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

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ACTTION

SEDATION CONSORTIUM ON ENDPOINTS AND PROCEDURES FOR TREATMENT, EDUCATION, AND RESEARCH (SCEPTER-III)

Clinical Trials to Evaluate Patient-Centered Outcomes of Sedation in Mechanically Ventilated Patients in the Adult ICU

Friday, March 29, 2019
8:00 a.m. to 2:38 p.m.

Westin Georgetown Hotel
Washington, DC

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

DR. WARD: It was really an exciting day yesterday with some controversies and some questions. We have a couple of talks this morning before we get into really kind of the meat of the meeting, and that is really to continue the discussion on how you would design a clinical trial for ICU sedation. At the end of the meeting, I will talk about some of the deliverables that we would like to have.

I think one of the things to keep in mind among the things we're talking about is -- Merv is going to talk about dexmedetomidine -- if a new dex that comes along, if a company's got the new dex, what do they have to do to get it approved? Probably the FDA is not going to say, well, if you show that the quality of life improves 6 months later and back to work, that's not going to get new dex approved as an ICU sedation drug.

Those are all great things, and we should be talking about them, and those are things we would

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like sedation in the ICU to accomplish, but indications have to be a lot tighter connected to the mechanism of action for the drug. The question that I asked yesterday, and at dinner last night, and I still haven't got an answer to -- I think it was Rich who said we should move past a RASS score minus 1 or 2 as the primary outcome. What is the primary outcome?

If you have the new dex, and you have a company that -- not to push the money too much, with Steve, but if the money was there to get new dex approved and you're the consultant, what would you say the primary outcome should be for that study?

DR. FLOOD: Why would a significantly improved talk about quality of life at 6 months not be an acceptable outcome?

DR. WARD: Could you use the microphone?

DR. FLOOD: Sure. Pamela Flood. Why would an improved quality of life at 6 months not be an acceptable outcome?

DR. WARD: Bob?

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DR. DWORKIN: There's no question it's an acceptable outcome -- [inaudible - mic distortion], and of course you'd want to know that, but it's a basis for approving a drug. I don't see anyone here from the FDA. I don't see Rigo or Marti [ph].

I think that if you want to approve a drug with a label for sedation, when you do it for ICU, [indiscernible - mic distortion] to talk about quality of life 6 months later. If there was someone from the FDA, I'm sure they could flush out that answer a little better.

DR. FLOOD: I was assuming that it was actually functional as an anesthetic, but it would definitely show a benefit over other sedatives if it was just as good acutely as a sedative but there was a recovery benefit. No?

DR. WARD: As a primary endpoint, if the labeling says it's a sedative, you've got to show it's a sedative for that. It's not going to be assumed that the regulatory agency level. I think that's a question that we need. If we're going to help people design clinical trials, we need to come up with some thoughts about what would be our primary endpoint for that.

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There's some housekeeping stuff. Sign in. Silence your cell phones. Remember, you're being audiotaped, and there's going to be no 18-minute blanks in these tapes. You're all going to be there for that. WiFi. Checkout is noon. You can bring your luggage down here. Lunch is the same place, and the usual transportation will be available to go to the airport, or train station, or wherever you're going afterwards.

This morning, before we have the first panel, Pratik is going to talk about what I kind of just talked about, is how do we define a major light versus moderate sedation analgesia. Then I want to finish up with the presentations. Dex is the only drug that has been specifically approved for ICU sedation, and Mervyn was one of the key people in that ever since he came down to UCLA and said, "I've got this drug. Would you like to do some phase 1 trials with it?" And I said, "How come you're not doing it first?" He said, "Well, I

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think we should do it in southern California first," and really got dex through the whole approval process. So I've asked Mervyn to talk about the story for getting that drug approved.

Pratik?

Presentation - Pratik Pandharipande

DR. PANDHARIPANDE: Good morning. When I initially had suggested this talk, I thought I was going to do a recap of the literature, talking about how light levels of sedation would be defined in the literature. Then after yesterday's discussion, realizing that a lot of people over here are knowledgeable and have actually created the literature that supports those definitions, as well as the fact that we already got off to a relatively robust discussion about what light level versus deep level should be.

I thought I'd split this talk about introducing the elements in the guidelines, how it was defined there to give us a framework, and then bring in some of the discussions we've already had yesterday to try and use that as a springboard for

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discussion so that we're actually moving forward and not just talking about what we've talked about in the past.

For disclosure, I do have a research grant from Hospira, now Pfizer, which makes dexmedetomidine, and it's a collaborative effort between the NIH for an RCT that we're doing on propofol versus dexmedetomidine. The study drug is provided by Pfizer. All other grant supports are shown over there. NIH R01s are what form the bulk of non-Vanderbilt [indiscernible] salary support.

As we think about light sedation, I think it's important to realize what are the indications, at least in the literature, for sedation use because as we move away from using sedatives and moving towards light sedatives, we need to remember why we initially at least taught sedation is required in some patients in the ICU. And while it's true that all these indications no longer may hold true, it's important to at least keep that in mind. So perhaps we still feel it's important that patients don't have anxiety in the ICU. Perhaps

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it's still important that patients in the ICU don't remove their devices, their endotracheal tubes, their central lines.

The question about whether it reduces physiological stress response, in some patients it may be important and we may want to consider that. Patient ventilator synchrony seems to be a big one that shows up in many articles regarding sedation levels, and that may be something that we have to think of. And I bring this up later on, whether there is a temporal change in sedation levels that one needs to consider. Is it one score at all times in critical illness or do we also need to think about how we define light sedation differentially as the time and the elements of critical illness results?

At least in the past, I think there's been a fair amount of concern that we needed to have patient sedated in the ICU so that they didn't remember anything about their ICU stay. This is an area that is debated. The question is whether we have strong enough evidence now to say that that

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entire concept of deep sedation associated with improved psychological outcomes, or the other way around, being awake, not associated with psychological, heavy debunked that complete association.

So the question is whether we have large enough studies, and most studies that I have at least looked at are relatively small. They're post doc analysis of other studies, so that's something I think we need to keep in mind.

Deep sedation, we all know is associated with worse outcomes, and I'm not going to belabor this point. At least some of the studies that have been looked at in the 2018 PADIS guidelines focused on RCTs that have shown that having a lighter level of sedation -- and we'll discuss about how those were defined -- were associated with shorter time on mechanical ventilation, shorter time in the ICU, et cetera. The question is whether light versus deep sedation makes an impact on mobility, and I think most of us, anecdotally at least, know that your comatose patients can't walk, so that may be

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something to obviously think about.

More recent data, at least starting with associations, I don't think we have gotten to causality over there; the associations of deep levels of sedation and mortality, deep levels of sedation or sedation levels higher than what should be probably prescribed to delirium, and then the question, again, about neuropsychological outcomes.

This is a study that I put up a couple of years ago. And I was telling Mona that only yesterday when I revised my reading of this study that I realized that Mona Hopkins over here was the senior author on this paper. This is ARDS survivors looking at recall of the ICU state. I think many of us years ago would see patients come back to the ICU and say, do you remember anything of the ICU state, and patients would say, "No, I don't," and I would consider that a victory on my part that I got you through the critical illness, the worst period of your life. I managed to erase all memories of that. What a great job I did. I think many of us now would think that perhaps not

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so fast; maybe we were actually doing patients harm.

In this study in particular, what they looked at was in 70 ICU survivors after ARDS, whether recall of the ICU stay was associated with neuropsychological sequelae, cognitive impairment, and other sequelae. What they showed was that at discharge, 1 year or 2 years, if you look at the no recall group in yellow, you had worse neurocognitive sequelae than the group that had recall. Other studies that Christina Jones, et cetera, have done have shown that if you have recall of ICU stay, as long as it's factual, even if it's painful, you tend to do better. You process it better than if you have delusional memories of your ICU stay. So the context of what kind of memory of the ICU stay, that's important as well.

Let's switch gears a little bit to the guideline recommendations of light versus modern deep sedation. The 2013 guidelines did look at this question, and the question that they

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specifically asked, with regards to the depth of sedation, is should ICU patients be maintained at a light level of sedation? It was an actionable item. It was a graded recommendation.

What their recommendations were was maintaining light levels of sedation is associated with improved short-term outcomes. So that was the focus of the question. The 2018 guidelines, as I show you, focused on more of the long-term outcomes. We did not want to revisit what was already shown to be decent quality data, so moderate quality data. These are B recommendations; associated with a shorter time on mechanical ventilation in ICU length of stay, that there may be some importance with regards to physiological stress response, and unclear about the psychological dysfunction, and therefore we try to look at it in the long term in the 2018 guidelines and still found that there was very little evidence.

They recommended that sedative medications be titrated to maintain a light rather than a deep

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level of sedation with a positive 1B recommendation; so strong recommendation based on moderate level of data.

If you look at the 2018 guidelines, there are some differences. We looked at the long-term outcomes. We actually defined the way we look at light versus deep sedation in these guidelines. The question was does light sedation versus deep sedation, regardless of the sedatives -- so the sedative was not considered in this discussion at all -- does it significantly impact outcomes? And the outcomes based on the priority scoring will focus on long-term outcomes, 90-day mortality, cognitive impairment, PTSD, so not any of the short-term outcomes, all 90 days and beyond.

The recommendations, and more importantly even the gaps -- the recommendations were we suggested light versus deep sedation. It's a conditional recommendation, low quality of evidence because there weren't many RCTs looking at long-term outcomes. There were a few, but not too many. And the evidence gap is I think what we need

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to focus on.

There was no consensus of definition of light versus deep in the literature, so we utilized certain definitions, which I'll get to in the next slide. The relationship between changing sedation level over time; is one time good enough? You have to figure out a way to capture sedation over time, over time in a day, over time in the ICU, et cetera. How do you factor that in?

Then ultimately, those light levels of sedation have to be associated with outcomes. When we talk about let's target light levels of sedation, we need to be able to show that those are consistently associated with outcomes, especially the long-term outcomes, and that's where the gaps were.

Here's how the 2018 guidelines defined light versus deep sedation for the purpose of the studies that were chosen for the recommendation. We utilized those studies where light versus deep sedation was explicitly stated by the authors as the criteria for randomization. They may have used

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

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

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

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

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

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

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subjective. Some people talk softly; some people talk loudly. Is there some element?

In general, there are some guidelines, so I would say that they're relatively objective versus moderate sedation, deep sedation, et cetera, but there is some element of subjectivity in these scales.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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changes. It's not as much. Then your definition of light sedation moves to zero to minus 1. So over a period of time should the definition of light sedation change with regards to the fact that critical illness is resolving or getting worse?

The third part, which was introduced over here yesterday in conversation, and whether this becomes an element as an outcome or it gets even incorporated into some of the objective scales, where we have a little bit of subjectivity added to an objective scale, is whether we should be looking at these elements. Is following commands an important outcome? Perhaps it's a number, but should we be going further? Is it ability to follow commands?

In JP's study, it was defined as three out of four objective actions. You had to open eyes to voice. You had to track the investigator and request. You had to squeeze hands on request or stick out the tongue on request. So is that where you should set the bar or is it just opening eyes and making eye contact for 10 seconds? That's one

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area to think about.

Is ability to communicate important? When you look at the PRODEX and MIDEX studies, looking at propofol versus dex or midazolam versus dex, some of the outcomes that were shown to be beneficial were the ability to communicate. And the ability to communicate is beyond just talking to your team or your family. That's important.

We already heard yesterday, when Dr. Shafer said the first thing that comes up was a big element in him realizing that we're going to get through this, and other patients have also communicated that with us.

You can communicate with your medical team and actually be a part of your management, being able to discuss goals of care, et cetera, which otherwise a surrogate has to do. You can communicate your pain needs. Some of the studies which have shown lighter levels of sedation have also shown more in medication requirements, perhaps because patients are now able to communicate that I'm not comatose. I'm in pain. Give me some

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medications for that.

Ability to participate in mobilization, I think that's another important outcome and whether that should be considered as a stand-alone outcome. Many of our survivors when we see them in clinics or when we have them come back to Vanderbilt, they note that the day they participated physically themselves actively in mobilization was the day that they felt that they were going to survive because that was the first time in their life that they actually had some control.

Everything else somebody else was doing. When they had a bowel movement, somebody else was cleaning them up. But if they were able to sit on their own or stand up on their own, that was a very big moment in their lives, and we'll see whether other patients represent, that we have that same thought. That is one thing that many of our ICU survivors in our clinic say, "That was the first time that I felt I'm going to survive and I can be independent. I can do something that I have control of. I decided to stand up or I decided to

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participate in physical therapy."

The other part is as we think about long-term outcomes, having a patient not comatose and interactive, apart from participating in physical therapy, there may be benefits, ability to participate in cognitive exercises. Is that something we should be looking at?

Again, there are data to show that being able to participate in some of these activities are associated with improved outcomes. So going back to JP and [indiscernible] study, looking at ability to mobilize, even though sedation regimens in this study have been reported that they were equal in both groups, the ability to mobilize is associated with improved outcomes.

If you're targeting a light level of sedation, which ends up in having more mobility, we have data which shows that that is associated with long-term outcomes, so perhaps an outcome that we should consider for our short-term benefits because it has impact on our long-term outcomes.

The next part is this relationship between

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changing sedation over time. I think this is an area that we do need to think about. It's one thing to be able to get a static measure, did somebody communicate. And the question is how do you look at level of sedation over time?

How do you summarize sedation over time? Looking at, again, the SPICE study and Yahya's observational study, looking at number of 4-hour epochs of light versus deep sedation, categorized as minus 3. Perhaps if we change that threshold, the same data set can probably be looked at, at minus 2, minus 1, and trying to figure out whether there's a difference in outcomes based on that.

Is there a way that we have an area under the curve approach, the minimal time? How long do you need to be light? However you define it, is it one time a day? Do you have to be there for at least 4 hours? Is it half a day? I think that needs to be defined. So some way to try and get a burden of the area under the curve, and we'll have to figure out how that outcome can be defined. But that needs to be considered, the length of time

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that one is light per day.

The [indiscernible] published the Sedation Index, looking at the number of negative RASS scores. You add them up. You divide with the number of evaluations, and that has an indication with mortality. Again, that's another way to summarize that. While it may not be a way to do it real time because you have to wait for evaluating that over time, it's something to at least think about, and perhaps every 12 hours you can re-evaluate the Sedation Index in the previous 12 hours to try and optimize the regimen for the next day, so it is something to think about.

Plasma levels, there have been some studies looking at it, not the greatest amount of correlation, at least with sedation levels based on some of the literature reading that I've done, but those are out there. Maybe we will get better at doing that. Maybe it will be faster. We can incorporate some of the changes that are going on in critical illness, but that's something out there.

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Then early work in objective sedation tools, EEG based, haven't really panned out with significant data, but at least they're out there, and in the future we probably need to get high fidelity instruments, and we may be able to assess light versus deep on that. I don't think we're there yet.

Ultimately, we're going to have to figure out whatever we define, so there are various ways -- I talk about how you can define light sedation. Ultimately, that has to be associated with improved outcomes. That's one thing because on the other side of it, there's risk.

So you have to make sure that whatever we decide as far as threshold, incorporating that time element, it has to be evaluated for short and long-term outcomes and then balanced against the perceived risk because, still, those self-extubations, those device removals, anxiety, et cetera, and perhaps some unintended consequences that we don't even know yet all have to be balanced.

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I'm going to end with that, and hopefully I'm on time. Thank you.

(Applause.)

DR. WARD: We can take some time for some questions now because we don't have a specific panel. I have a question. How do you incorporate sleep and the need for sleep into your sedation assessment every 4 hours? You wake somebody up? Is a sedation assessment different at 2 o'clock in the morning than it would be at 2 o'clock in the afternoon? Because there is a diurnal rhythm that still takes place in the ICU, I assume.

DR. PANDHARIPANDE: I think incorporation of sleep in some ways is important. The question is how. I really don't know the answer because adding 24-hour polysomnography is not a very easy option, practically, I mean. It can be done in the research setting. Whether some of the newer devices are going to be able to show you EEG patterns without doing full polysomnography, I think those are things that have to be considered.

So I think at this point with at least the

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definition of light versus deep sedation, I'm not sure how you can incorporate sleep in it as well. As we discussed yesterday, it would be great to incorporate pain in it as well and incorporate sleep in it as well. But all of these agents are not necessarily sleep promoting all the time. There are some data showing that perhaps dexmedetomidine is associated with better sleep outcomes.

Yoanna and John have done the nocturnal dex study, which showed those benefits. On the other hand, many of the other studies have all been done in normal human volunteers. So we don't really know whether we have the best drug. It does improve non-REM sleep but reduces REM sleep. The whole REM cycling, et cetera, none of these agents actually do that.

Michele and then -- lots of questions.

DR. BALAS: I'd like to start by saying, God bless the souls of the people who developed these tools and did the psychometric testing, something I swore I'd never do. I've been using these for over

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a decade.

I think it's interesting. If you could flip your slides back to whatever sedation scale you want.

DR. PANDHARIPANDE: Will you load my slides back up, please?

DR. BALAS: Oh, sorry. Anyway, I never considered this before, but the definition of agitation just popped out at me. Once again, bringing up the point about what we're trying to measure and the need for conceptual clarity, it's interesting to see how all of the different tools define the agitation.

Let's start with the first one.

DR. PANDHARIPANDE: Which one do you want to start with?

DR. BALAS: Whatever one is first.

DR. PANDHARIPANDE: John's going to answer the question since he validated the tool.

DR. BALAS: No external stimulation required to stimulate movement. Why is that bad? Why would that be considered agitation? Attempting to sit

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up, why would that be bad? So you need both of them. So if the patient's just awake moving around by himself trying to sit up, that would be considered part of agitation. I would consider that maybe part of normal behavior.

I could understand not consistently following commands, but then if you flip to the next one --

DR. PANDHARIPANDE: The next scale or next --

DR. BALAS: I think the next -- it's either the next scale or the following scale. There's something even about physical restraints. I've never noticed this before; requires physical restraints.

We know from the literature that almost everybody in American ICUs is restrained. Right? So that would necessarily -- I guess if you're falling the scale --

DR. PANDHARIPANDE: Good points.

DR. BALAS: And it's the same one -- there's something else with the next one. So I think my

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challenge is -- I think if we were to improve these slides, I think one of the things that we should look at is maybe those plus ones, the higher scales.

DR. SKROBIK: They've never been validated, right? That's the problem with them.

DR. BALAS: But the tools have.

DR. SKROBIK: No. If you look at the amount of validation on the original studies, you go back to the original studies, 95 percent of the evaluations were at zero or lower, or whatever the equivalent was.

DR. BALAS: So you mix them up?

DR. SKROBIK: I am saying -- that was what I was about to say, but sorry to be jumping in, is that the positive ones have never been validated. I think to your point -- so thank you for bringing it up --

DR. BALAS: Isn't that the exact same problem now; people are quoting with my [indiscernible] ICU study, that they didn't have enough agitated people in the study?

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

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

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

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

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

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

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

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

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

(Laughter.)

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

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

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

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

(Laughter.)

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

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

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

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

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

Steve?

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

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

(Laughter.)

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

(Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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not that familiar with it.

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

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

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

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

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And you can see you get a 10 to 20-point drop in blood pressure. This is the mean changes for the entire population, and then it rapidly comes back after the infusion stopped. Similarly, for the heart rate, you see a drop from about 10 beats per minute.

This is important, that the oxy sats [ph] were no different in between the control and dex group. Denny had already shown that the hypercarbic ventro [ph] response to dexmedetomidine was unchanged. Essentially, it didn't have any of the properties of, say, an opiate.

Now, I'm just going to show you one or two slides from the midazolam study. And I want to point out that 60 percent of the patients had no supplementation at all; zero. Now, that's important because one criticism of the way that the trial was done could be that all you're doing is changing the pharmacokinetics of existing sedatives and they become longer acting. Therefore, you're not dealing with a sedative; you're dealing with a drug that changes metabolism. In fact, that can't

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be the case because these patients had no drug at all, and that was significantly different between the two groups. Morphine was different between the two groups in the midazolam study.

Now, this is something that I didn't see used much at all anymore. It's called the critical flicker fusion test. Do people remember this? Okay. This is how much change you have in the rate at which the light flickers before you say the light is continuous, and it was significantly better improved with dexmedetomidine. They were more --

DR. SKROBIK: Could you clarify that for those of us who have not heard of it?

DR. MAZE: Sorry?

DR. SKROBIK: What light flickers? I'm sorry.

DR. MAZE: There's a light -- the patient sees a light, and they're supposed to indicate when it is that they see this light as a continuous light versus a flickering light, the cutoff. So the patient responds and says, "I now see this as

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continuous." In the dex group, they saw it as continuous at a higher frequency.

DR. SKROBIK: The light was indeed continuous.

DR. MAZE: Pardon me?

DR. SKROBIK: The light was continuous.

DR. MAZE: I didn't hear the --

DR. SKROBIK: The light was continuous.

DR. WARD: You start with a slow flicker, and you get the flicker going faster, and faster, and faster, and faster, to where at some point you can't tell that it's flickering anymore.

DR. SKROBIK: Thank you.

DR. COURSIN: Either that or you start seizing.

(Laughter.)

DR. SKROBIK: Thank you.

DR. MAZE: I just put this up here because this is the message that came from the FDA, or came to Abbott to those who were involved in the trial. This was obviously good news. This happened, by the way, that the entire enrollment of the study

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population occurred over 12 weeks. In the summer of 1998, the data was submitted to the FDA and approved by February '99. That was remarkable how quickly this study was done.

MALE VOICE: Joan Tambling [ph]?

DR. MAZE: What's that?

MALE VOICE: Joan Tambling.

DR. MAZE: Yes. Oh, you remember this person.

DR. NEEDHAM: It was 800 patients recruited in 12 weeks? This is Dale Needham.

DR. MAZE: Correct. All of them -- well, not all of them, but like 95 percent in European trial centers and just a few from Canada; none in North America, for an FDA-approved study.

DR. NEEDHAM: Roughly how many study sites?

DR. MAZE: Somewhere close to 20. It wasn't remarkable, but there was some sites that did a lot of patients. There are places that did more, some way close to 10 percent of all patients came from a single site.

MALE VOICE: Remarkable.

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

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

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

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

Presentation - Avery Tung

DR. TUNG: Good morning. I'm going to disclose in advance that I signed up for this in part so I could sit in the back of the room and listen to real experts talk about sedation. I have not been disappointed at that. It's been tremendously informative as I sit here. And I'm going to continue to listen because the goal of this panel is not for me to talk but for you to talk.

I'm also going to disclose an anesthesiologist bias, which is that, generally speaking, we anesthesiologists believe the magician is more important than the wand, so drug focus studies are likely to, in expert hands, lead only modest effects, if ever.

I added the critical care section of A&A, and we pushed this one through in mid 2016 and published it in print in 2017. Dr. Jerath is a huge fan of inhaled anesthetics for ICU sedation. She has subsequently published randomized-controlled trials supporting that. So

our job here was to push back the bias she had in her paper, discuss issues with light versus deep sedation and interruption.

You can see the kind of outcomes that she listed as secondary outcomes. This was the first one. I also do think that there's a huge need for outcomes that matter because if one were to publish a new drug study in 2019, I imagine that one would have a paper that looked roughly like this; these are your outcomes and this is your primary outcome, and any effect that you see as swamped by heterogeneity. So anything that's really interesting, you say, well, look at that. Time to obey verbal commands, but it's not significant because there's so much variability between studies.

I also wanted to put in a plea for the practicing intensivist, that really when the rubber meets the road, it's a lot more than propofol versus dex, or interruption versus not. It's very, very complicated stuff, and patients that are easiest to sedate are easy, and those that are hard

are hard.

I'm just going to take 4 minutes to recount the four different vignettes that I came up to in my head while listening to what was going on yesterday. This is what happens in our ICU, this gabapentin, lidoderm, melatonin triad. This pops up everywhere I look. Everybody's on gabapentin, and we are only now in our OR realizing the sedative effects of gabapentin because sometimes our patients, after their ERA protocols, don't wake up because they all get their 900 of gabapentin before they get surgery.

In this case you ask, why is this patient on so much stuff, and they describe the incremental adding of drugs when stuff that you use doesn't work. The question not really for me is whether dex or propofol is better, but how do I optimize this patient? What do I do to get this patient out? And my instinct, if a lung transplant, is to take off the stuff and wake them up; otherwise, they'll never get out of there. But is that patient centered or not?

Here's another thing that happens often, and as the former SOCCA president, I see this everywhere I go, and that is that the neuro ICU people extubate patients with zero mental status, and the cardiac people don't dare do that because those patients will never fly. It's sort of an interesting difference.

Here's an example of what happens when I wander into the neuro ICU and they extubate someone who had no mental status, and you say, "Really?" And they say, "Yeah, but usually it works pretty good." And you say, "Okay. Let me re-intubate them." So it sets up a whole bunch of questions as to whether time to extubation, the primary outcome in the Jerath trial I just showed you is relevant or not. Another question, which we're going to get to in design -- I have 12 design questions that the committee here is supposed to make recommendations on -- is weather ICU heterogeneity is an issue or not when you're designing trials.

You come back to your ICU and your residents -- and this is why you have to keep

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reading as an intensivist because residents just ask stuff that you have to know the answer to. This is, "Well, should we use Tylenol?" because everybody knows that Tylenol reduces delirium. And it's so recent that if you don't keep up with your reading, you might say, "What Tylenol? I never heard of that." But in fact, here's a 2 by 2 factorial trial with 120 patients, so that means 30 patients in a group finding less delirium with the use of IV Tylenol in patients sedated with either dexmedetomidine or propofol, so what am I supposed to do with that? I mean, is this -- what? What? What?

I searched this entire article for the words "hypo" or "hyperactive," and I did not see anything like that. One thing for the outcomes person is whether the world needs a hyper or hypo ratio for every single delirium trial so we understand that we're not just taking hyperactive patients and fixing their pain.

Finally, what is a patient-centered outcome? This is the last vignette. It occurred to me, as

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listening to what patients experienced in ICU, and this patient, severe mitral annular calcification, and the patient has the dreaded complication of AV groove disruption, which is almost impossible to fix.

Luckily, or not luckily, he was on ECMO, so he was able to wake up afterwards. And on the take-back, the realization is we simply cannot fix his heart. There is no exit from ECMO, and the question is do you wake him up and tell him he's going to die or do you just turn off the ECMO while he's still asleep, and what is patient-centered outcome there?

In this brave heart contrast between freedom and mercy, the question is while there may be those who argue for freedom, there might also be those who would prefer mercy. So that's a good question here as to what a patient-centered outcome should be.

This panel that is supposed to last an hour -- and I think I've chewed out 4 or 5 minutes of that -- is to identify, where possible, group

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recommendations regarding the conduct of clinical trials of ICU sedation, both for the new drug developer and I think for the practicing intensivist who wants to know what to do. It's not going to be measurement because that's panel 2, so anybody wanting to ask questions about patient-centered outcomes, or RASS, or SAS, or Ramsay, that is the next panel after the break. And anybody who wanted to talk about outcomes, including return to work 6-monty recovery, that is panel 3.

But instead we're going to talk about structural elements. We're going to talk about inclusion/exclusion criteria. I've got 12 different specific questions, and then trial design, I brought in Dr. Coursin here to close the discussion if I cannot do it.

DR. COURSIN: Comic relief.

Panel Discussion

DR. TUNG: Dr. Coursin is here to close it out. So we're going to go with structural, and the first question is -- and I've used this sort of

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language at the end in red here to frame what a paper might say. The first question for the -- and I'm just going to invite commentary now -- is whether there can be consensus on multi- versus single-center trials. For example, we could say, the paper could say, this committee could say that committee recommends that trials with station be multicenter if possible.

Agree? Disagree? Comment?

DR. SKROBIK: Can I just -- I'm sorry. We were having a conversation with a little bit earlier outside. You're not defining the model of the trial. When it comes to sedation, I wondered whether observational trials could also be considered rather than RCT.

DR. TUNG: That is a good question. I left off everything except the randomized-controlled trial thinking that you couldn't really get FDA --

DR. SKROBIK: I just would argue --

DR. TUNG: -- that's a good question.

DR. SKROBIK: that with large enough bodies of data, you can actually arrive at conclusions

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without having an RCT. And I think that if you're looking at depth of sedation, which is what we were talking about the first part of the morning, and if you had compelling data to say people at this level over cohorts of thousands, how would you then justify moving forward with an RCT?

That would be my only comment.

DR. TUNG: I will comment that this whole thing is not being scribed by me but being scribed by the people recording in the back. I guess the actionable thing is that the committee suggests that trial designs other than randomized-controlled trials is possible as strategies for investigating ICU sedation.

DR. DEVLIN: This is John Devlin. The other thing is maybe the importance if it's a new molecule of a pilot study, really looking at some of the key things with feasibility, looking at safety signals, validation of tools, or outcomes, or some of those other things that could really guide maybe a multicenter study. I know that's not quite answering your question, but if we're just

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going from single versus multi, there could be some gaps and mistakes made.

DR. SESSLER: The general rule is to do single-center studies if you can. It's more homogeneous, you have better control over things, and it's a lot less expensive and a lot faster to do a single-center study. There are advantages to multicenter studies. Obviously there are some where you need more patients than you can get at a single center, but you pay a penalty in terms of variability.

So you're adding patients, but you're adding variability, and that actually increases the number of patients that you need. Generalizability is increased in a multicenter study, but still, at least for an initial study, go with a single center if you can.

DR. TUNG: I know Dr. Pandharipande has done a multicenter sedation trial, and thus dealt with all the complications that that entails.

Would you recommend that the committee recommend single or multicenter for trials studying

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ICU sedation?

DR. PANDHARIPANDE: I again feel that for FDA approval, I think it's going to be important to have a more generalizable population as a start for a phase 2 study, perhaps, using a single-center model to try and get all the kinks worked out, but then moving on to a larger scale, phase 4, trying to see whether it's generalizable in the larger scale, not just in the research setting. I think it's important to get it as a multisite study.

DR. SESSLER: The FDA does usually require at least a few centers.

DR. SKROBIK: I was going to say I am -- best answer to that.

MALE VOICE: I think there are multiple --

DR. SESSLER: Rigoberto, do you want to comment?

DR. ROCA: Sorry to interrupt. This is Rico Roca. Yes, I agree with the comments that are being said, in particular with respect to the fact that perhaps early on, a single-center study will give you more control and all that, but as far as

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regulatory approval, we do want to see the ability to extrapolate to a more generalized population.

I also noted his comment that the magician is more important than the wand, so from that standpoint, we're going to get a lot more magicians that we can see how this drug performs and different things.

MALE VOICE: And my only comment was I think in passing you mentioned phase 4. I think you meant phase 3.

DR. PANDHARIPANDE: Phase 3. Sorry.

DR. ROCA: Phase 4 will be after approval.

DR. TUNG: Dr. Shehabi?

DR. SHEHABI: I think for testing grounds, single-center studies are effective [inaudible - mic fade] -- single-center studies that came with major claims end up being completely wrong.

MALE VOICE: Your microphone is not on.

DR. SHEHABI: Well, I think it's the clicker thing' it's not me.

(Laughter.)

DR. SHEHABI: I think for things that will

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

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

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

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

(Crosstalk.)

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

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

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

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

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

DR. TUNG: Panharipande?

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

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

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

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

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

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

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that, and they may or may not have a neurosciences unit.

DR. TUNG: We just became a trauma center, and our trauma ICU is full of wildly outlandish sedation practices, ketamine drips, dexmedetomidine drips, ketamine and dexmedetomidine, propofol, you name it, extubated patients. It doesn't matter.

DR. SKROBIK: Can I add to that you could also make the politically incorrect suggestion that it be stratified by type of hospital and patient population because if you look at Hannah Wunsch's work, looking at alcohol withdrawal, one of the more important factors is what socioeconomic population your hospital services.

So if you're in a county hospital in a town in an area where there is a lot of recreational drug use, the withdrawal syndromes are very different. So your sedation practices are necessarily going to reflect that unless those people are excluded.

DR. TUNG: I think the committee is suggesting that cardiac and neuro be carved out of

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any trial so that the heterogeneity doesn't swamp any signal, and that may be stratified on patient type and hospital.

DR. WARD: But listening to the group -- and I'm not an intensivist, but a trauma patient versus a community-acquired pneumonia patient is going to have very different analgesic requirements; somebody who's got a reason to have pain versus somebody who is having pain because they're in the ICU.

Is there a difference there between a trauma ICU versus a medical ICU that's dealing with more ARDS?

DR. COURSIN: Well, I think you're going to find in the U.S. that academic centers for the most part are going to do these studies, and academic centers are going to reflect the silo and increasing specialization of critical care and trauma. The problem I have -- Yoanna, I appreciate your fine suggestion, but what kind of end are you going to need to do these studies to be able to stratify them I think is one of the challenges I

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would see. Most community hospitals are not going to see level 1 trauma, and level 2 and level 3 trauma are two very different entities.

DR. TUNG: Dr. Shehabi?

DR. SHEHABI: I think there is like a rationale for departing [indiscernible] the patients in terms of homogeneity or heterogeneity, you would say, into a medical type part for your patients and then the surgical part, which you could include trauma, neuro, and cardiothoracic in an in-depth part.

I agree with you that if you're going to certify by [indiscernible], the more certification you do, you're just going to go much, much, much more. I think if you stick to medical, regardless of where they are, that would include the generalizability, whatever you would find. So whether they're in a community hospital or an academic center, if you apply the intervention, in that population you should see the same result.

So I think medical and surgical have their trauma, and neuro and cardiac under that is

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probably the best way forward.

DR. TUNG: Dr. Sessler?

DR. SESSLER: Well, all trials stratify by site, and then the general rule is that you should also stratify by things that you think will affect the outcome. So within a site, you might well stratify by type of ICU or type of patient, trauma versus not, for example.

DR. TUNG: The committee recommends, then, that outcomes of trials of ICU sedation be stratified by type of ICU and maybe even by site as well.

DR. SESSLER: Stratification always helps. It doesn't increase sample size; it reduces the risk of ending up by pure bad luck within homogeneous groups. There's just no reason not to stratify for pretty much everything you can think of.

DR. COURSIN: But Pratik, would you comment on what it was like to enroll in MENDS, both centers and centers with the ability to actively enroll, and thirdly, centers actively enrolled that

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

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

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

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

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team, so there are these anticipated things that might happen. Does an attending anticipate the patient is going to be mechanically ventilated for another 24 or to 48 hours? Are they anticipating that the patient is so unstable that they might die the next day?

Obviously, if there were a drug here, that's another whole discussion. It's funny how when I observe and have these discussions, how often the clinical team might not always get the accurate answer, and I realize they don't have all the data. And then looking back, we probably could have enrolled the patient, and they would have been an evaluable patient.

So it's a tricky domain to evaluate, but I think there could be a bias here of putting -- there could be some patients who could go into the study that we don't because of the way these inclusions/exclusions are written.

DR. COURSIN: That was John Devlin.

DR. NEEDHAM: Dale Needham. I don't have an answer, but I have a question. We've talked about

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patients with alcohol or substance abuse and whether they should be in or not. I don't know if this is the appropriate section to discuss it, but I think it's a pretty important thing for the paper to comment on.

DR. TUNG: So the committee would identify aspects of patients that are relevant to inclusion/exclusion.

Dr. Spies?

DR. SPIES: First, I would like to speak to the stratification because, otherwise, you have it too narrow and it takes too long to do the studies. In addition, you don't get approval for your drug. For this situation, I think it's too narrow.

The second point is, I think you talk a lot about patients. You don't talk about your staff. The staff is the major issue. So compared to that, what you have for the patients variability, you have much more with the behavior of your medical staff. So I think before you do the inclusion, I think I would include to have the staff trained and that there is a visit before, a peer review that

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you really check that the staff assessment and assessment by you is not differing too much.

The third point I think is appropriate is also to say that if you want to include patients, I think it's much more important also to include the organization and the system that it's based in. I think a lot of the trouble comes because you don't get your team data, a source data, into your medical records. This is a lot of validity of the data you're missing.

So I think there's a lot of data warehouse problems we have within the different ICUs and the different centers, and that's something I should really check because it's not only the patient; it's us and the hospital that's much more influencing the studies.

DR. TUNG: Dr Egan, and then we have to move on.

DR. EGAN: Just a quick comment about a very practically oriented consideration. We have to remember that the goals of the pharmaceutical company, which is what drives the drug across the

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finish line, and the goals of the clinical community are quite different as it relates to the kinds of studies one would want to do.

What the pharmaceutical company wants is to get the drug approved, and they're quite happy and satisfied with a relatively limited label; that is, in terms of the inclusion criteria, they'd be happy to have a very specific -- a defined patient population and a relatively narrow label because that's the easiest way to get the drug across the finish line, and then the clinical community can begin using the drug off label and define the rest of the usage patterns after the drug is approved.

So I think that's a very important thing to remember, that having relatively limited inclusion criteria is perfectly fine for the company. In fact, they'd probably prefer that in some respects because all they want to do is get the drug across the finish line, and then let the clinical community decide how it's going to be used off label.

DR. TUNG: We're trying to frame

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

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

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

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

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between a younger adult and older adult. And that's why I think the age needs to be taken in consideration when we design clinical trials for sedation.

DR. TUNG: I heard Dr. Riker mention time to sedation is a potentially relevant issue in trials of ICU sedation. Do you care to flesh that out?

DR. RIKER: Sure. I think Yahya really is the one who taught us this information about how important those first 2 or 3 days in the ICU may be as far as long-term outcomes. Clearly, that's also going to be a challenge regarding consent if we're doing a randomized trial with a new drug. So that may mandate an ethic approach or depending on the country we're doing the study, and deferred consent.

But I think it's an area that there may be ways to incorporate study design to address that early time frame. Even if we can't enroll patients in that time frame, perhaps we could, after consent is obtained and the patient's enrolled, go back and get that data. I don't know. It's a complex area

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but one that, prior to Yahya's data, I think we accepted with blinders on, and now I think we understand better how important that early phase is.

DR. TUNG: I imagine the question is if you're going to do a trial on a new drug, that you must analyze in part by time to sedation and where you are in the course of critical -- is that roughly the sense of what we're talking? Does the committee agree?

DR. WARD: Just to comment, in reviewing the papers that I did before this meeting, there was a lot of variability in time to enrollment, and most were after 24 or even 48 hours, with some sort of hand waving about what kind of drugs they got before they enrolled in the trial.

So I think this is one of our important recommendations because it is to me a change in what the current literature seems to have.

DR. TUNG: JP has a comment in the back.

DR. KRESS: I think these are important endpoints. Be careful in terms of what you choose

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as your primary versus your secondary. Time to sedation, to use layman's terms, is a kind of a soft endpoint. It's interesting and it's important, but if you targeted your study as that as your primary outcome, I suspect you'd probably miss the boat because it's not going to be the big ticket item.

But I think they're important pieces. Nowadays, the way these trials, they are more rigid than they used to be. When you submit a proposal through criticaltrials.gov, for example, you can only pick one primary outcome. It's kind of a rule that's rigid. So I wouldn't put this as primary, but certainly secondary.

DR. RIKER: Riker. I agree a hundred percent. I think Elizabeth had a nice description yesterday, uh, in her presentation, calling it a process variable. Perhaps the time and target sedation or the time to sedation, those are process but not necessarily meaningful outcomes for what's going to happen.

DR. WARD: I may have missed on interpreting

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that comment. I was not thinking of it as time to achieve sedation, but the time in which the study was initiated.

MALE VOICE: Yes.

DR. WARD: I think the time to achieve sedation clearly is not an accepted outcome, as a primary outcome.

DR. TUNG: One quick comment, and then we have to move on. Yes?

DR. AITKEN: Leanne Aitken. I do think we need to make a recommendation that we need to make the time to intervention as early as possible, bearing in mind all the ethical considerations. And I think we should make that quite definite in there, and whether that's 24 or 48 hours. But we can't be thinking that sedation studies can start 72 hours later.

DR. COURSIN: One of the limitations I see there -- I work, as many of you do, in a tertiary coronary care facility, and I often see patients 2 or 3 days into their course who've had a mish-mash of therapies, and then they show up on my doorstep.

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I may enroll them within 24 hours, but they're not the same as the de novo pneumococcal sepsis that's agitated and whatnot that I want to get under control.

DR. AITKEN: But maybe they don't belong in the study. Yes, we still have to manage them, but they maybe don't belong in the study.

DR. COURSIN: I understand that. I think it just makes -- again, in the world that most of us live in here, it's an increasing challenge to get patients enrolled and complete a timely study.

DR. TUNG: Okay. In this next bullet, what I've done is reach far and wide into the delirium literature to pull out everybody's delirium risk prediction model. And the weirdest risk predictor of co-factors in those models -- and I've come up with this list of -- and the question is whether the committee believes that if delirium is going to be an outcome of your sedation trial, you must match patients in the control and intervention groups on these factors. You need to know the A1C, for example, to match in the delirium trial.

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Isn't that why you're randomizing? I'm confused as to why you would match in a randomized-controlled trial.

Dr. Girard?

DR. GIRARD: I'd say you need to know the number, and you need to be able to report the number.

DR. TUNG: So tracking it --

DR. GIRARD: Tracking it.

DR. TUNG: -- not necessarily matching that at enrollment.

DR. SKROBIK: I don't think you should go there, myself. In all of the prediction models -- there are several, and you've reviewed them, and John and I have applied some of them in our study data, and I think that it is a slippery slope because a lot of different models will use different metrics, and none have used all of them.

When the Dutch did theirs and applied it to populations outside of their -- John, maybe you can comment on this because you've worked on it with them. But when pre-deliric is applied to other

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populations than theirs, it doesn't predict as well. So is it useful, really? And then you could really go crazy and say, and what is delirium? But I'm not going to --

DR. TUNG: You could go crazy, even delirious.

So the committee does not have a set of patient characteristics that we must know about when we --

DR. WARD: We should know, but not necessarily -- from what Dan just said, they may be things that you'd want to put --

DR. TUNG: But do you need to --

DR. WARD: -- you'd want to put in table 1.

DR. TUNG: Anyone see it for table 1? That's the question.

DR. SESSLER: The matching is largely taken care of by randomization in a sufficient and large trial. And if you're worried about it, stratify your randomization; that takes care of that. A different issue is should you write down stuff? The answer is of course. You should write down

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everything you think is conceivably relevant and put it into table 1.

MALE VOICE: If things are not --

DR. SESSLER: The current approach is to use absolute standardized differences, not p-values in table 1. Then you set some rules if the absolute standard difference is more than 0.1 or 0.2. You include that in a multivariable analysis, and you put that into your statistical plan ahead of time.

DR. TUNG: Does the committee have a recommendation on this question here?

DR. RIKER: Riker. I think it depends if you're talking about a new drug to market or an improvement in our sedation approach in the ICU. The second of course can be pragmatic. The former, I don't know the answer to.

DR. SESSLER: I couldn't agree more. This highly context-dependent, but a new chemical entity is going to be tightly controlled. It's not going to be a pragmatic trial. Something that's already approved, for example, could well be done in a pragmatic trial, which is less expensive, that

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enrolls faster, and tends to include a broader population. It would be more generalizable.

So I don't think you can answer this in a general fashion. It's going to be dependent on the trial and the drug and mistake.

DR. TUNG: Can they be adaptive?

DR. SESSLER: Of course.

DR. TUNG: Should they be adaptive?

DR. SESSLER: Of course.

MALE VOICE: Will they be adaptive?

MALE VOICE: With they be adaptive?

DR. RIKER: There's a large and growing body of literature refuting the role of RCTs in ICU studies because the primary effect is underestimated so often in the design of the study. The results are negative. People don't know what to do with that information and strongly recommending alternative designs. I think as we, as we move into adaptive responsive platform type designs, we may get more return on our investment and get much more meaningful information.

DR. SESSLER: I couldn't agree more. So

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many studies have overoptimistic sample size estimates, and they tend to be estimated based on time or budget or wishful thinking. You end up with a p-value 0.09, which is uninterpretable. That's statistical never-never land. You can't say that there's no effect because the point estimate suggests that there actually is a clinically important effect. You can't say that it's statistically significant.

It's the one place you really don't want to end up at the end of a clinical trial. You can avoid that by putting interim analyses in and putting in your protocol that you will re-estimate sample size as necessary, as strongly recommended.

DR. COLANTUONI: This is Elizabeth Colantuoni. I just wanted, since we have an FDA representative, maybe getting the FDA's perspective. I agree with everything that's just been said, but it would be nice to also have confirmation from the FDA and if they have preferences in terms of strength of evidence or preferences in terms of what sorts of adaptive

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trials they're open to.

DR. ROCA: Well, they're certainly open to adaptive trial designs. They have come into the discussions the last four or five years of so. Some divisions do them more than others. For example, hematology/oncology does a lot of them, a lot more than we do. So they do have a role.

I think one of the things would be, what you're describing, is whatever strategy you're going to be using, it really needs to be stated a priori as opposed to on the fly, so we would be looking at it. We do have statistical input, multidisciplinary input as the adaptive design comes in.

So it would be something we would consider. We would want to have discussions, but it is something.

DR. TUNG: Dr. Maze?

DR. MAZE: I could just add to that we're dealing with a different division from anesthesia with DCRP, and Dr. Temple has put out a lot of literature on the subject. I'm strongly

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recommending, in this post-cardiac arrest syndrome trial, that we do a -- we did adaptive design. And we may still do it because we haven't completed our SAP yet. So at the time that the SAP is finalized, it may be that we will do an adaptive for the very reason that Dan has stipulated. In fact, Dan is head of DSMB, so he would be in a position to plan that.

(Laughter.)

DR. TUNG: Does the committee recommend a composite outcome, single primary outcome, or does the committee have no comment on this question?

DR. NEEDHAM: This is Dale Needham. I fear that we don't yet know what the outcome should be, but it's the end of the discussion yesterday, so I'd say we have no comment yet.

DR. WARD: After Yoanna's panel, we'll have --

DR. SKROBIK: I was just going to say that I think a lot of the subsections through are going to be informed or over the next two groups, where I look forward to all of your comments because I

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think some of the sub-items, if you will, have to do with the process.

I've heard a lot of the local culture, the local availability of technology, the electric records versus not, I think you're allowed items that can talk to the content. So even in the question that you just asked, which we aren't answering, we can also say why we're not. And I think that's important, so thanks for the expert [indiscernible].

DR. TUNG: I'm going to push forward to the next one, which is I heard yesterday a discussion of how a placebo-controlled trial is hard to do in sedation for obvious reasons. Does the committee want to recommend a single standard against which, say, a new drug should be compared to?

DR. RIKER: I'll throw something out there. Riker. I think, as we learn from the MENDS trial and the complexity if you've got a wide range of acceptable sedation and how you have to supplement perhaps with other agents to get to your deeper levels, I would recommend that we recommend not

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having light and deep sedation, however we're going to define light, and that there may be different standards for those two approaches. In other words, based on the last PADIS guidelines and the previous PAD guidelines, light sedation, the standard may well be dexmedetomidine or propofol, and for deeper sedation would probably be propofol.

So I'll throw that out there for comment; not necessarily that it's the right answer.

DR. TUNG: Dr. Shehabi?

DR. SHEHABI: I think the comparator is very, very important. I think in terms of usual practice used as a comparator, you can do that, but I think it has to be stipulated that the sedation level, whatever that is, should be comparable in both groups. I think that's fundamental because we've seen trials that sedation targets were not comparable, and you don't know whether that is the effect of the intervention or the different sedation. So I think that's a fundamental part of the comparator.

Whether it's usual practice or controlled

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usual [indiscernible] practice, that really depends on whether you believe the interventions used are already considered standard practice. And if they are, then yes, you can use usual practice as a comparator. But if they're not, then you need to have a control to do your practice.

DR. TUNG: Do we think there's some comparator that's not only depth but also potentially drug?

Dr. Egan?

DR. EGAN: Just a quick reminder about an important point we discussed yesterday, and that is that dose matters. I think that the depth of sedation is a function more of the dose than it is the drug, assuming that most of the sedatives that we talk about are at least capable of approaching a near deep sedation state. Certainly, propofol has a more maximal effect than dexmedetomidine does, but you've got to control for the dose. The level of sedation, again, I think is more a function of the dose than it is the drug that's chosen. So that is an important consideration in terms of the

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comparator.

DR. TUNG: Dr. Kress?

DR. KRESS: I think Pratik touched on it in his talk this morning with regard to this light versus deep. The one thing I don't think we have good literature on is, is there a difference between light, where the patient comes up from the depths of being under water for a bit of time so that you know they're in there, but then the rest of their 23 hours, they spend under the water, or is that compared to a situation where they're alert for longer periods of time?

You could do that study reasonably easily using some kind of an area under the curve analysis. And I'm not sure which is better or even if they're the same. If I spend 23 hours sedated but 1 hour awake following instructions, is that fundamentally different? It is, but in terms of outcomes, then if I spend most of my time able to follow instructions and interact, certainly with dexmedetomidine, the chance to get that latter goal is much better I think. But I don't think

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

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

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

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

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

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

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

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

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this way, and we're not randomizing, so it's done without consent. I suppose you could make that argument.

DR. GIRARD: It has been done without consent, not in sedation, and maybe it wouldn't work in sedation. I'm not convinced that it would. But for other interventions, clearly this has been done. The two big -- crystalloid versus imbalanced --

MALE VOICE: Salt trials.

DR. GIRARD: -- like salts, REB [indiscernible], they did this. They didn't call it the alternating cohort; they called it a cluster randomized trial with crossover.

DR. TUNG: Cluster. That's the word I wanted.

DR. GIRARD: Right. One group would cross over to be the alternate strategy on a given month.

DR. SESSLER: It would be perfectly reasonable for comparative effectiveness study. Just suppose you want to compare propofol and dexmedetomidine. Both are commonly used drugs. It

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would be perfectly reasonable to use one drug for a month, and then you switch over and use the other drug for a month, and you keep switching back and forth. You'd have to have waived consent, but if you had that, you can enroll a huge number of patients relatively inexpensively.

DR. WARD: It may be more difficult if you've got a new molecule in the picture.

DR. SESSLER: You probably could not get waived consent for a new molecule. It's not designed for that.

DR. WARD: Let's take 25-minute break and get back here at 10:35.

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

DR. WARD: Well, we think about what are the indications for a sedation trial. We did inclusion and exclusion criteria, so it was a little bit in that one because the indication is the need for sedation because these are clinical trials for sedation. So we may need to do a little bit about more what the indications are.

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The second clarification -- and this always come up in this kind of meeting. It came up a lot in SCEPTER II, where we were talking about safety and the issue of a QI database is not a particularly good database to base your information about safety on. It's kind of the magician versus wand issue.

If you're studying the wand -- if you've got a new molecule you want to study, you want to study the wand. You don't want to study how the magician uses the wand. I may be pulling this analogy a little bit too far. There's still kind of a Harry Potter fan that's still a reasonable analogy for it.

A phase 4 trial, a more pragmatic trial, is where you want to get a bunch of magicians out there using the wand and see if everybody manages to use it the same way. This maybe covers a little bit of both types of trials, but one type of trial we're very interested in, of course, as Bob keeps calling it, new dex. If new dex is coming along, the new wand, we're going to talk about how would

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you design the trial for the registration. And that's different than some of the other kinds of things that we've been talking about that are valuable, phase 4 or NIH-funded kind of trials, and will add great information to it.

So I don't want to eliminate talking about either kind, but I think we need to remember there's kind of a different way that you would design a trial if it's new dex versus you've got a way to give propofol differently than we've been giving it and you want to compare it to a comparator.

Yoanna, you've got group 2.

DR. SKROBIK: Thank you.

DR. WARD: Thank you.

Panel Discussion

DR. SKROBIK: I was going to invite you all to sit down in a circle around the room because I think that what I would really like to ask are questions based on this mandate that we have. I've heard a lot of discussion over the last day and this morning that I found fascinating, and I also

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think, to your point, Denham, that we are actually discussing different kinds of trial models.

Lisa, help me, please, because we were talking about -- what Lisa pointed out is that there's the new drug, the new molecule, and what are you going to compare it to and how are you going to do that? Then there's the comparator trial between two different kinds of molecules that already exist.

What was the third category? Lisa, help me.

DR. BURRY: Sorry. As a pharmacist, I felt very much we were trying to put all different kinds of pills in the same container, and I had anxiety about doing that.

(Laughter.)

DR. BURRY: They needed to sedate me, yes. There were trials that I would have very specific design ideas about if it was a brand new drug coming to market and what I would expect, and I expect, as already have been indicated, the labeling would be rather narrow to start with and then expand over time. Then am I comparing two

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different molecules that are already available, and I need to think about the operating characteristics of that molecule so I'm not unfairly biasing one particular arm or another. Then am I going to take the same molecule and compare it with different methods of administration to tie in and accommodate for poor pharmacokinetics or things that are less than ideal to make the drug operate at a better standard.

So I felt there were different types of studies we were trying to address within the same questions. Although the questions were valid, I felt the answers would be very different depending on what we were trying to achieve.

DR. SKROBIK: The last category I think is -- the last item -- so I'm bringing up these points even though they're not on this list because as we're moving forward to answer, how to best et cetera, that answer may vary based on the type of trial that we're suggesting it for.

The last comment that I had to make -- and perhaps Dr. Roca [indiscernible] can comment on

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this. But my sense is that the FDA, just like Health Canada, if they're approving a new molecule, you have to choose which comparator you're going to choose it for. Dr. Maze was talking about it this morning. Sedation was what dexmedetomidine was chosen for when in fact it has analgesic properties. So you have to pick one category and how does that play into how you decide to structure the trial or these questions.

So with that, I'd like to open the discussion to the measurement of the level of sedation. What I have here is a list of suggested metrics, including the RASS and other sedation level measurements. Some of them are actually not only not validated but have been shown to not be useful, like the Ramsay and the Glasgow, which were ubiquitously used 20 years ago and no longer are because of the dissemination of other sedation scales.

There are other elements that are patient population specific. Pain evaluations in the neuro ICU population have been studied by Senengee [ph],

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and now who's in Montreal but also by others, but they're population specific answers to some of those questions.

What I would like before we address the scale issue is to talk about process, and I've heard -- Leanne, I didn't say a number of things that really spoke to me about how things happen at the bedside. All of these nice Cartesian, in the OR, anesthesia comments, where you are the magician and you're holding the wand in front of one recipient of whatever that wand contains, don't necessarily apply to the behavior at the bedside in ICUs.

So I'd like to hear Leanne, and I'd like to hear Michele, and I would like to hear Claudia, because they're all of the dimensions of cultural and behavioral bedside application that I think we have not highlighted sufficiently, and this is an opportunity to do that.

Take it away, girls. Come on.

DR. AITKEN: Leanne Aitken. I guess it depends on the specific questions, but --

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

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

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

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

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There are a lot of things you need to train, and we do that by blended learning concepts. We have that available for all German ICUs because it's --

DR. SKROBIK: But it's in German, right?

DR. SPIES: That's why I think other people need to do it. I think also it's not English itself. It needs to be adapted to the culture. So I think it's very important that we speak like we usually speak to our families, to our staff, and I think that needs to be reflected. That's at least my point.

DR. SKROBIK: Pamela?

DR. FLOOD: I have a comment both based on my observations as a patient and also on my observations as a clinician. one is that I think the variability is partially due to the burden on the clinical nurse because I think in some settings, they have a lot more burden of clinical care. They may have two patients rather than one patient. They have enormous documenting responsibilities just based on clinical care.

So when you throw another documenting

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responsibility on them, on the basis of this study, they're not really very interested, and you get the issue that you mentioned, that every blood pressure's the same and every sedation score is the same because they just can't live up to the burden because their clinical care is too much. In that case, in the best of all possible worlds, it would be better to have a more consistent study nurse or study personnel taking those, but of course money isn't everywhere.

DR. SKROBIK: I think there's nice data showing that sedation levels actually rise with burden. There's lots of literature on that.

To speak to the point of the assessments. -- and I'll give you, Steve, in just a second -- Mona was saying earlier to me -- I'll find it -- that once you've trained somebody, that that doesn't mean that you could assume that they stay trained.

DR. SPIES: No, that's wrong.

DR. SKROBIK: Let her answer.

DR. HOPKINS: So I can talk? I can tell you

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in the ALPA [ph] study, Dale organized training sessions. Before the study rolled out, people had to come and practice and reach a certain level on each assessment, both for RASS and CAM, and for all the ICU outcomes assessments we did. There was marked variability, and then when we would come back a year later to recertify, most of us failed in something, and we had to retrain and recertify to that level.

So I don't think it's quite the case that it's true, and in doing RASS and CAM, the variability, if we couldn't get a study RASS and CAM done, we would take the nursing RASS and CAM, and those were, often if we did them at the same time, markedly different. So I think there is an importance to training and keep training, and making sure -- maybe Dale wants to add any other comments.

DR. NEEDHAM: I think we presumed that the letters after somebody's name is associated with their competence. There was a faculty member who repeatedly didn't pass the QA and was very upset

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because this faculty member said, "Oh, I've done these things in animal models" and whatever, some of these things. I was like, "Oh. Sorry." That was Dale Needham.

DR. SKROBIK: Claudia had a comment, and Steve had a comment.

DR. SHAFER: All these scales involved at the deep end, it's physical stimulation, something noxious that the person responds to. Talmage and I shared the experience with the development of Sedasys, where the pivotal trial was a 1000-patient trial, and the device was intended to put patients in the area of moderate sedation, but trapezius squeeze and response to trapezius squeeze was used to define unarousable patients.

There were 5 patients in that trial who failed to respond to trapezius squeeze. All were assessed by the same nurse, and the same nurse had administered a trapezius squeeze, and this was a very somewhat -- a nurse who would not be expected to be particularly aggressive in this maneuver. The FDA interpreted that by saying this device puts

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people into general anesthesia, and that delayed the approval of the product by 4 years, those 5 patients.

We pointed out repeatedly to the FDA, that 2 minutes later those patients were awake and talkative, and you can't be awake and talkative 2 minutes after general anesthesia, and it was just a weak trapezius squeeze.

I mentioned this because much better things for noxious stimulation is electrical stimulation that can be readily reproduced and is not dependent on the strength and aggressive nature of the person doing the tests. So the noxious stimulation really has to be standardized because you may have people saying, "They're unarousable on the RASS scale," or they're a minus 5 when in fact nobody really tried.

DR. SKROBIK: I'm a little worried that you would be describing the noxious stimuli and that the patients would be that sedated, but that's a very personal response.

DR. SHAFER: But they really weren't; that's the problem.

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DR. SKROBIK: So in the sedative assessments, we talked about scales to measure a pharmacological agent administration. One of the points that Ingrid raised a little earlier was what do you do with patients when you're trying to decide whether to give them a sedative at all? I don't know if you wanted to speak to that.

DR. EGEROD: Yes. I just want to comment on the other problem of consistency. I was a part of the large Euro pain study with thousands and thousands of patients, and there was actually very good consistency in using the pain and discomfort scoring instrument.

So I think that it's important to have some kind of a research nurse in place, but that person of course isn't there all the time, but that person is responsible to see to it that the others are doing what they're supposed to do, and that usually does work pretty well.

So that was that. About the sedation, we've been discussing light sedation, but we haven't been discussing no sedation. I did a study in Denmark

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where on a single day, I asked every single ICU how many patients they had and how much they had sedated the patients. There were very few patients that had been sedated. And I asked them if they'd done the wake up, and of course they hadn't because they were awake.

So I think that that is very cultural, and I think more European countries are doing very close to no sedation, so I think we should think about that.

We were talking about light sedation this morning, and some of the interviews I've had with patients is that they would rather have no sedation than light sedation because light sedation can be uncomfortable to some patients because it takes away their sense of control. Some of the patients have described fighting sedation. So on top of all their other ailments, they're fighting sedation. So somehow, some patients would rather not be sedated.

If they're not sedated, communication is easier. One of my PhD studies did a year of

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observation in ICU, and what she saw was -- we don't use restraints, we've never used restraints, so we're not so concerned about patients pulling things. But what she saw was that if the patient was bothered by the tube that was pressing some place in the mouth, the patient could adjust his own tube.

What we see more and more is that we trust the patients because they're awake, we're communicating with them, and little discomforts can be very difficult to describe that -- where is the tube pressing or something -- they can do some of the adjustments themselves. So I just think we should also open this discussion to how we can work much more with awake patients and communicate with the awake patients.

DR. SKROBIK: Michele, did you have another comment? No?

So does that speak to some of the no sedation points, Claudia?

DR. SPIES: I fully agree with Ingrid. We have the same experience. We don't sedate all the

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patients except if they are agitated on the levels, and we titrate it, so it's no continuous, except the half-life because it's required for that. But the point is, in most of the cases, the half-life is too long, so we don't need any IV infusions.

DR. WARD: Ward. I think it speaks to our control group, and the control group could very well be no sedation would be an acceptable control group. But remember, the discussion is about if you have a new molecule that you want to have the registration be sedation, obviously a discussion about, well, if you don't need sedation, safety outcomes become the important piece, because if your control group is no sedation and you've got a new molecule that your indication is sedation, and now you find that the, pick one, delirium occurs more commonly with this new molecule, that has a worse safety profile than no sedation.

You don't necessarily need to have an active comparator. If the practice is no sedation, then that's a fine control group. But you need to still look at the safety outcomes for both your control

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group and your new molecule group.

DR. SKROBIK: But if we're discussing -- I'm sorry, Claudia, to be cutting you off. But regardless of whether we're testing a new molecule or comparing two, what we're talking about is delivering, as needed, sedatives in two groups that then should be triggered by the same threshold.

My question is, do you think that the RASS and the other methods that have been validated are actually good threshold metrics to begin the sedation? Because what they've been used for and validated for is comparison of drug effect, but nobody's actually said, to Ingrid's point, this is when you might consider starting.

I remember reviewing a lot of the -- well, not a lot. I reviewed some the earlier sedation papers. Agitation is actually very poorly defined. Sitting up in bed and moving, I agree with Michele, is not -- and one of the reasons that I think the RASS has become so popular is that everybody can agree on what 10 seconds means. My sense of what agitation is, is very different than what somebody

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else's sense of agitation is.

The minus whatever by subjective criteria, I think that's where you find your highest inter-rater reliability metrics. So do you think that a threshold for administering sedation is something that we should be thinking about and proposing? And if so, what should that threshold be?

I haven't heard you describe what the Israeli practices are like. I was curious whether you had any comments and thoughts on whether that would be something that you might --

DR. GOZAL: David Gozal from Jerusalem. [Indiscernible - mic distortion] American practice. There are not much difference between the North American practice and Israeli one. I agree the biggest problem must be, first of all, education and practice and training, and the second one, like Pamela said, burden on the nurse and staff. I think all over the world, nurse staffing is a big problem and of course a problem of money.

DR. SKROBIK: So the reliability of bedside

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monitoring, you should either consider a validation day to day with an expert or a supervising research nurse -- did I get that -- for the measurements of sedation?

What about sedation administration triggers? Any thoughts on that, Pratik?

DR. PANDHARIPANDE: I don't think it can be the lone trigger because it has to be in the context of whether someone's on the ventilator, et cetera. I would say greater than a RASS plus 2, or RASS plus 2 above, one might consider in the context of other things going on. It comes back to what is our indication for sedation.

Just talking to what Ingrid pointed out, in the morning, the discussion on light was the deep sedation for the PADIS guidelines. It was in the context of those who have indications for sedation. Every patient doesn't need to be lightly sedated because there are many patients who don't need to be. But in the context of the group that has an indication and whether that indication is ventilator patient dyssynchrony or that indication

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is perhaps dangerous agitation while on the endotracheal tube and with devices, I think that's where the discussion needs to be focused. So you could have some thresholds but in the context of other parts as well, not individually one thing.

DR. SKROBIK: So that's perhaps a good segue into the next part.

DR. WARD: Just a quick question. Are we sort of agreeing how best to base the level of sedation is RASS?

DR. SKROBIK: No. I think we're saying that whatever the measurement is, -- this is a personal thought. I think the Ramsay and the Glasgow don't necessarily belong here, but using a validated scale, I don't think it matters the one that you use. The problem is with the metric with the bedside. With a lot of the comments I've written down, it's all of the caveats about how to improve that methodologically and make sure it's consistent within a trial so that it improves the trial's quality.

Yahya?

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DR. SHEHABI: What about the frequency of the measurements?

DR. SKROBIK: Ah, great point. Thoughts?

DR. SHEHABI: I think that's really important because the more frequent it's done, the more comfortable the bedside nurse becomes with using the tool. In terms of within a context of a trial, there has to be a research support staff who checks that on a daily basis that people are doing what they're supposed to do. And the more frequently you do it, the more it reflects the time deeply sedated or lightly sedated.

DR. SKROBIK: In your units, is it done every shift, every 4 hours, every hour? How does it work? And do you have thoughts on whether there should be a standard?

DR. SHEHABI: We've mandated every 4 hours on this part, so we picked up the 4-hour records, but most units move to an hourly RASS. So it became on their flow chart, they do a RASS with the blood pressure and heart rate and urine output on every patient.

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DR. RIKER: Both within our unit and as part of SEDCOM, it was every 4 hours but before and 15 minutes after any change in dose. So if patient gets restless, or has pain, or is agitated, you'd document before you give the drug, then you give the drug, then you document a response to that, or if you change the infusion rate if it's a continuous infusion medication.

DR. SKROBIK: What about the segue to the next part, which is this patient and the family perspective?

DR. WARD: I want to switch back a little bit more on how best to measure sedation, because there is a paper out there that did psychometric comparison on sedation assessments. In fact, I think your name is on that paper, I believe. And it said that both --

DR. RIKER: It's a Robinson paper?

DR. WARD: RASS had a --

DR. SKROBIK: Can I just say it was Richard's fault, okay?

(Laughter.)

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DR. WARD: RASS had very good and the sedation agitation scale was very good. I didn't put all of them down here.

DR. SKROBIK: But there's other data suggesting that the Ramsay is not and that the Glasgow is not.

DR. WARD: Well, Ramsay was not. Ramsay was only medium.

DR. SKROBIK: That's it. So it's not just our work, there are others.

DR. WARD: Yes. Would this group recommend -- one of the things we did in the other sector is we said not necessarily have to use it, but we did recommend using the OAAS as a major for procedural sedation, having reviewed all the other sedation scales, including some of these, not many of them, because there is a difference between procedural sedation measurement and ICU sedation.

So is this group going to say that the RASS is the one we recommend?

DR. SKROBIK: This is what we said in the guidelines, right? So we recommended in the

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guidelines using a validated scale, and we recommended the RASS and the SAS because we had in the past. But we also didn't want to preclude somebody coming up with a new scale that you then couldn't use for whatever, direct comparison, if it had been subsequently validated.

DR. WARD: There's a difference between the clinical guidelines that you are promulgating and a paper coming out of this group, which will serve as a resource for people designing clinical trials for maybe a new molecular entity or some other combination. And I would think, and what I'm hearing, is that the recommendation would be the RASS.

DR. SKROBIK: Tim, do you have a comment?

DR. GIRARD: This is Tim Girard. I'm not sure we can justify there being a difference between the clinical recommendation and what's done in the research study precisely because of the approach that Rich just described, which I think is the right approach, which is if the drug is titrated, then the sedation level prior to

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titration and after should be documented.

Well, who's going to do that at 3AM? Is anybody here proposing that we do large clinical trials where research staff are at the bedside 24 hours a day? I cannot imagine that we would be able to do that. So if that's not possible -- and I welcome anyone to tell us that it is -- then the alternative is to do what has been recommended in a clinical setting.

DR. SKROBIK: So I think we're recommending a middle path for the purpose of trials because of the variability and the unreliability, variability within institutions and between institutions, and the unreliability of the patient record alone. What we're suggesting -- I think what I heard -- is that in a trial context, the reliability of the sedation measurement be fostered and the inter-rater reliability documented by the research cheerleader team, regardless of the format, but for the validation of the content if the results that you're getting --

DR. GIRARD: I agree with that, but it can

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only be done if the clinical nurse --

DR. SKROBIK: And your point --

DR. GIRARD: is using the tool that's already been validated in the clinical setting.

DR. SKROBIK: So I think that when you do research studies -- my personal belief is that when you do studies across multiple sites, you actually disseminate knowledge on how to do clinical practice in a way that isn't incorporated in the QA initiatives.

So I think there's a benefit to that, but I also think there's a practical dimension of not being able to rely on just the -- and I agree with you that it should only be validated scales, except let's say it's the RASS or the SAS, then there's a new scale that comes out in two years and there's no guideline, I wouldn't want it to be limited by that. That was my only thought.

Rich, you were going to say something.

DR. RIKER: I was just going to say the other thing is we heard yesterday about qualifying outcome measures or variables, and I don't think

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either SAS or RASS right now are qualified by the FDA, so that may be another thing for us to kind of consider. That may be an improvement.

DR. SKROBIK: One of the points that was raised yesterday is that the electronic medical record, which is a device, is not, right? The FDA doesn't approve the medical records, does it?

DR. SPIES: It depends. It depends. If you have open source and it's integrated, it's accepted, I think.

DR. SKROBIK: No, no. So they don't validate the -- as a technology, electronic medical records are not part of what the FDA looks at, right?

DR. SPIES: I think we had a study where we could.

DR. ROCA: This is Rico Roca. I'm afraid I can't answer that because I think that what you're describing would probably be in the Center for Devices, and I'm not sure where their purview is. So I don't know whether electronic records would be one of the things that they would look at.

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DR. WARD: I guess a question, but Rich brought up, no, none of the sedation scales are part of the validating. Is that something that would be worthwhile for the ICU community to do, would be to get -- and it's not a simple process -- it through the FDA.

Bob, you've got some experience with pain scales.

DR. DWORKIN: ACTTION is, at one point or another, in the process of qualifying for different novel measures, a new measure of pain intensity for pain clinical trials, a measure based on accelerometry of physical activity also for pain trials, and then potentially a measure of parasthesias and dysesthesias for peripheral neuropathy and a measure of craving for addiction clinical trials.

So we've got some experience doing this. I guess the thing to say about it is it's a substantial commitment and it doesn't happen overnight. The FDA sets a rigorous bar for the qualification of novel clinical outcome

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assessments. But sitting here for the last day and a half and listening, I think it would be a fascinating enterprise to develop and qualify a sedation measure, challenging but fascinating. But it is a substantial commitment, and you need someone who's going to spearhead the effort and devote considerable time to it.

DR. SKROBIK: John?

DR. DEVLIN: Just really quick, SCCM through its ICU Liberation effort is finalizing working with Epic and [indiscernible] and some of the things to put all the metrics in for ADAF, which of course is delirium scores, pain scores, and sedation scores. So it's not answering the question, but there is a lot of work trying to do this, but I don't know if that's for a research setting.

DR. SKROBIK: In my nominal reluctance, other than taking off names on the list that are there now, that are known to not be validated and has to do with things like the evolving delirium metrics, for instance, where people are starting to

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measure delirium not just with a tool that's a screening tool, but with a severity 7-item score, that I think has a lot of promise.

So I think if you say validated, then based on the guidelines, I think that that would be sufficient, but I'm a little bit biased towards the work that we did in the guidelines context.

I'd like to take this opportunity to move us onto the next topic because I don't have -- certainly I can't pretend to even dream of having Avery's speed, but I would like to get through some of the bullet points.

Do you think that there are family and patient dimensions to sedation administration? I'll kick it off by saying I have been in the clinical context of the patient's fine as far as I'm, and it's the family member that's getting agitated about that patient moving. Then of course there's the prospective of communication while you're being sedated that Ingrid mentioned, that Pam has spoken of, and I think it's huge, and I think it may be related to outcomes, which is what

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we'll be talking about in the next panel, but I don't know how to capture that, so I welcome your thoughts on both of those points.

When I said sometimes families get agitated about the patient not being sedated enough, I saw a few heads nod in the room.

DR. FLOOD: Pamela Flood. Well, I think the patient's viewpoint, if you can communicate with them, has to be primary. And I haven't heard anybody say anything about asking the patient when they appear agitated. If you can communicate with them, if they're responsive, if they want more sedation, saying to them, "You look uncomfortable. Would you like something to help you relax?" that's something we do with the patient very commonly. In terms of the family member, if the patient can communicate, then of course their view is primary. If they can't communicate, then certainly the family's opinion should be taken into account.

DR. SKROBIK: Other thoughts? Leanne?

DR. AITKEN: I just thought I'd mention there was a priority setting exercise that was done

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with patients, family members, and clinicians in the UK about four or five years ago, and I just pulled up the results, and the second highest ranked item for both patients and family members and clinicians was how can we enhance patient comfort during intensive care, i.e., minimize pain, discomfort, agitation, and anxiety, and does this improve patient outcome?

DR. SKROBIK: I know it's an important topic, but in the context of studies, what I'm hearing is that addressing whether the patient has preference for lighter or deeper sedation may be something that we might consider a metric to request. So if you have -- let's see, I have patients who are at minus 3. Is that because those patients said to the nurse, "Yeah, bring it on. Give me another bolus," and is that a justified comment?

Lisa and Pratik have thoughts.

DR. BURRY: Lisa here. I just wonder if that will influence consent for your trial, that families and patients may have a particular desire.

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Some will want to be more sedated and not know what's going on, and that will influence consent into your trial. I just wanted to put that out there.

DR. SKROBIK: I'm sorry. I have blonde hair. Can you explain why?

DR. BURRY: If a family member wants their patient to be awake -- I'm just thinking back to when we originally enrolled for SLEEP [ph] --

DR. SKROBIK: For SLEEP, yes.

DR. BURRY: -- it was a struggle because patients and families did not want to be awakened, and that you are going to turn off my analgesia and sedation and hurt my mother, or so on. And if I'm in an awakened state, am I going to suffer and have symptoms during that period? I think the issue of light versus deep will have a lot of family and contextual and culture issues that will influence enrollment into your study. I just wanted to put that out there.

DR. SKROBIK: I've never asked family members whether they wanted their family member

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deeply sedated or not because I think that's a reflection of their own discomfort, the family's discomfort. But ever since we had our patient representatives on our panel, I've asked patients because I who have never wanted to nap in my life, was astonished to discover that somebody would want to be knocked out the way Avery was suggesting that some people might prefer to, which is inconceivable to me. And in my limited observation over the last three or four years, it's about 50/50 in the patient preferences that are stated.

I don't know whether that should be in incorporated because we're here for a methodological recommendation. Should that be included in what people describe in trial content when it's adjusted to sedation? Is it ethical to not ask the patient whether they would prefer to be more -- or do you impose it on them because you say, you know it's bad for you, so I'm going to keep you awake.

Claudia and Tim have comments.

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DR. BALAS: If you have an intervention that's known to cause harm, how ethical is it to suggest or give the possibility that you're going to give that intervention? To say the patient -- would you do it with a catheter?

DR. SKROBIK: The huge majority of people who administer sedatives do it with avuncular intent. They believe they are providing relief. They believe they're helping asynchrony.

Tim?

DR. GIRARD: Tim Girard. At the risk of being provocative --

DR. SKROBIK: Let yourself go, Tim.

DR. GIRARD: -- we would not ask, unless it was a family member, which is a unique circumstance. In most cases, we would not ask the family member, where do you want the tidal volume? It looks like the patient -- or the patient for that matter; we wouldn't ask them, "It looks like you're feeling short of breath. Would you like for me to alter your tidal volume?"

I understand that, yes, sedatives are

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treating symptoms, but they have other effects, and that's very well established. So why is it that we sedation as being just a treatment for symptoms based on patient preferences rather than medical treatment that has numerous potential effects?

So yes, we want treatment preferences to guide therapy, but it's not the only consideration. I feel like the conversation is going down this path where we imply that it is the only consideration. We go up to the room. We ask the family do they want to be sedated or not, and then we do that. I'm confused by that rationale.

DR. BURRY: That's not what I meant to imply.

DR. GIRARD: And I wasn't speaking to what you said, but there have been multiple other comments --

DR. SKROBIK: So Tim, when I talk about patient preferences, I think in my mind what that means is either choosing to not sedate them at all and keeping them at zero, and maybe horrors between zero and plus 1, or leaving them at minus 1. So

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this is not a broad range, and I think that Ingrid's point, which was the descriptors of the patients who dislike light sedation because it makes them lose their sense of agency, is a provocative thought.

DR. GIRARD: And my comments were in response to what Lisa described, where in a clinical trial, the family members were saying we want this and we want that.

DR. SKROBIK: No. And I've experienced the same thing, and I've sweetly smiled. I agree with you on that.

DR. BURRY: I think I should clarify, it was the process of trying to get consent, not what they wanted in the trial. But trying to get them to consent to the trial, patients may have had preferences. I don't want to -- "This sounds great, Lisa, but I don't want to be randomized to the arm that's going to have the interaction because I don't want to be awake."

DR. SKROBIK: I don't want to suffer.

DR. BURRY: So I think it's the getting into

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the trial.

DR. SKROBIK: And I think the consent issue is a separate, distinct part. We had this very similar challenge with the dex trial when the patient's families would say why are you going to be giving a sleep drug when this patient's already sedated? Like what's the point?

DR. BURRY: And to go back to Claudia's point, once the patient was in the study, it required tremendous education of not only the bedside nurse, but actually the family. Now, we're in the trial, and this is what's going to happen, and if we are to do an awake, this is the level of sedation in the trial. But we had to repeatedly explain ourselves over and over as the shift changed and the family members fluxed in and out of the room, and it did require a lot of energy.

DR. SKROBIK: So there was pressure.

DR. BURRY: Tremendous pressure where I felt like I needed a Tefler [sic] vest at times because we were doing what people thought was unethical at that time, even though it had already been

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published by JP.

DR. SKROBIK: Claudia?

DR. SPIES: I think that's very good what was said. The point is I think it's very important that we consider the patient's wishes, but I think we have to inform the patients and the relatives as structured. I think that's not what we do. We say something, but that's nothing that comes up to the mind of the relatives because they feel helpless, and they don't listen to us so much.

So I think we need a structured element where people can take that home and see fact boxes or something like that, where they exactly know why we do that. I agree with Pam's point that I think at some point, when patients are agitated and you structure the family to according what to do with agitated patients, they can help the patients, and then you don't need any drug.

I think at some point we should consider in all of the studies that we should first go to nonpharmacological, and then if that's not working, then the next step should be to use a sedative. I

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think that's important because we don't -- well, to my impression, I think if we don't learn and educate our staff how to do nonpharmacological intervention, all our drugs are senseless because they are overdosed, and they are usually not doing what they should do.

DR. SKROBIK: JP and then Pam?

DR. KRESS: I think what you're basically outlining are two extremes. One of them is sort of a paternalistic approach, which says I know better than you do, so please just do as I say. I'm the care provider and you aren't. And the other extreme is sort of equal partnership where the patient or the family gets equal say. Probably either of those extremes is suboptimal.

We were talking, before when we were writing the guidelines, about the patient's input. It's certainly important, but I think it's important for us to realize -- and I think Michele's touched on this a little bit, the patient isn't as educated as the care provider. That isn't meant to be a derogatory statement, but it makes it really

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tricky.

The Kevlar vest experience, yeah. It's just, because you walk into the arena, and I think if you just simply say to the patient or the family, "Here are the options. We'll do whatever you think is best," that's foolish. On the other hand, we walk in and say, "You do as I say, and you don't have any say."

So I think there's an art to this, and the consent process for these studies is often very difficult, and it's very variable from place to place, and probably country to country, too, just because of social expectations and whatnot. I think it's fascinating, but it makes these studies tough to do.

DR. SKROBIK: I just want to ask one last question before we move onto the next topic, and I'll let you speak, Claudia. It won't be long. It was Pratik who was speaking a little earlier about using capacity to communicate as a metric for sedation level that speaks to the patient family perspective.

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I remember Pam mentioning how important it was to be able to merge and make contact and how crucial that was to a sense of wellbeing. This is something that I've heard over and over from various patients. I think maybe Ingrid could speak to that. Would it be useful to have a metric in future studies, particularly with the goal of saying how are you going to measure outcomes like PTSD or psychological fallout?

If the issue was that you couldn't make contact when you were in the ICU and the family member was lost, is there any interest in that ability to make contact a metric? Does anybody think that's a -- Ingrid?

DR. EGEROD: Yes. I think what we need is more common sense in the situation because there are so many factors. One important factor, of course, is communication, and the other one is pain medication. If they have been covered for their pain and they are communicating, I think you can get far. Also, some patients have been in ICU before and might have an opinion from an earlier

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visit.

I'm not sure the family is always so reliable because they might be trying to satisfy their own concerns, but I think that common sense -- I don't know where you put it in an algorithm, but it needs to be in there somewhere.

DR. SKROBIK: I've got Claudia, Yahya, and Denham, and I'll start with Claudia because you've been waiting for the longest.

DR. SPIES: There are structured interviews that can be done of both the patient and the family in a chat session. The point is that it's not paternalistic or you give the whole autonomy to the patient and the relatives. If you can measure how far patients want to be involved, that's a structured interview. That's a short, structured scale.

The second point is the patients and the relatives can assess how you did that. You say there's a decision to make. That's something you need to say, and then the relatives and the patient can say, "I came to that famous place. I want to

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be respected, but you make that decision." Then that's fine, but you said to the patient that this is a decision to be made.

The other thing is that patients can say, okay, I want to take all responsibility; I decide. And I think we don't measure that structured. We do that now with a shared decision process in our departments, and it's better to involve patients and relatives. I think that's easily implementable. However, it depends that the patient and the family wants to be informed; whatever they decide, they want to be informed. That's the major issue.

DR. SKROBIK: Perfect. Thank you.

Pam?

DR. FLOOD: Well, again, clinically you're getting back to the art, but in terms of a clinical trial, how do you measure the art? It might be something as simple as how integrated -- how much is the patient and how much is the family able to be usefully involved in their care because as a clinician, if the patient says, "Get the tube out,

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get the tube out, get the tube out," but they have no ventilation, then of course you're not going to pull the tube out. If the family says the same thing, of course you're not going to.

But it may be valuable to note whether or not the patient and the family are able to contribute to the care because there's so much variability. If they don't even speak the language and understand what you're talking about, and you can barely communicate with them, they probably can't add much.

DR. SKROBIK: Yahya, you were going to say something?

DR. SHEHABI: I just wanted to make a comment. Richard at dinner last night asked me would I have changed the outcomes in a new SPICE study. I think one of the things that I would definitely change is to make the RASS target from minus to plus 1, I would make it minus 1 to zero.

I think we found there's a big difference between minus 2 and minus 1 in terms of patient communication and also in terms of family

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interaction. We found that the nurse at the bedside, once we said the patient is eligible, we're going to go and randomize, they would say, "Please, make him in this arm because this family wants to communicate with the patient."

So I think there is a bit of that happening between the bedside nurse and the family and the patient. They know which one would like to be a bit more zontum [ph] [indiscernible] and which one likes to be a bit more awake, and tend to the family, interact, and so forth. So I think there's definitely a difference between that minus 2 level and minus 1 level. I can communicate with someone when it's minus 1 effectively, and so does the family, but I cannot do that effectively with someone at minus 2.

DR. SKROBIK: I think there's little time to cover a topic as huge sleep in our discussion. I think that the sleep group the guidelines was probably one of our most novel and informative panels because it's such a -- we assume that sedatives are good for sleep. They taught us that

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not only are they bad for sleep, but we ended up recommending that propofol not be used for sleep.

So begging the question of what you do with your patient on propofol, what are you supposed to do; turn it off at night? So I think that there's -- but I think methodologically also, sleep plays into agitation, recovery, and all of those different elements of sedation trial outcomes, and I would welcome the thoughts on how that could or should be integrated.

Should sleep metrics be included in a simplistic way? Obviously, you're not going to be doing PSGs in every sedation trial, but should a steep metric being incorporated in trials that compare sedative molecules, for instance?

Dr. Maze?

DR. MAZE: Before that question is addressed, can I just make the point that not only is sleep important in delirium and other consequences, but it also is very important for inflammation, and all these patients how inflamed in one way or another. I would say anything that

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you can do to improve sleep in the ICU, you should try and do.

DR. SKROBIK: My thought on the topic was a pragmatic one. I think that sleep is much more influenced by the environment than anything else, and it's a multimodal sort of thing. So the noise, the combination -- and we've had these discussions around the guideline panels where it's a question of how much light, how much noise, how much anxiety, this amalgam of things that contribute to the sleeplessness that we know occur in ICU patients.

In sedation trials, then, should we be either, A, capturing quality of the self-reported sleep in a simple metric to add that to the comparator, or should we be looking at environmental differences? When I listened to Margaret Prezannie [ph] describe her ICU, if I were ever going to go sleep in an ICU, which I wouldn't want to, that's the one I would want to go to because they actually dim the lights, turn off the sounds, or in southern Brazil, where they give you

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a warm massage back rub, and give you warm milk if you're not intubated

Thoughts on that, on that dimension of sedation comparator?

DR. RIKER: I think as researchers and clinicians, I think this is an area we want more information about. But if we come back to the goal of what we're trying to talk about, we're trying to come up with a standard list of things that new drug developers should provide, I don't know that we -- I would suggest that sleep and probably patient and family perspective are gaps that we don't yet understand what the effect is, and especially don't understand how best to measure it.

Ideally in the future, we would get that information, but I don't think it's reasonable for us to mandate that when a new dex comes down the pipeline next year, that that's got to be part of the data they provide because I don't think we understand that yet.

DR. SKROBIK: So I'll try and imitate Avery without much success, but would there be a panel

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consensus, or at least a coherent thought, that these are indeed gaps that should be explored in future studies? Yes, yes, yes; there's a lot of head nodding.

DR. RIKER: But not necessarily as a requirement for submission.

DR. SKROBIK: And that's not what I'm saying. That's not what I'm saying.

Claudia, you were going to say something?

DR. SPIES: I think it's very important that we consider to assess that because that's protocol violation. Usually we have decibels of 60 to 80 during nighttime, even 100. So if you really control for, you get to 40 to 60. This is even high, but it's much better.

The second point, at least we should assess noise. We should check if the alarms can go silent during nighttime and can go outside so that the supervision of the nurses is outside, so you have a supervision room; something like the context where we are living.

DR. SKROBIK: Are you saying that it's

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because it's an important confounder?

DR. SPIES: It's an important confounder, and what we've seen also with our patients in the new rooms we have -- so this is a new room, really, that's giving us all these settings you require, that you have better sleep, et cetera. I think it's very important that we need less analgesics for these patients. Analgesics are anticholinergic usually because they are opiates. So it's depending very much on the anticholinergic activity, and this is also decreasing your sleep level.

So there are a lot of things going on. We should at least check for it.

DR. SKROBIK: So confounders should be considered. Got it.

DR. SPIES: As a confounder, it's very important. And in addition for the sleep monitoring, I think polysomnography, it's not a major issue to apply it. It's the major issue to evaluate it. If they have data science people using that, we can use it. But I think that's the

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major issue. We have to have somebody get that analyzed because that's taking time.

Instead of polysomnography, what we are using if that's not possible, we use actigraphy. This is at least a measurement that's not perfect but at least some idea what's going on. That's not sleep, but that's at least a confounder that can be measured.

DR. SKROBIK: I think we have some more sleep thoughts.

DR. ABSALOM: Tony Absalom. I just wanted to say it is very easy to measure the environmental effects. We've done it in some studies, the environmental, the lights and sound levels and so on. I think it's less clear how much of an effect that has. We've done some studies with volunteers at sleeping at home, in an empty intensive care, and in a busy intensive care, and actually they slept quite well, although it was very noisy.

These were things that I think there's a lot of assumptions about the effects of the environment, but --

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DR. SKROBIK: There's some conflictual data, too, right?

DR. ABSALOM: Sorry?

DR. SKROBIK: Some conflictual data, too.

DR. ABSALOM: That's a knowledge gap. In terms of polysomnography, we've also done stuff for that, and it's not that difficult to do. There's a poor correlation with self-reported sleep in the work that we've done. There's a Somnolyzer. There's a product out there -- I don't know what Claudia thinks about it -- that does the assessment automatically, so it's not as difficult as a neurophysiologist assessment of 24 hours.

DR. SKROBIK: Thank you for those points.

I think the sleep state, changing the requirement for sedation, and the confounders for the need for sedation like noise or other elements, are things to consider but not -- my understanding is it shouldn't be mandated as part of study design if we're going to be looking at sedation trials.

DR. WARD: I wanted to be careful with the use of the word "mandated."

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DR. SKROBIK: You're right.

DR. WARD: I think we're trying to come up with a resource --

DR. SKROBIK: Suggested.

DR. WARD: -- to help people design trials.

DR. SKROBIK: Got it. Sorry about that. I didn't mean it in a directive way.

I think we've gone on a fair bit about the efficacy of both sedation and analgesia at some length until now and have highlighted a number of challenges in these two areas. So I'm not going to go over it in more detail unless anyone wants to go back to the topic. Yes? No? The topic of analgesia and its metrics.

DR. DWORKIN: So maybe I missed it, but I haven't heard an answer to Denham's question, I think, that he began the morning with, is what would be our recommendation, if someone was going to be starting a clinical trial tomorrow, of a novel approach to ICU sedation for a primary efficacy endpoint? Or did I miss that?

(Laughter.)

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DR. SKROBIK: With regard to the pain dimension, you mean?

DR. SEDATION: No, no, no. Sedation, the sedation trial; what's our primary --

DR. WARD: I think what I heard outside of Denham's presentation were a lot of answers that said, well, it depends what you're doing because there's a huge variability in the amount of trial questions that people would propose. If you're looking at let's say a psychological outcome focus trial versus a mechanical ventilation duration trial, a lot of points were made in a lot of -- did I answer that?

DR. DWORKIN: Well, maybe I'm not understanding; this is not my area. But it goes back to the quip about new dex. So I've got new dex, and I would like to do -- I've done some phase 1 and phase 2 studies. I have a sense of the dose, blah, blah, and now I want to do a confirmatory phase 3 trial, establishing that new dex has efficacy for sedation in the adult ICU. What's my primary endpoint?

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

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

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

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

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with modern technology. I don't think that's a big issue. I'm not aware of anybody who's routinely trying to use it in the states.

DR. SKROBIK: I have Steve and Claudia.

DR. SHAFER: I'm an anesthesiologist, not an intensivist, but these drugs are really associated with substantial levels of agitation at low levels. It's the stage 2 anesthesia. We see this on the way down; we see this on the way back up. They do accumulate substantially. If you run an anesthetic for 24 hours to reattach a digit, you can be there a very long period of time with any of the drugs that we use unless you're running it right at a level on the threshold between awake and asleep, but there is substantial accumulation with these drugs.

I'd be concerned about the agitation, and I just would be curious whether or not this is seen. You don't see agitation as people are going to sleep with propofol or as people are going to sleep with inhaled anesthetics.

DR. WARD: I'd like to just bring us back to

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the question that was asked. So here's the discussion, but you can design it to look at an anesthetic versus a drug, but that's really not what we're trying to discuss here.

DR. SKROBIK: So whether we should consider it isn't part of what you want to --

DR. WARD: It's just another drug. I mean, it's another new dex. What clinical trial should we use?

DR. SKROBIK: I am shocked by you saying that, so I think it's important to --

DR. WARD: But I want to get back to Bob's question. Again, is time at a RASS of zero or minus 1 the effective outcome to measure effectiveness?

DR. BALAS: Can I get back to Tim's point and ask Dr. Sessler a question about the composite outcomes? I think what you propose is very interesting. Is anybody aware of a clinical trial that combined the symptoms of pain, anxiety, level of arousal and delirium together?

My question for you is you mentioned that

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they can't be too common of occurrence, so I assumed that that would probably be a problem. But if the goal is not to have a common occurrence, can you do such a composite outcome?

DR. SESSLER: Sure. It's not a matter of being common. It's that each component of the composite has to have a relatively similar incidence. So that seems like a reasonable composite to me. You have to dichotomize these inherently continuous outcomes, but that's a reasonable thing to do.

DR. BALAS: So it has to be dichotomous.

DR. SESSLER: Let's say RASS should be in this range --

DR. BALAS: Zero to minus 1.

DR. SESSLER: -- to make it dichotomous. It's either in it or not. We actually had some discussion last night at dinner about this. We were saying that you could use the days that met a composite of delirium, arousability, and pain, and then you have a continuous or ordinal outcome that's based on a dichotomous --

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DR. BALAS: Like a symptom burden index.

DR. SESSLER: Right.

DR. BALAS: Well, not every symptom, but the common symptoms.

(Crosstalk.)

DR. SKROBIK: So delirium and como is one such example, that combination.

DR. SESSLER: It's actually a pretty attractive outcome.

DR. RIKER: I think it's a great discussion, but my concern with this is as you go to the other extreme as far as incidence goes, you run into the same problem as if you have very rare outcomes. Cardiologists use this all the time because the mortality with MI is 1 or 2 percent. So to avoid having to enroll 20,000 people, they put the composite together and then they can get by with 400 patients or whatever.

If we have an incidence of our composite outcome that includes coma, delirium, and pain, aren't we going to be having an incidence of 90 percent, and then we're fighting the other

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

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

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

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

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the definition or even if they report any adverse events; not drug events, adverse events.

DR. SKROBIK: So would you consider sedative withdrawal, benzo withdrawal as such an adverse event?

DR. BURRY: I would potentially consider drug withdrawal an adverse event if it's an anticipated side effect of continuous exposure of that drug.

DR. SKROBIK: So the risk factors for adults are 48 hours of administration. So do you think that that should be part of what is incorporated in sedation trials?

DR. BURRY: I don't have an answer for that because I don't even know how to assess for withdrawal in an adult, in an ICU. So at this point, there's no tool to even --

DR. SKROBIK: Or gaps.

DR. BURRY: -- there are more gaps. The other point I wanted to comment on is if it's a regulated trial and anticipating adverse side effects or unanticipated side effects, having gone

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through and running a regulated trial for probably the simplest molecule on the planet, melatonin, the reporting for adverse events for new drugs or off-label use is extremely difficult.

Deborah Cook has a great paper about assessing adverse drug events in a critically ill patient. We spent days battling with Health Canada about the definition of adverse drug events because you are often labeling something as a drug event, which really has nothing to do with the drug at all. And I think some of those things need to be factored into regulatory trials, and reporting is quite difficult

DR. SKROBIK: No. I've used that paper as an argument.

DR. BURRY: We were successful with that paper after many battles and advocates to move forward.

DR. SKROBIK: The paper, for those of you who don't know, is a paper that summarizes that some of the things that are considered severe events in fact are just standardized ICU stories,

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so dyspnea, hypertension, et cetera.

DR. ZHAO-WONG: In terms of what to report on adverse events, we can always refer to the International Council for Harmonization Standard. They have definitions on what needs to be reported. It doesn't have to be related to drug. If it happens during a clinical trial, it needs to be reported.

DR. FRASER: May I make one statement?

DR. SKROBIK: Yes.

DR. FRASER: I'd like to introduce the concept of obesity and how it affects drug deposition. Very often we have patients on 20 micrograms per kilogram per minute or propofol, and that sounds like a low dose, except for if it's in a 180-kilogram person, then all of a sudden the absolute exposure of this drug is meaningful. So any drug that is based on body weight without consideration for obesity is actually missing the boat.

DR. SKROBIK: Thank you.

DR. EGAN: A very good comment about that.

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This is something that perhaps our ICU colleagues have not yet run across because it's relatively new literature. Obviously whether the body weight affects the disposition of the drug is a testable hypothesis. This has been investigated for propofol and also for remifentanil by my lab. But for propofol by a lab in the Netherlands, Tony is one of the main investigators that have been, involved.

The question now for propofol is really an answered question. You now have a scientific foundation in terms of adjusting the weight that you would put in the pump as it relates to propofol infusions. These are manuscripts by Eleveld, et al. Tony is also a co-author. I think it would an important thing to get into the ICU community because you can avoid this problem of overdosing these patients by putting in an adjusted weight.

DR. FRASER: Or consideration there for the context-specific half-lives of these drugs or is that just a short-term issue that you guys are studying?

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

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with, A, one answer, but I think what you've heard is a smattering of various -- is there anybody who would like to suggest one standard for sedative delivery that you would consider to be clinically meaningful?
DR. DWORKIN: How about we wait until people get some food, and then do it after lunch?
DR. SKROBIK: Yes, which I will invite you to do now. Thank you.
(Applause.)
(Whereupon, at 12:01 p.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N
(1:01 p.m.)
DR. WARD: I will keep the trains running on time here, so we will be through promptly at 3 o'clock. Nobody ever thanks a professor for lecturing too long, so we'll make sure we'll stay on time.
Can I have my first slide there. I do want to usurp a little bit of Tim's time for the slide I was planning on using in the next steps. I do want to keep the conversation a little bit more about a primary outcome because if we're going to have a paper that's a resource for designing clinical trials, and since we don't know what the primary outcome is going to be, that paper is never going to be accepted anywhere, and it's not going to be particularly useful.
What's the best primary outcome? It's not could we use as a primary outcome? I've got a trial I'm designing today that I want to start ASAP because I got new dex here, and I've got a drug company that wants to fund it. What should I use

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

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But let me defer that a little bit because I think that's a little bit of a separate topic. If we have an indication for a sedative, what's the major of its effectiveness? I put a straw man up there at a RASS of zero minus 1. That's what I've been hearing from the group, and I've seen heads shaking no, and I've seen heads shaking no.

I think don't want to usurp a lot of Tim's time, but I think this is important. I think if we want to have an outcome from this meeting that's useful and publishable, effective is the first one on the list. So we have to agree, if we can, on what a measure of effectiveness is.

Steve?

DR. SHAFER: I assume by time, it's actually a fraction, time at RASS versus time on drug.

DR. WARD: Area under the curve --

DR. SHAFER: It's got to be a ratio. It can't just be time. The more longer in the ICU, the more time you spend at the RASS score.

DR. WARD: Right.

DR. SHAFER: So it's fractional time at

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rest.

DR. WARD: Yes.

DR. AITKEN: Leanne. I don't think you can have something like time at RASS because that's just how well implemented was the intervention. That's not how effective was the drug.

DR. WARD: But if I have a drug that doesn't cause sedation, then it wouldn't achieve that.

DR. AITKEN: But you could achieve the same outcome by giving 100 milligrams of the drug or 1 milligram of the drug. You still achieve that.

DR. WARD: It's not a dose-finding study. That you should have been doing in a phase 1 and phase 2 two trial.

DR. COURSIN: You seem to want to get an objective, which makes a lot of sense. But my sense is what we really want is much more subjective. We want patients to be safe so it can facilitate their care to recover or not recover.

Now, I don't know how you put that in a graded scale that you can compare drug A to drug B, but that interest is, in my mind, very directly,

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what's your indication, and there will be no sedation.

DR. SKROBIK: I think also part of the resistance to this answer is in having one primary outcome be ranked as the best primary outcome for sedative trials, whereas what I'm hearing now and I think what I'm understanding is what you would like is the identification of potential primary outcomes, and they can be safety related. They can be process related, and then that list can be made.

What I have heard from many members around the table and earlier today is that there isn't one item that all of us would agree is a good primary outcome for any sedative trial. It depends what you're looking for. Lisa was talking a little earlier.

DR. WARD: Bob is coming out of his chair.

DR. DWORKIN: I want to clarify. If our primary outcome is safety, that's fine, but that's a different trial. That's a trial where the primary outcome is a safety outcome. I think what Denham is asking, and that says "effective," and it

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could say "efficacy," what is our primary efficacy outcome if we're evaluating the efficacy of an agent intended for ICU sedation?

So safety's a different question. If we're doing a safety trial, it could be something totally different.

DR. SKROBIK: Off line, and from all of our patient representatives, and from qualitative work that Ingrid has done and others, and Mona, the answer to that is return to the best you can be. I don't think it's a peri [ph] ICU metric globally, if you want one global item that is the subject of consensus, whereas the metric at the bedside is problematic for all of the reasons that we've been talking about, and everyone on that list is problematic.

DR. DWORKIN: But maybe Yoanna and I should take it outside, which is totally fine with me.

DR. SKROBIK: No, no, but that's important.

DR. DWORKIN: I think returning to the best you can be from a patient perspective sounds terrific, but I would challenge you have, do we

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

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

DR. SKROBIK: So let me argue back.

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

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

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

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

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

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

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

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

DR. WARD: Yes, that's true.

Rich?

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

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

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

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

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because I think otherwise it negates -- it simplifies what is in fact not a reflection of the reality.

DR. WARD: Well, that's because there are secondary outcomes that relate to these other realities.

DR. SKROBIK: No. I'm not even going beyond sedation. I'm describing the variability between the way it's applied and variability in the way it's interpreted. If you're going to say this is the ideal world scenario, if you're recommending something that's an ideal world scenario and the real world doesn't have it 50 percent of the time --

DR. WARD: Well, that's good clinical practices for a clinical trial, which is different than the way it's out in a phase 4 trial and obviously being used by everybody out there. If you're conducting your randomized-controlled trial as a function with GCP, that very might give you a different answer.

DR. SKROBIK: I didn't think we were here

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just for the phase 3's, but thanks for clarifying.

DR. WARD: Claudia and then Pratik.

DR. SPIES: The first part, I have a quality assurance guideline for the whole hospitals involving all disciplines and all from different specialties. We agree on zero minus 1, but I have one point I think I would like to make also. I think it's time and talk.

So during the stay, the ICU stay, your target may change, and even the drug is then -- you don't have that primary outcome fulfilled if you keep it that tight. So the question is if it's zero and minus 1, I think if the target is different, I think it needs to be acute. Why? If there's a reason to do it that way -- for example, for proning a patient or something like that, sometimes you cannot keep zero minus 1. That's the point.

DR. WARD: I agree with that.

DR. SPIES: So maybe we say time and target and say, okay, the standard is zero minus 1, and if there's an additional target to be mentioned, that

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has to be done before, not afterwards.

DR. WARD: As long as your clinical trial prespecifies the reasons that you're changing the target, you should be able to change the target, but that shouldn't be as you go along in the trial. It should be for certain conditions, you change the target to minus 2.

DR. SPIES: Yes, but it's one patient, and then it's decreasing the fragmented time, the fractional time during the period, it's decreasing. If you really delete that out of here, you have a shorter period. I think if you come to the real world and people do it different, I think that's something we can consider because if we say it's targeted to some level, and that needs to be performed by the physician beforehand, the physician has to achieve that.

Also, I think it's important because in some patients you may target it lower for a certain period, and this is also effective if you do that that way. So I think if you have an argument why you do it and you target it that way, it can be

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compared, and it can be, to my impression, also be included as a primary outcome for the study. It doesn't need to be --

DR. WARD: Pratik?

DR. PANDHARIPANDE: I'm sort of repeating it now, but I think the time to time to target seems the most effective, an effectiveness outcome. Now what that target is over a period of time, that will be an educational mission if 5 years from now, we know that minus 1 is where it needs to be. But from a new drug coming on, the ability that if you want it to be a minus 1, we can get there. If it needs to be a minus 3, we can get there, patients and situations change.

I think all of that as a start, it's great. I'm thinking about the composite outcomes. We had this discussion over dinner yesterday and the thought that it would be so great if there's a pain element that can be added in. I think unfortunately it becomes unfair because if you're trying to look at the effectiveness of a sedative regimen and then trying to put in an element that

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it really doesn't impact it, it's differential. Then you have to selectively choose or try and market a drug which has sedative and analgesic properties because otherwise it will never hit the other composited points of primary pain.

Then one last point is why target is important, target sedation, the question is what is going to be the target. And we've learned this from some of our studies, is that having the ordered target in the chart is very different than what the bedside nurses are using as their target in their head that they're titrating.

So effectiveness is probably closely related to what the bedside nurses are actually targeting it. If they want this patient to be minus 3, the automate might say minus 1. The drug will not be effective because nobody's been titrating it to that. So the thought of having both those elements in what is your target probably needs to be considered.

DR. WARD: Tim, I think you're on.

DR. COLANTUONI: This is Elizabeth

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Colantuoni. Can I ask one more question before we leave this part? How do you envision incorporating mortality into this endpoint? If someone was randomized and alive for 4 days and then experienced death, would you incorporate the time at the target RASS up until mortality, or are all patient deaths ranked worse than the scale?

It's just a question that -- we have to think about the complication of mortality within this framework.

DR. WARD: I'm not the statistician, but you're absolutely correct. That's got to be part of how you measure this time at RASS.

DR. DWORKIN: I've got to answer for Elizabeth.

Elizabeth, we're going to ask you to help us write that section of the paper.

(Laughter.)

DR. DWORKIN: Okay?

DR. COLANTUONI: Sure.

DR. DWORKIN: Thank you.

DR. SHAFER: Actually, can I just as one

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question --

(Crosstalk.)

DR. SHAFER: You're assuming that otherwise mortality is the same, because as a safety endpoint, if one group increases mortality, nothing else matters.

DR. COLANTUONI: But that's a challenge. So if there is differential mortality and you exclude it, then the treatment evaluation is no longer a randomized trial. If you're only computing this endpoint among survivors and there is differential mortality across the treatment arms, then the randomization doesn't hold anymore.

DR. SHAFER: But in thinking about your question, I can't imagine there's a clinical trial that would favor something which actually increased mortality.

DR. COLANTUONI: Yes, I agree. I'm just putting it out there as part of the discussion.

DR. SESSLER: It often is not significant. It often is this small change. It's not statistically significant [inaudible - off mic].

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DR. SHAFER: That's why I asked the question. We're assuming that there's no statistically significant difference in mortality.

DR. SESSLER: Right.

DR. COLANTUONI: Right, but in a couple of the sedation trials that I read, there was like a 7 percent difference in absolute mortality, which wasn't significant. I don't know this content area very much, but that seemed big to me. I'm just throwing it out there as a point that we need to consider an emphasize. If you're going to make a recommendation that this would be an endpoint, we have to think of all the potential complicating features of it.

Panel Discussion

DR. GIRARD: Which is a good segue into the last topic.

Denham asked me to moderate the session on acute, subacute, and chronic outcomes after ICU sedation, and I asked Mona and Dale if they would join me on the stage -- I guess this is a stage -- because they have done so much work in

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this area. Obviously, like the other two sessions today, we want this to be an open discussion. I don't really think I have to encourage that.

(Laughter.)

DR. GIRARD: I get the sense that it just happens naturally. Actually, as I thought about this topic, I think we've actually covered, either intentionally or unintentionally, a lot of ground regarding acute outcomes. So I'm intending that we mostly focus subacute or chronic, or what we would call long-term outcomes, although I'm guessing that there will be some conversation about shorter term outcomes as well.

On that note, I wanted to just quickly throw out this list and ask if there are thoughts that haven't already been covered, and I'm intending that we'll move quickly past this question. But we've alluded to the fact that even if the primary outcome is one that's related directly to the intended effect of the drug, which is sedation, you have to evaluate other short-term outcomes.

We just discussed that survival has to be

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one of those short-term outcomes. We've talked a lot about [indiscernible] proceduralization, including time to extubation. I inserted the word "successful" as being extubated only to be re-intubated within a day is not a good outcome. We all know that. So time to successful extubation, time to successful discharge, I would propose that hospital discharge matters much more than ICU discharge. I think probably many of us work in environments where you put the order in to discharge someone and, and whether they actually move is an entirely different question.

Short term, many of these outcomes that we've discussed could be assessed. Whether or not they could be assessed reliably in every patient or in the same percentage of patients in multiple treatment groups is a different question. But anxiety, depression, cognition, functional status, pain, quality of life, and costs all could be measured over the short term.

DR. DEVLIN: Tim, do you mean like short term, maybe like hospitalization?

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DR. GIRARD: That is a good question, and my second question when we get into long-term outcomes is what time frame would you consider long term, so you could also ask that question here. But as I said, I would like for us to focus more on long-term outcomes because I feel like we've focused primarily on the acute outcomes.

That said, are there additional comments that either Mona, or Dale, or any of you would like to make about the inclusion of these outcomes? And remember, at this point I think we're all in agreement that we're talking about secondary outcomes, whether you consider them safety. Certainly survival would be a safety outcome, but many of these others could be viewed as safety or could be viewed as efficacy outcomes.

DR. DEXTER: I can't comment involving patients who aren't surgical because those are the ones I've studied, obviously, although we're talking about non-surgical patients as well. But when it comes to these time to events, if you think of it in terms of time to successful extubation,

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time to ICU, discharge, time to hospital discharge, all these could be censored if the patient dies; time to being at home or whatever is the original status.

So you have 4 separate times. Although they're countable numbers, they can be units of days, and it's highly, highly correlated in terms of costs and things like that. So I think that this concept, when you're talking about countable days, it isn't like a binary type of endpoints that are being combined, but it's relatively straight forward from an economic point of view in terms of analysis.

DR. URMAN: Rich Urman. Just a quick question. Would quality-of-life survey involve satisfaction? The patients were able to answer those questions because that's slightly different. Obviously, you to have someone who was actually able to --

DR. GIRARD: Right.

DR. URMAN: -- have access to that.

DR. GIRARD: I think that's a good question.

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Many of the validated quality-of-life measures and what population they've been validated in is a question that's been raised. But many of those would not include satisfaction that could be added.

Time frame of when you would administer that I think would greatly affect whether or not the results were reliable in terms of measuring what you're trying to measure.

DR. URMAN: Right, and a lot of satisfaction scores are influenced by so many other factors, medical factors, things that have really nothing to do with what you're trying to measure, but just a thought.

DR. GIRARD: Right. Good points.

DR. RIKER: Riker. We heard earlier in this meeting about the challenges of assessing anxiety in our patients, how hard it is for patients to do a HADS score or whatever other tool we're going to use, and ditto the concept of earlier acute depression while they're receiving sedatives, versus hypoactive delirium, versus septic encephalopathy, that's a very challenging

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differentiation.

I'd be eager to hear what kind of time frame you had in mind for when we would assess anxiety and depression. Would that be pre-discharge, or within a month of discharge, or during their ICU stay, or how do you vision that?

DR. GIRARD: I should have clarified. I am not proposing necessarily measuring many of these in the short-term period, but rather I wanted to open it up to the group. My personal thought is -- and I'm curious if you guys agree or if others agree or disagree. My personal thought is that many of these are going to be very difficult to measure in the short term within the hospital period, and that the cost to benefit ratio in terms of the work that needs to be done to measure them relative to the reliability of the information you gain in that acute setting is probably not a good ratio, one that would warrant the work. But I wonder if others disagree with that.

DR. COLANTUONI: In terms of anxiety, it's easily measurable. There's a visual analog scale

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very similar to the pain that's been tested in the ICU. So I think we can do anxiety, or you can even do anxiety, yes/no. I'm not aware of any short-term depression scales that have ever been used in any studies.

DR. SKROBIK: It would be nice to use. [Inaudible - off mic] she did that in chronic inflammation ICU and was suggesting that the cutoff -- and we were talking about this point a little earlier, that the cutoff for the HADS is different in that population and in fact lower and associated with the worst functional outcome.

To speak to your anxiety comment, we've done it also in the A&A paper that we published with a pre post-implementation of pain, analgesics for pain. We did the RASS scores, and we asked about anxiety, and there was a 30 percent proportion of the population, roughly, that had a RASS score of zero to minus 1 but that was experiencing anxiety. We didn't even put it on the scale. It was a tick box, are you anxious right now?

So it's very feasible to incorporate these

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features. I'm just going to say, I'm not sure that in those patients medication is the answer because the medications that they were administered was the same because one of the options in that study was a nonpharmacological intervention. Would you rather listen to music or have a drug? So I think, yes.

DR. HOPKINS: Could I just speak to doing this after the ICU? Our 2005 paper, we assessed all of this stuff before they were discharged, and I will tell you, it was incredibly difficult, and the visits were repetitive, and you'd walk into the room, and they were having a treatment or they'd been sent down to x-ray, or MR, or wherever, or back to surgery.

So doing this and trying to really understand what their long-term outcomes are, are difficult at that point in time. And for cognitive, we know, between our study and Christina Jones' studies, that the rate of cognitive impairments at this point in time is almost 100 percent, between 90 and 100 percent, take your pick. So it has a lot to do with drugs and

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

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

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

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

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show it's not necessarily just a cross-section at one time. Usually it's much more advantageous to be able to see it and track it over time.

DR. GIRARD: Okay. So speaking of over time, let's move to this question of long-term outcomes. We've touched a little bit on this question, but I think it's worth revisiting, should sedation trials in general, all sedation trials -- I guess if you wanted to be really provocative, should all sedation trials include long-term outcomes? I'm seeing some nodding yes and nodding no. Speak up.

DR. KRESS: I would say that's wonderful in theory, but it's just not practical. It's too expensive. You're just not going to be able to do that with every trial. I think it should be something to consider, but I would reason to say the major rate-limiting step is going to be human power and money.

DR. SKROBIK: [Inaudible - off mic] But you're looking at the safety as a short-term molecule.

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Sorry. It's Yoanna. If you're looking at the safety of a short-term molecule, that may not be the point that you're looking at. But we're looking at the big picture of trajectories because we've learned that that's what we do. And thanks to all of you sitting up there on the podium and others in the room, I think we've become much more mindful that it's a continuum, but not all questions are related to that.

If you wanted, for instance, to say what is the usefulness of a sedative as a co-analgesic in the ICU, then you wouldn't -- well, you could look at chronic pain if you really got excited.

DR. KRESS: One thing, and we touched on it a little bit yesterday, I certainly have learned over the years is the importance of getting every email, phone number, text number, Snapchat, Instagram, whatever I can find is a way to reach people, or second cousin, because losing people later is frustrating if that's your intent.

So maybe you could imagine that people that weren't going to look at long-term outcomes to at

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least make a concerted effort to try to keep the people that are in their trials in the proverbial queue so that perhaps down the road someone else maybe who actually found money for a different purpose could try to capture those patients, so you could pass the baton so to speak.

DR. GIRARD: Others? Steve?

DR. SHAFER: It seems to me that certainly for initial trials, just to get the dose right to figure out if something is able to achieve the pharmacological effects of interest know, but any trial that's going to either go for registration of a drug or change practice, I think needs long-term outcomes.

DR. GIRARD: So phase 3 trials you would say --

DR. SHAFER: Yes.

DR. GIRARD: Okay. What is your thought to Yoanna's comment that -- it sounded like you're confident that many of these drugs won't have any long-term effects. How would you respond to that?

DR. SHAFER: We have a lot of examples in

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medicine of things where we say -- like take blood pressure -- even better, take tight control of glucose, and we know we can give basically drugs like insulin and try to get tight control of glucose, but we also know, when we look at long-term outcomes, we can really cause a lot of damage with what we think -- short-term, narrow-focused measurements are actually okay.

I think that you're going to have to know in the long term is this actually doing anything if you're really going to try to change practice.

DR. WARD: As a general question, do we think there is no effect, no signal there in long-term outcomes related to sedation in the ICU? Do we think it just doesn't matter how you do sedation, it's not going to affect a long-term outcome?

DR. GIRARD: Well, I certainly don't believe that.

DR. SKROBIK: That's not what I -- you can have a trial that looks at a short-term effect of a short-acting drug over a 5-day period in the ICU,

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or you can look at sedation practice over the ICU stay. Those are two different questions.

DR. WARD: My point followed Steve, that if we think there might be a signal there at some point in the phase 1, 2, 3 trial, and this is probably a phase 3 trial because you need a big enough end, you should be looking at is there something that's going to change cognition or something at the 6-month point.

I think some looking at what you three have done would say there's probably a signal there. And if there is, that's something that should be looked at.

MALE VOICE: And if there isn't, why are we doing this?

DR. NEEDHAM: I'm sort of skeptical. I think if you've got the new drug that you're trying to get FDA approval for, I don't think that post-discharge outcomes need to be mandated as part of it. And I suspect that if in this more modern age -- so I think more modern clinical trials -- all of them are going to be aiming for

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lighter sedation in both groups. And I suspect that the new drug's not going to have a signal in a phase 3 FDA trial. I think it's sort of a phase 4 thing, and it might be an even bigger population.

DR. DWORKIN: So the language we've often used is something along these lines, quote, "In most circumstances, investigators should consider including long-term outcomes in their clinical trials." No one ever objects to that sentence, and it's a kind of soft recommendation that if you're putting all of this effort into designing a phase 3 trial, also think about some long-term outcomes. There's no mandatory at all.

DR. WARD: That's the wording we used a lot in the papers for SCEPTER I and II.

DR. GIRARD: So if it was a recommendation rather than a mandate, would you then disagree with that?

DR. NEEDHAM: Dale Needham. Yes, I would agree for a recommendation rather than a mandate.

DR. GIRARD: So JP's comment about the cost and the work that goes into measuring the long-term

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outcomes, I don't think that any of us who have done these types of studies would disagree that it's expensive and it takes a lot of work. I hesitate to presume that I know what goes into, on the industry side, doing a clinical trial because I'm not in industry, but from the numbers I've seen, it wouldn't be a major part of the budget to add long-term outcomes. It would be I think a negligible part of the budget, considering how much is spent on the other aspects of the trial.

Pratik?

DR. PANDHARIPANDE: I think going back to some of the things I said earlier on looking at it from funding agencies, again, most funding agencies are now looking for those long-term outcomes. So looking at the three sedation studies that we've sent to the NIH recently, all have come back with saying make sure that the long-term outcomes are robust because we at least want you to be doing that. That's one part.

The other part is from the publication standpoint, I think most journals, to have an

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impact of your new drug, to get it to actually practice, are looking for things beyond the short-term outcome. So I think we need to keep that in mind. It may not be the primary outcome like we've discussed, but it has to be in the consideration.

DR. GIRARD: And I think we should also remember that -- I think it's actually a great thing that many of us in the room -- I wouldn't include myself, but many of us are skeptical that there would be a difference in long-term outcomes between two different sedatives or two different sedative regimens, when 15 years ago, or 20 years ago -- I think JP would agree with this. Twenty years ago, when JP published his paper in the New England Journal on daily interruption, there was an outcry that this is almost certainly going to lead to adverse long-term outcomes.

At that time, the assumption was widely that without heavier sedation, patients are going to do poorly in terms of long-term outcomes. And now we've come to the point where we're wondering if

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there will be any difference. It's not that hard to imagine that 20 years from now, we'll have more information and may view this whole thing in a different way.

DR. HOPKINS: Can I just add one thing to that? If you look at the trials to date that have long-term outcomes and show these adverse affects, most of them do not show differences between trial arms. So the bad outcomes that we all study are occurring in both trial arms, so that could be a rationale that we're not having them.

It's not that we're preventing bad outcomes; they're happening in both arms of the trials. I just went back and looked at the ABC data. I looked at Jim's paper from the brain ICU study, the brain ICU paper that Pratik published, and there isn't really a difference in outcomes, but there are bad outcomes in both arms at rates that are concerning.

DR. NEEDHAM: The other thing to add, in the few studies that are specifically designed to improve patients' outcomes after discharge, almost

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none of them show any signal of benefit, and they're specifically designed to improve that. So something that we're going to do in the ICU to affect sedation, that's why I'm sort of skeptical that they would. I've got two other quick comments.

Pratik, to your NHLBI or NIH funding application, you're right. I think now all of our grants say, "We will use the NHLBI-funded core outcome measurement set in our study" to hopefully have study sections go, yes, there's been a lot of thought put into what should be measured, and we're going to do it.

Back to a question on funding, if we're trying to fund this using like NIH-funded capitation, I think it is hard to squeeze out the money to do long-term outcomes assessments. Having tried to do this, I think it's very hard to squeeze it out because the budgets are so narrow, despite within the entire trial budgeted really being a drop in the bucket.

These trials are so expensive for the ICU

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part of them that it becomes hard, but hopefully we can get funding agencies and industry to recognize that it's important and make sure that there's some budget for that. Probably for a centralized call center that's probably in a large study, it's probably the most cost efficient and the most effective, but there needs to be a separate budget for that.

DR. GIRARD: Actually, along those lines, I want to skip down to the third question here. We can come back to the question of what's considered long term if anyone feels strongly that we need to discuss that. But moving to the core outcomes set, there's a core outcomes set that Dale and others published for acute respiratory failure survivors, and that is shown here, I believe.

One question that I have, if we are going to recommend but not mandate long-term outcomes be assessed in survivors who are enrolled in a clinical trial of sedation in the ICU, would this be the recommendation? These were developed with acute respiratory failure patients in mind. Those

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I believe are the same patients that we would be including in sedation trials.

So is this a natural fit or would there be some concern that, well, the core outcomes set wasn't specifically developed with the sedation trial in mind? what are your thoughts? Would this be an appropriate recommendation? Pratik?

DR. PANDHARIPANDE: I think it's a great start. You can always add more, but at $3, if those figures are correct over there, and I'm sure they are correct, Dale --

(Laughter.)

DR. PANDHARIPANDE: -- $3, I see very little excuse for not having that, given that, yes, most of the indication nowadays -- whether right or wrong, most of the indications right now for sedation is patients with respiratory failure who are difficult to manage on the ventilator. So I would say yes, one vote at least.

DR. NEEDHAM: This is Dale Needham. To clarify, the cost is the cost of the instrument,

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

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

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

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

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DR. RIKER: Riker. Mona, do you have a parameter or an idea as far as dropout goes, the longer you go? I imagine with this sick population, we're going to see drop out, not just from lost to follow up but mortality and other things like that. Do you see an obvious endpoint for long term?

DR. HOPKINS: I'll let Dale help answer this as well, but we have done when we implement the tools to maintain cohort retention, our long-term outcomes and my single-center studies, and our multicenter studies, and Dale's other multicenter studies have been very high in the 94 to 98 percent follow-up rate, but it is a lot of work to do that. Certainly, there is some mortality that continues at 6 and 12 months, and even longer, but it dramatically drops off the longer time you go.

I think an interesting question that you didn't ask is what happens with cognitive impairment? Is there some recovery, or same thing with depression, anxiety, PTSD, and physical function. What we do see is that there is some

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recovery but it appears to plateau between 6 and 12 months, but we don't really know exactly where because we've measured hospital discharge 3 months, 6 months, 12 months.

So there does seem to be some recovery, and a question that hasn't really been addressed in any study is can we facilitate that recovery? I should take that back. Jim's recover study, and Nate's study, and there are a couple of others that are showing that we can get increased improvement, but they're very small studies.

Okay.

DR. NEEDHAM: A couple of other comments. We have an interesting paper that actually used data to look at trajectories of recovery over time, and in fact it's a minority of patients that have a stable or improvement over a 5-year follow-up. That's a minority of patients. So the word "recovery" really is a misnomer. In fact, there's a proportion of patients who are bad and just get worse., and then there's proportion of patients who are bad, maybe stay the same, or get better over

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one year, and then have a decline between 1 and 5 years.

So there are lots of bad things that are happening to people after they are discharged and go home, high rates of readmission. So I think if we're trying to draw a cause and effect relationship, we can't go too far because maybe the intervention did cause the readmission, caused the medical and caused readmission, or maybe it's something else.

Interestingly, I think that we should stick to 3, 6, 12-month time points because that's virtually what everybody does. So I don't like a 30-day. I don't like a 45-day or some other random number. I think we should pick to those.

Interestingly, we have more difficulty with cohort retention at 3 months than at 5 months because patients are very overwhelmed at 3 months. So you might kind of want to capture that in a way, that might be an argument, but that sort of is not a steady state either, and it's an interesting observation around patient distress and lost to

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follow-up.

So in fact, we have higher retention rates at 6 months. What happens at 3 months, they just are overwhelmed or they can't be reached, but then you can get them at 6 months, and they're happy to participate, or they can be reached but they're still in a SNP or some other setting.

DR. GIRARD: If I could summarize what I've heard so far -- and this is your opportunity to tell me I've not been listening; my wife would be willing to tell me that --

(Laughter.)

DR. GIRARD: -- if I could summarize, it sounds like actually we agree that all of the long-term outcomes would not be mandated in sedation trials, that they would be recommended, and that it would be recommended that this core outcomes set be a good place to start. Perhaps you could add other outcomes if you had a specific hypotheses you wanted to test, but at a minimum, that it would be recommended that you would include this core outcome set.

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

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

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

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

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family is. But that's a very different question than assessing their view of the patient and what's happening.

DR. NEEDHAM: Also, it's not on any of these measures, we have created from scratch and used in thousands of assessments a standardized approach for measuring return to work that could then allow you to measure lost income and also health care utilization that had been published numerous times. They're freely available, and other people from around the world for comparability reasons are using the exact instruments.

Both of those instruments around health care utilization, after hospital discharge and returned to work, actually take a fair bit of detailed time to actually do based on an interview. And of course it's based on an interview, which may not be the same as other methods of getting health care utilization, but they are available and they are freely available on that same website, improveltl.com.

DR. AITKEN: If I could just pick up on

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that, Dale, I wondered why something like return to work wasn't in the core outcomes set.

DR. NEEDHAM: Interestingly, among the qualitative work and all of the work leading up, that social health was a consistent signal, but that social health never made it into a core outcome that should always be measured, and therefore there's not a measurement instrument for it. And that may be because in the empirical literature, it's measured much less often as opposed to signals from the qualitative literature.

DR. GIRARD: And in many of these trials, more than half of the participants were not working prior to their acute illness and enrollment in the trial. It certainly is an important outcome for a portion of the participants, but not for all of them.

Pratik?

DR. PANDHARIPANDE: Two questions. We said for the long term, it would be great to do it at 3 months, 6 months, and 12 months. If given that there's a pragmatic part of it, we have to choose

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just one time point, would you say at 6 months?

DR. NEEDHAM: This is Dale. I would say 6 months, and I say it because 3 months is really tough. Three months is pretty early. Six months isn't steady state, but 3 months really isn't steady state, and 12 months, it delays your outcomes by another 6 months, and you've got to do a lot of cohort retention activities between 6 and 12 months.

DR. PANDHARIPANDE: Thanks. The second part is if we were to do it more often, do all these tests in the core outcome set have the test/retest issues taken care of? Are there alternate versions of all these or is there a test/retest issue if you're doing it more than once with the core outcome?

DR. NEEDHAM: These ones, there are no multiple versions. I don't have the test/retest psychometrics in my head, and certainly they've never been evaluated in ICU survivors. But they commonly are used repeatedly over time in ICU survivors, and they seem to change over time in

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ways that seem to reflect reality. So I think that they have responsiveness.

DR. HOPKINS: This is Mona. I completely agree. HADS is how have you been in the last 2 weeks? You could administer that multiple times, and it's been used. They don't have alternate forms. IES-R has been used multiple times. There's not as much data there as there is on the HADS, EQ-5D. The bigger problem is going to be your MoCA Blind because you're asking the same questions, and there is psychological and psychiatric literature about cognitive learning to the test. So that's going to be your most problematic test for close retest.

DR. GIRARD: Close retest meaning what time frame? Would 6 months and 12 months be a concern there?

DR. HOPKINS: Most people would like you to go to 12 months, but if you use the regular MoCA in person, there are alternate forms. There's just not for the MoCA Blind.

DR. GIRARD: Okay. I think I had maybe -- I

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have two more questions. We're running early, so if you want --

DR. WARD: This is good.

DR. GIRARD: This is good. Running early is good. I've never learned that lesson --

(Laughter.)

DR. GIRARD: -- but I've heard that that's the case.

One question, and this is one that Elizabeth raised yesterday in her presentation, but I want to revisit it. Even though in critical care in general, we rarely, if ever, do see differential survival -- we have seen it a few times, including one sedation trial, and we simply don't know what new molecules' effects may be, and we have to always at least consider the possibility of a difference in survival, whether that's because the new drug is harmful or helpful, it has be considered.

So how should we account -- I think you've heard yesterday some options for accounting for confounding by differential follow-up due to either

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differential survival or differential functional status. If everybody in one group is still SNF and they can't do the testing, that would also lead to differential follow-up.

What do you think this group, if anything, would recommend for how to account for that? Is the composite endpoint the recommended approach? Is everyone satisfied with recommending survivors-only analysis even though that could potentially be biased? What are your thoughts?

I raise this specifically in the conversation about long-term outcomes because I think the longer term the outcome is, the more likely you will have differential follow-up. If you're measuring something in the ICU within hours or days of administering a treatment, you're less likely to have that problem.

DR. COLANTUONI: This is Elizabeth Colantuoni. If mortality is going to be an endpoint in the trial, I think that you have to plan to do an analysis by the counts for the possibility of differential mortality. It could be

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a stepped approach in the statistical analysis plan that says if the mortality's not statistically significant and/or within a absolute difference of some percentage that you don't think is clinically relevant, then the survivors-only analysis would be utilized, but I think it has to be planned in the trial.

I'm doing a systematic review right now of the last 5 years of papers published in the top five medical journals, and in studies where there's a decent amount of mortality, everyone's only doing the survivors-only analysis. So I'm not saying that those trials are biased because a lot of them, there is no difference in mortality, but no one's thinking about this, and I think that the standard should just be a staged analytic plan, and that would be a good, long-term approach.

DR. GIRARD: Just to add to that, what the potential values of a group like this making a recommendation along these lines is that it not only could influence how trials are designed, but also how they're interpreted.

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For example, in the ABC trial, when we published the long-term outcomes, we published the survivor -- you know this because we've discussed it. We published the survivors-only analysis, but that was not because that was our plan. That's because what the journal editors hired us to do. We actually presented to them initially a composite outcome, and they didn't accept that.

So I think that if, for example -- I've also revealed now that I have a bias about this ad an opinion, but if a prespecified plan based on a recommendation is followed through, then that may change the way a trial is interpreted.

JP?

DR. KRESS: I think no matter what choice you make, you're going to have pros and cons. One thing, having said that, that has in the last 15 or 20 years gotten a lot more attention is this concept of whatever badness is: free days, ventilator-free days, ICU-free days, hospitals.

One of the things that we've used, and I think others have as well, your disposition after

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the hospital, at least in the United States, has about 7 different bins you could go into.

So there's home, there's acute care, there's subacute care, there's LTAC, there's hospice, there's death, there's nursing home, a whole bunch of different places. But one way that might simplify that is over the course of whatever your denominator is, what are your institution-free days? That would allow you to deal with the varying outcomes but also take into account that if you end up home, no matter where else you go, it's not as good as home.

DR. RIKER: I tend to agree with you, Tim. If we only look at the people who are well enough to drive themselves to the follow-up appointment, we're going to be missing a lot of differences between the groups. So somehow, whether it's a composite outcome that includes death or skilled facility and unable to present, or unable to complete the evaluation, those are important outcomes that we need to capture I think somehow.

DR. GIRARD: So I'm going to push Elizabeth

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a little so we're specific. If we say how it's a staged approach and mortality is different, then we've got a choice, based on your work, around a composite outcome versus a causal inference method, like a SACE correct?

DR. COLANTUONI: Yes.

DR. GIRARD: Do you have any advice around anything that the paper should talk about in terms of how that decision should be considered?

DR. COLANTUONI: That's a really loaded question. Myself, I would lean towards doing a patient ranking, knowing that that's subjective and that there could be a whole discussion around how to rank someone's PTSD symptoms with respect to mortality at 6 months post-critical illness. But I think that the assumptions that go into the SACE model, like actually estimating the SACE, are also challenging and can equally be -- people can buy it or not buy it.

I would personally prefer to see us rank patients in terms of function or --

DR. GIRARD: To put that into a specific

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context, for instance, Rich was just talking about you can't do the test if you're not alive. So for example, say that your outcome or your primary outcome, we've got a randomized-controlled trial where this is their primary outcome, the 6-minute walk distance, and we do use a composite outcome in a rank-based analysis.

So if you're dead, then you get a score, for example, of minus 1. If you're unable to walk, you get a score of zero. And if you can walk, then it's whatever distance you actually walk. I think most people would agree that -- no, not everybody, but most people would agree that death is worse than not being able to walk. There may be some people that would rather be -- there may be, right? Some people who are bed bound that would rather be dead than unable to walk, but at least that's a decision that we had made, and that's an example of how this ranked-based method that Elizabeth presented about could be done.

I think that's a feasible method. Not everybody has to have a causal inference

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statistician to do that approach.

DR. COLANTUONI: And that allows you to do any host of sensitivity analyses to modifications of the rankings.

DR. BALAS: Who's going to make sed rankings? Should we add to that conversation like someone deciding is a nursing home worse than an LTAC versus --

DR. GIRARD: You're right. Within our group, for the clinical trial that I'm referring to, we had 3 rounds of international consultation. When we designed the study design, we had the luxury of doing that before we submitted it, so we had some sort of input. But fortunately -- and then we made the decision regarding a priori statistical analysis plan. We could also do a sensitivity analysis if say that there were big differences in patients that were unable to walk.

Death was the same, but unable to walk, we could do a sensitivity analysis and say how would the results look differently if we changed the ranking? But we put our nickel down and said this

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is the ranking that we're going to use, and other people seemed to think it was appropriate.

DR. COLANTUONI: I think also it's clear from our discussion, I think, that these are still going to be considered secondary endpoints. So no one's going to be -- we have to keep that in mind, that a lot of this will be exploratory, and over time will evolve into stronger hypotheses, and then these conversations can happen to kind of fine tune the analytic approaches.

DR. GIRARD: Good. So it sounds like in terms of after sedation outcomes, we're in agreement that long-term outcomes will be recommended at 6 or possibly 12 months and that those outcomes -- that the plan to analyze those outcomes should be prespecified and account for the possibility of confounding by differential follow-up.

Is that correct?

DR. COLANTUONI: Could you add -- so we have the patient-centered ones, it sounds like, to be in the cool. Could we add the family-centered outcome

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that was suggested over there, and maybe caregiver burden, recommend but not require a measure of caregiver burden?

DR. GIRARD: I think that makes sense.

DR. COLANTUONI: I think some have been shown valuable and reliable in critical care.

DR. GIRARD: The last question that came to my mind as I was thinking about the questions to discuss, maybe one that we've already inadvertently answered, and that is how should these long-term outcomes be assessed? By virtue of the fact that we've agreed to recommend the core outcome set for acute respiratory failure survivors, that would imply that we're recommending assessment over the phone.

Is there any interest in considering that some or all -- or maybe a better way to put it is, all or more feasibily, a subset of patients were assessed in person. Do you think there will be any additional value to doing that?

DR. NEEDHAM: That's the approach that we've used in -- like a large national clinical trial

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from a clinical trials network, all patients were assessed by phone through two centralized call centers, and then 5 of the 12 study centers through supplemental funding through an ancillary grant had more in-depth testing through in-person. And in-person may be in your research clinic or it may be in the patient's home or institution, so you need funding time and skills and safety issues to go out to people's homes.

But yes, I think that's great. It provides -- if somebody did a patient-reported physical functional outcome, that is going to be different than a performance-based physical function outcome. They measure different things even though they're both physical function measures. So it does reveal new information.

DR. HOPKINS: This is Mona. I agree.

DR. WARD: Is there also a role for a qualitative study and that subset that you can do the interviews with; not 200 your patients obviously, but in a few patients?

DR. NEEDHAM: I would agree, and I think

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some of us have talked about how that would be very helpful, especially in sedation trials where we don't have a measurement tool to capture the patient experience that we've heard about, I think that would be very rich.

I'm not a qualitative researcher, so other people correct me, but we have done qualitative research by phone, which allowed us to capture patients across all the 45 hospitals in the research network, or some of them, rather than just from a single center through phone, and obviously input from qualitative research and lots of training.

DR. GIRARD: Okay. So I think that it was okay that we donated some time for this session to the previous session.

DR. WARD: I think I can still finish up early.

DR. GIRARD: Yes. Any other comments about post-ICU sedation outcomes that we did not address, that you've just got a burning desire to bring up because now is your chance?

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DR. NEEDHAM: I've got one quick comment. We need to think about when we talk about discharge location or institution-free days, as JP said, we need to recognize that these things, especially in the United States, are directly affected by people's insurance status and also by family support status, and wealth, whether you can hire somebody to come into your home, or not, to provide the services that might otherwise be provided in the skilled nursing facilities. So those are important kind of confounders as well.

DR. GIRARD: All right. Denham, I think you're up.

DR. WARD: Great. Thank you.

(Applause.)

Group Discussion

DR. WARD: Well, thanks everybody for hanging in there the last day and a half. It's been exciting for me. As a pharmacologist, respiratory physiologist, clinical trialist, this is a little out of my wheelhouse, but it goes along with what we've been doing in the SCEPTER realm, in

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the 9 months it took to put this group together, and I appreciate -- almost everybody who I asked, and most of you I didn't know personally -- almost everybody who I asked responded very quickly and said, yes, I'd be interested. So in that sense, this was a great meeting to put together.

There are a couple of things I want to go over for kind of the next steps for us. This is complex. This was a great diagram that I had found in my background work. The interaction with what we're trying to do with sedation between pain, delirium, and unpleasant awareness is obviously very complex and much more difficult than the procedural sedations that we worked on in SCEPTER I and II.

What the deliverable is, this meeting is one of the deliverables. I think we have had a discussion with the FDA, both representatives, both directions, both hearing from them, and they're listening to what we're talking about. So we've accomplished one of the deliverables. We've brought together experts in the

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field -- clinicians, clinical trialists, sedationists -- and we've talked about how we would look at clinical trials for drug device protocols for ICU sedation and analgesia.

The next deliverable, as we did with SCEPTER I and II, is a paper that would serve as a resource. It's not a practice guideline. It's not in the sense of a consensus document, although we like to have some consensus in it. But it will serve as a resource for the design of clinical trials.

I would like to go back through what I first talked about for the IOM report and healthcare quality domains, and I would like to organize the paper along this same line, that the IOM talked about 6 domains of which 4 I think are directly applicable to our topic of safety, patient centered, and I would say patient/family centered there, effective and efficient.

We've had a lot of discussion over these 4, and the first one was our most difficult one. I actually put this slide together before we had the

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discussion this afternoon. There's obviously some modification to that first one. But I think we've come up with some sort of measure of -- and probably RASS, although there are some alternatives. And again, there's no must in these kinds of papers as it serves as a resource -- that a RASS at a sedation level that may vary throughout the time of the use of sedation if it's being used.

I think we will spend some time on email understanding a little better the indication for sedation because I think that's been a topic that's come up, and we haven't really resolved that. The target RASS may not be a zero and minus 1 throughout the whole sedation period, and that's fine, too.

Clearly, there's also some safety related outcomes beside the usual measurement of the SAEs and the AEs that terminology like MedDRA uses so we can report these adverse events in a systematic and a systematic way. But as you discussed with procedural sedation, there are things you kind of expect. If you're using an opioid procedural

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sedation, you better be looking for what the saturation is going to be doing as a safety outcome.

So there are probably some things that we need to look at when you're doing ICU sedation, that it's not the usual AEs and SAEs, and I would think the measurement of delirium not cooperating, a variety of things, agitation, that would be a safety outcome. Then there are other secondary outcomes that are more patient centered perhaps.

To me, pain is the one that is patient centered. You can argue you want more sedation or less sedation, but saying I only want more pain, probably most patients would say, "I don't want to have any pain." So to me, if all of these outcomes, pain is the main patient-centered outcome that we all -- unless there's a masochist -- want for our patients, and really don't want to have pain, and then other longer terms.

Pam?

DR. FLOOD: Not to mince words, but I think that certainly everybody wants less pain; nobody

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wants more pain, but some people would trade a little bit of pain for consciousness.

DR. WARD: These all interact, absolutely, and that's the kind of things that need to be taken into consideration, obviously, for the design of the trial.

Then there are the secondary outcomes that include both patient centered as on short-term, behavioral pain scores, and longer term -- a longer term consensus came a lot easier than I thought it was going to be. That turned out to be the easiest part of the meeting. I think a lot of that comes from all the great work that Dale and his group has done to set the stage for the validated tools that are available.

Then I would put things like time to discharge, hospital, ICU as really the efficiency parts. As I said, with efficiency, you have to be careful of whose efficiency. So it's not just cost shifting off the institution or healthcare system to the patient and the family and their insurance company, and those are the kind of things.

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So I think we've got ideas in all four of the IOM domains for high-quality health care. If we could come to some level of agreement for recommendations for these, along with indications, and study design, and some of the statistical things, that Elizabeth's going to be able to write that section for us.

A few things for next steps. Is everybody comfortable with distributing everybody's slides to everybody? Any objection to having your slides sent out?

(No audible response.)

DR. WARD: So along with the picture of everybody, I will send out everybody's slides to everybody.

I've had some but not a lot of experience with Delphi technique. Dale has had a lot, obviously. He and I discussed using Delphi before this meeting, and I decided not to. I was kind over overwhelmed with getting the whole thing organized without adding that to it. But after this meeting, I'm wondering what you all think

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about using a Delphi survey to see what kind of agreement we've got on some of these. And I would probably ask the group to provide the questions that we put on the Delphi as it goes around.

What do most people think about doing that? There's one thumb up there. Do you think it will be worthwhile? I think it would add to the paper. The methods of these kinds of papers are not the usual methods section. The methods section is about the information we distributed to the group beforehand, and that was the PADIS and papers that I sent around to everybody ahead of time. That was all we had. So we talked about here, and then Rigo said part of the methodology for reaching our recommendations was a post-meeting, Delphi of the meeting disciplines.

DR. GIRARD: I think it's a good idea. I do have one question both for you, Denham and Dale, having done this before. It seems like we're highly motivated to come up with a recommendation about primary outcome. We've revisited that question multiple times. The one thing with

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Delphi, though, there is no consensus. Are we then going to make the recommendation that someone develop one because we couldn't come up with one, or what would be your plan in that case?

DR. WARD: Yes.

(Laughter.)

DR. WARD: I think we'll be stuck with that as we recommend that there is no consensus, and that needs to be one of the key things we'd have to develop because you can't really move forward looking at a new molecule if you don't have some consensus on how you measure efficacy.

Coursin? Doug?

DR. COURSIN: Could we look at modulating the Delphi to come up with a PICO question or two? We know the population for the most part, but what's our real question?

DR. WARD: I think the Delphi would have multiple question, and certainly all the elements of the PICO could be -- we discussed that a little bit, should we be moving beyond, and how important it is to do your clinical trial in a homogeneous

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unit, 100 percent agree or don't agree. That's the kind of way the Delphi would work.

Dale, do you have any comments on how we --

DR. NEEDHAM: This is Dale Needham. I guess the way I envisioned it, which may be not what Denham does or anyone, but we've come up with a bunch of recommendations or whatever, and those will be in the manuscript, I think maybe your irrespective, and this is sort of recommendations. But then the Delphi allows people to objectively anonymously really say if they agree with it or not because some people may not have agreed with and may not have expressed it.

So we may still have something in the paper, and then we can express the level of agreement with that recommendation.

DR. RIKER: I think Delphi also allows you to comment on the areas of what's proposed that you have a problem with, and then you can tweak that and then revote. So it may be that if we're having trouble coming to consensus about this primary outcome, through the process, in addition to

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identifying the level of support for the group, you can also find a common ground with that.

DR. WARD: If you don't agree with including this, you get to get a recommendation on what you would agree for, and then that goes in the next Delphi, in the next Delphi round for it.

DR. DEVLIN: I saw critical care medicine up there. Is that your target journal, potentially?

DR. WARD: A thought, yes.

DR. DEVLIN: [Indiscernible] I'm on the editorial board. I would also, if that's your target journal, it might be strategic to reach out to hand that this group's convened to talk about what we're putting together. He's a pretty hands-on editor, and he might provide a little bit of informal feedback about what he'd like to see rather than just submitting something and hope for the best.

DR. WARD: Sure, yes.

DR. DEVLIN: And that could inform some of us a little.

DR. WARD: A little bit an anecdotal story

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on that, the first paper at the first SCEPTER meeting went through a fair amount of editorial discussion, shall we say, at Anesthesia & Analgesia, and they finally accepted it as part 1. I said, "Great," because now I can send them part 2, and they've already said they've got part 1, so now I get part 2 in.

I would probably, with your help, communicate with him and show him part 1 and part 2, and this would be a similar kind of -- but I think the audience will be better in CCM than in Anesthesia & Analgesia for that.

DR. SHAFER: In the Delphi process, is there any sort of assumption among the participants that we are going to try to reach consensus? In other words, this is not the U.S. Senate --

(Laughter.)

DR. SHAFER: -- and the hope would be -- my hope would be -- that people would really try to find a consensus viewpoint rather than putting stakes in the ground. Is that part of the Delphi, or is that just assumed, or does that not happen?

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DR. SKROBIK: Can I comment on just the consensus notion because John and I had a discussion about this. This is Yoanna Skrobik. When we were doing the guidelines, we swayed from the party line because we thought that if we said consensus or made it sound like we wanted or needed consensus, there would be two problems with that. One, it would suggest that there was one right way of doing things all the time, so we shied away from that, but also it wouldn't represent variability in patient populations, or practice, or opinion.

The way we got around that was we tried to ensure the communication about the content. Once we had clarified what you meant by a metric for a sedative, then there was much greater agreement. So we fostered, and hammered, and encouraged, and we're exhausted from all we learned about the communication piece. And at the last minute, we stepped back and we let people vote whether they agreed or disagreed, and then published the dissenting percentages and allowed people to comment.

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I wanted to put that on the table as an alternative to consensus because there are going to be different points of view. I think it's rich, but I also think that we should agree on something.

DR. WARD: Talmage?

DR. EGAN: Talmage Egan. I recently participated in Enhanced Recovery After Surgery, which is a society that's gaining some traction in the anesthesia world -- recently participated in the Society for Enhanced Recovery After Surgery pre-operative quality initiative, which is another cool acronym, POQI.

This POQI task force, which is a group that operates under the auspices of this ERAS society was tasked with putting together some guidelines, a consensus statement regarding neurophysiologic monitoring in the perioperative period. Anyway, we used the Delphi process. It was a 2-day conference like this, actually, and the groups were charged with putting forward statements, then the entire group would get together and refine these statements.

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This was an iterative process where we'd put the straw man together, people would vote, and then they'd get comments and they'd take them back, redo them, and bring a refined statement back. And ultimately, the idea was to have this Delphi method described in the methods section of the paper.

Anyway, the point I wanted to make is that the deliverable from this Delphi process were these statements. The voting of the statements were ultimately to be part of the deliverable so that it was clear whether there was a consensus or not. Then the same people were able to describe the elements of their dissent in the actual text of the paper.

So that was the way this group approached the Delphi process, and I think it worked out reasonably well. But a key thing is that you have to get everybody to vote so that there's not an implicit bias of some kind.

DR. WARD: There are multiple rounds. If you agree to come in on the first round, you really have to agree -- usually 3 rounds is one of the

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standards that I've seen and what I've done. You have to agree to come in on round 2 and round 3 so you don't get a dropout as it goes through.

Dale, do you have any comments?

DR. NEEDHAM: I think those are both great ideas. To make this less painful, many Delphis, if we reach consensus on 75 percent of this, you don't vote on it again. It's just what there isn't consensus on. At least in my mind, maybe it's like this was the original statement. This was the level of consensus. This was some revision after more discussion during a Delphi maybe.

DR. SKROBIK: [Inaudible - off mic] -- gap identification might be -- if what we want to do is build, give to the patient and to future generations, a tool that they can use to better the way they ask and answer questions and the way we serve that patient population, if that's the goal, and you haven't got consensus on 25 percent of Delphi -- I don't know what you think of, because you were looking for answers, but you were looking for outcome measures. That's a very different

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thing than disagreeing because -- and I think maybe it might be -- just as we did with the guidelines to say there's a gap/here's the gap, if we can identify it, then naming it because it would also be constructive.

I'm putting it on the -- obviously, I think it's a good idea because we did it for the guidelines, but I'm proposing it as a novel way of addressing these limitations for instance.

DR. WARD: To answer Steve's question directly, the government will give you a chance to report the level of agreement. You can pre- -- most Delphis say, okay, if it's 75 percent agreement and there's no vetoes, then it goes on. But you can also report this is a recommendation, but there was only 65 percent agreement.

DR. SKROBIK: I'm always suspicious of 100 percent agreement, unless it's something like pain should be assessed, I'm stunned at that. I think what did they do, what did they give you?

DR. WARD: It sounds like the Delphi, people

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are going to participate if I start a Delphi process.

The third one is help writing the paper. Is that something everybody wants to participate in? Because that's what I did for the first two papers. I wrote it, and then everybody participated, everybody's a little asterisk on it because there were degrees of participation.

I won't obviously use his name. One of my friends, who's actually on the editorial board of one of the other journals, never heard from him the whole time, and this was like 5 rounds of getting everybody to agree, until I sent it out to everybody and said, okay, I think we finally got agreement. This is what I'm going to send in, and I immediately got back from him 10 pages of modifications that he wanted.

So if you're going to participate --

DR. SHAFER: Delete.

DR. WARD: -- everybody gives their name on -- it's like these are the people and the group. But I was willing on the other SCEPTER to put

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everybody's name up there in the headline. But would people be willing to put a writing group together that would get the primary piece of credit or blame, and then everybody gets -- does that sound like a reasonable approach? Because I'm being a little gun shy from having written up this twice.

So if that's reasonable, would you let me know by email your willingness to participate on the writing group.

Elizabeth, you don't have a choice. You have to be on this. You have to be on the writing group -- to be on the writing group to help me put this together for that.

DR. SKROBIK: I sent you some of the summaries from yesterday morning, and I've written up a bullet point summary of what I understood from this morning's session between 10:30 and 12. And what I would also like, regardless of participation in the writing group, is just vetting for some of -- if I send it around and you have time to look at it, it's not long. It's a bullet point list, if

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there are things that I've forgot. Lisa and -- were kind enough to do it with yesterday's group.

DR. WARD: One more slide I think. Any other questions, comments? Egan?

DR. EGAN: I just want to make two quick questions just for your transcript because these two issues didn't come up. One is because of the profound synergy between these sedative agents and the analgesics, the opioids, the analgesic regimen really does have to be carefully controlled. We didn't really mention that, but that drug interaction is so profound that that's very important.

The second thing is if TCI were to be entertained as a trial method, we're not going to use that in the real world, so why would we do that for a new dex? I think that the FDA combination products group could evaluate the drug and the delivery system as an entity together, and it can be approved in that way. It's not a non-starter from the beginning.

DR. WARD: Any other final comments or concerns?

(No response.)

Adjournment

DR. WARD: Thank you all for participating. ACTTION appreciates you.

(Applause.)

DR. DWORKIN: Denham, and thank you very much. You did a great job.

(Applause.)

(Whereupon, at 2:38 p.m., the meeting was adjourned.)

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