. But
18 we've alluded to the fact that even if the primary
19 outcome is one that's related directly to the
20 intended effect of the drug, which is sedation, you
21 have to evaluate other short-term outcomes.
22 We just discussed that survival has to be

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1 one of those short-term outcomes. We've talked a
2 lot about [indiscernible] proceduralization,
3 including time to extubation. I inserted the word
4 "successful" as being extubated only to be
5 re-intubated within a day is not a good outcome.
6 We all know that. So time to successful
7 extubation, time to successful discharge, I would
8 propose that hospital discharge matters much more
9 than ICU discharge. I think probably many of us
10 work in environments where you put the order in to
11 discharge someone and, and whether they actually
12 move is an entirely different question.
13 Short term, many of these outcomes that
14 we've discussed could be assessed. Whether or not
15 they could be assessed reliably in every patient or
16 in the same percentage of patients in multiple
17 treatment groups is a different question. But
18 anxiety, depression, cognition, functional status,
19 pain, quality of life, and costs all could be
20 measured over the short term.
21 DR. DEVLIN: Tim, do you mean like short
22 term, maybe like hospitalization?

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1 DR. GIRARD: That is a good question, and my
2 second question when we get into long-term outcomes
3 is what time frame would you consider long term, so
4 you could also ask that question here. But as I
5 said, I would like for us to focus more on
6 long-term outcomes because I feel like we've
7 focused primarily on the acute outcomes.
8 That said, are there additional comments
9 that either Mona, or Dale, or any of you would like
10 to make about the inclusion of these outcomes? And
11 remember, at this point I think we're all in
12 agreement that we're talking about secondary
13 outcomes, whether you consider them safety.
14 Certainly survival would be a safety outcome, but
15 many of these others could be viewed as safety or
16 could be viewed as efficacy outcomes.
17 DR. DEXTER: I can't comment involving
18 patients who aren't surgical because those are the
19 ones I've studied, obviously, although we're
20 talking about non-surgical patients as well. But
21 when it comes to these time to events, if you think
22 of it in terms of time to successful extubation,

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1 time to ICU, discharge, time to hospital discharge,
2 all these could be censored if the patient dies;
3 time to being at home or whatever is the original
4 status.
5 So you have 4 separate times. Although
6 they're countable numbers, they can be units of
7 days, and it's highly, highly correlated in terms
8 of costs and things like that. So I think that
9 this concept, when you're talking about countable
10 days, it isn't like a binary type of endpoints that
11 are being combined, but it's relatively straight
12 forward from an economic point of view in terms of
13 analysis.
14 DR. URMAN: Rich Urman. Just a quick
15 question. Would quality-of-life survey involve
16 satisfaction? The patients were able to answer
17 those questions because that's slightly different.
18 Obviously, you to have someone who was actually
19 able to --
20 DR. GIRARD: Right.
21 DR. URMAN: -- have access to that.
22 DR. GIRARD: I think that's a good question.

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1 Many of the validated quality-of-life measures and
2 what population they've been validated in is a
3 question that's been raised. But many of those
4 would not include satisfaction that could be added.
5 Time frame of when you would administer that
6 I think would greatly affect whether or not the
7 results were reliable in terms of measuring what
8 you're trying to measure.
9 DR. URMAN: Right, and a lot of satisfaction
10 scores are influenced by so many other factors,
11 medical factors, things that have really nothing to
12 do with what you're trying to measure, but just a
13 thought.
14 DR. GIRARD: Right. Good points.
15 DR. RIKER: Riker. We heard earlier in this
16 meeting about the challenges of assessing anxiety
17 in our patients, how hard it is for patients to do
18 a HADS score or whatever other tool we're going to
19 use, and ditto the concept of earlier acute
20 depression while they're receiving sedatives,
21 versus hypoactive delirium, versus septic
22 encephalopathy, that's a very challenging

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1 differentiation.
2 I'd be eager to hear what kind of time frame
3 you had in mind for when we would assess anxiety
4 and depression. Would that be pre-discharge, or
5 within a month of discharge, or during their ICU
6 stay, or how do you vision that?
7 DR. GIRARD: I should have clarified. I am
8 not proposing necessarily measuring many of these
9 in the short-term period, but rather I wanted to
10 open it up to the group. My personal thought
11 is -- and I'm curious if you guys agree or if
12 others agree or disagree. My personal thought is
13 that many of these are going to be very difficult
14 to measure in the short term within the hospital
15 period, and that the cost to benefit ratio in terms
16 of the work that needs to be done to measure them
17 relative to the reliability of the information you
18 gain in that acute setting is probably not a good
19 ratio, one that would warrant the work. But I
20 wonder if others disagree with that.
21 DR. COLANTUONI: In terms of anxiety, it's
22 easily measurable. There's a visual analog scale

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1 very similar to the pain that's been tested in the
2 ICU. So I think we can do anxiety, or you can even
3 do anxiety, yes/no. I'm not aware of any
4 short-term depression scales that have ever been
5 used in any studies.
6 DR. SKROBIK: It would be nice to use.
7 [Inaudible - off mic] she did that in chronic
8 inflammation ICU and was suggesting that the
9 cutoff -- and we were talking about this point a
10 little earlier, that the cutoff for the HADS is
11 different in that population and in fact lower and
12 associated with the worst functional outcome.
13 To speak to your anxiety comment, we've done
14 it also in the A&A paper that we published with a
15 pre post-implementation of pain, analgesics for
16 pain. We did the RASS scores, and we asked about
17 anxiety, and there was a 30 percent proportion of
18 the population, roughly, that had a RASS score of
19 zero to minus 1 but that was experiencing anxiety.
20 We didn't even put it on the scale. It was a tick
21 box, are you anxious right now?
22 So it's very feasible to incorporate these

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1 features. I'm just going to say, I'm not sure that
2 in those patients medication is the answer because
3 the medications that they were administered was the
4 same because one of the options in that study was a
5 nonpharmacological intervention. Would you rather
6 listen to music or have a drug? So I think, yes.
7 DR. HOPKINS: Could I just speak to doing
8 this after the ICU? Our 2005 paper, we assessed
9 all of this stuff before they were discharged, and
10 I will tell you, it was incredibly difficult, and
11 the visits were repetitive, and you'd walk into the
12 room, and they were having a treatment or they'd
13 been sent down to x-ray, or MR, or wherever, or
14 back to surgery.
15 So doing this and trying to really
16 understand what their long-term outcomes are, are
17 difficult at that point in time. And for
18 cognitive, we know, between our study and Christina
19 Jones' studies, that the rate of cognitive
20 impairments at this point in time is almost
21 100 percent, between 90 and 100 percent, take your
22 pick. So it has a lot to do with drugs and

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1 half-lives of drugs, and other kinds of factors.
2 So it depends on the question. If you want
3 to know if they're anxious on the ventilator, I
4 absolutely agree you can get that data in the ICU,
5 but if you really want to understand what their
6 longer term outcomes are, I don't think in the ICU
7 is the time to assess it.
8 DR. WARD: Is it something that should be
9 assessed -- I understand the logistics are
10 difficult -- at the time of hospital discharge?
11 Because that's the point that you still at least
12 have them there; 60 days, 120 days later, there's
13 going to be fewer patients you can perhaps contact
14 without a lot of work.
15 So is this something that we would recommend
16 at hospital discharge? I understand the logistics
17 issues. Should the intensive care unit experience
18 questionnaire or something that should be
19 administered at hospital discharge?
20 DR. HOPKINS: I think it's an interesting
21 question, and to me it depends on what the purpose
22 of the study, what you're trying to find out and

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1 what you're trying to measure. I hate saying a
2 universal yes, it should be measured in anybody
3 there. There's an SCC meeting that will be held in
4 May at ATF, where they're trying to look at ways to
5 predict these things, and there's this move to try
6 to do predictors in the ICU. And at least my sense
7 from the phone calls -- we haven't had the meeting
8 yet -- is that it's moving farther and farther away
9 because of the confounds of the high rates of
10 impairment.
11 So there is this need to understand what
12 people are going to have them, and can we predict
13 who's going to have them, or can we risk stratify,
14 or can we do some kinds of prevention, but I don't
15 think we have the data yet.
16 Maybe Dale?
17 DR. NEEDHAM: I agree.
18 DR. AITKEN: Leanne Aitken. Perhaps the
19 only other thing that's sort of tied up with
20 cognition is memories. I'm not thinking in ICU,
21 but if we're talking hospital phase, then it might
22 be worth adding memories to the list.

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1 DR. GIRARD: Okay. JP?
2 DR. KRESS: I apologize if somebody already
3 mentioned this because I had to step out, but ease
4 or success rate with mobilization would be another
5 endpoint that might be worth considering because
6 the most common reason that people can't be
7 mobilized is that they can't follow any
8 instructions.
9 DR. GIRARD: I agree. Just to clarify what
10 I had in mind, that word "after" is -- I was
11 viewing this conversation as all outcomes that you
12 might measure after the period of time the patient
13 was no longer receiving sedation, however, that may
14 still be affected.
15 Gilles?
16 DR. FRASER: I was just wondering if
17 discharge disposition was an acute or short-term
18 outcome.
19 DR. GIRARD: I would consider it as an acute
20 outcome. Yes, I think that makes sense.
21 DR. TANG: I just want to really quickly
22 revisit the point on quality of life. I think

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1 depending on the measures and instruments that you
2 adopt to look at quality of life, you can have
3 anything from something that's really quantifiable.
4 I think we talked about presenteeism, absenteeism,
5 that level of productivity, all that is
6 quantifiable, whereas you also have PROs,
7 patient-reported outcome validated measures where
8 it's more about how the patient feels and very
9 subjective on how the patient is experiencing it.
10 So I think it's worthwhile to kind of
11 balance both ends of the spectrum when talking
12 about quality of life and taking into those
13 considerations when you choose whichever is most
14 appropriate for the population.
15 DR. GIRARD: Would those be measured within
16 the hospital, during the hospital, or at the time
17 of discharge, or long term?
18 DR. TANG: It would be a spectrum, so you
19 definitely would want a baseline at specific time
20 points. I think it just depends on the instrument
21 and how it was validated as well. That could have
22 influence. But the idea is that you would want to

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1 show it's not necessarily just a cross-section at
2 one time. Usually it's much more advantageous to
3 be able to see it and track it over time.
4 DR. GIRARD: Okay. So speaking of over
5 time, let's move to this question of long-term
6 outcomes. We've touched a little bit on this
7 question, but I think it's worth revisiting, should
8 sedation trials in general, all sedation
9 trials -- I guess if you wanted to be really
10 provocative, should all sedation trials include
11 long-term outcomes? I'm seeing some nodding yes
12 and nodding no. Speak up.
13 DR. KRESS: I would say that's wonderful in
14 theory, but it's just not practical. It's too
15 expensive. You're just not going to be able to do
16 that with every trial. I think it should be
17 something to consider, but I would reason to say
18 the major rate-limiting step is going to be human
19 power and money.
20 DR. SKROBIK: [Inaudible - off mic] But
21 you're looking at the safety as a short-term
22 molecule.

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1 Sorry. It's Yoanna. If you're looking at
2 the safety of a short-term molecule, that may not
3 be the point that you're looking at. But we're
4 looking at the big picture of trajectories because
5 we've learned that that's what we do. And thanks
6 to all of you sitting up there on the podium and
7 others in the room, I think we've become much more
8 mindful that it's a continuum, but not all
9 questions are related to that.
10 If you wanted, for instance, to say what is
11 the usefulness of a sedative as a co-analgesic in
12 the ICU, then you wouldn't -- well, you could look
13 at chronic pain if you really got excited.
14 DR. KRESS: One thing, and we touched on it
15 a little bit yesterday, I certainly have learned
16 over the years is the importance of getting every
17 email, phone number, text number, Snapchat,
18 Instagram, whatever I can find is a way to reach
19 people, or second cousin, because losing people
20 later is frustrating if that's your intent.
21 So maybe you could imagine that people that
22 weren't going to look at long-term outcomes to at

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1 least make a concerted effort to try to keep the
2 people that are in their trials in the proverbial
3 queue so that perhaps down the road someone else
4 maybe who actually found money for a different
5 purpose could try to capture those patients, so you
6 could pass the baton so to speak.
7 DR. GIRARD: Others? Steve?
8 DR. SHAFER: It seems to me that certainly
9 for initial trials, just to get the dose right to
10 figure out if something is able to achieve the
11 pharmacological effects of interest know, but any
12 trial that's going to either go for registration of
13 a drug or change practice, I think needs long-term
14 outcomes.
15 DR. GIRARD: So phase 3 trials you would
16 say --
17 DR. SHAFER: Yes.
18 DR. GIRARD: Okay. What is your thought to
19 Yoanna's comment that -- it sounded like you're
20 confident that many of these drugs won't have any
21 long-term effects. How would you respond to that?
22 DR. SHAFER: We have a lot of examples in

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1 medicine of things where we say -- like take blood
2 pressure -- even better, take tight control of
3 glucose, and we know we can give basically drugs
4 like insulin and try to get tight control of
5 glucose, but we also know, when we look at
6 long-term outcomes, we can really cause a lot of
7 damage with what we think -- short-term,
8 narrow-focused measurements are actually okay.
9 I think that you're going to have to know in
10 the long term is this actually doing anything if
11 you're really going to try to change practice.
12 DR. WARD: As a general question, do we
13 think there is no effect, no signal there in
14 long-term outcomes related to sedation in the ICU?
15 Do we think it just doesn't matter how you do
16 sedation, it's not going to affect a long-term
17 outcome?
18 DR. GIRARD: Well, I certainly don't believe
19 that.
20 DR. SKROBIK: That's not what I -- you can
21 have a trial that looks at a short-term effect of a
22 short-acting drug over a 5-day period in the ICU,

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1 or you can look at sedation practice over the ICU
2 stay. Those are two different questions.
3 DR. WARD: My point followed Steve, that if
4 we think there might be a signal there at some
5 point in the phase 1, 2, 3 trial, and this is
6 probably a phase 3 trial because you need a big
7 enough end, you should be looking at is there
8 something that's going to change cognition or
9 something at the 6-month point.
10 I think some looking at what you three have
11 done would say there's probably a signal there.
12 And if there is, that's something that should be
13 looked at.
14 MALE VOICE: And if there isn't, why are we
15 doing this?
16 DR. NEEDHAM: I'm sort of skeptical. I
17 think if you've got the new drug that you're trying
18 to get FDA approval for, I don't think that
19 post-discharge outcomes need to be mandated as part
20 of it. And I suspect that if in this more modern
21 age -- so I think more modern clinical
22 trials -- all of them are going to be aiming for

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1 lighter sedation in both groups. And I suspect
2 that the new drug's not going to have a signal in a
3 phase 3 FDA trial. I think it's sort of a phase 4
4 thing, and it might be an even bigger population.
5 DR. DWORKIN: So the language we've often
6 used is something along these lines, quote, "In
7 most circumstances, investigators should consider
8 including long-term outcomes in their clinical
9 trials." No one ever objects to that sentence, and
10 it's a kind of soft recommendation that if you're
11 putting all of this effort into designing a phase 3
12 trial, also think about some long-term outcomes.
13 There's no mandatory at all.
14 DR. WARD: That's the wording we used a lot
15 in the papers for SCEPTER I and II.
16 DR. GIRARD: So if it was a recommendation
17 rather than a mandate, would you then disagree with
18 that?
19 DR. NEEDHAM: Dale Needham. Yes, I would
20 agree for a recommendation rather than a mandate.
21 DR. GIRARD: So JP's comment about the cost
22 and the work that goes into measuring the long-term

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1 outcomes, I don't think that any of us who have
2 done these types of studies would disagree that
3 it's expensive and it takes a lot of work. I
4 hesitate to presume that I know what goes into, on
5 the industry side, doing a clinical trial because
6 I'm not in industry, but from the numbers I've
7 seen, it wouldn't be a major part of the budget to
8 add long-term outcomes. It would be I think a
9 negligible part of the budget, considering how much
10 is spent on the other aspects of the trial.
11 Pratik?
12 DR. PANDHARIPANDE: I think going back to
13 some of the things I said earlier on looking at it
14 from funding agencies, again, most funding agencies
15 are now looking for those long-term outcomes. So
16 looking at the three sedation studies that we've
17 sent to the NIH recently, all have come back with
18 saying make sure that the long-term outcomes are
19 robust because we at least want you to be doing
20 that. That's one part.
21 The other part is from the publication
22 standpoint, I think most journals, to have an

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1 impact of your new drug, to get it to actually
2 practice, are looking for things beyond the
3 short-term outcome. So I think we need to keep
4 that in mind. It may not be the primary outcome
5 like we've discussed, but it has to be in the
6 consideration.
7 DR. GIRARD: And I think we should also
8 remember that -- I think it's actually a great
9 thing that many of us in the room -- I wouldn't
10 include myself, but many of us are skeptical that
11 there would be a difference in long-term outcomes
12 between two different sedatives or two different
13 sedative regimens, when 15 years ago, or 20 years
14 ago -- I think JP would agree with this. Twenty
15 years ago, when JP published his paper in the New
16 England Journal on daily interruption, there was an
17 outcry that this is almost certainly going to lead
18 to adverse long-term outcomes.
19 At that time, the assumption was widely that
20 without heavier sedation, patients are going to do
21 poorly in terms of long-term outcomes. And now
22 we've come to the point where we're wondering if

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1 there will be any difference. It's not that hard
2 to imagine that 20 years from now, we'll have more
3 information and may view this whole thing in a
4 different way.
5 DR. HOPKINS: Can I just add one thing to
6 that? If you look at the trials to date that have
7 long-term outcomes and show these adverse affects,
8 most of them do not show differences between trial
9 arms. So the bad outcomes that we all study are
10 occurring in both trial arms, so that could be a
11 rationale that we're not having them.
12 It's not that we're preventing bad outcomes;
13 they're happening in both arms of the trials. I
14 just went back and looked at the ABC data. I
15 looked at Jim's paper from the brain ICU study, the
16 brain ICU paper that Pratik published, and there
17 isn't really a difference in outcomes, but there
18 are bad outcomes in both arms at rates that are
19 concerning.
20 DR. NEEDHAM: The other thing to add, in the
21 few studies that are specifically designed to
22 improve patients' outcomes after discharge, almost

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1 none of them show any signal of benefit, and
2 they're specifically designed to improve that. So
3 something that we're going to do in the ICU to
4 affect sedation, that's why I'm sort of skeptical
5 that they would. I've got two other quick
6 comments.
7 Pratik, to your NHLBI or NIH funding
8 application, you're right. I think now all of our
9 grants say, "We will use the NHLBI-funded core
10 outcome measurement set in our study" to hopefully
11 have study sections go, yes, there's been a lot of
12 thought put into what should be measured, and we're
13 going to do it.
14 Back to a question on funding, if we're
15 trying to fund this using like NIH-funded
16 capitation, I think it is hard to squeeze out the
17 money to do long-term outcomes assessments. Having
18 tried to do this, I think it's very hard to squeeze
19 it out because the budgets are so narrow, despite
20 within the entire trial budgeted really being a
21 drop in the bucket.
22 These trials are so expensive for the ICU

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1 part of them that it becomes hard, but hopefully we
2 can get funding agencies and industry to recognize
3 that it's important and make sure that there's some
4 budget for that. Probably for a centralized call
5 center that's probably in a large study, it's
6 probably the most cost efficient and the most
7 effective, but there needs to be a separate budget
8 for that.
9 DR. GIRARD: Actually, along those lines, I
10 want to skip down to the third question here. We
11 can come back to the question of what's considered
12 long term if anyone feels strongly that we need to
13 discuss that. But moving to the core outcomes set,
14 there's a core outcomes set that Dale and others
15 published for acute respiratory failure survivors,
16 and that is shown here, I believe.
17 One question that I have, if we are going to
18 recommend but not mandate long-term outcomes be
19 assessed in survivors who are enrolled in a
20 clinical trial of sedation in the ICU, would this
21 be the recommendation? These were developed with
22 acute respiratory failure patients in mind. Those

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1 I believe are the same patients that we would be
2 including in sedation trials.
3 So is this a natural fit or would there be
4 some concern that, well, the core outcomes set
5 wasn't specifically developed with the sedation
6 trial in mind? what are your thoughts? Would this
7 be an appropriate recommendation? Pratik?
8 DR. PANDHARIPANDE: I think it's a great
9 start. You
10 can always add more, but at \$3, if those figures
11 are correct over there, and I'm sure they are
12 correct, Dale --
13 (Laughter.)
14 DR. PANDHARIPANDE: -- \$3, I see very little
15 excuse for not having that, given that, yes, most
16 of the indication nowadays -- whether right or
17 wrong, most of the indications right now for
18 sedation is patients with respiratory failure who
19 are difficult to manage on the ventilator. So I
20 would say yes, one vote at least.
21 DR. NEEDHAM: This is Dale Needham. To
22 clarify, the cost is the cost of the instrument,

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1 not the actual staff time, of course.
2 DR. PANDHARIPANDE: Right, but the staff
3 time, still it's a great bar to have the
4 instruments at \$3. We have other studies where our
5 instruments are \$300, and then you add staff time
6 et cetera, and that's completely different.
7 DR. NEEDHAM: And the question that was
8 asked, to derive this for the Delphi panel, was any
9 type of study that's going to choose to measure
10 outcomes after hospital discharge, what should they
11 do? So it wasn't specific to -- in a patient
12 population, but it wasn't specific to an
13 intervention or anything. And as Pratik touched
14 on, the exact idea is this is the bare minimum, and
15 then studies would add something on top of that
16 that's specific to their intervention.
17 DR. BALAS: And these are all telephone
18 administered?
19 DR. NEEDHAM: They are, and the time that it
20 would take to administer an acute respiratory
21 failure of survivors on this slide.
22 DR. DWORKIN: Dale, do you recall why it

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1 ended up with SF-36 rather than SF-12?
2 DR. NEEDHAM: SF-12 was on the list of
3 things that the Delphi panel looked at? I'm going
4 to guess. Obviously, I'm not on the Delphi panel,
5 but I read every single response. I think it's
6 because in the field of critical care survivorship
7 research, almost nobody uses the SF-12, so there
8 isn't comparable data. And I think people like
9 specifically to look at the physical function
10 domain within the SF-36 that you can't get out of
11 an SF-12.
12 To make another note, for people that don't
13 have funding to license the SF-36, the RAND
14 version, which is the SF-36 version 1, is free of
15 charge, so it doesn't eliminate the time that it
16 takes, but it reduces the cost back to the \$1.50.
17 DR. GIRARD: So I'm guessing that most of
18 you are familiar with these outcomes, but just so
19 that I don't assume, maybe we should just quickly
20 review them.
21 The IES measures symptoms of PTSD. The HADS
22 is symptoms of anxiety and depression. The EQ-5D

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1 is an historic quality-of-life measure, in contrast
2 to the SF- 36, which is also quality of life but
3 longer. Then of course, I think you're all
4 familiar with survival as an outcome.
5 On the far left is the minimum core outcome
6 set, and then the determination was if you're going
7 to add cognition, the MoCA Blind, which our
8 president apparently passed at some point, what
9 would be included. Then if you wanted a longer
10 quality-of-life assessment, SF-36, and then you
11 could even do both. And doing all of that leads to
12 the 26-minute assessment on the phone.
13 DR. NEEDHAM: That's correct. It's
14 important to note, remember, there were 2 domains
15 that didn't reach consensus, so there's no
16 consensus -- a core outcome that the Delphi panel
17 believes should be evaluated in every study
18 included muscle and nerve function and physical
19 function. They could not reach consensus in how to
20 evaluate that because the panel thought -- this is
21 Dale Needham -- that a performance-based measure
22 would be better and couldn't come up with what a

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1 survey-based measure would be.
2 So there are a couple of outcomes that are
3 missing. And I would say to people, if you think
4 that's important, then maybe you need to think
5 about an instrument, but then that also adds time
6 and cost. So this is the minimum that everyone
7 agreed on.
8 DR. RIKER: Were you going to address time
9 of these assessments? Is it 30 days, 90 days, or
10 when do we do these?
11 DR. GIRARD: Yes, I did want to address
12 that. What time frame -- first of all, should we
13 even consider long term, and then second of all,
14 what would be the recommended time frame for a
15 long-term outcomes assessment? Opinions on that?
16 DR. HOPKINS: I can just tell you the longer
17 we go in follow up, then the comments we get in
18 reviews is that's not long-term outcome. So when
19 we were doing 3 months, it was long term. When we
20 did 6 months, 3 months, no longer a long-term
21 outcome. So I think it's hard to define and it
22 depends on your frame.

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1 DR. RIKER: Riker. Mona, do you have a
2 parameter or an idea as far as dropout goes, the
3 longer you go? I imagine with this sick
4 population, we're going to see drop out, not just
5 from lost to follow up but mortality and other
6 things like that. Do you see an obvious endpoint
7 for long term?
8 DR. HOPKINS: I'll let Dale help answer this
9 as well, but we have done when we implement the
10 tools to maintain cohort retention, our long-term
11 outcomes and my single-center studies, and our
12 multicenter studies, and Dale's other multicenter
13 studies have been very high in the 94 to 98 percent
14 follow-up rate, but it is a lot of work to do that.
15 Certainly, there is some mortality that continues
16 at 6 and 12 months, and even longer, but it
17 dramatically drops off the longer time you go.
18 I think an interesting question that you
19 didn't ask is what happens with cognitive
20 impairment? Is there some recovery, or same thing
21 with depression, anxiety, PTSD, and physical
22 function. What we do see is that there is some

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1 recovery but it appears to plateau between 6 and 12
2 months, but we don't really know exactly where
3 because we've measured hospital discharge 3 months,
4 6 months, 12 months.
5 So there does seem to be some recovery, and
6 a question that hasn't really been addressed in any
7 study is can we facilitate that recovery? I should
8 take that back. Jim's recover study, and Nate's
9 study, and there are a couple of others that are
10 showing that we can get increased improvement, but
11 they're very small studies.
12 Okay.
13 DR. NEEDHAM: A couple of other comments.
14 We have an interesting paper that actually used
15 data to look at trajectories of recovery over time,
16 and in fact it's a minority of patients that have a
17 stable or improvement over a 5-year follow-up.
18 That's a minority of patients. So the word
19 "recovery" really is a misnomer. In fact, there's
20 a proportion of patients who are bad and just get
21 worse., and then there's proportion of patients who
22 are bad, maybe stay the same, or get better over

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1 one year, and then have a decline between 1 and 5
2 years.
3 So there are lots of bad things that are
4 happening to people after they are discharged and
5 go home, high rates of readmission. So I think if
6 we're trying to draw a cause and effect
7 relationship, we can't go too far because maybe the
8 intervention did cause the readmission, caused the
9 medical and caused readmission, or maybe it's
10 something else.
11 Interestingly, I think that we should stick
12 to 3, 6, 12-month time points because that's
13 virtually what everybody does. So I don't like a
14 30-day. I don't like a 45-day or some other random
15 number. I think we should pick to those.
16 Interestingly, we have more difficulty with
17 cohort retention at 3 months than at 5 months
18 because patients are very overwhelmed at 3 months.
19 So you might kind of want to capture that in a way,
20 that might be an argument, but that sort of is not
21 a steady state either, and it's an interesting
22 observation around patient distress and lost to

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1 follow-up.
2 So in fact, we have higher retention rates
3 at 6 months. What happens at 3 months, they just
4 are overwhelmed or they can't be reached, but then
5 you can get them at 6 months, and they're happy to
6 participate, or they can be reached but they're
7 still in a SNP or some other setting.
8 DR. GIRARD: If I could summarize what I've
9 heard so far -- and this is your opportunity to
10 tell me I've not been listening; my wife would be
11 willing to tell me that --
12 (Laughter.)
13 DR. GIRARD: -- if I could summarize, it
14 sounds like actually we agree that all of the
15 long-term outcomes would not be mandated in
16 sedation trials, that they would be recommended,
17 and that it would be recommended that this core
18 outcomes set be a good place to start. Perhaps you
19 could add other outcomes if you had a specific
20 hypotheses you wanted to test, but at a minimum,
21 that it would be recommended that you would include
22 this core outcome set.

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1 Are we in agreement about that? I think
2 we're doing a lot better than the short-term --
3 (Laughter.)
4 DR. GIRARD: Okay. All right. Then I think
5 we've in part answered this question, but are there
6 other elements -- so that core outcomes set, to
7 recap, includes survival. It includes anxiety,
8 depression, cognition, and in some way functional
9 status. Pain is at least one question on the EQ-5D
10 and quality of life. So most of these are covered
11 by the core outcome set.
12 Of course, I should have changed that second
13 bullet point. My intention was to point out that
14 resource use could also be a long-term outcome,
15 certainly not in the way that it's described here,
16 time to extubation, but are there any costs or
17 resource utilization outcome measures that would be
18 recommended in a long-term data set or would we
19 limit our recommendation to core?
20 DR. WARD: Maybe Franklin would want to
21 comment on, too. I think the cost, you always have
22 to be careful by whose perspective. Is this the

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1 patient's perspective, the insurance company's
2 perspective, the healthcare system perspective.
3 You may have an earlier time to discharge, which
4 saves money for the hospital, but the family now
5 has to stay home and take care of the patient
6 because they are not in as good a shape as if
7 they'd stayed in the hospital an extra week.
8 So I think those are important efficiency.
9 To go back to the 4 things we're looking at from
10 the IOM, these are all measures of efficiency, but
11 I think we need some sort of statement in the paper
12 that when costs are measured, it has to be clear
13 about what the perspective of the costs are and not
14 just say this is great because the time to
15 discharge, you got 3 days shorter because that may
16 or may not be good as an efficiency measure without
17 understanding what the patient was like when they
18 were discharged, and there are lots of examples
19 like that.
20 Is Franklin still back there or is he gone?
21 Okay.
22 DR. RIKER: Tim, do any of these tools,

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1 either in the package or others, assess the family
2 or the caregiver perspective? I think what we've
3 noticed in many of our patients is that the patient
4 thinks they're doing just fine and the family is
5 pulling their hair out because they are nowhere
6 close to fine.
7 So that disagreement doesn't get assessed if
8 we don't ask the caregiver what their perspective
9 is. And there are some very quick and easy to use
10 tools that have been used like primarily in the
11 cardiac arrest population, but I think they would
12 easily apply to this population as well.
13 DR. GIRARD: Do you want to comment on the
14 validity of these tools as a self-reported measure
15 of the outcomes relative to what the family may say
16 about how the patient's doing?
17 DR. NEEDHAM: So we have looked at patient
18 versus family member for both the EQ-5D and the
19 SF-36, and they're in ADRS survivors through
20 reporting different things. The truth, who knows?
21 But it is a patient-reported outcome, so the
22 patient should be the gold standard if they're

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1 cognitively able to answer.
2 So they're not measuring the same thing, and
3 mental health instruments or psychological
4 wellbeing instruments, we've got to rely on the
5 patient. We also know -- I presented a little bit
6 of data yesterday showing us that the cognition, we
7 can't rely on the patient's memory or perception;
8 we need to test that with a standardized test.
9 There are a couple of other quick things I
10 wanted to say that are relevant. So Mona and I,
11 other people in the room, were part of an NHLBI
12 workshop on the research agenda for acute
13 respiratory failure research, and the manuscript's
14 not yet written, but I think it's going to say that
15 this core outcome measurement set should be part of
16 all NHLBI funded randomized -- or whatever, studies
17 around acute respiratory failure that choose to
18 measure long-term outcomes, is I think what it will
19 say. So this would be jiving with that.
20 DR. HOPKINS: This is Mona Hopkins. I think
21 the question about does this reflect families, no,
22 but you can use these tools to assess where the

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1 family is. But that's a very different question
2 than assessing their view of the patient and what's
3 happening.
4 DR. NEEDHAM: Also, it's not on any of these
5 measures, we have created from scratch and used in
6 thousands of assessments a standardized approach
7 for measuring return to work that could then allow
8 you to measure lost income and also health care
9 utilization that had been published numerous times.
10 They're freely available, and other people from
11 around the world for comparability reasons are
12 using the exact instruments.
13 Both of those instruments around health care
14 utilization, after hospital discharge and returned
15 to work, actually take a fair bit of detailed time
16 to actually do based on an interview. And of
17 course it's based on an interview, which may not be
18 the same as other methods of getting health care
19 utilization, but they are available and they are
20 freely available on that same website,
21 improvetl.com.
22 DR. AITKEN: If I could just pick up on

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1 that, Dale, I wondered why something like return to
2 work wasn't in the core outcomes set.
3 DR. NEEDHAM: Interestingly, among the
4 qualitative work and all of the work leading up,
5 that social health was a consistent signal, but
6 that social health never made it into a core
7 outcome that should always be measured, and
8 therefore there's not a measurement instrument for
9 it. And that may be because in the empirical
10 literature, it's measured much less often as
11 opposed to signals from the qualitative literature.
12 DR. GIRARD: And in many of these trials,
13 more than half of the participants were not working
14 prior to their acute illness and enrollment in the
15 trial. It certainly is an important outcome for a
16 portion of the participants, but not for all of
17 them.
18 Pratik?
19 DR. PANDHARIPANDE: Two questions. We said
20 for the long term, it would be great to do it at
21 3 months, 6 months, and 12 months. If given that
22 there's a pragmatic part of it, we have to choose

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1 just one time point, would you say at 6 months?
2 DR. NEEDHAM: This is Dale. I would say
3 6 months, and I say it because 3 months is really
4 tough. Three months is pretty early. Six months
5 isn't steady state, but 3 months really isn't
6 steady state, and 12 months, it delays your
7 outcomes by another 6 months, and you've got to do
8 a lot of cohort retention activities between 6 and
9 12 months.
10 DR. PANDHARIPANDE: Thanks. The second part
11 is if we were to do it more often, do all these
12 tests in the core outcome set have the test/retest
13 issues taken care of? Are there alternate versions
14 of all these or is there a test/retest issue if
15 you're doing it more than once with the core
16 outcome?
17 DR. NEEDHAM: These ones, there are no
18 multiple versions. I don't have the test/retest
19 psychometrics in my head, and certainly they've
20 never been evaluated in ICU survivors. But they
21 commonly are used repeatedly over time in ICU
22 survivors, and they seem to change over time in

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1 ways that seem to reflect reality. So I think that
2 they have responsiveness.
3 DR. HOPKINS: This is Mona. I completely
4 agree. HADS is how have you been in the last
5 2 weeks? You could administer that multiple times,
6 and it's been used. They don't have alternate
7 forms. IES-R has been used multiple times.
8 There's not as much data there as there is on the
9 HADS, EQ-5D. The bigger problem is going to be
10 your MoCA Blind because you're asking the same
11 questions, and there is psychological and
12 psychiatric literature about cognitive learning to
13 the test. So that's going to be your most
14 problematic test for close retest.
15 DR. GIRARD: Close retest meaning what time
16 frame? Would 6 months and 12 months be a concern
17 there?
18 DR. HOPKINS: Most people would like you to
19 go to 12 months, but if you use the regular MoCA in
20 person, there are alternate forms. There's just
21 not for the MoCA Blind.
22 DR. GIRARD: Okay. I think I had maybe -- I

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1 have two more questions. We're running early, so
2 if you want --
3 DR. WARD: This is good.
4 DR. GIRARD: This is good. Running early is
5 good. I've never learned that lesson --
6 (Laughter.)
7 DR. GIRARD: -- but I've heard that that's
8 the case.
9 One question, and this is one that Elizabeth
10 raised yesterday in her presentation, but I want to
11 revisit it. Even though in critical care in
12 general, we rarely, if ever, do see differential
13 survival -- we have seen it a few times, including
14 one sedation trial, and we simply don't know what
15 new molecules' effects may be, and we have to
16 always at least consider the possibility of a
17 difference in survival, whether that's because the
18 new drug is harmful or helpful, it has be
19 considered.
20 So how should we account -- I think you've
21 heard yesterday some options for accounting for
22 confounding by differential follow-up due to either

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1 differential survival or differential functional
2 status. If everybody in one group is still SNF and
3 they can't do the testing, that would also lead to
4 differential follow-up.
5 What do you think this group, if anything,
6 would recommend for how to account for that? Is
7 the composite endpoint the recommended approach?
8 Is everyone satisfied with recommending
9 survivors-only analysis even though that could
10 potentially be biased? What are your thoughts?
11 I raise this specifically in the
12 conversation about long-term outcomes because I
13 think the longer term the outcome is, the more
14 likely you will have differential follow-up. If
15 you're measuring something in the ICU within hours
16 or days of administering a treatment, you're less
17 likely to have that problem.
18 DR. COLANTUONI: This is Elizabeth
19 Colantuoni. If mortality is going to be an
20 endpoint in the trial, I think that you have to
21 plan to do an analysis by the counts for the
22 possibility of differential mortality. It could be

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1 a stepped approach in the statistical analysis plan
2 that says if the mortality's not statistically
3 significant and/or within a absolute difference of
4 some percentage that you don't think is clinically
5 relevant, then the survivors-only analysis would be
6 utilized, but I think it has to be planned in the
7 trial.
8 I'm doing a systematic review right now of
9 the last 5 years of papers published in the top
10 five medical journals, and in studies where there's
11 a decent amount of mortality, everyone's only doing
12 the survivors-only analysis. So I'm not saying
13 that those trials are biased because a lot of them,
14 there is no difference in mortality, but no one's
15 thinking about this, and I think that the standard
16 should just be a staged analytic plan, and that
17 would be a good, long-term approach.
18 DR. GIRARD: Just to add to that, what the
19 potential values of a group like this making a
20 recommendation along these lines is that it not
21 only could influence how trials are designed, but
22 also how they're interpreted.

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1 For example, in the ABC trial, when we
2 published the long-term outcomes, we published the
3 survivor -- you know this because we've discussed
4 it. We published the survivors-only analysis, but
5 that was not because that was our plan. That's
6 because what the journal editors hired us to do.
7 We actually presented to them initially a composite
8 outcome, and they didn't accept that.
9 So I think that if, for example -- I've also
10 revealed now that I have a bias about this ad an
11 opinion, but if a prespecified plan based on a
12 recommendation is followed through, then that may
13 change the way a trial is interpreted.
14 JP?
15 DR. KRESS: I think no matter what choice
16 you make, you're going to have pros and cons. One
17 thing, having said that, that has in the last 15 or
18 20 years gotten a lot more attention is this
19 concept of whatever badness is: free days,
20 ventilator-free days, ICU-free days, hospitals.
21 One of the things that we've used, and I
22 think others have as well, your disposition after

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1 the hospital, at least in the United States, has
2 about 7 different bins you could go into.
3 So there's home, there's acute care, there's
4 subacute care, there's LTAC, there's hospice,
5 there's death, there's nursing home, a whole bunch
6 of different places. But one way that might
7 simplify that is over the course of whatever your
8 denominator is, what are your institution-free
9 days? That would allow you to deal with the
10 varying outcomes but also take into account that if
11 you end up home, no matter where else you go, it's
12 not as good as home.
13 DR. RIKER: I tend to agree with you, Tim.
14 If we only look at the people who are well enough
15 to drive themselves to the follow-up appointment,
16 we're going to be missing a lot of differences
17 between the groups. So somehow, whether it's a
18 composite outcome that includes death or skilled
19 facility and unable to present, or unable to
20 complete the evaluation, those are important
21 outcomes that we need to capture I think somehow.
22 DR. GIRARD: So I'm going to push Elizabeth

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1 a little so we're specific. If we say how it's a
2 staged approach and mortality is different, then
3 we've got a choice, based on your work, around a
4 composite outcome versus a causal inference method,
5 like a SACE correct?
6 DR. COLANTUONI: Yes.
7 DR. GIRARD: Do you have any advice around
8 anything that the paper should talk about in terms
9 of how that decision should be considered?
10 DR. COLANTUONI: That's a really loaded
11 question. Myself, I would lean towards doing a
12 patient ranking, knowing that that's subjective and
13 that there could be a whole discussion around how
14 to rank someone's PTSD symptoms with respect to
15 mortality at 6 months post-critical illness. But I
16 think that the assumptions that go into the SACE
17 model, like actually estimating the SACE, are also
18 challenging and can equally be -- people can buy it
19 or not buy it.
20 I would personally prefer to see us rank
21 patients in terms of function or --
22 DR. GIRARD: To put that into a specific

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1 context, for instance, Rich was just talking about
2 you can't do the test if you're not alive. So for
3 example, say that your outcome or your primary
4 outcome, we've got a randomized-controlled trial
5 where this is their primary outcome, the 6-minute
6 walk distance, and we do use a composite outcome in
7 a rank-based analysis.
8 So if you're dead, then you get a score, for
9 example, of minus 1. If you're unable to walk, you
10 get a score of zero. And if you can walk, then
11 it's whatever distance you actually walk. I think
12 most people would agree that -- no, not everybody,
13 but most people would agree that death is worse
14 than not being able to walk. There may be some
15 people that would rather be -- there may be, right?
16 Some people who are bed bound that would rather be
17 dead than unable to walk, but at least that's a
18 decision that we had made, and that's an example of
19 how this ranked-based method that Elizabeth
20 presented about could be done.
21 I think that's a feasible method. Not
22 everybody has to have a causal inference

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1 statistician to do that approach.
2 DR. COLANTUONI: And that allows you to do
3 any host of sensitivity analyses to modifications
4 of the rankings.
5 DR. BALAS: Who's going to make sed
6 rankings? Should we add to that conversation like
7 someone deciding is a nursing home worse than an
8 LTAC versus --
9 DR. GIRARD: You're right. Within our
10 group, for the clinical trial that I'm referring
11 to, we had 3 rounds of international consultation.
12 When we designed the study design, we had the
13 luxury of doing that before we submitted it, so we
14 had some sort of input. But fortunately -- and
15 then we made the decision regarding a priori
16 statistical analysis plan. We could also do a
17 sensitivity analysis if say that there were big
18 differences in patients that were unable to walk.
19 Death was the same, but unable to walk, we
20 could do a sensitivity analysis and say how would
21 the results look differently if we changed the
22 ranking? But we put our nickel down and said this

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1 is the ranking that we're going to use, and other
2 people seemed to think it was appropriate.
3 DR. COLANTUONI: I think also it's clear
4 from our discussion, I think, that these are still
5 going to be considered secondary endpoints. So no
6 one's going to be -- we have to keep that in mind,
7 that a lot of this will be exploratory, and over
8 time will evolve into stronger hypotheses, and then
9 these conversations can happen to kind of fine tune
10 the analytic approaches.
11 DR. GIRARD: Good. So it sounds like in
12 terms of after sedation outcomes, we're in
13 agreement that long-term outcomes will be
14 recommended at 6 or possibly 12 months and that
15 those outcomes -- that the plan to analyze those
16 outcomes should be prespecified and account for the
17 possibility of confounding by differential
18 follow-up.
19 Is that correct?
20 DR. COLANTUONI: Could you add -- so we have
21 the patient-centered ones, it sounds like, to be in
22 the cool. Could we add the family-centered outcome

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1 that was suggested over there, and maybe caregiver
2 burden, recommend but not require a measure of
3 caregiver burden?
4 DR. GIRARD: I think that makes sense.
5 DR. COLANTUONI: I think some have been
6 shown valuable and reliable in critical care.
7 DR. GIRARD: The last question that came to
8 my mind as I was thinking about the questions to
9 discuss, maybe one that we've already inadvertently
10 answered, and that is how should these long-term
11 outcomes be assessed? By virtue of the fact that
12 we've agreed to recommend the core outcome set for
13 acute respiratory failure survivors, that would
14 imply that we're recommending assessment over the
15 phone.
16 Is there any interest in considering that
17 some or all -- or maybe a better way to put it is,
18 all or more feasibly, a subset of patients were
19 assessed in person. Do you think there will be any
20 additional value to doing that?
21 DR. NEEDHAM: That's the approach that we've
22 used in -- like a large national clinical trial

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1 from a clinical trials network, all patients were
2 assessed by phone through two centralized call
3 centers, and then 5 of the 12 study centers through
4 supplemental funding through an ancillary grant had
5 more in-depth testing through in-person. And
6 in-person may be in your research clinic or it may
7 be in the patient's home or institution, so you
8 need funding time and skills and safety issues to
9 go out to people's homes.
10 But yes, I think that's great. It
11 provides -- if somebody did a patient-reported
12 physical functional outcome, that is going to be
13 different than a performance-based physical
14 function outcome. They measure different things
15 even though they're both physical function
16 measures. So it does reveal new information.
17 DR. HOPKINS: This is Mona. I agree.
18 DR. WARD: Is there also a role for a
19 qualitative study and that subset that you can do
20 the interviews with; not 200 your patients
21 obviously, but in a few patients?
22 DR. NEEDHAM: I would agree, and I think

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1 some of us have talked about how that would be very
2 helpful, especially in sedation trials where we
3 don't have a measurement tool to capture the
4 patient experience that we've heard about, I think
5 that would be very rich.
6 I'm not a qualitative researcher, so other
7 people correct me, but we have done qualitative
8 research by phone, which allowed us to capture
9 patients across all the 45 hospitals in the
10 research network, or some of them, rather than just
11 from a single center through phone, and obviously
12 input from qualitative research
13 and lots of training.
14 DR. GIRARD: Okay. So I think that it was
15 okay that we donated some time for this session to
16 the previous session.
17 DR. WARD: I think I can still finish up
18 early.
19 DR. GIRARD: Yes. Any other comments about
20 post-ICU sedation outcomes that we did not address,
21 that you've just got a burning desire to bring up
22 because now is your chance?

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1 DR. NEEDHAM: I've got one quick comment.
 2 We need to think about when we talk about discharge
 3 location or institution-free days, as JP said, we
 4 need to recognize that these things, especially in
 5 the United States, are directly affected by
 6 people's insurance status and also by family
 7 support status, and wealth, whether you can hire
 8 somebody to come into your home, or not, to provide
 9 the services that might otherwise be provided in
 10 the skilled nursing facilities. So those are
 11 important kind of confounders as well.
 12 DR. GIRARD: All right. Denham, I think
 13 you're up.
 14 DR. WARD: Great. Thank you.
 15 (Applause.)
 16 Group Discussion
 17 DR. WARD: Well, thanks everybody for
 18 hanging in there the last day and a half. It's
 19 been exciting for me. As a pharmacologist,
 20 respiratory physiologist, clinical trialist, this
 21 is a little out of my wheelhouse, but it goes along
 22 with what we've been doing in the SCEPTER realm, in

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1 the 9 months it took to put this group together,
 2 and I appreciate -- almost everybody who I asked,
 3 and most of you I didn't know personally -- almost
 4 everybody who I asked responded very quickly and
 5 said, yes, I'd be interested. So in that sense,
 6 this was a great meeting to put together.
 7 There are a couple of things I want to go
 8 over for kind of the next steps for us. This is
 9 complex. This was a great diagram that I had found
 10 in my background work. The interaction with what
 11 we're trying to do with sedation between pain,
 12 delirium, and unpleasant awareness is obviously
 13 very complex and much more difficult than the
 14 procedural sedations that we worked on in SCEPTER I
 15 and II.
 16 What the deliverable is, this meeting is one
 17 of the deliverables. I think we have had a
 18 discussion with the FDA, both representatives, both
 19 directions, both hearing from them, and they're
 20 listening to what we're talking about. So we've
 21 accomplished one of the deliverables. We've
 22 brought together experts in the

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1 field -- clinicians, clinical trialists,
 2 sedationists -- and we've talked about how we would
 3 look at clinical trials for drug device protocols
 4 for ICU sedation and analgesia.
 5 The next deliverable, as we did with
 6 SCEPTER I and II, is a paper that would serve as a
 7 resource. It's not a practice guideline. It's not
 8 in the sense of a consensus document, although we
 9 like to have some consensus in it. But it will
 10 serve as a resource for the design of clinical
 11 trials.
 12 I would like to go back through what I first
 13 talked about for the IOM report and healthcare
 14 quality domains, and I would like to organize the
 15 paper along this same line, that the IOM talked
 16 about 6 domains of which 4 I think are directly
 17 applicable to our topic of safety, patient
 18 centered, and I would say patient/family centered
 19 there, effective and efficient.
 20 We've had a lot of discussion over these 4,
 21 and the first one was our most difficult one. I
 22 actually put this slide together before we had the

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1 discussion this afternoon. There's obviously some
 2 modification to that first one. But I think we've
 3 come up with some sort of measure of -- and
 4 probably RASS, although there are some
 5 alternatives. And again, there's no must in these
 6 kinds of papers as it serves as a resource -- that
 7 a RASS at a sedation level that may vary throughout
 8 the time of the use of sedation if it's being used.
 9 I think we will spend some time on email
 10 understanding a little better the indication for
 11 sedation because I think that's been a topic that's
 12 come up, and we haven't really resolved that. The
 13 target RASS may not be a zero and minus 1
 14 throughout the whole sedation period, and that's
 15 fine, too.
 16 Clearly, there's also some safety related
 17 outcomes beside the usual measurement of the SAEs
 18 and the AEs that terminology like MedDRA uses so we
 19 can report these adverse events in a systematic and
 20 a systematic way. But as you discussed with
 21 procedural sedation, there are things you kind of
 22 expect. If you're using an opioid procedural

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1 sedation, you better be looking for what the
2 saturation is going to be doing as a safety
3 outcome.
4 So there are probably some things that we
5 need to look at when you're doing ICU sedation,
6 that it's not the usual AEs and SAEs, and I would
7 think the measurement of delirium not cooperating,
8 a variety of things, agitation, that would be a
9 safety outcome. Then there are other secondary
10 outcomes that are more patient centered perhaps.
11 To me, pain is the one that is patient
12 centered. You can argue you want more sedation or
13 less sedation, but saying I only want more pain,
14 probably most patients would say, "I don't want to
15 have any pain." So to me, if all of these
16 outcomes, pain is the main patient-centered outcome
17 that we all -- unless there's a masochist -- want
18 for our patients, and really don't want to have
19 pain, and then other longer terms.
20 Pam?
21 DR. FLOOD: Not to mince words, but I think
22 that certainly everybody wants less pain; nobody

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1 wants more pain, but some people would trade a
2 little bit of pain for consciousness.
3 DR. WARD: These all interact, absolutely,
4 and that's the kind of things that need to be taken
5 into consideration, obviously, for the design of
6 the trial.
7 Then there are the secondary outcomes that
8 include both patient centered as on short-term,
9 behavioral pain scores, and longer term -- a longer
10 term consensus came a lot easier than I thought it
11 was going to be. That turned out to be the easiest
12 part of the meeting. I think a lot of that comes
13 from all the great work that Dale and his group has
14 done to set the stage for the validated tools that
15 are available.
16 Then I would put things like time to
17 discharge, hospital, ICU as really the efficiency
18 parts. As I said, with efficiency, you have to be
19 careful of whose efficiency. So it's not just cost
20 shifting off the institution or healthcare system
21 to the patient and the family and their insurance
22 company, and those are the kind of things.

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1 So I think we've got ideas in all four of
2 the IOM domains for high-quality health care. If
3 we could come to some level of agreement for
4 recommendations for these, along with indications,
5 and study design, and some of the statistical
6 things, that Elizabeth's going to be able to write
7 that section for us.
8 A few things for next steps. Is everybody
9 comfortable with distributing everybody's slides to
10 everybody? Any objection to having your slides
11 sent out?
12 (No audible response.)
13 DR. WARD: So along with the picture of
14 everybody, I will send out everybody's slides to
15 everybody.
16 I've had some but not a lot of experience
17 with Delphi technique. Dale has had a lot,
18 obviously. He and I discussed using Delphi before
19 this meeting, and I decided not to. I was kind
20 over overwhelmed with getting the whole thing
21 organized without adding that to it. But after
22 this meeting, I'm wondering what you all think

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1 about using a Delphi survey to see what kind of
2 agreement we've got on some of these. And I would
3 probably ask the group to provide the questions
4 that we put on the Delphi as it goes around.
5 What do most people think about doing that?
6 There's one thumb up there. Do you think it will
7 be worthwhile? I think it would add to the paper.
8 The methods of these kinds of papers are not the
9 usual methods section. The methods section is
10 about the information we distributed to the group
11 beforehand, and that was the PADIS and papers that
12 I sent around to everybody ahead of time. That was
13 all we had. So we talked about here, and then Rigo
14 said part of the methodology for reaching our
15 recommendations was a post-meeting, Delphi of the
16 meeting disciplines.
17 DR. GIRARD: I think it's a good idea. I do
18 have one question both for you, Denham and Dale,
19 having done this before. It seems like we're
20 highly motivated to come up with a recommendation
21 about primary outcome. We've revisited that
22 question multiple times. The one thing with

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1 Delphi, though, there is no consensus. Are we then
2 going to make the recommendation that someone
3 develop one because we couldn't come up with one,
4 or what would be your plan in that case?
5 DR. WARD: Yes.
6 (Laughter.)
7 DR. WARD: I think we'll be stuck with that
8 as we recommend that there is no consensus, and
9 that needs to be one of the key things we'd have to
10 develop because you can't really move forward
11 looking at a new molecule if you don't have some
12 consensus on how you measure efficacy.
13 Coursin? Doug?
14 DR. COURSIN: Could we look at modulating
15 the Delphi to come up with a PICO question or two?
16 We know the population for the most part, but
17 what's our real question?
18 DR. WARD: I think the Delphi would have
19 multiple question, and certainly all the elements
20 of the PICO could be -- we discussed that a little
21 bit, should we be moving beyond, and how important
22 it is to do your clinical trial in a homogeneous

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1 unit, 100 percent agree or don't agree. That's the
2 kind of way the Delphi would work.
3 Dale, do you have any comments on how we --
4 DR. NEEDHAM: This is Dale Needham. I guess
5 the way I envisioned it, which may be not what
6 Denham does or anyone, but we've come up with a
7 bunch of recommendations or whatever, and those
8 will be in the manuscript, I think maybe your
9 irrespective, and this is sort of recommendations.
10 But then the Delphi allows people to objectively
11 anonymously really say if they agree with it or not
12 because some people may not have agreed with and
13 may not have expressed it.
14 So we may still have something in the paper,
15 and then we can express the level of agreement with
16 that recommendation.
17 DR. RIKER: I think Delphi also allows you
18 to comment on the areas of what's proposed that you
19 have a problem with, and then you can tweak that
20 and then revote. So it may be that if we're having
21 trouble coming to consensus about this primary
22 outcome, through the process, in addition to

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1 identifying the level of support for the group, you
2 can also find a common ground with that.
3 DR. WARD: If you don't agree with including
4 this, you get to get a recommendation on what you
5 would agree for, and then that goes in the next
6 Delphi, in the next Delphi round for it.
7 DR. DEVLIN: I saw critical care medicine up
8 there. Is that your target journal, potentially?
9 DR. WARD: A thought, yes.
10 DR. DEVLIN: [Indiscernible] I'm on the
11 editorial board. I would also, if that's your
12 target journal, it might be strategic to reach out
13 to hand that this group's convened to talk about
14 what we're putting together. He's a pretty
15 hands-on editor, and he might provide a little bit
16 of informal feedback about what he'd like to see
17 rather than just submitting something and hope for
18 the best.
19 DR. WARD: Sure, yes.
20 DR. DEVLIN: And that could inform some of
21 us a little.
22 DR. WARD: A little bit an anecdotal story

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1 on that, the first paper at the first SCEPTER
2 meeting went through a fair amount of editorial
3 discussion, shall we say, at Anesthesia &
4 Analgesia, and they finally accepted it as part 1.
5 I said, "Great," because now I can send them part
6 2, and they've already said they've got part 1, so
7 now I get part 2 in.
8 I would probably, with your help,
9 communicate with him and show him part 1 and part
10 2, and this would be a similar kind of -- but I
11 think the audience will be better in CCM than in
12 Anesthesia & Analgesia for that.
13 DR. SHAFER: In the Delphi process, is there
14 any sort of assumption among the participants that
15 we are going to try to reach consensus? In other
16 words, this is not the U.S. Senate --
17 (Laughter.)
18 DR. SHAFER: -- and the hope would be -- my
19 hope would be -- that people would really try to
20 find a consensus viewpoint rather than putting
21 stakes in the ground. Is that part of the Delphi,
22 or is that just assumed, or does that not happen?

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1 DR. SKROBIK: Can I comment on just the
2 consensus notion because John and I had a
3 discussion about this. This is Yoanna Skrobik.
4 When we were doing the guidelines, we swayed from
5 the party line because we thought that if we said
6 consensus or made it sound like we wanted or needed
7 consensus, there would be two problems with that.
8 One, it would suggest that there was one right way
9 of doing things all the time, so we shied away from
10 that, but also it wouldn't represent variability in
11 patient populations, or practice, or opinion.
12 The way we got around that was we tried to
13 ensure the communication about the content. Once
14 we had clarified what you meant by a metric for a
15 sedative, then there was much greater agreement.
16 So we fostered, and hammered, and encouraged, and
17 we're exhausted from all we learned about the
18 communication piece. And at the last minute, we
19 stepped back and we let people vote whether they
20 agreed or disagreed, and then published the
21 dissenting percentages and allowed people to
22 comment.

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1 I wanted to put that on the table as an
2 alternative to consensus because there are going to
3 be different points of view. I think it's rich,
4 but I also think that we should agree on something.
5 DR. WARD: Talmage?
6 DR. EGAN: Talmage Egan. I recently
7 participated in Enhanced Recovery After Surgery,
8 which is a society that's gaining some traction in
9 the anesthesia world -- recently participated in
10 the Society for Enhanced Recovery After Surgery
11 pre-operative quality initiative, which is another
12 cool acronym, POQI.
13 This POQI task force, which is a group that
14 operates under the auspices of this ERAS society
15 was tasked with putting together some guidelines, a
16 consensus statement regarding neurophysiologic
17 monitoring in the perioperative period. Anyway, we
18 used the Delphi process. It was a 2-day conference
19 like this, actually, and the groups were charged
20 with putting forward statements, then the entire
21 group would get together and refine these
22 statements.

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1 This was an iterative process where we'd put
2 the straw man together, people would vote, and then
3 they'd get comments and they'd take them back, redo
4 them, and bring a refined statement back. And
5 ultimately, the idea was to have this Delphi method
6 described in the methods section of the paper.
7 Anyway, the point I wanted to make is that
8 the deliverable from this Delphi process were these
9 statements. The voting of the statements were
10 ultimately to be part of the deliverable so that it
11 was clear whether there was a consensus or not.
12 Then the same people were able to describe the
13 elements of their dissent in the actual text of the
14 paper.
15 So that was the way this group approached
16 the Delphi process, and I think it worked out
17 reasonably well. But a key thing is that you have
18 to get everybody to vote so that there's not an
19 implicit bias of some kind.
20 DR. WARD: There are multiple rounds. If
21 you agree to come in on the first round, you really
22 have to agree -- usually 3 rounds is one of the

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1 standards that I've seen and what I've done. You
2 have to agree to come in on round 2 and round 3 so
3 you don't get a dropout as it goes through.
4 Dale, do you have any comments?
5 DR. NEEDHAM: I think those are both great
6 ideas. To make this less painful, many Delphis, if
7 we reach consensus on 75 percent of this, you don't
8 vote on it again. It's just what there isn't
9 consensus on. At least in my mind, maybe it's like
10 this was the original statement. This was the
11 level of consensus. This was some revision after
12 more discussion during a Delphi maybe.
13 DR. SKROBIK: [Inaudible - off mic] -- gap
14 identification might be -- if what we want to do is
15 build, give to the patient and to future
16 generations, a tool that they can use to better the
17 way they ask and answer questions and the way we
18 serve that patient population, if that's the goal,
19 and you haven't got consensus on 25 percent of
20 Delphi -- I don't know what you think of, because
21 you were looking for answers, but you were looking
22 for outcome measures. That's a very different

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1 thing than disagreeing because -- and I think maybe
2 it might be -- just as we did with the guidelines
3 to say there's a gap/here's the gap, if we can
4 identify it, then naming it because it would also
5 be constructive.
6 I'm putting it on the -- obviously, I think
7 it's a good idea because we did it for the
8 guidelines, but I'm proposing it as a novel way of
9 addressing these limitations for instance.
10 DR. WARD: To answer Steve's question
11 directly, the
12 government will give you a chance to report the
13 level of agreement. You can pre- -- most Delphis
14 say, okay, if it's 75 percent agreement and there's
15 no vetoes, then it goes on. But you can also
16 report this is a recommendation, but there was only
17 65 percent agreement.
18 DR. SKROBIK: I'm always suspicious of 100
19 percent agreement, unless it's something like pain
20 should be assessed, I'm stunned at that. I think
21 what did they do, what did they give you?
22 DR. WARD: It sounds like the Delphi, people

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1 are going to participate if I start a Delphi
2 process.
3 The third one is help writing the paper. Is
4 that something everybody wants to participate in?
5 Because that's what I did for the first two papers.
6 I wrote it, and then everybody participated,
7 everybody's a little asterisk on it because there
8 were degrees of participation.
9 I won't obviously use his name. One of my
10 friends, who's actually on the editorial board of
11 one of the other journals, never heard from him the
12 whole time, and this was like 5 rounds of getting
13 everybody to agree, until I sent it out to
14 everybody and said, okay, I think we finally got
15 agreement. This is what I'm going to send in, and
16 I immediately got back from him 10 pages of
17 modifications that he wanted.
18 So if you're going to participate --
19 DR. SHAFER: Delete.
20 DR. WARD: -- everybody gives their name
21 on -- it's like these are the people and the group.
22 But I was willing on the other SCEPTER to put

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1 everybody's name up there in the headline. But
2 would people be willing to put a writing group
3 together that would get the primary piece of credit
4 or blame, and then everybody gets -- does that
5 sound like a reasonable approach? Because I'm
6 being a little gun shy from having written up this
7 twice.
8 So if that's reasonable, would you let me
9 know by email your willingness to participate on
10 the writing group.
11 Elizabeth, you don't have a choice. You
12 have to be on this. You have to be on the writing
13 group -- to be on the writing group to help me put
14 this together for that.
15 DR. SKROBIK: I sent you some of the
16 summaries from yesterday morning, and I've written
17 up a bullet point summary of what I understood from
18 this morning's session between 10:30 and 12. And
19 what I would also like, regardless of participation
20 in the writing group, is just vetting for some
21 of -- if I send it around and you have time to look
22 at it, it's not long. It's a bullet point list, if

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1 there are things that I've forgot. Lisa
2 and -- were kind enough to do it with yesterday's
3 group.
4 DR. WARD: One more slide I think. Any
5 other questions, comments? Egan?
6 DR. EGAN: I just want to make two quick
7 questions just for your transcript because these
8 two issues didn't come up. One is because of the
9 profound synergy between these sedative agents and
10 the analgesics, the opioids, the analgesic regimen
11 really does have to be carefully controlled. We
12 didn't really mention that, but that drug
13 interaction is so profound that that's very
14 important.
15 The second thing is if TCI were to be
16 entertained as a trial method, we're not going to
17 use that in the real world, so why would we do that
18 for a new dex? I think that the FDA combination
19 products group could evaluate the drug and the
20 delivery system as an entity together, and it can
21 be approved in that way. It's not a non-starter
22 from the beginning.

1 DR. WARD: Any other final comments or
2 concerns?
3 (No response.)
4 Adjournment
5 DR. WARD: Thank you all for participating.
6 ACTTION appreciates you.
7 (Applause.)
8 DR. DWORKIN: Denham, and thank you very
9 much. You did a great job.
10 (Applause.)
11 (Whereupon, at 2:38 p.m., the meeting was
12 adjourned.)
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