

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

November 19, 2016

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1	measure them?	1	many trials, but we also included a lot of trials.
2	We're going to spend a little bit more time	2	And I think it gives us a state of the play of what
3	on respiratory because that's obviously the most	3	these trials are including when they are trying to
4	common and most devastating adverse events that	4	look at safety.
5	happen with sedation. But we're also going to	5	We obviously excluded for this meeting,
6	cover gastrointestinal, cardiovascular,	6	we excluded ICU trials, general anesthetic, general
7	neurological, and liver-kidney.	7	anesthesia, and retrospective studies. We ended up
8	Then this afternoon we're going to try to	8	with 500 studies, of which we excluded about 400
9	pull it together with some discussions. When I say	9	initially. It left us with about 141 which met the
10	panel discussions on the agenda, it's really	10	exclusion criteria, and we looked at 133 articles
11	discussions of everybody here.	11	for this analysis.
12	I know we all have flights to catch this	12	No information was put in 1 percent of the
13	afternoon, so what I will propose to do is to come	13	studies. We looked at what or generally
14	back from lunch at 1:00, and then we'll have a	14	classified them into two different classes. Some
15	two-hour session looking at recommendations that we	15	studies just said, we recorded vital signs as
16	can be making because I'm going to go home and	16	safety assessment, and others were much more
17	start writing the paper to send around to	17	specific on what they were recording.
18	everybody and get through at 3:00. And there'll	18	About 50 percent, 54 percent, of studies
19	be some snacks out there that you can take with you	19	were specific on what classified as safety
20	as you go out the door. And that way people who	20	measurements, and of those 54 percent, 46 actually
21	have 5:00, 6:00 flights can make them without a	21	also included interventional techniques or
22	problem. So if that's agreeable to everybody,	22	interrupting procedure as items included in their
	Page 6		Page 8
1	we'll come back at 1:00 and adjourn at 3:00.	1	safety assessment. And 11 percent of those
2	So we'll start out this morning with a	2	54 percent used a standardized tool, such as Beck
3	review of the literature that we have started,	3	or World SIVA, to try to assess their safety
4	what's out there for clinical trials, and Mark is	4	outcomes.
5	going to start out with that.	5	Reviewing which safety outcomes they looked
6	Presentation - Mark Williams	6	at, as mentioned, respiratory, every one of the
7	MR. WILLIAMS: Thank you, Denham. Welcome	7	studies that defined their safety outcomes used a
8	and good morning, everyone.	8	respiratory item as a measure of safety.
9	So as Denham said, we started with a review	9	Surprisingly, only 69 percent used some
10	of the literature just to give us a platform of	10	cardiovascular measure; and then fewer, about a
11			
	what trials are out there, what safety aspects they	11	third, for neurological and gastrointestinal items.
	what trials are out there, what safety aspects they are using, trying to cover. And the initial search	11 12	
12		12	
12 13	are using, trying to cover. And the initial search	12 13	These were two studies for the efficacy of
12 13 14 15	are using, trying to cover. And the initial search was performed we did eventually, unfortunately, end up with quite a restrictive search because the search terms "sedation" and "safety" bring up	12 13 14	These were two studies for the efficacy of fospropofol, but they also captured safety data.
12 13 14 15	are using, trying to cover. And the initial search was performed we did eventually, unfortunately, end up with quite a restrictive search because the	12 13 14 15	These were two studies for the efficacy of fospropofol, but they also captured safety data. And this is similar to some of the studies that
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12 13 14 15 16 17 18	are using, trying to cover. And the initial search was performed we did eventually, unfortunately, end up with quite a restrictive search because the search terms "sedation" and "safety" bring up hundreds of thousands of articles. To bring this down to some manageable amount of articles, we ended up looking at procedural	12 13 14 15 16 17	These were two studies for the efficacy of fospropofol, but they also captured safety data. And this is similar to some of the studies that went through safety. These are actually similar across the studies, looking at desaturation.
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12 13 14 15 16 17 18 19 20 21	are using, trying to cover. And the initial search was performed we did eventually, unfortunately, end up with quite a restrictive search because the search terms "sedation" and "safety" bring up hundreds of thousands of articles. To bring this down to some manageable amount of articles, we ended up looking at procedural sedation studies, which were clinical trials. And we ended up keeping it quite restrictive into randomized clinical trials, which were double-	12 13 14 15 16 17 18 19 20	These were two studies for the efficacy of fospropofol, but they also captured safety data. And this is similar to some of the studies that went through safety. These are actually similar across the studies, looking at desaturation. Here they used less than 90 percent for more than 30 seconds, and heart rate less than 50, requiring an intervention, or blood pressure less than 90 or so, requiring an intervention; so similar across the fospropofol studies here.
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1	the FDA license for efficacy, also including the	1	classifications.
	2 safety. These are slightly different, definitely	2	Serious adverse events, not often discussed.
	different from the fospropofol, slightly different	3	Serious adverse events from the good clinical
	between the studies. These use the time of blood		
	pressure outside of the range. I think this was an	5	Then, as we mentioned yesterday, time frame,
	5 area-under-the-curve study.	_	
7			these parameters before you classify its ranging,
8			in these studies that we looked at, anyway, from
	baseline. And the other study was		10 seconds to 1 minute, and then some recorded the
	25 percent and for 30 percent, and for		cumulative time, cumulative repeated times outside
	respiratory rate was less than 8 breaths,		-
			of the range.
	 25 percent. So a bit of a difference across 3 studies and between studies. 	12	So there's not really good consensus on
			which items are important to capture, what should
14	5		be mandated to be captured throughout the studies,
	5 just some of the studies that we went through		which parameters to use, what time frame to use, or
	5 trying to just capture what they looked at, again		how to classify them for severity.
	just showing the lack of consistency across studies	17	So with that lack of consensus, we hoped we
	in not only timing, but the adverse events also,		could get some consensus across the group with your
	the actual values that were used.		feelings across some questions. So I'll hand it
20			over to Denham, and he'll take it.
	studies captured maybe a saturation or a resp rate.	21	Q&A
22	2 A lot of studies are starting to use end-tidal	22	DR. WARD: I think we're going to open up
	Page 10		Page 12
1	monitoring. What that value actually means isn't	1	for questions first from the others. I have a
2	2 often clear, but they at least capture it, and then	2	couple.
	other important respiratory items, cardiovascular,	3	How common in those papers were there an
	usually blood pressure, heart rate. And then GI,	4	
	predominately nausea and vomiting.	5	MR. WILLIAMS: An active?
6	5 Neurological was often a wide span if they	6	DR. WARD: We pointed out yesterday, did we
7	include. Sometimes excessive sedation was	7	run into a clinical trial that
8	3 classified as an adverse event. Even looking at	8	MR. WILLIAMS: Yes. So we only looked at
9	not unpleasant recall but recall, were they able to	9	
	form a three-object recall later on, or did they	10	So that was the randomized, double-blind,
	have persistent amnesia for events or mini-mental		controlled trial, yes.
	2 scale assessment decrease. Then generally	12	DR. WARD: Do you know what kind of control
	3 capturing other side effect data.		group, what drugs and procedures they used for the
14			controls for some of those?
	5 that we discussed it was discussed well	15	MR. WILLIAMS: It was usually if they
	5 yesterday often ambiguously classified.		were looking at ketamine, it might be enzo
	Sometimes it interfered with a patient's		and enzo, that they were looking at, yes, and
	g function that was classified differently or		other sedative medications.
	met a certain intensity or a certain deviation from	19	DR. KOCHMAN: Mike Kochman. So the problem
	o normal physiology. Otherwise, classified as an		with these constructs of safety
	interrupting procedure or not, or requiring		outcomes sorry of the adverse events that are
	 reatment or not, those seem to be the usual 		being looked at is that often they can be
44			soling looked at lo that often they dan be

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1	relatively insensitive to what we would look at and	1 with a systemic review, besides the computerized
2	say are really important, as opposed to physiologic	2 literature searches, ask the experts in the field
3	changes that may occur.	3 if they know of any other papers or unpublished
4	So in GI, one of the things, for example,	4 papers, or we'll send around the list of papers
5	that we look at is there are a whole bunch of	5 that we have found, and for you to add any to them
6	different scales to grade pancreatitis. And we can	6 that you think should be added.
7	argue that those scales are insensitive for the	7 Rick?
8	detection of significant pancreatitis, moderate	8 DR. RIKER: There's a study in press in JAMA
9	pancreatitis, and mild pancreatitis. We throw	9 called the SIESTA trial. It's ischemic stroke
10	those terms about, but we don't know what they	10 thrombectomy, general anesthesia versus conscious
11	actually mean.	11 sedation. It's by the Heidelberg group. And I
12	So one of the things I'll just throw out is,	12 think to me it brings in a couple of issues.
13	does it become an AE, an SAE, when we have to alter	13 Excluding general anesthesia would have lost
14	the intended procedure that the interventionalist	14 that study, although maybe it would have popped up
15	is performing, or you have to change your	15 with conscious sedation. But it was a very
16	anesthetic plan from what you intended to do, a	16 interesting study because they looked at long-term
17	priori, with an intervention that was not part of	17 safety and efficacy, and actually showed an
18	the goal of that anesthetic plan?	18 improved, modified rank in 3 months in the general
19	MR. WILLIAMS: Good question. I don't know.	19 anesthesia group. So it may change our focus a
20	(Laughter.)	20 little bit on what we consider the duration of
21	DR. KOCHMAN: I'm looking for help here.	21 effect of a sedation or a procedure.
22	DR. WEISS: Like many things at least about	22 There were some time differences between the
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1	the anesthetic plan, the answer is, I would think	1 groups. It took 10 minutes extra to get an
2	that depends on the situation, and what the patient	2 arterial puncture. Maybe the anesthesiologist was
3	is presenting to us at the time, and what the needs	3 having lunch or something. But time from puncture
4	of the proceduralist are presenting to us at the	4 to reperfusion was actually quicker in general
5	time.	5 anesthesia.
6	There are times where we certainly have to	
		6 So some things you don't necessarily think
1.7	change the anesthetic plan, or what we're doing,	So some things you don't necessarily thinkabout. And counter-intuitively, the incidence of
	change the anesthetic plan, or what we're doing, because now we're in trouble. And there are times	
8		7 about. And counter-intuitively, the incidence of
8 9	because now we're in trouble. And there are times	7 about. And counter-intuitively, the incidence of8 pneumonia was higher in the general anesthesia
8 9 10	because now we're in trouble. And there are times where you may not be in trouble, but I know that I	7 about. And counter-intuitively, the incidence of8 pneumonia was higher in the general anesthesia9 group, kind of the opposite of what I might have
8 9 10 11	because now we're in trouble. And there are times where you may not be in trouble, but I know that I can give a proceduralist a better feel, which will	 7 about. And counter-intuitively, the incidence of 8 pneumonia was higher in the general anesthesia 9 group, kind of the opposite of what I might have 10 expected. So I don't know.
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	Tage 17		Tage 19
	MR. WILLIAMS: No. And some didn't define	1	They may be an issue in that an opioid that
	2 how they were assessing these. They just said that	2	was administered is going to have a more untoward
	3 they were assessing them. So obviously, the	3	effect in those patients. And that can surface as
	4 methodology is important.	4	an adverse event.
	5 Going back to how long do you follow them	5	So excluding those patients is somewhat
	٥ up, it's a very good question. If you're looking	6	important. If they actually have documented
	7 at adverse events, if you don't have them within	7	polysomnigrams and nocturnal hypoxia.
	3 the first 5 minutes after they recover, is that	8	DR. WARD: Well, you can probably do better
	9 okay or do you have to follow them for months?	9	trying not to include high-risk patients than you
1	DR. RIKER: Yes. I guess the other issue is	10	could being
1	L long-term cognitive issues. Right? I know this is	11	DR. LERMAN: Well, certainly, but that's
1	2 a very controversial area, but probably should at	12	what I'm addressing is the fact that you're going
1	3 least mention it.	13	to trap them, generate AEs, SAEs, unwittingly.
1	4 Group Discussion	14	DR. KOCHMAN: I would argue that the
1	5 DR. WARD: I asked the group if you had any	15	question in the phase 3 trial is what is that phase
1	6 questions you wanted to survey the rest of the	16	3 trial? Is that the pivotal labeling trial or
1	7 group. I didn't get many responses, so I made up	17	not? If we're looking at a pivotal labeling trial
1	3 my own. So if you don't like the questions I made	18	and exclude certain patient populations
1	9 up, you can just blame yourselves for not sending	19	deliberately, then what is the onus later?
2	me better questions.	20	To get the manufacturers to go back and
2	So I thought we'd just go through these one	21	change label so that we're operating within the
2	2 at a time and discuss them as we go through. And	22	label becomes very, very difficult. And I would
	Page 18		Page 20
	Page 18 L as I said, I make no claims of validity of these	1	Page 20 argue that properly trying to size and properly
	-		-
	L as I said, I make no claims of validity of these	2	argue that properly trying to size and properly
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1	groups. So you've got that comparator to balance	1 know what the routine treatment is. So generally,
2	the increased risk.	2 it's best to specify the controls or the actual
3	DR. WARD: Exactly. If you were trying to	3 [inaudible – of mic] period.
4	compare propofol with dexmedetomidine in obese	4 DR. WARD: So you'd recommend that if we
5	patients with sleep apnea going for a GI procedure,	5 were going to do a clinical trial with a new, to
6	you'd have both groups.	6 actually not do this kind of trial but to really
7	DR. BERKENBOSCH: If you've got appropriate	7 specify.
8	comparators, it may not. Those continue to wash	8 DR. SESSLER: A specified control is always
9	out a little bit more.	9 better.
10	DR. WARD: So how about a noninferiority	10 DR. WARD: Frank?
11	pragmatic clinical trial with a new sedative agent	11 DR. DEXTER: I know the goal is the safety
12	protocol compared to a current regime? By	12 issues, but yesterday when people talked about the
13	pragmatic, I mean, you let with the current	13 time reduction, one of the other problems with the
14	regime is you let the people do what they usually	14 routine care is that it can differ endogenously
15	do, and not as this not specify quite as	15 related to the work flow.
16	rigorously as you would for a non-pragmatic trial.	16 In other words, it's routine care at one
17	So pretty well split between yes, you should	17 organization because their work flow versus another
18	and recommended but not required. Dan?	18 one, but that work flow is oftentimes not
19	DR. SESSLER: Suppose you do a study testing	19 characterized, not described in papers. And so
20	a new agent against placebo and you find that it's	20 then it's so difficult to figure out whether the
21	better than a placebo?	21 economic result, the time reduction results, would
22	DR. WARD: Can you ever do a sedative study	22 be generalizable or not.
	Page 22	Page 24
1	against a placebo in a late-phase trial?	1 DR. WARD: Rick?
	against a placebo in a late-phase trial? Certainly, in phase 1 that's what you're doing. So	
2		1 DR. WARD: Rick?
2	Certainly, in phase 1 that's what you're doing. So	 DR. WARD: Rick? DR. RIKER: I would say we'd have to be
2 3 4	Certainly, in phase 1 that's what you're doing. So that's why I said compared to current regime.	 DR. WARD: Rick? DR. RIKER: I would say we'd have to be 3 careful of not throwing the baby out with the bath
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4 5 7 8 9 10		2 3 4 5 7 8 9 10 11	in your talk? Okay. Great. Because nausea, really, as opposed to what? Vomiting is more of a measurable outcome. So I was trying to get at an outcome that was a little bit more continuous than the dichotomous vomiting or no vomiting. Frank? DR. DEXTER: The issue in terms of nausea, "Anesthesia and Analgesia" had a series of articles. One of the challenges is that not only would it be an ordinal scale, it's a highly skewed ordinal scale. And so that when you see, for example, is that even when you try using relatively
13 14	Our scale actually specifies three scales on the DSM delirium criteria, which includes inability		valid instruments, you will see, for example, a difference by a Mann-Whitney test. I get the
16	to associate with the environment, fails to perform purposeful movement, and out of touch with the environment, I think.	16	medians are identical or near identical. So I think that one of the things that is better in the past two, three years is mathematical
18	The other two may be overlapping with pain,	18	
19			
20	come up here, which is if you measure or attempt to	20	currently uncorrectable for covariance.
21	measure emergence delirium in a procedure for which	21	So in a purely randomized trial, reasonable,
22	there is post-op pain and you haven't controlled	22	but beyond that, it's a real challenge to deal with
	Page 26		Page 28
	the sector constraints to be a filler to sector a structure of the sector of the secto		The second state of the state o
	the pain completely with a block or some other		it because the methods designed for the ordinal
2	means, you risk some interaction between post-op	2	variables rely upon a very symmetric distribution
2	means, you risk some interaction between post-op pain and an emergence delirium.	2	variables rely upon a very symmetric distribution within the rank scale.
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1	they value? What's important to them?	1	think we see very many studies for procedural
2	So I think for every one of these things, it		sedation that has given follow-up for a month or
3	gets a little complicated to know how do we	3	more.
4	actually quantify and score, and what's the	4	DR. DEXTER: Yes. That's what I was going
5	important aspect of it to us and to patients.	5	to ask, if Mark came across any papers that
6	DR. ROBACK: Maybe it's my pediatric	6	actually went to postoperative behavioral outcomes,
7	orientation, but like Jerry says, it's really hard	7	nightmares, cognitive issues, up to a month
8	to measure in children. And so we go back to	8	afterwards.
9	interventions, and was it enough that they received	9	MR. WILLIAMS: Not up to a month, but some
10	an antiemetic for it? And that would say that	10	certainly looked at the immunological outcomes over
11	maybe it's significant. But again, you don't get	11	the next 48 hours, including nightmares. But yes,
12	gradation of what the actual degree is.	12	I didn't come across any out to a month.
13	DR. WARD: Again, I was trying to get at	13	DR. LITMAN: Denham, the best we have in
14	non-dichotomous outcomes to help. But I thought	14	this area are some very old studies that looked at
15	that in fact, when the adverse events may be rare,	15	not sedation per se but hospitalizations, and that
16	then you're trying to find out some non-dichotomous	16	the whole hospitalization data and what happens to
17	outcome.	17	these kids' fear of doctors, regressive behaviors,
18	DR. DEXTER: So I have the paper, the one	18	it's just so foreign from the hospital environment
19	Devine, where we had a series of studies on the	19	that there is today, where back in those days they
20	statistical analysis and so forth that was part	20	didn't even let parents in, and kids got a lot more
21	of studies of aromatherapy and stuff like that.	21	shots than they do now. It's so hard to know.
22	The thing with the clearly, it's all going to be	22	DR. WARD: Yes?
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1	adults, and it very much becomes one in terms of	1	DR. LIGHTDALE: And there's the fact that
2	almost binary.	2	kids, unlike adults, are probably undergoing
3	The reason being is because you're going to	3	procedures because they are ill. They're going to
4	have patients with large amounts of nausea, and if	4	have so much confounding in terms of that month
5	you think about, for example, a Wilcoxon test, all	5	interim as opposed to, let's say, a screening
6	the ties completely go away. So it essentially is	6	colonoscopy, which everybody needs.
7	going to become mathematically as if it were to be	7	DR. WARD: What I'm sort of hearing, though,
8	binary. Think of it as extreme amounts of nausea	8	is different than what everybody responded.
9	become average or zero, is the way that essentially	9	DR. LIGHTDALE: Or you had a bunch of
10	works.	10	adult
11	DR. WARD: Okay. So in pediatric patients,	11	DR. WARD: Yes. Yes.
12	how long should the follow-up be after the	12	DR. BERKENBOSCH: I think there's potential
13	sedation? Regression in milestones, nightmares,	13	value to looking our further. But the question is
14	long-term neurological. I guess the majority	14	finding a control group where you've undergone a
	long-term neurological. I guess the majority wanted to go at least a month for follow-up, with		finding a control group where you've undergone a procedure with maybe there's going to be very
15		15	
15 16	wanted to go at least a month for follow-up, with	15	procedure with maybe there's going to be very few procedures, at least in kids, because it's
15 16 17	wanted to go at least a month for follow-up, with only a few as 48 and a week. So that speaks to	15 16 17	procedure with maybe there's going to be very few procedures, at least in kids, because it's
15 16 17	wanted to go at least a month for follow-up, with only a few as 48 and a week. So that speaks to somewhat longer follow-up than what we normally	15 16 17	procedure with maybe there's going to be very few procedures, at least in kids, because it's probably more of interest in kids than it well, the question's in kids.
15 16 17 18	wanted to go at least a month for follow-up, with only a few as 48 and a week. So that speaks to somewhat longer follow-up than what we normally see.	15 16 17 18 19	procedure with maybe there's going to be very few procedures, at least in kids, because it's probably more of interest in kids than it well, the question's in kids.
15 16 17 18 19 20	wanted to go at least a month for follow-up, with only a few as 48 and a week. So that speaks to somewhat longer follow-up than what we normally see. Jerry?	15 16 17 18 19 20	procedure with maybe there's going to be very few procedures, at least in kids, because it's probably more of interest in kids than it well, the question's in kids. You almost have to look at that age group
15 16 17 18 19 20	wanted to go at least a month for follow-up, with only a few as 48 and a week. So that speaks to somewhat longer follow-up than what we normally see. Jerry? DR. LERMAN: Oh, I'm sorry. I thought you	15 16 17 18 19 20 21	procedure with maybe there's going to be very few procedures, at least in kids, because it's probably more of interest in kids than it well, the question's in kids. You almost have to look at that age group where you could or you couldn't get the MRI with or

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		Page 33		Page 35
	1	those who underwent with, to try to tease out some	1	probability of yield, very small. But you won't be
	2	of those confounders procedure-related anxiety,	2	criticized if you've made it a 24-hour cover; then
	3	not just the sedation-related stuff.	3	you may end up missing something. You don't know,
	4	But I think that unfortunately takes out	4	with any new drug.
	5	some of the age group that's really at risk for	5	DR. WARD: We're trying to come up with some
	6	these longer-term behaviors, at least as has been	6	recommendations with this group.
	7	described in previous anesthesia literature.	7	DR. LERMAN: Yes. Well, I just throw out a
	8	DR. WARD: Dan?	8	week and say a week is a compromise time-wise and
	9	DR. SESSLER: I guess I'm a little confused.	9	for efficiency of doing studies, and see what
	10	If you compare the novel treatment with the usual	10	everybody else thinks.
	11	treatment, if you're using a randomized design,	11	DR. WARD: Jenifer?
	12	there is no confounding. Both groups will have	12	DR. LIGHTDALE: Wouldn't the phase 1 study
	13	some baseline effort, but	13	really need to focus beyond nightmares, even, on
	14	DR. LIGHTDALE: You're going to have so	14	neuropsychiatric testing, pre and post? That
	15	many	15	really needs to be sorted out early on with this
	16	DR. SESSLER: you're looking at the	16	controversy going on.
	17	difference between the two.	17	DR. WARD: Is there a need for clinical
	18	DR. LIGHTDALE: I'll put it back. There's	18	intervention? Reversal agent? Treatment? We've
	19	heterogeneity in what's going on with the patients.	19	been talking about this a lot; particularly a lot
	20	And so unless you	20	of the QI databases are really run by intervention,
	21	DR. SESSLER: Sure. Sick patients are	21	intervention plus, and something, and something
	22	inherently more variable than well patients, yes.	22	else.
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		Page 34		Page 36
	1	Variability is one of the factors in sample size.	1	
	2	Variability is one of the factors in sample size.	2	Is that the best primary outcome measure for
	2 3	Variability is one of the factors in sample size. We need to study more patients [inaudible].	2	Is that the best primary outcome measure for a sedation clinical trial? Is reasonable consensus there that it's not?
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1	that sort of outcome, you need to define it very	1	desaturation, if you're using high-flow oxygen, you
	carefully, and they have to be interventions that	2	
	matter with enough content.	3	and never lose that. But yet an intervention such
4	DR. WARD: So I would say if you've got a	4	
	clinical trial in which you're collecting the data		measure of something with a clinically important
	that generally would indicate what the need for the		respiratory depression.
	intervention is, do you really need the	7	DR. WARD: So again, differentiating between
	intervention piece?		a QI-type database and designing a clinical trial,
9	You've got the saturation data. You've got		so could you design a clinical trial in which if
	the respiratory rate. You've got the nausea scale		you define the intervention, if there's an
	that you're measuring. So I'm really asking it, is		intervention using MRIs, then putting on nasal
	the intervention which is the clinical outcome;	12	
	right? The quantitative data that we're measuring		it's in the GI suite, that might not be. But could
	is not the clinical outcome. That's a surrogate		a clinical intervention be the primary outcome of a
	for it.		clinical trial that you are designing?
16	I agree it'll be dependent on the procedure	16	I see Dan shaking his head yes. We said no
	and the risk tolerance of the provider. Somebody		here, but maybe my question wasn't very clear.
	may put oxygen on. There's a lot of things	18	DR. SESSLER: The question was, is it the
	that other psychological research says if your		best?
	previous patient had a saturation of 85, then your	20	DR. WARD: Okay.
	next patient you'll probably tolerate a lower	20 21	DR. CARLSON: But if we don't choose
	saturation.		intervention, which is measurable, then we have to
22		22	
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1	That's been well-documented, that we have	1	agree upon whether the biophysical markers, of
2	biases based on our situation. So there's a lot of	2	which that nets. Maybe intervention is a proxy,
3	difficulties with a straight clinical intervention,	3	not perfect, but actually coming to agreement about
4	but yet that's the real outcome, is having to	4	what is the measure would be really hard if it
5	intervene.	5	wasn't an actual act.
6	DR. RIKER: I think if we moved in that	6	DR. WARD: Dan?
7	direction, I would echo Dan's comment. It's got to	7	DR. SESSLER: Maybe the consensus here is
8	be a clinically significant outcome that we talk	8	
9	about, not something that is 5 seconds in duration	9	helpful because they often change in ways that
10	and has no long-term impact.	10	don't really mean anything; saturations, for
11	DR. WARD: Or something that interrupted the	11	
12	procedure.	12	important, and it's highly context-dependent.
13	DR. RIKER: Interrupted the procedure,	13	It's probably not going to be possible for
	extended beyond the procedure, caused harm in some		us to come up with a simple solution. We're going
	way.		to have to recommend to the investigators we have
16	DR. GREEN: Yes. I'm certainly a fan of		reasonable endpoints. In a given context, even,
	interventions because then they let you know what	17	the procedure, the type of sedation, and who's
	is clinically important. We keep talking about	18	
	this hypoxia. Some people do procedural sedation	19	DR. WARD: Yes. The difficulties we had
	without supplemental oxygen. Other people do it		with midazolam decades ago illustrate that, when I
	with high-flow oxygen.		was a junior faculty I was a junior faculty and
22	So trying to just say, was there a		you as a resident, and we were squirting midazolam
1			

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1	when it first came, we didn't have any problems	1	You're going to design it from the beginning.
	with it. But then they started using it with some	2	DR. WARD: I'll talk a little bit more on
	fentanyl out on the [indiscernible] suite, and then	3	respiration. But should a provocative test be used
	there was a lot of problems with it.	4	in early clinical trials for a new agent to provide
5		5	more information about possible propensity for
	different drugs have different expected	6	adverse events? And you see most of that in the
	complications. So if you're evaluating ketamine	-	respiratory studies.
	versus midazolam, you're looking for different sets	8	Kind of split, most with no opinion. And
	of side effects.	9	let me expand on that when I give my subsequent
10			talk. The difficulty of that just is that very few
	on a primary outcome, it's an efficacy outcome, not		of the provocative tests that we have, have any
	a safety outcome. And I would think for a sedation		validity in connection to adverse events in
	trial, the successful completion of the procedure		clinical use.
	or something along those lines would be the more	14	DR. DAHAN: And they're very difficult to
	likely primary outcome, and then there'd be a		perform, especially in patients. It may be
	number of safety outcomes.		impossible.
17		17	DR. WARD: Well, some of them. I mean,
18		18	hypercapneic response is the traditional one that
	just interested that you listed that as a primary		people have used.
	outcome measure. I would think that these are not	20	DR. DAHAN: Still difficult to do.
	primary outcome measures. It may be primary safety	21	DR. WARD: The end tidal CO2 as an outcome
	outcome or a secondary outcome outright.		during sedation clinical trials? Maybe outcome's
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1	The primary outcome is that you're	1	the wrong word there, but should it be reported in
2	delivering sedation, how the procedure is	2	sedation clinical trials? I was surprised by that.
3	completed, and the patient left the hospital. The	3	I thought that would be much more yes than a
4	secondary outcomes are everything else that	1	resounding maybe.
5	happened. And you can call them mild, moderate,	- 4	resounding maybe.
	happeneu. Anu you can can them milu, mouerate,	4 5	DR. PRATIK: [Inaudible – off mic].
6	and severe.		
6	and severe.	5	DR. PRATIK: [Inaudible – off mic]. DR. CONWAY: But it's not really the number
	and severe. I think it's crucial that we record these	5 6	DR. PRATIK: [Inaudible – off mic]. DR. CONWAY: But it's not really the number
7 8	and severe. I think it's crucial that we record these	5 6 7 8	DR. PRATIK: [Inaudible – off mic]. DR. CONWAY: But it's not really the number of the end tidal CO2 that you're wanting to report
7 8 9	and severe. I think it's crucial that we record these interventions because anybody else who is beginning	5 6 7 8	DR. PRATIK: [Inaudible – off mic]. DR. CONWAY: But it's not really the number of the end tidal CO2 that you're wanting to report in the sedation clinical trial. It's the changes
7 8 9	and severe. I think it's crucial that we record these interventions because anybody else who is beginning to give this drug would like to know, for example, that 50 percent of the patients need a jaw thrust.	5 6 7 8 9	DR. PRATIK: [Inaudible – off mic]. DR. CONWAY: But it's not really the number of the end tidal CO2 that you're wanting to report in the sedation clinical trial. It's the changes and the wave forms or periods of apnea, increase or
7 8 9 10 11	and severe. I think it's crucial that we record these interventions because anybody else who is beginning to give this drug would like to know, for example, that 50 percent of the patients need a jaw thrust.	5 6 7 8 9 10 11	DR. PRATIK: [Inaudible – off mic]. DR. CONWAY: But it's not really the number of the end tidal CO2 that you're wanting to report in the sedation clinical trial. It's the changes and the wave forms or periods of apnea, increase or decrease of 10.
7 8 9 10 11 12	and severe. I think it's crucial that we record these interventions because anybody else who is beginning to give this drug would like to know, for example, that 50 percent of the patients need a jaw thrust. A, they may not want to use that drug, or B,	5 6 7 8 9 10 11	DR. PRATIK: [Inaudible – off mic]. DR. CONWAY: But it's not really the number of the end tidal CO2 that you're wanting to report in the sedation clinical trial. It's the changes and the wave forms or periods of apnea, increase or decrease of 10. DR. WARD: Right. But should it be
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1	use blow-by, oxygen blow-by, to get through an MRI	1	example, in an MRI scanner, and it's not never
	or whatever. Sometimes we put the kids on their		seen it used in a child or in a pediatric study.
	side.		It may be used, but it's just not practical to
4	DR. WARD: But we're talking about a	4	
5	clinical trial, right, so we're talking about	5	pediatrics, in my opinion.
	something that you're designing	6	DR. SESSLER: I imagine the most common
7	DR. LITMAN: Who volunteer. Volunteers.	7	response was generally, but not always.
8	DR. WARD: You've got volunteers in	8	DR. LERMAN: I suspect
9	patients. But you've designed a clinical trial to	9	DR. SESSLER: You can say it should be done
10	look at a new sedative. Are you going to require	10	if you can, and recognize that in certain cases, it
11	that you have end tidal CO2 in that clinical trial?	11	may be difficult.
12	DR. LITMAN: If you could control for it	12	DR. WARD: James?
13	easily. If you think it would be accurate. I	13	DR. MINER: I think if you're looking
14	just when I think about children, I think about	14	at we're always going to use apnea and airway
15	how hard that is.	15	obstruction as major outcomes in any sedative
16	DR. LERMAN: Well, I think it's more or	16	trial. And if you're expecting an observer to
17	less mandatory. And part of the reason is the	17	record those based on their impression, it would be
18	implications of sedating perhaps a child with a	18	so biased it's almost useless, especially apnea.
19	particular disease, who has already pulmonary	19	Nobody sees apnea because they don't want to.
20	hypertension or may have a congenital heart	20	End tidal CO2 always picks it up. It
21	difference, who cannot tolerate an increased CO2,	21	doesn't matter if you're doing blow-by. It doesn't
22	if we knew that sedative regiment caused an	22	matter if they're standing on their head, it's
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	-		
	increase in CO2, we would clearly avoid it.	1	going to pick up apnea accurately and without
2	, 3	2	, , , , , , , , , , , , , , , , , , , ,
	the sedative regimen is on end tidal CO2 compared		measurement.
	to the standard regimen, assuming and we	4	DR. WARD: This is from Aaron, actually,
	generally do in every case, including MRI for		suggested this. Transcutaneous PCO2 be reported?
	children having sedation. So I think it would have		It gets around some of the problems that Ron was
	to be part of the study.		talking about.
8		8	AUDIENCE MEMBER: There are always problems
	but there's no reason to think that other		with that, too. It's more serious problems.
	parameters won't be predictive of end tidal CO2.	10	DR. WARD: I'm going to move ahead here
	Like I can't think of a situation where your	11	o i
	ventilation would be normal but your end tidal CO2	12	(Laughter.)
	would be higher than you expected. DR. LERMAN: That's right. But how do you	13	DR. WARD: So these are applied to adults. Critical value of end tidal CO2 be considered an
14	measure tidal ventilation, except with my little		adverse event? And most people wanted greater than
	monitor, not invasively? Because there is no		55, which goes to speak that CO2 is not a
	technique except the one that	17	particularly good biomarker of an adverse event.
18		18	
19			problems, long-term problems.
20		20	AUDIENCE MEMBER: One of the problems we get
	ventilation.		into with CO2 in trials is that when people
22			obstruct, it makes more room air. And if they're
		1	

1 using nasal cannula, the value drops. I don't	1 were still less than 40, would be an absolute
2 think it works really that accurately for picking	2 change, entire cardiac greater than 120. So both
3 up a high-end value.	3 outside, the usual normal range of 60 to 100.
4 DR. WARD: Right. I'm just assuming you can	4 Okay. So that was the opinions that people
5 get an accurate measurement, and there are	5 had. And again, I put those out more to help
6 obviously a lot of technical difficulties with	6 people think a little bit and be a little
7 measuring end tidal CO2.	7 controversial than to really collect anything that
8 AUDIENCE MEMBER: I think recognizing that's	8 we were going to go from.
9 not the only CO2 value that's of importance. I	9 Could I have my slides? So the rest of the
10 mean, the maximum value isn't the only thing of	10 morning we're going to spend talking about more
11 importance. Again, if you're obstructing and the	11 specific measures. We've gone through the very
12 CO2 suddenly plummets, that's also something that's	12 high level yesterday, and we're going to get down
13 worth looking at.	13 into what were the kind of things if you're
14 DR. WARD: Right. That's more of airway	14 designing a clinical trial for a new sedative, what
15 obstruction, which end tidal CO2 is probably not a	15 were the things that you'd want to measure?
16 good way to measure airway obstruction.	16 Respiratory, so I allotted more time to
DR. MINER: But it's consistent, though. If	17 respiratory than the other areas because that's
18 your value all of a sudden drops, it's consistent	18 clearly the one that we have spent the most time
19 from obstruction.	19 on. And I'll talk some about it, and Albert will
DR. WARD: A lot of other things, too, a lot	20 talk some about it, too.
21 of mixing of not a good exhale.	21 Unfortunately, I thought I'd have to go back
Is there a difference in CO2? We want to	22 and do a little respiratory physiology with
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-	
1 have CO2 that'll go up pretty high to be not any	1 everybody because there was a few missed concepts
 have CO2 that'll go up pretty high to be not any worse than existing regimen. Blood pressure 	 everybody because there was a few missed concepts that I was hearing yesterday.
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Sa	lety Outcomes in Frocedural Sedation	11070116	(11), 2010
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1	way of thinking about it for procedural sedation is	1 selection.	
	to think about ventilatory control coming from	2 So monitoring ventilation is something that	t
	three areas. There's the traditional metabolic	3 we can do clinically. Methodologically, that's n	
	control, the CO2/O2 chemoreceptors that when your	4 necessarily the easiest thing to do. We've hea	
	O2 goes down or your CO2 is up, or your pH is low,	5 little bit about CO2 monitoring. Albert yesterda	
	there's stimulation through the closed metabolic	6 mentioned humidity monitoring. Thermistors a	-
	loops for the chemoreceptors.	7 used by the pulmonologist to measure air flow.	
8		8 the laboratory, there's ways with pneumotacho	
		9 and face masks and mouthpieces and things th	
9	that I can manage to not only walk and chew gum at	Lo can measure it accurately.	lat you
		-	
	the same time, but I can breathe and talk at the	L1 In the clinical situation, measuring	
	same time. And I can do it fairly efficiently,	L2 ventilation, tidal volume, and breathing rate is	
	without very much disturbance of my blood gases.	L3 not a trivial task. Measuring apneas and	
	If you measured my blood gases right now, they'd be	L4 differentiating between central and peripheral	
	essentially normal. My CO2 might be a couple	L5 apneas, measuring the CO2, measuring the	
	millimeters low. So I got voluntary control.	L6 saturation, depending on whether or not you ha	ave
17		L7 supplemental O2, and recalling without airway	
	talking, probably the most important control is	L8 obstruction with a patient that has supplementa	
19	behavioral, wakefulness control, that in spite of	L9 O2, saturation is going to be a very poor monit	or.
20	5 5	20 In fact, a concept called apneic	
	intersection of the CO2 response and the metabolic	21 oxygenation, if you've got an open airway and	
22	hyperbola that controls our resting ventilation,	22 you're on 100 percent O2, you will never get	
	Page 54		Page 56
1	that's probably not true. What's controlling my	1 hypoxic because sufficient gas will flow because	e of
2	resting ventilation is what Ray Fink termed back in	2 the gas exchange ratio.	
3	Columbia in the 1960s as behavioral wakefulness	3 Then the apnea-hypoxic, hypercapneic in	dex,
4	drive.	4 so the respiratory disturbance index, looking at	
5	So in the normal resting and maybe during	5 ventilatory arrhythmias; and then the need for	
6	light exercise, this mixed control really controls	6 clinical intervention. These can all be done jus	t
7	all three, but the primary effect is a behavioral	7 monitoring a patient without any provocative	
8	control. And obviously, the procedural drugs that	8 intervention.	
9	we use can have effects on any of those three	9 In the laboratory, and these are generally	
10	areas, and they do.	L0 more phase 1 type trials, hypercapneic ventilat	ory
11			
	Examples to start off with is with opioids	L1 response, so you can give patients a traditiona	
	Examples to start off with is with opioids that severely depresses the hypercapneic and	L1 response, so you can give patients a traditiona L2 CO2 rebreathing study, where you can have su	
12			ıbjects
12 13	that severely depresses the hypercapneic and	L2 CO2 rebreathing study, where you can have su	ıbjects
12 13 14	that severely depresses the hypercapneic and hypoxic response, may reduce their wakefulness	L2 CO2 rebreathing study, where you can have su L3 rebreathe CO2 and look at the slope and interc	ibjects ept;
12 13 14 15	that severely depresses the hypercapneic and hypoxic response, may reduce their wakefulness control a lot, but voluntary control is still intact. You can ask an apneic narcotized patient	L2 CO2 rebreathing study, where you can have su rebreathe CO2 and look at the slope and interce L4 hypoxic response. The pulmonologists look at L5 negative airway pressure, called Pcrit, negative	ibjects ept;
12 13 14 15	that severely depresses the hypercapneic and hypoxic response, may reduce their wakefulness control a lot, but voluntary control is still intact. You can ask an apneic narcotized patient to take a deep breath, and they can still take a	L2 CO2 rebreathing study, where you can have su L3 rebreathe CO2 and look at the slope and interce L4 hypoxic response. The pulmonologists look at L5 negative airway pressure, called Pcrit, negative L6 pressure that causes the airway to obstruct; an	ıbjects æpt; d
12 13 14 15 16	that severely depresses the hypercapneic and hypoxic response, may reduce their wakefulness control a lot, but voluntary control is still intact. You can ask an apneic narcotized patient to take a deep breath, and they can still take a deep breath for you.	L2 CO2 rebreathing study, where you can have su rebreathe CO2 and look at the slope and interce L4 hypoxic response. The pulmonologists look at L5 negative airway pressure, called Pcrit, negative pressure that causes the airway to obstruct; an L7 you can find that between normal sleep, general	ibjects æpt; d d
12 13 14 15 16 17	that severely depresses the hypercapneic and hypoxic response, may reduce their wakefulness control a lot, but voluntary control is still intact. You can ask an apneic narcotized patient to take a deep breath, and they can still take a deep breath for you. So I want to divide up the idea of testing	L2 CO2 rebreathing study, where you can have su rebreathe CO2 and look at the slope and interce 4 hypoxic response. The pulmonologists look at 15 negative airway pressure, called Pcrit, negative 16 pressure that causes the airway to obstruct; an 17 you can find that between normal sleep, general 18 anesthesia, and sedation, there's a change in the	ibjects æpt; d al vhat
12 13 14 15 16 17 18	that severely depresses the hypercapneic and hypoxic response, may reduce their wakefulness control a lot, but voluntary control is still intact. You can ask an apneic narcotized patient to take a deep breath, and they can still take a deep breath for you. So I want to divide up the idea of testing sedative drugs into two areas, with an overlap	L2 CO2 rebreathing study, where you can have su rebreathe CO2 and look at the slope and interce 4 hypoxic response. The pulmonologists look at 5 negative airway pressure, called Pcrit, negative 6 pressure that causes the airway to obstruct; an 17 you can find that between normal sleep, genera- 18 anesthesia, and sedation, there's a change in v 19 that Pcrit or negative airway pressure could be	ibjects æpt; d al vhat
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	Page 57		Page 59
1	or a sedative on breathing.	1	saturation than perhaps you're used to seeing.
2	Other measurements in the laboratory were	2	Then this is what's known as a RespiTrace,
3	the EEG or EMG for the genioglossus muscle,	3	so it has bands around the abdomen and the chest
4	esophageal pressure. And then finally, most of the	4	wall, that measures the excursions of both. So
5	time it's not a single drug, so how are you going	5	normally they're in sequence, and as there's
6	to measure the drug interaction between two drugs,	6	degrees of obstruction, they become out of
7	looking at PK/PD or response surface kinds of	7	sequence. So here we've got three different ways
8	modeling.	8	of measuring a respiratory effect, a tidal volume
9	So we've got lots of options. If you've got	9	measurement, saturation measurement, and a
10	a brand new drug and you say, I want to	10	synchrony between the abdomen and rib cage.
11	characterize this drug's respiratory effects, we've	11	Here we see, just monitoring the patient,
12	got lots of options, both early at a phase	12	that we have some apneic episodes here, with a
13	1/phase 2 trials and maybe phase 2 to 4 kind of	13	subsequent time delayed decrease in saturation
14	trials.	14	there. And it's a little hard to tell without
15	So a clinical intervention index, something	15	blowing this up whether this is a central or a
16	that we put together, not validated, but one that	16	peripheral apnea.
	we wanted to have. But it's based on other	17	Anybody want to guess what drug this is?
18	studies. We used this in a study that we did in	18	(No response.)
	GI, that Suzie did, looking basically at a clinical	19	DR. WARD: Nobody wants to guess what drug,
	intervention score.	20	what sedative this is?
21	It's based on the kinds of desaturations,	21	DR. RIKER: Midazolam?
22	things that we talked about, the need for a chin	22	DR. WARD: No.
	Page 58		Page 60
1	Page 58 lift, desaturation of a greater amount, so some	1	Page 60 AUDIENCE MEMBER: Opioid?
	-	1	
2	lift, desaturation of a greater amount, so some		AUDIENCE MEMBER: Opioid?
2 3	lift, desaturation of a greater amount, so some sort of scoring system. That's been mentioned a	2	AUDIENCE MEMBER: Opioid? DR. WARD: No.
2 3	lift, desaturation of a greater amount, so some sort of scoring system. That's been mentioned a couple times; there are a lot of areas for	2 3 4	AUDIENCE MEMBER: Opioid? DR. WARD: No. AUDIENCE MEMBER: Dexmed?
2 3 4 5	lift, desaturation of a greater amount, so some sort of scoring system. That's been mentioned a couple times; there are a lot of areas for intervention; pancreatitis.	2 3 4 5	AUDIENCE MEMBER: Opioid? DR. WARD: No. AUDIENCE MEMBER: Dexmed? DR. WARD: Dex. This is dexmedetomidine.
2 3 4 5 6	lift, desaturation of a greater amount, so some sort of scoring system. That's been mentioned a couple times; there are a lot of areas for intervention; pancreatitis. We have scoring systems. We don't really	2 3 4 5 6	AUDIENCE MEMBER: Opioid? DR. WARD: No. AUDIENCE MEMBER: Dexmed? DR. WARD: Dex. This is dexmedetomidine. This is 2 micrograms per kilogram given over
2 3 4 5 6 7	lift, desaturation of a greater amount, so some sort of scoring system. That's been mentioned a couple times; there are a lot of areas for intervention; pancreatitis. We have scoring systems. We don't really have any validated scoring any that I'm aware	2 3 4 5 6	AUDIENCE MEMBER: Opioid? DR. WARD: No. AUDIENCE MEMBER: Dexmed? DR. WARD: Dex. This is dexmedetomidine. This is 2 micrograms per kilogram given over 2 minutes. It's a pretty high dose given pretty
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	Page 61		Page 63
1	We see this patient, or subject, was going	1 increa	asing CO2 with a change in the slope and
2	along breathing quite nicely, and then had an	2 interc	ept of the hypercapneic response, and you can
3	apneic episode. But you see it's a central apneic	3 decre	ase the PO2 and look at a linear increase in
4	episode, that the tidal volumes were decreased, but	4 ventil	ation with a decrease in saturation. Each
5	they stayed in synchrony. So we can differentiate	5 dot's	a breath to breath, with pretty good
6	a central and an apneic episode. This I think it	6 correl	lation.
7	was with midazolam and remi.	7	Sedative and analgesic drugs have been well
8	The central episode came on for a number of	8 classi	ified with these. You can go back to Santiago
9	seconds. So we can actually quantify the apneic	9 and E	delman, but maybe even before that,
10	episode. And as we've pointed out, I think we're	.0 0.2 m	illigrams of morphine IM and looking at the
11	relying on clinical observation for length of an	1 shift i	n the and the decrease in slope of the
12	apneic episode as pretty subjective.	2 hyper	capneic response, and the decrease in slope of
13	But an interesting thing on this particular	3 the C	O2 response. Ventilation went down. Tidal
14	one was when we started to get a respiratory	4 volum	ne went down. Respiratory rate went down just
15	arousal, we started out obstructed. So we started	.5 a little	e bit.
16	out with the abdomen and chest wall out of sequence	.6	These are pretty substantial shifts. But I
17	for three breaths, and then the patient cleared the	7 don't	think anybody would say that 0.2 milligrams
18	obstruction, started getting an arousal, and	.8 perki	logram IM morphine in an adult is a dose
19	started breathing again with airflow and synchrony.	.9 that's	going to be particularly a problem for
20	Or you can do this even more so. This is	o multip	ble adverse events. So these are very
21	from one of the studies that Dr. Karan did, where	1 sensi	tive measures of the respiratory system, and
22	you can look at a full montage EEG, a thermistor	2 they'r	e done almost invariably with any new
	Page 62		Page 64
1	Page 62 measurement of flow at the mouth, and the	1 sedat	Page 64 ive analgesic drug.
	-		-
2	measurement of flow at the mouth, and the	2 l	ive analgesic drug.
2	measurement of flow at the mouth, and the saturation, and the respiratory thorax and	2 I 3 much	ive analgesic drug. But we don't have any correlation with how
2 3 4	measurement of flow at the mouth, and the saturation, and the respiratory thorax and abdominal movement.	2 I 3 much 4 ventil	ive analgesic drug. But we don't have any correlation with how this changes to how much that decreases
2 3 4 5	measurement of flow at the mouth, and the saturation, and the respiratory thorax and abdominal movement. He had no flow with this. You can clearly	2 l 3 much 4 ventil 5 metal	tive analgesic drug. But we don't have any correlation with how this changes to how much that decreases ation, and again, that's because this is a
2 3 4 5 6	measurement of flow at the mouth, and the saturation, and the respiratory thorax and abdominal movement. He had no flow with this. You can clearly see they're out of sequence, with the thorax going	2 l 3 much 4 ventil 5 metal	tive analgesic drug. But we don't have any correlation with how this changes to how much that decreases ation, and again, that's because this is a bolic controller, and you've probably left the fulness drive and the voluntary controllers
2 3 4 5 6 7	measurement of flow at the mouth, and the saturation, and the respiratory thorax and abdominal movement. He had no flow with this. You can clearly see they're out of sequence, with the thorax going in and the abdomen going out, thorax going out,	2 I 3 much 4 ventil 5 metal 6 wake 7 intact	tive analgesic drug. But we don't have any correlation with how this changes to how much that decreases ation, and again, that's because this is a bolic controller, and you've probably left the fulness drive and the voluntary controllers
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1 remifentanil. Right, Suzie? Yes, with	
I Termentarin. Right, Suzie: Tes, with	1 change. Ventilation started recovering here about
2 remifentanil, and looking at the difference between	2 an hour later, so that would be consistent with the
3 resting, eyes closed, pain, or audiovisual	3 pharmacokinetics. Midazolam by itself, and there
4 stimulation.	4 were no desaturations.
5 We found different effects depending on	5 Fentanyl by itself, 2 mics per kilo, caused
6 whether the subject was laying there with their	6 a big decrease in ventilation, as you'd expect, and
7 eyes closed, they had a painful stimulus, or they	7 6 out of 12 of the subjects desaturated. Adding
8 had audiovisual stimulation, with interesting	8 midazolam to it, there was no further decrease in
9 audiovisual stimulation being more than a painful	9 ventilation. So there was no synergy between
10 stimulation.	10 fentanyl and midazolam as far as the ventilation to
11 We looked at midazolam and propofol on	11 hypercapnia was concerned. But now 11 out of 12
12 collapsibility using dynamic negative airway	12 got hypoxic. So there was much bigger instances of
13 pressure. In that case, we were actually lowering	13 apneic episodes. When they were just laying there
14 the pressure at the mouth and seeing what that did	14 breathing normally as opposed to being stimulated
15 to ventilation, so lowering this down to minus 4.	15 by hypercapnia, that would cause desaturations for
16 The flow was decreased, and we had partial	16 that.
17 obstruction. We started to see some out of	17 So again, illustration that the laboratory
18 synchrony there.	18 measurements of ventilation in response to
19 Lower the pressure even more, we started to	19 hypercapnia is not necessarily a good predictor of
20 see a further decrease in the flow and more	20 what the apneic episodes would be.
21 dyssynchrony in the ventilation with a partial	21 Albert's lab has done a lot of work looking
22 airway obstruction. And finally, lowering this	22 at multiple drugs. This was a study that I did
Page 66	Page 68
1 down to minus 10, we saw complete obstruction and	1 with him when I was on a sabbatical there, looking
2 complete asynchrony in the thorax and the chest.	2 at remi/propofol interaction and ventilation with
3 What the pulmonologists then do is then plot	3 the function of CO2 for control, propofol
4 this, or with each of the pressures, and measure	4 decreasing the slope, remi-fentanyl causing a
5 where the airway-closing pressure would be. And	5 shift, and the two of them together causing a big
5 where the airway-closing pressure would be. And6 there is work in general anesthesia done by Eastman	5 shift, and the two of them together causing a big6 decrease, both in slope and a right shift, the
6 there is work in general anesthesia done by Eastman	6 decrease, both in slope and a right shift, the
6 there is work in general anesthesia done by Eastman7 in Australia that looks at that critical closing	6 decrease, both in slope and a right shift, the7 synergism between the drugs.
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1	on the bis, no synergism at all. The remi didn't	1	So I'll leave it open to your comments on
	have any effect on the bis.		these questions.
3	Albert, do you remember the OAAS? Did we	3	DR. RIKER: It was a nice review. Thanks.
4	measure that? I think we just had the bis, just	4	Should we move beyond ventilatory impairment,
	had the bis data for that, because the bis is not	5	though, and talk about the respiratory events that
6	sensitive for the remifentanil.	6	could happen, aspiration with pneumonitis, with
7	So finally, as we think about respiratory	7	pneumonia, with neither, which half of the patients
8	measurements it's complex, I guess would be the	8	who aspirate will fall into? Does that precipitate
9	answer to that, but I think it's useful when	9	airways disease? And I don't mean upper airway
10	they're doing some of the trials to think about	10	obstruction; I mean, small airways disease,
11	these three drives to ventilation, voluntary,	11	wheezing, bronchospasm, blah blah blah?
12	behavioral, and metabolic.	12	DR. WARD: Yes. Those are important
13	We've got lots of changes between them,	13	clinical outcomes. Again, those are going to be
14	between I'm not going to go through	14	the rare events and clearly should be reported.
15	them anaerobic exercise, which is low pH; it's	15	Because I'm not sure if it's moving beyond this.
	probably just metabolic control; REM sleep non-	16	Those are clearly in addition.
	REM sleep is probably just metabolic control,	17	DR. RIKER: I just think of them as
	whereas REM sleep is more like a wakefulness drive,		respiratory events but not related necessarily to
	and there's not much metabolic control during REM		ventilatory drives.
20	sleep. Singing and talking is all voluntary.	20	DR. WARD: Yes. Yes, yes. Clearly should
21	Then looking at the drug effects, then you		be looking for and reporting non-respiratory drive-
22	have to think about the particular kind of sedation	22	related events. I think what I'm hung up on, and
	Page 70		Page 72
1	-	1	
	protocol you're doing. Is there a painful		I've been hearing it, too, is looking at just
2	protocol you're doing. Is there a painful stimulus? Is it an x-ray procedure, which there's	2	I've been hearing it, too, is looking at just saturation is probably not an adequate measure.
2	protocol you're doing. Is there a painful stimulus? Is it an x-ray procedure, which there's no other stimuli?	2 3	I've been hearing it, too, is looking at just saturation is probably not an adequate measure. So if we agree on that, then what are the
2 3 4	protocol you're doing. Is there a painful stimulus? Is it an x-ray procedure, which there's no other stimuli? So I think there's questions that we've been	2 3 4	I've been hearing it, too, is looking at justsaturation is probably not an adequate measure.So if we agree on that, then what are thethings that we should be measuring? Should we be
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1	data.	1	DR. KARAN: Do you need a show of hands?
2	So it is a relevant issue, and your examples	2	DR. SESSLER: So we won't specify the type
3	are exquisite examples of mechanistic studies to	3	because it might be context-dependent, or is
4	understand if you have a new drug, is it better	4	sometimes transcutaneous, sometimes end tidal,
5	than the previous drug. That's my opinion about	5	sometimes bands around the chest, sometimes
6	it, and I'll talk a little bit on how I see how you	6	impedance. But there probably should be some
7	should [inaudible]. I do agree outcome, of course,	7	measure of ventilation, because otherwise you miss
8	is most important. Yes.	8	a lot, especially in patients on oxygen if you're
9	DR. WARD: Jenifer?	9	just looking at saturation.
10	DR. LIGHTDALE: I think drugs get a	10	DR. DAHAN: Personally, I would go for flow
11	reputation. I am really fascinated by the concept.	11	rather than ventilation.
12	Some drugs, you'd say, they don't have many	12	DR. SESSLER: Okay. I would accept flow as
13	respiratory effects. Maybe we do need to do these	13	a type of ventilation.
14	provocative tests early on to really make sure we	14	DR. DAHAN: Well, it's close to passage of
15	have the right reputation for the drug. People	15	air.
16	have a sense of, well, actually, you can push this	16	DR. SESSLER: I'm saying something besides
17	drug, and it will do something. We need to know	17	saturation.
18	that.	18	DR. WARD: Rick?
19	DR. WARD: Yes. I think that's what	19	5
	dexmedetomidine is. The early studies including		a move towards risk-based monitoring. So maybe we
	mine, in spite of what I showed you there, did have		should apply a similar model here. So if we're
22	minimal respiratory I mean, if you didn't push	22	looking at low-risk patients, maybe it's not a
	Page 74		Da
	Faye 74		Page 76
1	-	1	
	2 mics per kilo over 2 minutes, it didn't have much		critical piece of it. But if we're certainly
	2 mics per kilo over 2 minutes, it didn't have much for respiratory effects.	2	critical piece of it. But if we're certainly looking at these sleep apnea, obese patients who
2	2 mics per kilo over 2 minutes, it didn't have much for respiratory effects.	2 3	critical piece of it. But if we're certainly looking at these sleep apnea, obese patients who are at much higher risk for these kinds of events,
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1	to the adverse effects, especially ventilatory	1 have an apneic peak.
	ones. The sicker the patient is, the higher the	2 DR. SEXTON: Because it seems like that
	rate, the easier it is to compare agents and find a	3 would be something you'd want to measure so you
	difference that's meaningful.	4 don't have to wait till they desaturate, and they
5	DR. WARD: You're correct, Albert, that some	5 have already have some options.
_	of these more sophisticated tools are difficult to	6 DR. WARD: And the abdomen and thorax
	use. But I look at our pulmonology colleagues	7 measurements are the kinds of measurements that let
	doing sleep studies who have a pretty sophisticated	8 you do that. So I think Dan's point was a good
	array of instrumentation that they do hundreds and	9 one, is that if you're doing clinical trials, you
	thousands of patients every night in sleep. And if	10 should be first we have said we need to measure
	you can do it in a polysomnographic laboratory, why	11 ventilation, that just maybe saturation is not
	couldn't you it may be provocative why	12 sufficient. And then it was brought up that if
	shouldn't you be doing it in a clinical trial in a	13 you're going to do a clinical trial, then you
	few hundred patients?	14 should be using the most sophisticated way to
15	DR. DAHAN: You can. It's expensive. It	15 measure what you want to measure as you can. So
	requires a lot of teaching.	16 that moves us into things like abdomen and thoracic
17	DR. KARAN: It's cheaper now. The	17 bands.
	ambulatory monitors are a little bit cheaper now.	18 Bill?
	They keep evolving. Every month there's newer,	19 DR. CHAPPELL: I have a comment. I would
	more robust monitors out there that are in the	20 imagine I could be wrong but I think that if
-	ambulatory environment that are meant to be robust	21 you were developing a new chemical entity, that
	to the surrounding, and that are applied just by	22 types of provocative and mechanistic physiologic
	Page 78	Page 80
1	patients themselves without a lot of teaching. So	1 studies with these very intensive measurements you
2	it's evolving.	2 described would probably be best situated maybe in
3	DR. WARD: Dan?	2 described would probably be best situated maybe in
	BR. WARD. Ball	3 early development.
4	DR. SESSLER: The general rule for clinical	
		3 early development.
5	DR. SESSLER: The general rule for clinical	3 early development.4 DR. WARD: Phase 1.
5 6	DR. SESSLER: The general rule for clinical trials is to use the best available methods to	 3 early development. 4 DR. WARD: Phase 1. 5 DR. CHAPPELL: Then as you push the compound
5 6 7	DR. SESSLER: The general rule for clinical trials is to use the best available methods to measure whatever you're trying to measure. And the	 3 early development. 4 DR. WARD: Phase 1. 5 DR. CHAPPELL: Then as you push the compound 6 farther down into development, you're going to have
5 6 7 8	DR. SESSLER: The general rule for clinical trials is to use the best available methods to measure whatever you're trying to measure. And the fact that it's expensive or difficult only gets you	 3 early development. 4 DR. WARD: Phase 1. 5 DR. CHAPPELL: Then as you push the compound 6 farther down into development, you're going to have 7 to do larger scale trials, and you'll have to move
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5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	DR. SESSLER: The general rule for clinical trials is to use the best available methods to measure whatever you're trying to measure. And the fact that it's expensive or difficult only gets you so far. If you're doing a clinical trial, that's inherently a difficult and expensive process. You should use the best metrics you can. DR. SEXTON: As an anesthesiologist, what are the things that let you know, if you're doing a case, before they start to desaturate? What tips you off? DR. WARD: Well, I don't know. I'll leave it to the other anesthesiologists in the group. But to me, it's watching the patient and the signs and symptoms of airway obstruction. DR. DAHAN: I have some slides that show irregular breathing.	 3 early development. 4 DR. WARD: Phase 1. 5 DR. CHAPPELL: Then as you push the compound 6 farther down into development, you're going to have 7 to do larger scale trials, and you'll have to move 8 to simpler designs and simpler data, as Albert was 9 commenting. You need both, really, depending on 10 the development stage of the project. 11 DR. WARD: Yes. But I think the preclinical 12 trials in animals on respiratory effects don't 13 correlate very well with the early clinical trials 14 of respiratory effects. Opioids are an example in 15 cats. They don't correlate very well with what 16 happens in humans. So some of the preclinical data 17 needs to be repeated, and physiological data needs 18 to be repeated in humans. 19 So I'd think, paraphrasing Dan and Albert, 20 and a few others, is it sort of the consensus

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	1 as the size of the trial and as we move further	1	DR. WARD: Right. Early on, if you've got a
	2 along. But the concept would be that as we start	2	new sedative that you're looking for approval for
	3 out, we want to use better measurement devices and	3	it as a sleep medicine, then it's very much
	4 not just rely on a clinical trial that has	4	analogous to the way you progress.
	5 saturation and clinical observation of respiratory	5	Bob?
	6 rate. It would not be adequate for a clinical	6	DR. DWORKIN: The other analogy, it seems to
	7 trial.	7	me, [inaudible – off mic] can show that there's a
	8 Is that kind of and Mark, you said you		pretty standard phase 2 design where you study that
	9 saw a lot of those kind of trials in the	9	drug against positive comparators in recreational
1	0 literature.		substance abusers, and see if they have great drug
1	1 MR. WILLIAMS: That's right, yes.		liking or that they would pay a lot for it on the
1			street.
1	3 something that's different than the current things	13	That's a kind of intense, small phase 2
	4 that are being done. So I think that's an	14	design, costly, in highly selected patients. And
	5 important outcome for this.		you do that before you study your drug in the
1	·		phase 3 trial in patients with low back pain or
1			whatever. And that seems analogous to me, too,
1	8 can be studied in these are not exactly real		here, a targeted phase 2 trial in a group of
	9 world because they'll be held to a higher standard		subjects that you expect to be informative, but
	o of measurement as we're looking at this, but things		that doesn't necessarily generalize to the ultimate
	1 we can apply in MRI in children, things we can		population.
	2 apply to that as to how we measure those.	22	Rigo, does that seem analogous to you, that
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	Because most of these sedations we're doing	1	kind of intense phase 2, get to know your drug?
	2 in kids, and then we have to get through an IRB,	2	DR. ROCA: Yes, I think so. And I
	3 and efficiencies in hospitals, and say we're going	3	think which is another comment I think you guys
	4 to do this, but you can only do two MRIs a day	4	were talking about, that will also help you design
	5 because of the level of monitoring; who are the	5	your phase 3 because you can identify certain
	6 funding to not just the funding for that	6	things that you would like to focus on. And at the
	7 patient, but the lost income for institutions who	7	same time, you may be able to identify certain
	8 are asking to do these studies.	8	things that you don't need to focus on. But yes,
	9 DR. WARD: Right. And I think that's a	9	your example is very analogous.
1	o great point and couples with what Phil said, is	10	DR. WARD: Any other comments on the
1	1 that the studies have to be designed such that as	11	respiratory?
1	2 you move further along in the drug development,	12	(No response.)
1	3 your monitoring doesn't have to be as sophisticated	13	DR. WARD: And sorry to bore you with all
1	4 as it was earlier on. I think that's an important	14	the physiology, but I thought we did have to have a
1	5 concept.	15	little physiology lesson before we got a reality
1	6 DR. CHAPPELL: You mentioned sleep studies	16	check on how difficult it is to actually make some
1	7 earlier, and that is exactly the paradigm for the	17	of these physiological measurements if we want to
1	8 development of hypnotic medications. As you	18	move beyond simple saturation and clinical
1	9 probably know, the FDA typically requires sleep	19	observation.
2	Iaboratory studies, but then you move beyond that	20	So let's take a break. I think we're just a
2	1 and do outpatient studies where you're not really	21	little bit ahead of schedule. So let's come back
-	2 doing sleep EEG work.		at about 10:00, and we can keep the day maying and
2		22	at about 10:00, and we can keep the day moving and

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1	get through in time for us to all make our flights	1	happened.
	this afternoon. Thanks.	2	This is sort of a list of what we typically
3	(Whereupon, at 9:320 a.m., a brief recess	3	commonly see in a clinical trial setting. But
4	was taken.)	4	talking about adverse events, I listed adverse
5	DR. WARD: So there's more to life than	5	events, presumably, these are what people don't
6	breathing. We have to eat and do some other	6	like. Does anyone here like vomiting? I hope not.
7	things, so the complications are not just	7	(Laughter.)
8	respiratory complications. There's also other	8	DR. GAN: You may laugh, but sometimes it's
9	organ system complications. So I thought we'd	9	surprising that some people actually enjoy
10	spend a few minutes on looking at some of the other	10	vomiting. And this was a description of somebody
11	possible complications, both as I went through what	11	who actually derived pleasure from vomiting. So
12	to measure and how to measure them. So we will	12	while we called it adverse, it may not be adverse
13	start out with TJ Gan on GI adverse events.	13	to some people. So it's all relative.
14	Presentation – TJ Gan	14	So anyway, we're not going to go there.
15	DR. GAN: Good morning, everyone. First of	15	Let's talk a little bit about this. This is a
16	all, I want to thank Denham for inviting me to	16	slide that is not to be included in the public
17	this I think this event is great. And those of	17	domain, I hope.
18	you yesterday and today, I think you don't get a	18	Anyway, so nausea and vomiting, I'm just
19	lot of opportunity where you can have multi-	19	going to concentrate on one that I think happens
20	specialty people having a common interest come	20	particularly frequently, and one that we sort of
21	together in a room to discuss something that we're	21	think that patients really don't like and hopefully
22	all passionate about. And I'm sorry I missed the	22	can reduce it.
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1	first round, so I'm delighted that I'm here.	1	This is one of them. It's one of the GI
2	I'm asked to talk about GI events, what and	2	events, nausea and vomiting. It happens commonly.
3	how to measure. I'm going to just really show you	3	And this is actually a 10-center observational
4	a few slides and just to set the scene. And again,	4	study, just look at across the board, what is
5	you are not here to come and listen to me talk, but	5	insulin nausea and vomiting.
6	it's more about discussion and what we can get out	6	Again, these are people having general
7	of it. So I'm just going to quickly go through	7	anesthesia, and I'll show you some data on people
8	some slides, give you some perspective as I see it,	8	under sedation. But you can see here, a common
9	and then have lots of discussion.	9	practice is that we give a lot of prophylactics,
10	So as far as GI events are concerned, I am	10	antiemetics, right, either one, and probably more
11	an anesthesiologist, so the GI events that I am	11	appropriately, two or three, depending on their
12	accustomed to may be a little bit different from	12	risk factors.
13	the GI events gastroenterologists are accustomed	13	But nevertheless, if you see that these are
14	to, emergency medicine accustomed to.	14	one antiemetics two or three, nausea, about 30 to
15	I'm just going to put out a list of what	15	50 percent of people with nausea, vomiting about 10
16	hospital GI events could be in clinical trials	16	to 30 percent, so it still happens commonly. And
17	based on adverse events reporting, looking at	17	about a third of these patients say nausea and
1.0	druge and again thinking about Clayente Arelif	1	vention a interfere with their functional receiver.

- 18 drugs, and again, thinking about GI events. And if 18 vomiting interfere with their functional recovery.
 - 19 And I guess this is probably more important, that
 - 20 these are people sort of bothered by nausea and
 - 21 vomiting.22 Some peop
 - Some people may say, "I'm a little bit

19 you think about from the mouth all the way down,

20 the esophagus, the stomach, small intestine, large

22 probably pretty capture some of these events that

21 intestine, all the way to the other end, you can

1 queasy, one or two on a scale of zero to 10. I 2 don't like it, but it's not going to kill me," for

6

13

22

3 example. But this is where I think we need to pay 4 attention, that these are people who say that it 5 does interfere with my functional recovery.

7 vomiting following sedation, this was a study that

8 we reported a few years ago, looking at patients

10 intent of the study was just looking at the depth

11 of sedation, whether it has any implication in

14 include respiratory, apnea, saturation, all the

15 rest of it. And we found an incidence of about 5

17 And vomiting is pretty rare, in the region of 2 or

19 undergoing routine endoscopy, and it comes in.

20 They go out. Again, these are patients who use

21 midazolam fentanyl. This is not propofol sedation.

Now, let's talk a little bit about nausea

16 to 10 percent sort of nausea, including all-comers.

18 3 percent. And these again are fit, healthy people

12 terms of adverse events.

9 undergoing upper and lower GI endoscopy. And the

We recorded a number of adverse events to

Now, as far as the incidence of nausea and

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	1 is that, if nausea at a certain point is bad
	2 enough, then you ask for something. And that
/	3 something that you ask for, an antiemetic, is a
	4 proxy for sort of bad nausea.

- 5 Then there are other things that are less
- 6 commonly mandated by the FDA, but increasingly
- 7 being asked to be collected by sponsors who want to
- 8 do a phase 3 trial interference with daily
- activities as well as patient satisfaction, again 9
- 10 recognizing the limitations of some of these
- scoring because patient satisfaction sometimes is 11
- 12 not well validated in terms of who say their
- 13 satisfaction.
- In fact, people could be sick, and if a 14
- nurse is there, really be with them all the time 15
- 16 and console them, they were happy even though they
- were sick, just like in other pain studies as well. 17
- So just to quickly run through some of the 18
- 19 scales here that have been used, this is typically
- 20 called a verbal rating score, no nausea, 1N, and
- 21 then 1 to 10 was nausea. And then for children, as
- 22 Denham earlier brought up, this is called the BARF

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1	and vomiting. How do we measure it? And again,	1	scale.
2	adverse events reporting and how we normally	2	(Laughter.)
3	measure it when we look at efficacy is a little bit	3	DR. GAN: It actually stands for Baxter
4	different. Right?	4	Animated Retching Facial Scale. And hopefully,
5	But yesterday, as you heard, there is some	5	when you're a kid, you can pick up which are the
6	overlap between efficacy and adverse events	6	faces that you would like to be associated with.
7	reporting. But this is typically when we are to	7	So these are typically for children.
8	do a nausea and vomiting study, this is typically	8	Then there is the VAS, Visual Analog Scale,
9	the outcome. If you have a phase 3 study, this is	9	which is basically one line without these
10	typically what the FDA people will tell you these	10	descriptors. And then there is also the Likert
11	are the outcomes.	11	scale that basically have descriptors such as
12	So I want to look at nausea, which can be	12	slight, mild, moderate, and severe.
13	assessed using a variety of scales. Vomiting is	13	So there are a variety of scales that are
14	another outcome. Incidence, typically, severity is	14	being used and have been validated in many stud
15	a little bit difficult to quantify. How do you	15	As to whether how valid this is, as we talked about
16	quantify severity of vomiting? Retching is	16	yesterday, is it linear? Probably not, but we
17	typically lumped together with vomiting. It just	17	don't really have a better scale than this to
18	means that you have nothing to there is no	18	recommend to investigators.
19	content that is expelled.	19	If you look into the literature, I mean,
20	Often in clinical trials, the use of rescue	20	these are pretty standard. And I would say that if
21	antiemetic is used as a surrogate for nausea,	21	somebody had asked me, if you wanted to do a n
1			

22 because nausea is so subjective. And the thought

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- y studies.
- d about
- that if
- do a nausea
- 22 and vomiting study, what scale should I use, I

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1	would say that, for adults, it would be either VAS	1	potentially scoring in nausea and vomiting, looking
	or VRS scale for nausea, vomiting, incidence of		at really three aspects of it. One is looking at
	vomiting, and collect use of rescue antiemetics.		the frequency, how frequent and how often does it
4	That's what I would recommend. But if you		happen, rare or very common, or how severe it is
5	go to the literature and look at what people use,		from mild to very severe, and how bothersome to
	it's really all over the place. I mean, there are		them. Does it bother a lot or is it really just
	people who use this scale. How do you interpret		very little?
	that? I can see that I mean, it's all over the	8	So maybe they're using this sort of
9	place. And so sometimes, it's very difficult to	9	composite scoring that we can make a better
10	interpret.	10	assessment in terms of these qualitative
11	Then there is people using the Likert scale.	11	experiences of these adverse events. In fact, we
12	And then you've got a vomiting score, how many	12	actually correlated with the opiate doses and found
13	episodes within a certain time to indicate some	13	there's a good correlation in terms of these
	sort of severity of vomiting, not as well	14	scoring, the symptom distress score. The more
15	validated. And there are also people using this		severe it is, the higher opiate doses is associated
16	sort of grade 1 to 5. And I was intrigued to find	16	with higher symptom distress scoring.
17	out, in fact, if you got vomiting, grade 5, that	17	So I'm going to stop there, and I don't know
18	means death, which sounds a bit drastic. I haven't	18	whether we then want to open the questions or we
19	seen anyone sort of vomiting until death, but	19	want to wait for the rest.
20	anyway, you can see that people use all sorts of	20	DR. WARD: Thank you. We'll take a few
21	scales.	21	questions now. I would comment that, 100 years
22	This is one of the chemotherapy ones, again,	22	ago, people did die of vomiting making oceanic
	Page 94		Page 96
	i age 34		-
	from no nausea, severe nausea, and also look a	1	passes with seasickness. So it used to be
	little bit about daily interference of their	2	
	activity. So you can see it's all over the place	3	seasickness today.
	in terms of scoring is concerned.	4	DR. GAN: Also, in the days when ether
5	Now, the other question that got raised		anesthesia was a regular anesthetic and again, I
	yesterday is that collecting this incidence and		think everyone in the room may be too young for
	subjective experience is one thing, but maybe we	7	that, but ether anesthesia, you pretty much
	should look at how much does it bother the	8	
	patients. I mean, some people may be bothered by		patients, they were sick from ether anesthesia.
	it, but some people may not, not that I think	10	Any other questions, comments, thoughts?
	people enjoy nausea, but as you can see earlier,		Yes?
	people may enjoy these adverse events.	12	DR. MINER: For the visual analog scores for
13	But the question is how frequently does it		nausea, I always try to use those, but I always
14	hannan haw aavara it in and also haw hatharaass		seem to end up with binary data, where everybody
	happen, how severe it is, and also how bothersome		
	to that individual it is, to the patient. So a few	15	says, yeah, I'm on one side or I'm on the other,
16	to that individual it is, to the patient. So a few years ago, we sort of validated this symptom	15 16	says, yeah, I'm on one side or I'm on the other, and there'll be like one person at 50. I don't
16 17	to that individual it is, to the patient. So a few years ago, we sort of validated this symptom distress score, which is a bondification from the	15 16 17	says, yeah, I'm on one side or I'm on the other, and there'll be like one person at 50. I don't know [indiscernible] any more.
16 17 18	to that individual it is, to the patient. So a few years ago, we sort of validated this symptom distress score, which is a bondification from the Portenoy Pain Score.	15 16 17 18	says, yeah, I'm on one side or I'm on the other, and there'll be like one person at 50. I don't know [indiscernible] any more. Does anyone else find that? I think it's
16 17 18 19	to that individual it is, to the patient. So a few years ago, we sort of validated this symptom distress score, which is a bondification from the Portenoy Pain Score. This is as a result of doing some pain	15 16 17 18 19	says, yeah, I'm on one side or I'm on the other, and there'll be like one person at 50. I don't know [indiscernible] any more. Does anyone else find that? I think it's been hard to get it distributed score.
16 17 18 19 20	to that individual it is, to the patient. So a few years ago, we sort of validated this symptom distress score, which is a bondification from the Portenoy Pain Score. This is as a result of doing some pain study. And part of it is opiate-related side	15 16 17 18 19 20	says, yeah, I'm on one side or I'm on the other, and there'll be like one person at 50. I don't know [indiscernible] any more. Does anyone else find that? I think it's been hard to get it distributed score. DR. GAN: What I find is the Visual Analog
16 17 18 19 20 21	to that individual it is, to the patient. So a few years ago, we sort of validated this symptom distress score, which is a bondification from the Portenoy Pain Score. This is as a result of doing some pain	15 16 17 18 19 20 21	says, yeah, I'm on one side or I'm on the other, and there'll be like one person at 50. I don't know [indiscernible] any more. Does anyone else find that? I think it's been hard to get it distributed score.

	Page 97		Page 99
1	when you're sedated, a line may become two or may	1	But I think we probably all would like to have
	become 3, and you just couldn't quite focus.		whatever scales to be used to have some data to
	Usually, in those settings, I find that a verbal		show that it is a validated scale for that
	rating score seems to capture a better response,	4	particular study.
5	from zero to 10.	5	DR. GAN: Right. And I think those I'd
6	As to your point about whether people	6	describe typically are the most commonly used, so
7	cluster it on the left or the right, I've looked at	7	the FDA doesn't raise questions about validity.
8	that. In fact, that's what we commonly thought.	8	DR. DWORKIN: So in the pain world, it's
9	But if you actually look at all the studies, it's	9	been shown, going back a couple of decades, the
10	actually pretty well I mean, if a patient is	10	10-centimeter visual analog scales are problematic
11	awake enough to interpret it, it's actually not a	11	with older patients and patients with mild
	bad score provided a patient actually understands		cognitive impairment. So given that older patients
13			and patients with MCI can be in a clinical trial,
14	I think, sometimes, it's difficult to		we almost always prefer a zero to 10 scale rather
	explain it to the patient. That's why, in the		than a 10-centimeter line. And perhaps especially
	clinical trial setting, we try to explain to them		when they're also sedated, that might push towards
	before we actually do the procedure, so that they		the numerical rating scale or the verbal scale.
	somewhat understand because, when you're trying to	18	DR. GAN: I totally agree. I think that was
	explain to them when you are sedated, groggy, I		what my recommendation is, would be zero to 10,
	think it is impossible.		which would make it much easier. And while we have
21	DR. WARD: It sounds like a somewhat similar		done both and, often, I get complaints from my coordinator or nurses saying that the patient can't
44	issue that we had at the first meeting, looking at	22	cooldinator of nuises saying that the patient can t
	Page 98		Page 100
1	-	1	
	Page 98 the number of validated sedation efficacy scales, the number of validated nausea scales. Is there		do it. And when you ask them zero to 10, then
2	the number of validated sedation efficacy scales,		
2 3	the number of validated sedation efficacy scales, the number of validated nausea scales. Is there	2 3	do it. And when you ask them zero to 10, then usually they can. Absolutely.
2 3	the number of validated sedation efficacy scales, the number of validated nausea scales. Is there any consensus or is it possible to reach a	2 3	do it. And when you ask them zero to 10, then usually they can. Absolutely. DR. WARD: Maybe even the faces scale, even
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	Page 101		Page 103
1	The thinking is that, if the patient is bad enough,	1	intervention? And it can be procedure specific and
	at some point they're going to ask for rescue		nervousness specific. I mean, if you have a
3	antiemetics. It could be vomiting. But for those	3	patient who's at high risk for aspirations, you may
4	who didn't have vomiting, that is typically as a	4	be treating prophylactic or nausea quicker than you
5	proxy for the duration of nausea. But some studies	5	would for somebody who [inaudible – off mic].
6	do collect the duration of nausea.	6	If the same issue keeps coming up when you
7	You're right. I think if people just keep	7	use clinical intervention, then how do you define
8	getting sick and I happen to have a firsthand	8	the provider, physiology of procedure indications
9	experience it's just the worst experience you	9	so that [inaudible – off mic.]?
10	can ever imagine.	10	DR. GAN: By making trials also have some
11	Yes?	11	sort of definition or another criteria when you can
12	DR. RIKER: Did you find anything on	12	administer rescue antiemetic. Maybe you have
13	surrogate assessment versus patient self-report? I	13	vomiting, or your nausea scale is above 3, or some
14	mean, in pain, there's clearly a lot of data that	14	sort of duration, at least somehow to control that
15	says surrogates are horrible at estimating pain.	15	variability.
16	Is there similar data in nausea and vomiting? I	16	Any other thoughts, questions? Thank you
17	mean, vomiting is pretty easy.	17	very much.
18	DR. GAN: When you say surrogate, can you	18	
19	define which surrogate are you thinking of?	19	DR. WARD: John is going to tell us about
20	DR. RIKER: Well, a clinician, for instance,	_	cardiovascular.
	estimating the degree of nausea based on that.	21	
22	DR. GAN: Yes. You can't. I don't think	22	DR. BERKENBOSCH: I can't promise that this
	Page 102		Page 104
1	Page 102 the clinician can assess in any way, shape, or form	1	-
	-	1 2	will be nearly as entertaining.
	the clinician can assess in any way, shape, or form		will be nearly as entertaining.
2 3	the clinician can assess in any way, shape, or form accurate in terms of patient's nausea.	2 3	will be nearly as entertaining. (Laughter.)
2 3 4	the clinician can assess in any way, shape, or form accurate in terms of patient's nausea. DR. RIKER: All right. So outside the	2 3 4	will be nearly as entertaining. (Laughter.) DR. BERKENBOSCH: So I'm going to just jump
2 3 4	the clinician can assess in any way, shape, or form accurate in terms of patient's nausea. DR. RIKER: All right. So outside the setting of young children, then, we would say the	2 3 4 5	will be nearly as entertaining. (Laughter.) DR. BERKENBOSCH: So I'm going to just jump into this. A little bit, by way of background
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	Page 105		Page 107
1	obviously the things that are going to be pretty	1	I think, really, at the base of looking at
	universally reported, cardiac arrests, the need for	2	cardiovascular adverse events, though, to me, the
	CPR, just really basically requiring either		question is, what is the adequacy or is there still
	electrical or medical conversion. Those are some		adequate cardiac output and/or tissue oxygen
5	of the things that have been typically reported in		delivery? How do we assess that?
	the literature.	6	Clinically, we often use it with organ-
7	I'll throw out the question. We've sort of	7	system-based approaches. Clinically, right? We
8	bounced around this already. But when does an		look at mental status. We look at urine output for
	event become an adverse event, and when do we want		the kidneys, things like that. Those are often
	to report those things? And another question is,		masked during sedation because you can't assess
	when does an adverse event become an adverse		them.
	outcome, because I don't think that those are	12	<u> </u>
	necessarily the same thing.		are very short-lived procedures. So if a decrease
14	When we're designing trials, I think we need		in urine output during a 15-minute sedation for a
	to be transparent up front about how we're going to		fracture reduction, or lumbar puncture, or
	make those definitions, and then if we choose one		something like that, that's clearly not something
	thing, then call it what it is.		that's going to be clinically meaningful.
18	A little bit about what's been reported and	18	There are issues related to access to the
	how things have been reported from a cardiovascular		patient. And again, I'm thinking to my own
	standpoint, early studies have been relatively		practice as a pediatrician, about half of what we
	simplistic in that they were predominantly		sedate for is MRIs, where you have very limited
	event-based, hypotension, bradycardia, and again,		access to the patient. That may be different than
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	Page 106		Page 108
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	Page 109		Page 111
1	one attempt to look at are there other surrogates	1	The FDA, people that were here yesterday
	of cardiac output and tissue oxygen delivery that		clearly said these are events that we're mandated
	we can look at that aren't necessarily available to	3	by law to report, hypotension, bradycardia,
	us as clinicians when patients are sedated.	4	· · · · · · · · · · · · · · · · · · ·
5	Obviously, NIRS monitoring is going to have some	5	interesting to us from a, do we think that this was
6	limitations as to where you can use it as well.	6	an event that caused harm to the patient, but there
7	I think another question we have to	7	are events that were mandated to report in those
8	ask and again, this has been discussed round and	8	early studies.
9	round; I won't belabor the point is which events	9	Later on, perhaps some of the more
10	are clinically relevant. So we see these	10	interventional based types of things to get a
11	statements in numerous studies: Regimen X resulted	11	better handle on, the clinician felt that, that
	in more hypotension, but the clinical relevance of	12	blood pressure dropped to the 70s in a 5-year-old
	this is questionable; Drug X resulted in	13	was actually clinically important and decided to
	significant cardiovascular changes compared to	14	intervene in whatever way, shape, or form he or she
	baseline, but these changes were not associated	15	
16	with adverse events.	16	
17	I think we all probably believed that those	17	
	are true statements all throughout there, and you		consider.
	can do with that what you will. The question,	19	We've talked about the Quebec guidelines and
	without actually measuring cardiac output or tissue		the TROOPS tools. I think I'm not going to belabor
	oxygen delivery, can we really say that these are true? Probably, but what's the degree of		those points, other than I think there are probably some things on those tools that could be added if
22	inde: Trobably, but what's the degree of	22	some unings on those tools that could be added if
	Page 110		Page 112
1	-	1	Page 112 we would like, cardiovascular interventions in
1	confidence that we have in those things?		
2	confidence that we have in those things?		we would like, cardiovascular interventions in
2 3	confidence that we have in those things? I'll also throw out the question of what do	2 3	we would like, cardiovascular interventions in particular on the TROOPS tool, I thought.
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	Page 113		Page 115
1	enrolling high-risk patients in clinical trials,	1	least considering what the third party needs, maybe
	but I think that the role of comorbidities is		within the setting of sedation. So industry has
	something that's particularly important to		different interests in reporting events than
	cardiovascular events, the cardiomyopathy patient		regulatory organizations such as the FDA do, versus
	for whom small changes in blood pressure, small		what institutions are interested in, because they
	changes in preload may be very much more clinically		want to know are people doing this safely.
	relevant than in an otherwise healthy patient; the	7	So differences between me, my partners, the
8	patient with single-ventricle physiology, which our	8	hospitalists, the intensivists, the emergency
9	group and others that do pediatric sedation are		medicine people, all of those may play into what
10	going to be seeing a lot more than on the adult	10	our institution is looking at as far as are you on
11	side.	11	benchmark. And maybe that's not as relevant to
12	Patients with brain injury, where you're	12	clinical trials. But if you've got institutions
13	looking at cerebral perfusion and patients with	13	where multiple different providers are engaged in a
14	vasculopathies, the Moyamoyas, blood pressure	14	clinical trial, that may be something that's
15	changes, they're exquisitely sensitive to those	15	important.
16	compared to patients that would be ASA1s and 2s,	16	So as final thoughts, I probably should have
17	where relatively marked changes are probably of	17	reworded this as final thoughts to look at rather
18	much less clinical relevance.	18	than recommendations, per se, but I think the
19	I think that we, at our institution,	19	question then becomes what to assess. Obviously,
20	probably struggled somewhat with reporting during	20	the big events are something that we look at. Was
21	the procedure versus during the recovery. I think	21	there cardiac arrest? Was CPR performed? Was
22	that recovery is done by people. I know that	22	either medical or electronic conversion of the
	Page 114		Dogo 116
	-		Page 116
	recover is done by, in most places, by people		dysrhythmia did that need to occur? That's
2	recover is done by, in most places, by people different than the proceduralist who may have		dysrhythmia did that need to occur? That's important.
2 3	recover is done by, in most places, by people different than the proceduralist who may have different motivations behind what they report.	2 3	dysrhythmia did that need to occur? That's important. I think there is certainly a role for
2 3 4	recover is done by, in most places, by people different than the proceduralist who may have different motivations behind what they report. Vital sign frequency typically is something	2 3 4	dysrhythmia did that need to occur? That's important. I think there is certainly a role for looking at bradycardia, hyper or hypotension.
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1	age-appropriate norms versus a percentage change,	1	very much, solid recommendation, but just some
2	particularly and Jerry talked about this earlier	2	thoughts and questions that I think we need to
	as well for me, in pediatrics, a lot of these		ponder as a group.
	kids come in agitated. Their heart rates are sky	4	
	high. A 30 percent drop from a heart rate of 170	5	you had mentioned about urine output monitoring.
	to 130 or 120, big deal as opposed to if a child	6	
	goes below a certain threshold, that's probably		around the perioperative period, can be difficult
	more physiologically relevant.	8	
9	Intervention-based, I think there's lots of	9	
	increasingly good reasons to think about using		anything. It's just patient response to surgical
	intervention-based approaches, but the question		stimulus.
	becomes, what's the trigger or rationale for	12	
	intervening or not intervening for an event?		collecting urine output other than if there's no
14	Ron, you talked about the kid who becomes		urine at all?
	hypotensive during dexmedetomidine, and we just	15	
	sort of go, "Yeah. They're probably fine," or		it's probably completely unhelpful, because we're
	bradycardia, and we just kind of watched them.		not going to be able to get good data, partly
	They may a little bit below normal, but they		because the time frame that you're looking at is so
	otherwise look fine.		short. We're certainly not going to put urinary
20	So it may be worth looking at an		catheters in these kids because that's just an
	intervention-based if we're looking at those		unacceptable risk.
	outcomes to think about tying not just	21	
22	outcomes to think about tying not just	22	
	Page 118		Page 120
1	-	1	
	Page 118 intervention, but maybe tying some sort of rationale questions into the intervention.	1	DR. BERKENBOSCH: I'm sorry?
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2 3 4 5	intervention, but maybe tying some sort of rationale questions into the intervention. Did you do it because you were anxious? Did you do it because of how long it occurred, that	2 3 4 5	DR. BERKENBOSCH: I'm sorry? DR. GAN: Even in adults. DR. BERKENBOSCH: But what's the frequency of a normal adult voiding? It certainly is much
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1	trial that you require more continuous cardiac	1	And then which one of those are which? I think
2	output monitoring? Would that be acceptable as	2	that it's got a lot of sorting out to do. I think
3	part of the obviously not standard monitoring, but	3	it has a lot of potential.
4	additional monitoring to get additional data? How	4	DR. BERKENBOSCH: Yes. And we found the
5	valid these are? Any thoughts on that?	5	same thing with the study that we did with NIRS
6	DR. ROCA: I think a general statement would	6	monitoring that we found cerebral desaturations
7	be that we are definitely flexible from the	7	were not common, but often were not associated with
8	standpoint of somebody would like to try a new type	8	changes in respiratory rate, pulse oximetry values,
9	of monitoring and new type of information. I think	9	and so on.
10	it's safe to say that we are very much interested	10	So they may be giving us different
11	in getting data, getting information. And even if	11	information. I'm not sure that they're necessarily
12	it's a new monitor, we'd be interested in it.	12	correlated, but there is certainly different
13	Consequently, with that, though, it would be	13	information. Yes?
14	important for whoever's proposing it to give us	14	DR. RIKER: Many of the non-invasive cardiac
15	information to make us feel that it is a reasonable	15	output monitors have clinical scenarios where
16	way of monitoring. If they have information that	16	they're known to be non-reliable, primarily
17	would compare to other methods of monitoring, then	17	spontaneously breathing patients with variable
18	we can get an idea of a comparison. That would	18	title volumes, and venous return, et cetera. I
19	also be useful.	19	wonder, if we are going to go into this area, if we
20	But the bottom line is, yes, we're always	20	should describe situations, or monitors, or types
21	open, flexible, but it needs to be supported with	21	of patients where maybe these are not felt to be
22	additional information and more data.	22	reliable and cut that off at the pass, so to speak.
	Page 122		Page 124
1	Page 122 DR. BERKENBOSCH: I guess one of the reasons	1	
	-	1	DR. BERKENBOSCH: That's a good point.
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1	(Laughter.)	1	practice.
2	DR. MINER: So that's a pretty hard thing to	2	People weren't reporting it well, so having
3	do, and we talked about it a lot at the last	3	
4	meeting. Neurological adverse events, you can't		really important, because understanding that you're
	talk about without talking about level of sedation.	5	not supposed to do general anesthesia during
	But we're talking about adverse events now more	6	procedural sedation, people are reluctant to
	than just measuring that level of sedation, which		self-report that this person indeed was not
	can be really hard to do. We'll talk a little bit		responsive to any form of pain unless someone else
	about awareness and recall, paradoxical responses,		was doing it for them and not telling them what
10	and then permanent complications last.	10	they're measuring.
11	For the level of sedation, there's a lot of	11	So they'll try to wake them up, and harder
12	different scales out there. I think a lot of	12	for you, or wait a few seconds until they're not
13	people have been settling on the OAAS scale, which		generally anesthetized and not report it. But I
	is pretty universal. It tracks really well with a		think this is a more concrete outcome. Usually, we
15		15	can get in there.
16	If you look at it, it really fits with general	16	Deeper level implant is much harder just
	anesthesia, deep sedation, moderate sedation, and	17	because eye opening falls in those scales a lot,
18	the levels that work.	18	and that's a hard one to use, because if we really
19	I think it's got some good external	19	use eye opening as a hard scale, people close their
20	validity, and we all accept that these are levels	20	eyes all the time when they're being sedated. It
21	that probably mean something in our practice and	21	has nothing to do with them being more deeply
22	are associated with increasing risk.	22	sedated. We've all seen very, very deeply sedated
	Page 126		Page 128
1	Page 126 There's a lot of different scales out there,	1	Page 128 patients whose eyes really aren't closed.
	-	1 2	
2	There's a lot of different scales out there,	2	patients whose eyes really aren't closed. So this one gets a little harder to use, but
2 3	There's a lot of different scales out there, and every couple years, someone will come up with a	2 3	patients whose eyes really aren't closed. So this one gets a little harder to use, but
2 3 4	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or	2 3 4 5	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report
2 3 4	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same	2 3 4 5	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical
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2 3 4 5 6 7 8 9	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate	2 3 4 5 6 7 8	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both
2 3 4 5 6 7 8 9	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate versus deep sedation so many times, and the	2 3 4 5 6 7 8 9	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both levels of sedation, and it comes up for
2 3 4 5 6 7 8 9 10 11	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate versus deep sedation so many times, and the confounder is people just call it what they want to	2 3 4 5 6 7 8 9	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both levels of sedation, and it comes up for credentialing purposes.
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate versus deep sedation so many times, and the confounder is people just call it what they want to call it based on how they wanted the patient sedated for the procedure. So it gets really, really hard to compare just because it's so vague. But as we're talking about what can be the adverse event, I think we can all pretty much agree	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both levels of sedation, and it comes up for credentialing purposes. For example, a drug like propofol, where you can get moderate sedation with propofol, but you're going to end up with deep sometimes. And if a person isn't good at managing deep sedation, then it all ends up being a problem. So I think it's a
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate versus deep sedation so many times, and the confounder is people just call it what they want to call it based on how they wanted the patient sedated for the procedure. So it gets really, really hard to compare just because it's so vague. But as we're talking about what can be the adverse event, I think we can all pretty much agree that if you're trying to do procedural sedation and	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both levels of sedation, and it comes up for credentialing purposes. For example, a drug like propofol, where you can get moderate sedation with propofol, but you're going to end up with deep sometimes. And if a person isn't good at managing deep sedation, then it all ends up being a problem. So I think it's a valuable thing for us to try to record and report.
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate versus deep sedation so many times, and the confounder is people just call it what they want to call it based on how they wanted the patient sedated for the procedure. So it gets really, really hard to compare just because it's so vague. But as we're talking about what can be the adverse event, I think we can all pretty much agree that if you're trying to do procedural sedation and you end up with a generally anesthetized patient,	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both levels of sedation, and it comes up for credentialing purposes. For example, a drug like propofol, where you can get moderate sedation with propofol, but you're going to end up with deep sometimes. And if a person isn't good at managing deep sedation, then it all ends up being a problem. So I think it's a valuable thing for us to try to record and report. Missed target level is much harder. That'd
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate versus deep sedation so many times, and the confounder is people just call it what they want to call it based on how they wanted the patient sedated for the procedure. So it gets really, really hard to compare just because it's so vague. But as we're talking about what can be the adverse event, I think we can all pretty much agree that if you're trying to do procedural sedation and you end up with a generally anesthetized patient, that's an adverse event.	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both levels of sedation, and it comes up for credentialing purposes. For example, a drug like propofol, where you can get moderate sedation with propofol, but you're going to end up with deep sometimes. And if a person isn't good at managing deep sedation, then it all ends up being a problem. So I think it's a valuable thing for us to try to record and report. Missed target level is much harder. That'd be an outcome I'd love to be able to say, where you
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate versus deep sedation so many times, and the confounder is people just call it what they want to call it based on how they wanted the patient sedated for the procedure. So it gets really, really hard to compare just because it's so vague. But as we're talking about what can be the adverse event, I think we can all pretty much agree that if you're trying to do procedural sedation and you end up with a generally anesthetized patient, that's an adverse event. When we first started looking at this, the	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both levels of sedation, and it comes up for credentialing purposes. For example, a drug like propofol, where you can get moderate sedation with propofol, but you're going to end up with deep sometimes. And if a person isn't good at managing deep sedation, then it all ends up being a problem. So I think it's a valuable thing for us to try to record and report. Missed target level is much harder. That'd be an outcome I'd love to be able to say, where you wanted to hit a target and you couldn't because the
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	There's a lot of different scales out there, and every couple years, someone will come up with a new one and name it after their institution or friend. But they all essentially do the same thing. Whoever's measuring it can say whatever they want. It's not an objective measure. You can try bringing other people in to measure, and they almost never agree. I've tried to study moderate versus deep sedation so many times, and the confounder is people just call it what they want to call it based on how they wanted the patient sedated for the procedure. So it gets really, really hard to compare just because it's so vague. But as we're talking about what can be the adverse event, I think we can all pretty much agree that if you're trying to do procedural sedation and you end up with a generally anesthetized patient, that's an adverse event.	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	patients whose eyes really aren't closed. So this one gets a little harder to use, but I think it's important because when we're talking about what's clinically useful out in clinical practice from the research we're going to report when we study things, if an agent consistently brought people deeper than they intended to bring them, at least from training purposes, people who use the agent probably need to be trained for both levels of sedation, and it comes up for credentialing purposes. For example, a drug like propofol, where you can get moderate sedation with propofol, but you're going to end up with deep sometimes. And if a person isn't good at managing deep sedation, then it all ends up being a problem. So I think it's a valuable thing for us to try to record and report. Missed target level is much harder. That'd be an outcome I'd love to be able to say, where you

Sai	ety Outcomes in Procedural Sedation	1	November 19, 2016
	Page 129		Page 131
1	measure as we come up with more tight ways to	1	there if we can come up with good ways. Salivary
2	measure it.	2	amylase is a rough measure of synthetic
3	Objective monitoring, EEG and Bis scores	3	stimulation. It goes up very, very quickly when
4	still work pretty well. They're not great from	4	somebody is in distress or pain. It could be
	clinical practice, but from study purposes, we've	5	
6	had some luck. This monitor I think has been	6	patient when you're doing research, which limits
7	pretty useful from research purposes in terms of	7	our ability to do the trial.
8	giving an objective measure, especially for	8	The same with salivary cortisol, it goes up
	predicting who's in that recall or not from the	9	the next day if people had a stressful response,
10	sedation.	10	the problem being adverse respiratory events seem
11	I think it's got some value to it. I've	11	to stimulate that response much, much more so than
12	kind of moved away from using it because it can be	12	pain or being awake. So there's a confounder
13	time consuming and mess up the trial from that way.		there.
14	But I think there's some value there and trying to	14	What's stressful to a person? Probably
15	come up with a non-scale, something that you can't	15	under-perfusion or not respirating is much more
16	change based on not being blinded to a drug or	16	stressful than some pain you don't recall to the
17	figuring out what the person looks like.	17	point where it's heard to use biomarkers that we
18	Capnography can give us a little clue into	18	currently have identified.
19	people's level of sedation. There's more	19	Other things you can use that have a lot of
20	variation. Just we haven't been able to come up	20	inherent sense to them but are hard to pull into
21	with a really good way to do it. So I think that's	21	the adverse event territory are the duration of
22	still just something that's out there. Maybe	22	procedure and difficulty for the provider. If
	Page 130		Page 132
1	someday, we'll be able to look at the variation in	1	you're under-sedated or over-sedated, the duration
2	breathing and predict people's level of	2	will expand or contract relative to a procedure.
3	consciousness from it.	3	Also, recovery time tends to get longer when
4	I think it would be very useful and a lot of	4	people are over-sedated or there was a complication
5	us can do it clinically. We just can't report it	5	from it. As with the patient satisfaction, under-
6	in a way that's useful for anyone else to pick up	6	sedated patients tend to be dissatisfied with the
7	or we could write it down on a paper that a	7	event unless they have a ton of opioid on board
8	reviewer would accept.	8	when they were awake.
9	Biomarkers have tried to look	9	For awareness and recall, recall is not that
10	at specifically I've looked at salivary amylase	10	hard to study, but it's not great. There's not a
11	and cortisol and serum catechols, and it's not	11	lot of great tools out there that we all accept.
12	ready for really big use. I think what I've seen	12	I've tried a number of them. Probably a lot of you
13	is that when you've sedated a person, people who	13	have tried a number of different recall tools. You
14	have an adverse respiratory event have huge	14	get mixed results.
15	catecholamine surges, but people who get a pain	15	Probably the best way is to just ask the
16	medicine or don't, and then get a procedure done,	16	person do you remember anything and was it bad or
17	the changes are too small for us, or the variation	17	was it not bad. My experience has been that if
18	is so high that we can't pick up a change in the	18	you're using an opioid, say, just give somebody
19	size trials that I'm capable of doing because it's	19	
20	a lot more expensive.	20	but say, "Well, it really wasn't that bad," which
21		i.	is a sufarrow line is a surger in supersoful the surger lt
	So really, again, it's not really ready for	21	is confounding, because in propofol, they won't
22	So really, again, it's not really ready for us to use. But I think there's some potential		remember at all. And if they remember at all,

1	they'll say it was horrible if you don't give them	1	the whole procedure really, really well. What
2	an opioid, too.	2	they're really remembering is somebody finishing,
3	But it's useful, and it makes a lot of	3	putting a bandage on at the end of a fracture
4	inherent sense. If somebody remembers something	4	reduction, or cleaning up and they heard some
5	and it bothers them, it probably was bad and, if	5	clanging and it made them upset because they were
6	they remember something and it doesn't bother them.	6	slightly sedated.
7	It just gets very imprecise as you're trying to	7	Then they're fully alert three minutes
8	measure it for trying to do studies.	8	later, and they form that into a well-formed
9	For non-procedural things, I've tried a lot	9	memory, where they filled in all the gaps with gory
10	of different cues, and I think a bunch of us have	10	details that they were worried about before it
11	tried different cues. Reading words to people and	11	happened. And you get this confabulatory, very
12	having to repeat it back is really valuable for	12	clear memory from the patient, but you start to
13	objectively assessing their level of consciousness		pick up clues that this is not actually something
	because whether or not they can hear you and repeat		that happened, and they just kind of put it
	a word back is a pretty good measure of how sedated		together in the confusion of waking up, which makes
	they are.		recall as an adverse event very difficult.
17	But on the recall end, even when we do this	17	Again, stress response, same thing,
18	experiment just to wake people who haven't been	18	biomarkers for recall, this is a little bit harder
19	sedated at all, they miss words kind of randomly in	19	
20	a hard-to-predict fashion. So it's not a very good	20	
	cue of what they're remembering and what they're		can't recall pain to where somebody did not appear
	not. Although it's been used a lot, I think most		alert when they had something painful happen, the
			5
	Page 134		Page 136
1	Page 134 of the evidence we have for retrograde amnesia	1	Page 136 distress biomarkers, at least of catechols,
	-		-
2	of the evidence we have for retrograde amnesia	2	distress biomarkers, at least of catechols,
2	of the evidence we have for retrograde amnesia comes from word studies like that, and they've been	2 3	distress biomarkers, at least of catechols, cortisol, and amylase. It doesn't seem to show
2 3 4	of the evidence we have for retrograde amnesia comes from word studies like that, and they've been okay.	2 3	distress biomarkers, at least of catechols, cortisol, and amylase. It doesn't seem to show anything relative to the magnitude of response
2 3 4 5	of the evidence we have for retrograde amnesia comes from word studies like that, and they've been okay. We've tried some pictures. I was having a	2 3 4 5	distress biomarkers, at least of catechols, cortisol, and amylase. It doesn't seem to show anything relative to the magnitude of response received from hypotension or hypoxia.
2 3 4 5 6	of the evidence we have for retrograde amnesia comes from word studies like that, and they've been okay. We've tried some pictures. I was having a little bit more luck with picture cubes now, giving	2 3 4 5 6	distress biomarkers, at least of catechols, cortisol, and amylase. It doesn't seem to show anything relative to the magnitude of response received from hypotension or hypoxia. Other things, excitatory movements, muscular
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- 21 investigators to all use similar tools that we can
 - 22 compare our data from study to study. But these

21 we've all seen it. When you ask people, do you 22 remember stuff, they're like, oh yeah, I remember November 19, 2016

Sai	ety Outcomes in Procedural Sedation	1	November 19, 2016
	Page 137		Page 139
1	are clear adverse events I think most of us can	1	Should we be looking at delirium in kids or
2	agree on.	2	adults? And in fact, much of the delirium is
3	Lastly, on permanent complications, I've	3	hypoactive. It's not hyperactive. They just don't
4	heard a lot discussions about is there cognitive	4	respond with their environment appropriately. And
5	deficits or any permanent neurological injury from	5	I know that's really hard to assess in a kid, but
6	sedation, from people who get sedated multiple	6	should we be looking at the acute post-operative
7	times, or for any of the adverse events that occur.	7	cognitive deficits, not just the permanent ones?
8	It's really hard to measure because we've	8	DR. MINER: I think that's a great idea.
9	been talking about very subtle changes by	9	Some of that gets lumped into when we measure
10	definition. And picking up these subtle changes	10	recovery time now, assuming that the person is
11	can be pretty hard. I don't think we have precise	11	truly measuring getting back to baseline. That's
12	enough tools maybe to pick up the level of deficit	12	the only surrogate for that that I've seen
13	we're picking up unless someone gets sedated	13	consistently reported. But it seems to me that
14	regularly for a long period of time, which are the	14	would be a really important thing to know about an
15	people there's been reports that maybe we're seeing	15	agent.
16	some cognitive deficit there.	16	There's a question. Yes?
17	I think, getting towards what John was	17	DR. IRWIN: Yes. I was just going to
18	talking about a few minutes ago, maybe we should be	18	comment on the use of processed EEG, because I
19	looking at something else like cerebral perfusion	19	don't think it's a good monitor of consciousness,
20	or something that would cause that problem. It's	20	actually, because there's a lot of intra-individual
21	an easier step that we're closer to achieving.	21	variability.
22	This is definitely something we need to think of a	22	DR. MINER: Sure.
	Page 138		Page 140
1	Page 138 good way to measure it or come up with a surrogate	1	
		1	DR. IRWIN: And it's very drug specific. So
2	good way to measure it or come up with a surrogate	2	DR. IRWIN: And it's very drug specific. So
2	good way to measure it or come up with a surrogate at least to measure risk for it so we can look at	2 3	DR. IRWIN: And it's very drug specific. So if you're doing a trial comparing one drug against
2 3 4	good way to measure it or come up with a surrogate at least to measure risk for it so we can look at it going forward.	2 3 4	DR. IRWIN: And it's very drug specific. So if you're doing a trial comparing one drug against another, at sort of equi-sedation levels, you would
2 3 4 5	good way to measure it or come up with a surrogate at least to measure risk for it so we can look at it going forward. Death, obviously that's the adverse event	2 3 4 5	DR. IRWIN: And it's very drug specific. So if you're doing a trial comparing one drug against another, at sort of equi-sedation levels, you would actually likely find, even if they were genetically
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1	what do we need to measure concerning these kind of	1	anybody here asked me to sedate an ALS patient.
2	adverse events?	2	When I was statistician conducting a study
3	If there is a organ dysfunction, does it	3	concerning ALS patients, one underwent bone marrow
4	really change our sedation plan or strategy? Are	4	aspiration. And we were concerned about how this
5	there really some limitations concerning our	5	patient could breathe, and could we send them
6	sedation plan? Anyone in the group?	6	directly after the procedure home? Any
7	DR. LIGHTDALE: I mean, David, I could talk	7	suggestions?
8	mostly thinking liver. Right? So let's just say	8	DR. LITMAN: Well, we know that some
9	you have a terrific sedative, but it makes your	9	anesthetics in some patients can cause muscle
10	AST/ALT go up into 400, 800 range, and I don't know	10	damage. And we usually measure that with post-
11	how long that's going to last, yes, I would say	11	operative CK, creatine kinase. That seems to be a
	that matters.	12	reliable marker.
13	The same for kidneys, you wouldn't want to	13	DR. GOZAL: Actually, we had a serial for
14	cause kidney damage, even if the sedative has no	14	about 80 to 90 patients with ALS, and we did
15	cardiovascular effects.		propofol and alfentanil, and they were on
16	DR. GOZAL: Yes?		spontaneous respiration, lying on their left side,
17	DR. IRWIN: Yes. There's also the effect on		and they did very well, actually.
18	PK/PD of the organ dysfunction itself in terms of	18	What do we need to measure? Does it really
	the duration of oxygen of the drug or the	19	matter? I put here some muscle strength tests. We
	sensitivity of the individual to the		can discuss it. Liver, we should look after some
	pharmacodynamic effects. Is that what you're		neuropsychiatric science concerning hepatic
	thinking of?		encephalopathy. Propofol is said to be a better
	-		
	D 440		
	Page 142		Page 144
1	Page 142 DR. GOZAL: But in practical, does it really	1	Page 144 drug than anything else in patient with liver
	DR. GOZAL: But in practical, does it really		drug than anything else in patient with liver
2 3	DR. GOZAL: But in practical, does it really change	2 3	drug than anything else in patient with liver disease.
2 3 4	DR. GOZAL: But in practical, does it really change DR. IRWIN: It would change your dosing, I	2 3 4	drug than anything else in patient with liver disease. Kidney, instead of measuring potassium and
2 3 4	DR. GOZAL: But in practical, does it really change DR. IRWIN: It would change your dosing, I guess, and maybe change your choice of drug for	2 3 4 5	drug than anything else in patient with liver disease. Kidney, instead of measuring potassium and creatinine, we should measure the GFR. That is
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2 3 4 5 6	DR. GOZAL: But in practical, does it really change DR. IRWIN: It would change your dosing, I guess, and maybe change your choice of drug for that reason also. DR. DAHAN: Well, take for instance a child	2 3 4 5 6	drug than anything else in patient with liver disease. Kidney, instead of measuring potassium and creatinine, we should measure the GFR. That is much more [indiscernible] on these kind of patients. Thank you. DR. WARD: I guess a question is,
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	Page 145		Page	147
1	DR. WARD: Looking at [inaudible – off mic].	1	a lot in my own institution about education in	
2	So that was a kidney effect. There are other	2	sedation.	
3	kidney effects [inaudible – off mic].	3	We have two large programs in which we	
4	DR. GOZAL: Thank you.	4	educate both non-anesthesiologists as well as	
5	DR. WARD: I'm trying to be complete.	5	nurses. In our institute, non-anesthesiologists	
6	So a little different topic that I asked	6	apply mild sedation, and people that we call	
7	Dr. Dahan to do was sometimes we can do,	7	sedationists, which are nurse anesthetists with a	
8	interventions from respiratory, nausea and	8	three-year additional training to give sedation,	
9	vomiting. We've heard about pharmacological	9	they apply deep sedation in our institute, but all	
10	interventions to prevent adverse events.		supervised by us. So we do not have nurse	
11	Not thinking about a clinical trial for a	11	anesthetists that work on their own.	
	new sedative, but thinking about a clinical trial	12		
	if you have a new compound that would prevent		cause less respiratory depression? That's not an	
	adverse events, how would you design a clinical		easy answer to give. There has been recent	
15	trial to do that? Thank you.		publications on so-called biased ligands. These	
16	Presentation – Albert Dahan		are opioids that affect the new receptor	
17	DR. DAHAN: Thank you. Thank you, Denham,		differently from classical opioids.	
	for inviting me. It's a great pleasure to be here.	18		
19	Well, I've changed the topic a little bit,		pathways, at least in animals they've shown the	
	to be honest. And I will be talking a little bit		beta-arrestin pathway, which induces respiratory	
	on the trials that we've been performing on the		depression and the G proteins that induce	
22	effect of especially opioids on ventilatory	22	analgesia. And there are specific opioids being	
	Page 146		Page	148
1	Page 146 control.	1	Page developed aimed at G protein and not at the	148
1	-			148
2	control.	2	developed aimed at G protein and not at the	148
2 3	control. Most of the studies were on drugs that were	2 3	developed aimed at G protein and not at the beta-arrestin. However, I've seen various human	148
2 3 4	control. Most of the studies were on drugs that were used in chronic pain because most of the studies	2 3	developed aimed at G protein and not at the beta-arrestin. However, I've seen various human studies that were extremely disappointing in this respect, but I might be mistaken.	148
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1	this is the result. This is a parameter that	1	This was a patient without any respiratory
2	Denham already showed, isohypercapnic ventilation	2	activity for more than 3 minutes. We put her on
3	at 55 millimeters of mercury. This is the placebo.	3	mask ventilations, or this, artificial ventilation
4	These are crossover trials, so every subject was	4	because I did not want to have a patient in a study
5	tested 4 times placebo.	5	that stopped breathing for over 3 minutes.
6	The opioids, we're talking about and	6	I recently replicated a similar study post-
7	oxycodone. And this is an equianalgesic dose	7	operatively and had some of my patients that were
8	because we also did pain testing analgesia,	8	without any respiratory activity on oxygen for over
9	nociceptive testing. And as you can see, in terms	9	5 minutes. To me, it's totally surprising, no
10	of depression of isohypercapnic ventilation, the	10	effect on saturation.
11	effect is quite large.	11	So this shows you how dangerous it is to
12	I'm not really sure how this extrapolates to	12	just look on desats in your studies. I don't even
13	the clinical setting, but in my hands, we showed	13	use it as an outcome parameter anymore at all. And
14	that, for the first time, this drug produces an	14	I hope that, in did it hit the United States,
15	equianalgesic dose as compared to oxycodone, less	15	remifentanil PCA, for labor pain?
16	respiratory depression.	16	DR. KOCHMAN: I know that some people have
17	What it means, I do not know, but it's an	17	experimented with it at Penn. One person wants to
18	interesting concept that, if you want to use an	18	use it a lot more than others. I think most of us
19	opioid for chronic pain, and you have a patient	19	have a fear of this.
20	prone to respiratory depression, an obese patient,	20	DR. DAHAN: Well, we've done already over
21	a patient with pulmonary disease, this might be an	21	50,000 patients with it. I'm not really much in
22	attractive alternative.	22	favor of it because there are side effects, and we
	Page 150		Page 152
1	Now, another way that I am looking at	1	have had several resuscitations, because it's a
2	sedation is the use of ultra-short-acting opioids.	2	potent opioid, and flushing is an issue.
3	In my country, labor pain is now being addressed	3	DR. KOCHMAN: What dose do you use?
4	apart from using epidurals with PCA remifentanil.	4	DR. GAN: I use a bolus dose of
5	I'm not sure if this already hits the United	5	30 micrograms with a lock-out time of 5 minutes.
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infusion? No?

19 synapse increases.

DR. GAN: And do you put any continuous

So now, about co-medication to prevent or

DR. DAHAN: No. That's all they get.

10 reverse adverse events, again, respiratory

depression. There are several drugs being

developed for this purpose. There are several

trials with that. Physostigmine is a possibility,

talk about it later a little bit. Tianeptine is an

antidepressant. It is non-specific anti-

ampakines, although I haven't seen any phase 3

depressant. It reduces the amount of serotonin in

the brain. But the turn-over of serotonin at the

I am working on that drug. So far, the

21 results are limited; disappointing, I would say.

22 Animal studies do show large effects on

- 5 I'm not sure if this already hits the United
- 6 States. It's an epidemic in my country. The main
- 7 reason is that many of my colleagues,
- 8 anesthesiologists, refuse to give women in labor an
- 9 epidural outside of the daily hours, the daytime
- 10 hours, I have to say.
- 11 So they came up with this solution,
- 12 remifentanil PCA. I did a very large number of
- 13 trials to test the safety of this approach. Just
- 14 to give you one example -- this was published a
- 15 couple years ago -- this is a single-bolus PCA dose
- 16 of remifentanil. And as you can see, this minute
- 17 ventilation goes down.
- 18 If you add oxygen, so if these patients
- 19 would have been on oxygen, you can see two things.
- 20 By the way, this is respiratory rate and this is
- 21 saturation. First of all, you miss the occurrence
- 22 of saturation.

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	Page 153		Page 155
1 r	espiration. Again, in humans, maybe it's a dosing	1	observed some interesting observations. One of
2 is	ssue. I'm not really sure yet. We're still	2	them was the reduction in apnea-hypopnea index.
3 V	vorking on it.	3	But what surprised me from that study, and I
4	Serotonin agonist ketamine, I am in	4	liked it very much, is that, in oxygen, the
5 fa	avor I use ketamine quite a lot in my practice,	5	severity of apnea-hypopnea index increased, while
6 b	both perioperatively and for sedation. It's not a	6	after the application of physostigmine, the events
7 C	drug that actually stimulates breathing in the	7	decreased significantly. Maybe Suzie can talk
8 S	sense that your minute ventilation increases, but	8	about it a little bit later.
9 it	t reduces the variability that you see and I	9	Now, like I said before, I always perform
10 V	vill give you some examples of that so that	10	analgesia experiments together with respiratory
11 b	preathing becomes more stable, and the probability	11	depression experiments. Why is that? Because I'm
12 C	of an apneic event decreases significantly.	12	very much interested in the whole picture of it.
13	So this is really important. It's not a	13	If you have a certain amount of analgesia,
14 r	espiratory stimulant like, for instance, drugs	14	how much respiratory depression is connected to
15 t	hat I show here below, drugs like doxapram,	15	that? And I call that a utility function. In
16 (GAL021, and other experimental drugs. This is an	16	fact, a utility function is just a probability of
17 e	example of this GAL021 drug.	17	analgesia minus the probability of an adverse
18	This is an alfentanil-induced respiratory	18	event.
19 C	lepression at isohypercapnia. In orange is the	19	An adverse event can be anything. In my
20 p	placebo response. You see severe respiratory	20	studies, I use respiratory depression. And this is
21 C	lepression by over 50 percent. And adding this	21	an example that we published in Pain I think a year
22 C	drug, GAL021, increases respiration.	22	ago, in which we looked at a utility function of
	Page 154		Page 156
1	Page 154 It does so by blocking potassium channels at	1	Page 156 fentanyl. And what we did, we made a distinction
			-
2 t	It does so by blocking potassium channels at	2	fentanyl. And what we did, we made a distinction
2 t 3 b	It does so by blocking potassium channels at he carotid body, mimicking hypoxic event. The	2	fentanyl. And what we did, we made a distinction between subjects that had a high analgesic potency for fentanyl and the ones that did not.
2 th 3 b 4 th	It does so by blocking potassium channels at he carotid body, mimicking hypoxic event. The body is not hypoxic, but the carotid bodies think	2 3 4	fentanyl. And what we did, we made a distinction between subjects that had a high analgesic potency for fentanyl and the ones that did not.
2 th 3 b 4 th	It does so by blocking potassium channels at he carotid body, mimicking hypoxic event. The body is not hypoxic, but the carotid bodies think he body is hypoxic. Sadly, the company that	2 3 4 5	fentanyl. And what we did, we made a distinction between subjects that had a high analgesic potency for fentanyl and the ones that did not. What was quite surprising to me, something
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		Page 157		Page 159)
	1	of respiratory depression.	1	So we wanted to have a look at the	
	2	Now, we know this. You know when you have a	2	interaction between ethanol and oxycodone on	
	3	patient that does not respond to your analgesic	3	respiratory events, and we measured apneic events.	
		treatment, you keep treating them with higher		In my lab, an apneic event is the cessation of flow	
		dosages. Stop. There are many case reports in the		at the mouth for over 1 minute, 1 minute or more, I	
		literature that show that you should not treat your		have to say. And we looked at 2 populations.	
		patients like that. At one point, you have to stop	7	I talked about it a little bit already,	
		and revert to another therapy.	8	although that was another study. In this study, we	
	9	Why do I think the utility function is		looked at the interaction between two levels of	
-		extremely interesting also in the development of		alcohol, 0.5 grams per liter and 1 gram per liter.	
		drugs? Because you can compare drugs. For	11	This alcohol was delivered intravenously,	
		instance, here, we again have the fentanyl		and you can compare it to 3 to 5 beers per hour in	
		function. This is the total population, so there's		this population. And believe me, patients like	
		a negative effect, as expected from the last slide		this take their oxy. I have many examples of	
		as well, and compared to, for instance, morphine		patients that take their oxycodone with a very nice	
		that has a predominantly positive effect.		glass of whiskey.	
	17	So to treat for instance pain patients with	17	So it's not academic at all. Look at the	
		either morphine or fentanyl, I would choose	18	literature. And what we showed, there was a	
		morphine in the sense that the probability of an		tremendous explosion of apneic events in the	
		analgesic effect exceeds the probability of a		elderly population at the highest concentrations of	
		respiratory event.		alcohol. So this is a relevant and non-academic	
	22	Now, what should we measure? Like I said		observation that predicts the occurrence of a	
		-			
		Page 158		Page 160	
	1	Page 158 before, you can make it as complex as you wish.	1	Page 160 deleterious, fatal events at home.)
		-	1 2	deleterious, fatal events at home.	1
	2	before, you can make it as complex as you wish.	2	deleterious, fatal events at home.	
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2 3 4 5 6 7 8 9 10 11 12	measured these four measures on the IPI device. And there are certain indications that there might have been going on something, a sudden increase in heart rate here, a large increase in heart rate. Respiratory rate at one point was low. Entitled CO2 was low, which is an indication that the patient is hyponeic or something else. Maybe	2 3 4 5 6 7 8 9 10 11 12	of the things that I like very much of adding ketamine is that if you give for instance propofol/remifentanil, there are lots of expiratory pauses. The patient exhales and there is no breathing activity for some time. All of a sudden, he inhales or she inhales and, when the catheter is positioned at the spot where the surgeon or the cardiologist wants to ablate, there's small movement. I've had repetitive discussions with the cardiologists on this, and we decided to move on to
	some obstruction is going on. And the IPI gave us values below, let's say, 7 and certain indications.		a new way of dealing with that. How it changes the respiratory rhythm, difficult people -
15	But the problem I have with these kind of		claim because in Rett syndrome, R-E-T-T, which
	· · · · · · · · · · · · · · · · · · ·		is a complex pediatric syndrome you might know
17	patient did well. I saw this the next day. I	17	all about it; I am not a pediatric
18	withdrew data from the system. I asked the nurses	18	anesthesiologist, but I've read a lot about
	what happened. They said, "Well, nothing happened.		it ketamine also helps to make breathing more
	What do you think happened?" I said, "I don't		regular because these children also have a
	know." So it's really, really difficult to link		breathing problem.
22	the things that we measure in our patients with	22	I think it works for the AMPA system in
	Page 162		Page 164
1	actual outcome.	1	which there is more tonic activity from specific
1	actual outcome. Okay. I think this is it. Any questions or		which there is more tonic activity from specific areas in the brain, like the pre-Botzinger complex,
2		2	which there is more tonic activity from specific areas in the brain, like the pre-Botzinger complex, but this is very complex, and breathing becomes
2	Okay. I think this is it. Any questions or other items that I might have missed?	2 3	areas in the brain, like the pre-Botzinger complex,
2 3 4	Okay. I think this is it. Any questions or other items that I might have missed?	2 3 4	areas in the brain, like the pre-Botzinger complex, but this is very complex, and breathing becomes
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2 3 4 5 6	Okay. I think this is it. Any questions or other items that I might have missed? DR. GAN: Question Albert, that's a wonderful summary. I have two questions. One, you mentioned about ketamine making the respiratory pattern more regular.	2 3 4 5	areas in the brain, like the pre-Botzinger complex, but this is very complex, and breathing becomes more regular in the sense, like I said before, the probability of irregularity decreases. I really
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1	This is a matter of coaching. I coach them through	1	this is not new.
2	it. In the end, there's a minority of patients	2	In my opinion, when you give potent opioids
3	that dislike it, I do agree. Yes. There are side	3	to patients, they all become OSA patients,
4	effects.	4	obstructive sleep apnea patients, especially in
5	DR. GAN: Do you find that by adding a bit	5	their sleep. But the fact that they obstruct
6	of benzo, that	6	awake no. I'm not saying obstruct wide awake,
7	DR. DAHAN: I never do that. I don't think	7	become apneic awake. It was a big discussion with
8	it's necessary. Some of my colleagues use	8	the referee [indiscernible] also. Yes, he was
9	clonidine, which is an alpha 2 agonist, to dampen	9	right. Okay.
10	the side effects. I dislike midazolam, long	10	DR. GAN: Sorry, just one quick question.
	acting, interaction with all kinds of effects. Why	11	Do you believe that, for kappa opioids, it reduces
	do that? Talk to your patient.		respiratory depression?
13	Another issue is I use esketamine. I'm not	13	DR. DAHAN: The drug that I just showed you,
14	using the racemic ketamine. This is relevant in	14	the mu delta drug, also is a kappa agonist. There
	the sense that the equianalgesic, equianesthetic		was a big discussion on the mechanism of the
	doses produce less salivation. I like that. With		reduction of respiratory depression. The company
	racemic ketamine that I used years ago, there was		claims that it's the delta agonist that reverses
	lots of production of saliva. You know what I		the respiratory effect.
	mean? The mouth might be full of saliva that	19	I am not really happy with kappa agonists
20	interacts with breathing as well. But this is my	20	because they cause dysphoria. They claim that it's
	personal opinion. It's not evidence based.	21	the new agonism that counteracts the dysphoria. o
22	Yes, Suzie?	22	we're dealing here with very complex molecules
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1	DR. KARAN: Respiratory arrhythmias that you		that, in the end, I have no idea how they work.
2	DR. KARAN: Respiratory arrhythmias that you said that you observed before you have the apneas,	2	that, in the end, I have no idea how they work. And if you would take out one component, what would
2	DR. KARAN: Respiratory arrhythmias that you said that you observed before you have the apneas, are you measuring any duty cycles or any	2	that, in the end, I have no idea how they work. And if you would take out one component, what would make it do, I have no idea. Okay. Thank you.
2 3 4	DR. KARAN: Respiratory arrhythmias that you said that you observed before you have the apneas, are you measuring any duty cycles or any DR. DAHAN: I'm measuring expiratory time,	2 3 4	that, in the end, I have no idea how they work. And if you would take out one component, what would make it do, I have no idea. Okay. Thank you. DR. WARD: Everybody else come back up,
2 3 4 5	DR. KARAN: Respiratory arrhythmias that you said that you observed before you have the apneas, are you measuring any duty cycles or any DR. DAHAN: I'm measuring expiratory time, to be honest. I'm looking at the variability in	2 3 4 5	that, in the end, I have no idea how they work. And if you would take out one component, what would make it do, I have no idea. Okay. Thank you. DR. WARD: Everybody else come back up, speakers, and get some summary before we have
2 3 4 5 6	DR. KARAN: Respiratory arrhythmias that you said that you observed before you have the apneas, are you measuring any duty cycles or any DR. DAHAN: I'm measuring expiratory time, to be honest. I'm looking at the variability in expiratory time. I have a set-up that allows me to	2 3 4 5	that, in the end, I have no idea how they work. And if you would take out one component, what would make it do, I have no idea. Okay. Thank you. DR. WARD: Everybody else come back up, speakers, and get some summary before we have lunch, Jenifer, I think, around the topic of
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2 3 4 5 6 7	DR. KARAN: Respiratory arrhythmias that you said that you observed before you have the apneas, are you measuring any duty cycles or any DR. DAHAN: I'm measuring expiratory time, to be honest. I'm looking at the variability in expiratory time. I have a set-up that allows me to do that. So when the variability is increased by a factor of 2, I know something is going to happen.	2 3 4 5 6	that, in the end, I have no idea how they work. And if you would take out one component, what would make it do, I have no idea. Okay. Thank you. DR. WARD: Everybody else come back up, speakers, and get some summary before we have lunch, Jenifer, I think, around the topic of [indiscernible] measure. Q&A and Panel Discussion
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	Page 169		Page 171
1	guess, saturation went up.	1	actually is going to be a risk factor for something
2	So some of these events are not at all	2	that matters, that we see 1 in 10,000 or 1,000
3	transient and might occur. I do not know the	3	times.
4	clinical effect of these long-term hypoxemic	4	DR. WARD: Yes. And I think that's
5	events. I do know that I'm quite afraid, because I	5	absolutely the right point. Almost everything that
6	didn't speak about the fact that, in my study, I	6	we're measuring is a biomarker, and the literature
7	had to ventilate one or two of the patients or	7	is full of biomarkers that turned out to be either
8	stimulate them to take a deep breath.	8	no good or bad.
9	So even a short apneic event is significant	9	I think we've got some that are at least no
10	if it is not restored to normal breathing. But in	10	good. I don't know if I got any examples of
11	normal sedation, there's always somebody there that	11	biomarkers are bad, other than they maybe create
12	doesn't look at the patient and looks at the pulse	12	situations that had too many interventions. But
13	oximeter or the respiratory rate monitor.	13	yeah, I think, for clinical trial, we've got a lot
14	DR. WARD: I think in a clinical trial, you	14	of biomarker data across all the organ systems
15	could define the length of time for the transient		fixed.
	event when it becomes important. But I think it	16	I thought nausea was not the one that
17	was Suzanne yesterday that kind of separated the	17	counted, but TJ came up with one in which nausea
18	measurement instrument from the interpretation	18	actually could be good.
19	instrument. And I think that's an important	19	DR. BERKENBOSCH: The degree of transience
20	concept.	20	is also somewhat dependent upon the frequency and
21	You could be measuring these things	21	method with which you are monitoring. And I'm
22	continuously, and can report continuously, and then	22	thinking of things like respiratory rate and oxygen
	Page 170		Page 172
1	Page 170 decide in this particular relevance that none of	1	Page 172 saturation, heart rate.
	-	1	
2	decide in this particular relevance that none of	2	saturation, heart rate.
2 3	decide in this particular relevance that none of these were long enough to really get to the point	2 3	saturation, heart rate. Those are measured continuously, so you can
2 3 4	decide in this particular relevance that none of these were long enough to really get to the point where they're really considered adverse events, but	2 3 4	saturation, heart rate. Those are measured continuously, so you can see transient versus things are a little bit longer
2 3 4 5	decide in this particular relevance that none of these were long enough to really get to the point where they're really considered adverse events, but not to try to kind of pre-select and ignore a	2 3 4 5	saturation, heart rate. Those are measured continuously, so you can see transient versus things are a little bit longer lasting, whereas with blood pressure, we're
2 3 4 5	decide in this particular relevance that none of these were long enough to really get to the point where they're really considered adverse events, but not to try to kind of pre-select and ignore a transient event. If you can measure it, you should	2 3 4 5 6	saturation, heart rate. Those are measured continuously, so you can see transient versus things are a little bit longer lasting, whereas with blood pressure, we're measuring every 5 minutes most of the time, every
2 3 4 5 6 7	decide in this particular relevance that none of these were long enough to really get to the point where they're really considered adverse events, but not to try to kind of pre-select and ignore a transient event. If you can measure it, you should record it.	2 3 4 5 6 7	saturation, heart rate. Those are measured continuously, so you can see transient versus things are a little bit longer lasting, whereas with blood pressure, we're measuring every 5 minutes most of the time, every 15 to 30 minutes during recovery. And once they've
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	Page 173		Page 175
1	curious about Dan. But it strikes me now we're	1	recommendations for what constitutes an important
2	starting to get repeated measures within each		outcome.
	patient, and we may need some statistical	3	DR. LIGHTDALE: Suzie?
	workaround in how you get at that.	4	DR. KARAN: On the lines of the continuous
5		5	monitoring and patterns, does anybody on the panel
6	obviously, a lot of stats right now on how to start		
	to wade through just too much data. So I don't		arterial tonometry?
	know. Maybe some statistical thought on how to	8	DR. LIGHTDALE: With what?
9		9	DR. KARAN: Pulse arterial tonometry. It's
10		10	with the sleep that you're using as a surrogate
11	DR. WUNSCH: Yes. Actually, this follows on	11	measure of respiratory arrhythmias. Okay.
12	that. In critical care, there's a lot of interest	12	DR. GAN: How does that work?
13	in trying to predict who's going to fail	13	DR. KARAN: I'm not actually sure. I'm
14	extubation. It's in early phase, but looking at	14	curious. And somebody who has a brand of a device
15	sort of patterns and variability in respiratory	15	to measure respiratory arrhythmias during sleep has
16	status prior to extubation.	16	told me that it definitely correlates with some
17	There's been a little bit of mention of	17	degree of respiratory arrhythmias during sleep. I
18	that. I'm not sure it's the answer to what we	18	don't have a very good understanding of it yet, so
19	measure right now, but it may be something for the	19	maybe this would be a good group to run it by.
20	group to think about in terms of what to recommend	20	I think it's got some relevance in people
21	for what should we be looking at.	21	who are not beta-blocked, and measures some kind of
22	Is it about some of these patterns, as	22	sympathetic tone or response in response to a
	Page 174		Page 176
1	people have mentioned, rather than any specific	1	respiratory arousal.
2	transient event that we're ultimately, maybe 10	2	DR. GAN: Well, there are a number of
3	years down the line, going to be most interested	3	monitors as has been again, this recent ASA, for
4	in, in terms of what is a harbinger of a true bad	4	at least 3 sympathetic monitors in one fashion or
5	event, which I think is what we're really trying to	5	another, that potentially might be useful in
6	get at.	6	looking at a certain degree of sympathetic
7	DR. LIGHTDALE: Yeah, Dan?	7	activity, which probably when one was part of
8	DR. SESSLER: Albert was kind enough to	8	breathing came into that algorithm.
9	mention our paper on Ward hypoxemia. I think there	9	DR. WARD: It also mentioned looking at some
10	were two lessons that came out of that. What we	10	bio stress markers for sedation. And I recall a
11	found was that hypoxemia was common, severe, and	11	dexmedetomidine study that I did years ago, where
12	persistent. So first lesson might be that if you	12	we actually majored a lot of bio stress markers,
13	don't look, you won't see things.	13	particularly catecholamines, epi and norepi.
1		1	

That gets back to my plea for continuous
monitoring. It's easy to do now. It should be the
standard of care. But the more serious problem,
which John just mentioned, is that we don't know
what this means. And everything we're talking
about here is just a marker for the severe events
that we're concerned about, and we simply don't
know what that link is. And that really limits our
ability to come up with any convincing

14

17

18

19

22

21 the time of discharge.

We didn't get those results back for days

when we eventually got the epi and norepi back, we

unmeasurable in every single subject, that they had

DR. GAN: One of the questions maybe I could

15 afterwards. So we had discharged all our subjects

16 12 hours after they received the compound. And

discovered that, at time of discharge, it was

20 no measureable levels of either epi or norepi at

	Page 177		Page 179
1	ack Albert and you know that we did recorded to	-	a lat of kataming also in the word, but it's really
	ask Albert and you know that we did respiratory arrest project with Frank [indiscernible]. And		a lot of ketamine also in the ward, but it's really low dose, and I'm not really sure if this was
	what obviously that is, is sort of extreme when		still it's just to induce opioid sparing.
	somebody has a respiratory problem and then had a		
		4	DR. WEISS: When you're saying low dose, like 1 to 2?
	respiratory arrest.		
6	Do you think we are at a state where devices	6	DR. DAHAN: 0.1 milligram per kilogram.
	can sort of help to try to prevent, or mediate,	7	
	sort of predict some of the people who are at risk	8	DR. DAHAN: Very low. DR. WARD: That's not the racemic. That's
	for this catastrophic event, maybe hours or maybe	9	the
	days before that?		
11	DR. DAHAN: Of course, I'm not sure. But	11	DR. DAHAN: Esketamine. So you have to
	imagine what you're saying means that you need to		double or triple it with I'm currently doing a
	have a device, if there is a device, in each bed in		study to compare the analgesic effects of the
	your hospital. But it is possible. I know, in the		racemic and the ketamine. We know the comparison
	U.S., there are hospitals that now are buying		for anesthesia, but not for pain relief. I'm doing
	systems for every bed.		that right now.
17	We still do not know if we can predict this.	17	I was surprised how low the potency is of
	What I'm doing are small, very well controlled,		racemic ketamine compared to esketamine.
	high-dose opioid studies in otherwise healthy young		Esketamine is really a more potent drug than the
	and elderly volunteers. It might well be that in		racemic mixture. So I will tell you, in the future
	patients, there are so many co-factors, that this		what dose you need to use.
22	predictability is reduced tremendously by whatever	22	AUDIENCE MEMBER. To which patient do you
	Page 178		Page 180
1	-	1	-
	other underlying disease they have, drugs they use	1	give ketamine?
	-	2	give ketamine? DR. DAHAN: I use it for large abdominal
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	Fage 101		Fage 105
1	If you looked at that data and you	1	DR. SESSLER: Decide on what basis?
2	said ahead of time, you would say, okay, if you	2	DR. CONWAY: Would it be like a
3	use midazolam alone, it should be okay, but if you	3	physiologically significant difference or a safety
4	use it with an opioid, you're going to probably	4	difference?
5	have more true adverse outcomes, coming back to	5	DR. WARD: Yes. I think that's kind of the
6	you? What's an event? What's an adverse event?	6	next step, what I was just saying. Peter defined
7	What's an adverse outcome?	7	apneic episodes in a certain way. We have no idea
8	So I think we do have some limited data	8	if defining those differently would have made a
9	further on the respiratory system that more	9	tighter correlation or not. I mean, I think that
10	frequent apneic events in a phase 2/3 clinical	10	goes along with defining the event and the severity
11	trial is probably going to be predictive of more	11	of the event, how does that predict an adverse
12	adverse outcomes when used clinically. But it's	12	outcome.
13	not a tight connection.	13	DR. LIGHTDALE: What is the barrier to
14	DR. LIGHTDALE: That, I think, again gets	14	simply collecting continuous data in every sedation
15	back to, you're capturing small little things that	15	and dumping it?
16	don't see very relevant, but perhaps they're	16	DR. WARD: Right. And I think for clinical
17	predictive.	17	trials, that's exactly what we need to be doing.
18	DR. WARD: Right, but perhaps there might	18	Just looking at the pulse oximeter and looking at
19	be.	19	clinically how the patient is breathing is not
20	DR. LIGHTDALE: Yes.	20	adequate, and recording the pulse oximeter every
21	DR. WARD: And I think we're limited	21	5 minutes and the blood pressure every 5 minutes is
22	by we've got these clues, but we're limited by	22	not going to be an adequate way to get enough data
	Page 182		Page 184
1	Page 182 not having a very tight connection there. And part	1	Page 184 that we can finally look at this.
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1	sample-size calculation, you get numbers between	1	it around to everybody. And if you want to
2	10,000 and 20,000.	2	participate as an author, let me know, and if you
3	DR. WARD: Yes. That even sounds small.	3	don't, that's okay, too.
4	I think what we'll do is break for lunch.	4	But please help me out getting the paper
5	If we could get back at 1:00. I want to make the	5	written. It'll probably come around as a true
6	discussion this afternoon. We'll do a 2-hour, 1:00	6	draft and not as a final, final, final draft. So
7	to 3:00, and make sure we're through at 3:00.	7	don't expect it to be perfect the first time
8	There will be sandwiches and things available to	8	through, and I'm looking forward to a lot of input.
9	take with you as you go to your airplanes.	9	It's always difficult with a big group.
10	I want to focus on what are the	10	Having gone through the big group last time, it's
11	recommendations that we can maybe "consensus" is	11	too big to do a round robin, but it's a little
12	not the right word, but maybe have some level of	12	difficult when I get all the input in at the same
13	agreement on that I can start putting in the paper.	13	time. So use track changes on it, and I'll see if
14	So I've been putting together a list of some	14	I can so don't feel bad if you send this in part
15	possible recommendations. If you have some, would		on modification, and then when you get the next
	you please write them down and give them to me		draft, it's not there. I didn't do it on purpose.
17	during lunch? And I will put them in the slide	17	It just kind of fell through the cracks. So put it
18	that's got the list of things, that we can see if		again, and we'll work our way through it.
19	we can get some agreement on. Thank you.	19	Since part 1 was published in Anesthesia and
20	(Whereupon, at 11:50 a.m., a lunch recess	20	Analgesia, we'll probably send it there again.
21	was taken.)	21	I've had a nice discussion about where to send
22		22	these papers because it is multidisciplinary, and
	Page 186		Page 188
1	AFTERNOON SESSION	1	maybe the anesthesia journal is not necessarily the
2	(1:01 p.m.)	2	best place for it for everybody to be reading. I
3	Group Discussion	3	don't think it's a New England Journal kind of
4	DR. WARD: Okay. In order to keep	4	paper, but maybe PLOS or one of the more general
5	everything running on time, what I had laid out on	5	kind of journals, so we can talk about that.
6	the schedule for this afternoon was always a little	6	I think this one because Anesthesia and
7	bit tentative because I didn't know where we would	7	Analgesia did publish part 1, I'll probably send it
8	be at this point in the meeting and what we would	8	in there for part 2. Because they let me call the
9	still have to discuss.	9	first one on efficacy part 1, it sort of gave them
10	So we're really going to, as I mentioned	10	a little bit of a commitment.
11	earlier, combine the last couple of sessions, and	11	(Laughter.)
12	we'll be through by 3:00. Val is going to tell the	12	DR. WARD: Okay guys, here's part 2.
13	hotel staff that people will be needing taxicabs at	13	Remember, you told me you wanted me to call that
14	3:00, so she'll arrange for having extra cabs out	14	part 1. I'm going to call this one part 2, and
15	there for those of you who need to catch a cab to	15	there we go. It should be in the next month or so,
16	the airport.	16	to try to get early drafts of that out.
17	Once we get through, I'm going to back and	17	I want to thank you all for the
18	get the transcripts of this in a couple of weeks,	18	participation in both SCEPTER I and SCEPTER II.
19	and see if I can't put some stuff together, maybe	19	We'll think about what we're going to be doing next
20	with a consensus or recommendations like we did on	20	for SCEPTER. This is part of Bob's action, so I
21	SCEPTER I. And those of you who would like to	21	have to work with Bob on what action we'd like to
1	norticinate as outhers, latima know, or Illiand	00	and done in this area
22	participate as authors, let me know, or I'll send	22	see done in this area.

	Page 189		Page 191
1	Please send me or Bob or Val any comments	1	all phases of clinical trials.
	you have on the organization of this and the other	2	Physiological profile of new compounds
	meeting, things that we could do better and do		should be well-characterized in phase 1 clinical
	differently in organizing. It's a different kind		-
			trials, particularly the respiratory,
	of meeting; it's not a CME meeting where we go and		cardiovascular effects, even though we don't know
	listen to people talk. So this has been a great		that it's going to necessarily have a strong
	group, great networking, and good participation.		connection to outcomes.
8	In combining this, what we thought we would	8	The MEDRA/TROOPS system should be used to
	do is I put together some points that we might be		classify adverse events. Data should be collected
	able to agree upon, and then Steve and Mark are		in ways that facilitate pooling for meta-analysis.
	going to talk about some issues that they have. I		For many outcomes, both severity and length of time
	thought we would get this panel up here with		data should be collected, and we heard that as
13	Albert, TJ, John, Jim, and David, up here as kind	13	diverse as saturation and nausea, particularly for
14	of leaders of the discussion along with Steve and	14	the length of the time.
15	Mark.	15	The relationship or lack of relationship
16	So let me go through this one first, and	16	between events, adverse events, and adverse
17	then when Steve and Mark come up, we'll all become	17	clinical outcomes should be defined as much as
18	part of the panel, but I think it's a panel of the	18	possible in a clinical trial.
19	whole.	19	When clinical intervention is used as an
20	So things that we can agree upon, points we	20	outcome, it should be procedure specific. It's
21	can agree upon. What I think I want to do with	21	been brought up several times that putting nasal
22	this is go through them, not necessarily, unless	22	cannula on an endoscopy is not the same as putting
	Page 190		Page 192
1	somebody starts jumping up and down, spend a lot of	1	a nasal cannula on in an MRI, and have well-defined
2	time on them, think about them, and then we'll go	2	criteria for the intervention.
3	back to ones make a note of ones that you think	3	Particularly in a clinical trial, this has
4	are great or ones that you think are horrible. And	4	come up several times, that if an intervention is
5	then in the panel discussion we're going to have	5	the outcome, then the definition of what it is that
6	two hours now to go through all these we can	6	triggers that intervention needs to be very well
7	back to them after Steve and Mark give their	7	defined.
8	presentation.	8	It's useful to consider the measurement
9	So I've got some points that a couple people	9	instrument and the relevance instrument separately,
10	gave me. These are from my notes that I've taken.	10	and I think Susan was the one that gave that
11	So the disclaimer is all the errors are mine. This	11	concept out yesterday, and I like that idea. We
12	is how I've kind of interpreted it, and certainly	12	have a lot of things that we measure whether or not
13	it needs to be more of an agreement among the	13	it's going to be relevant. Will it be procedure,
14	group.	14	patient, drug specific?
15	I think the scope, from what I've been	15	If you do the relevance instrument too soon,
16	hearing, covers all the phases, 1 to 4. It may	16	you may not measure things that need to be
	make the paper writing a little difficult, because	17	measured. So you can measure things, and then
	things that might be happening, things that	18	decide whether or not they're going to be relevant:
	particularly Albert and I talked about, are more	19	saturation, nausea, variety of things.
	phase 1 kinds of things, and some of the other	20	The cause of the AE needs to be separated by
	things more phase 4, but that'll come out in the	21	drug or drugs, the disease, the procedure, the
	paper. But I think I heard things that would cover		provider, particularly as we're doing sicker and

	Page 193		Page 195
1	sicker patients. It may be more the patient and	1	Patient recall may be useful, but will need
2	the disease than the drug itself, and that's	2	to be defined in relation to expectations.
3	important to distinguish.	3	Unexpected, painful, unpleasant recall. In seeing
4	Decrease sophistication in the measurement	4	patients before surgery, I've had a lot of patients
5	techniques can be used as the compound progresses	5	tell me, "Oh, the last time I had anesthesia, I
6	through phases 1 to 4. Expenses and things that	6	remember the whole thing."
7	you would instruments in an early clinical trial	7	"Oh, what did you have?" "Oh, I had a
8	are needed, but may not be needed as the clinical	8	colonoscopy." You know, well maybe you weren't
9	trial gets to larger and larger populations.	9	anesthetized for it. So the expectations of the
10	High-risk populations need to be included in	10	patient as far as recall is a very important piece
11	phase 2/3 clinical trials. Non-standard monitors	11	of it.
12	that is cardiac output may be useful in clinical	12	The difficulty relating the occurrence
13	trials, but the accuracy should be defined if	13	of we talked a lot about this for lack of a
14	they're going to be used in that trial.	14	better word, of biomarkers, desaturations,
15	Major ventilation is needed in phase 3	15	et cetera, in phase 3 trials to rare SAEs mandates
16	clinical trials. Clinical observation and	16	postmarketing studies and data collection.
17	saturation only is not adequate for a clinical	17	So those are kind of the points that I came
18	trial. In some studies, longer follow-ups, as	18	up with. I don't know if we agree upon them, but I
	weeks to months of adverse events is appropriate.		would like to spend the next time thinking about
20	We talked about that for neurological in		some of these and some of the ones that Steve and
21	particular.		Mark will present, because those will form the
22	Recognizing it's limitations. Patient	22	basis of the paper as I write it.
	Page 194		Page 196
1	Page 194 satisfaction should be measured in late phase	1	
	-		
2	satisfaction should be measured in late phase	2	So Steve and Mark, and if I could have the
2	satisfaction should be measured in late phase clinical trials, and TJ gave us a symptom distress	2	So Steve and Mark, and if I could have the rest of the panel members, Albert, TJ, John, Jim, and David.
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San	ety Outcomes in Frocedural Sedation		1000ember 19, 2010
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1	department studies, largely of ketamine, and	1	These intermediate outcomes and
2	investigating adverse events with various different	2	interventions then represent things that should be
3	ketamine and ketamine adjunct combinations.	3	reported in a timely fashion and periodic peer
4	That's when we kind of started thinking	4	scrutiny.
5	about adverse events. I was part of Maala's	5	Then the final piece in green are the minor
6	consensus panel on the Quebec guidelines, and	6	outcomes and interventions, which we'll go over,
7	that's when my thinking about adverse events began	7	but this is really more for peer research or for
	to evolve, and from the threshold duration to the	8	certain specific clinical situations.
9	intervention type model.	9	This is the primary tool. You can see we
10	Maala presented her work to Joe Cravero and	10	have them broken into organ systems in the first
11	to John Berkenbosch in the Society for Pediatric	11	
12	Sedation Group. And we had further discussions,	12	then the sedation quality and patient experience,
13	some quite spirited, about this concept. And after	13	much like what was presented earlier today.
14	the thoughts yesterday and today, for me this is	14	We have the severity of the outcomes,
	kind of been a déjà vu all over again type of a	15	
		16	
17	So as a quick summary, the goal of this	17	related to the organ system of note. So we thought
18	tracking and reporting outcomes of procedural	18	we would go through these and get people's thoughts
19	sedation tool was to have a standardized approach,	19	about our current proposed approach.
20	something that was very practical, intended for	20	DR. GREEN: Of course it's worth nothing
21	everyday use. More of the surveillance, safety	21	that this is geared for clinical use, and what
22	surveillance, phase 4 type of trials, but also can	22	we're talking now about is research. So this can
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1	be used for greater sensitivity and specificity in	1	guide the discussion, but obviously there will be
2	phase 1 and 2 trials, interested in adverse events,	2	differences.
3	interventions performed, and then outcomes.	3	DR. ROBACK: So under airway and breathing,
4	Again, this should be for any tool that is	4	the point was made earlier that they're definitely
5	proposed, really needs to be for all patients in	5	distinctly different, and I think that's a very
6	all settings, as has been discussed.	6	important point. But the things that we felt, our
7	We talked about severity, and it was	7	group felt, were important, were patients that had
8	important to rank it. We have our sentinel events	8	problems apnea, respiratory depression,
	in red. Those are life-threatening. They'll	9	laryngospasm which resulted in them receiving
	warrant immediate reporting within sedation care	10	positive-pressure ventilation, unplanned reversal
	systems and the highest level of peer review.	11	of opioid or benzodiazepine, tracheal intubation,
	Intermediate outcomes and interventions were	12	neuromuscular blockade, and then of course,
	serious enough to endanger patients, if not	13	
	promptly managed, or reflect sub-optimal sedation	14	Yes, please?
15	quality or patient experience.	15	DR. RIKER: How do you view interventions
16	The thought about our discussions in the	16	like requiring oxygen post-procedure that you
17	last couple of days about the outcomes for sedation	17	didn't require before, or need for bronchodilator
18	and efficacy, I think it's really important that we	18	
	emphasize how do we measure sub-optimal sedation	19	DR. ROBACK: So those are obviously
	quality, and how do we really take into account the	20	important things to consider, and we've included
	very important considerations for patient	21	• •
22	experience.	22	more in-depth for research part of the tool.

Saf	fety Outcomes in Procedural Sedation		November 19, 201
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1	DR. WARD: What about the bronchodilators,	1	you chemically paralyze somebody, you're going to
2	intermediate or minor? I mean, sometimes somebody	2	be intubating them.
3	really gets a bad asthmatic episode. That seems to	3	DR. GAN: I'm just trying to see why there
4	be more intermediate kind of intervention.	4	were two separate
5	DR. ROBACK: So I think that that's a really	5	DR. ROBACK: I think that one of the
6	good point. And I believe we have it under minor,	6	criticisms were that we were a little too coarse
7	but if you're needing to do it aggressively, it's	7	with these, and we needed to have some greater
8	probably going to impact their length of stay, are	8	definition of what occurred. Tracheal intubation
9	they going to now require hospital admission, or	9	is a physical placing of the tube in the airway,
10	are they going to require intensive care. So it	10	and then there's also a pharmacologic response, and
11	would be captured under those, which were more of	11	we wanted to acknowledge both.
12	our intermediate outcomes.	12	DR. WARD: You didn't include any
13	Yes?	13	superglottic airways there, which I would
14	DR. PRATIK: Mark, where does airway	14	think in an anesthesiologist's hands, if I'm
15	obstruction, which requires oral airway, does that	15	having trouble, I'm going to put an LMA in a lot
16	come under minor? Where does that fit in?	16	sooner than I do tracheal intubation. So somewhere
17	DR. ROBACK: That's also in the research	17	in between positive-pressure ventilation and
18	tool. Under minor, we would have the visual or the	18	tracheal intubation, I'm going to put a
19	tactile stimulation or breathing cues. Here we	19	superglottic airway in.
20	have under respiratory then, airway positioning,	20	DR. ROBACK: Right. So we thought that
21	suctioning, capnography. Then here we have your	21	positive-pressure ventilation would be acknowledged
22	oral or nasal airway under intermediate.	22	in that, and then in the research tool have the
	Page 202		Page 204
1	DR. GAN: If you can, sorry, go back to that	1	LMA.
2	first slide, and I'm just trying to in my mind	2	DR. GREEN: Actually, LMA is in the footnote
3	distinguish between tracheal intubation and	3	under positive-pressure ventilation.
4	neuromuscular blockade. I assume you have both up	4	DR. ROBACK: Oh, that's right. No, that
5	there to signify that one may be different from the	5	makes sense.
6	other? What are you thinking about?	6	DR. WARD: I might put an LMA in without
7	DR. GREEN: Yes. Certainly, they overlap,	7	positive-pressure ventilation.
8	and I guess there would be a scenario in which the	8	DR. ROBACK: Rob, can you bring up
		1	

9 patient could be intubated without neuromuscular

10 blockade, or another scenario in which

11 neuromuscular blockade is done, but then the

12 intubation doesn't ultimately occur. So we just

13 wanted to cover both of those bases.

14 DR. GAN: So neuromuscular blockade was 15 happening without intubation? How could that be 16 possible?

17 (Crosstalk.)

18 DR. BERKENBOSCH: It breaks. They start 19 ventilating, because the succs will wear off fairly 20 quickly, and you may not end up progressing to 21 intubation. Probably I would bet that that's a 22 very unlikely scenario. But most of the time that

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21

22 they'll start breathing.

9 the -- okay, and then go over airway -- under

10 positive pressure to -- right there, the next one

So there it defines positive-pressure

DR. WARD: Like I said, I would most likely

DR. WARD: Because if I just have some

13 ventilation. It includes BiPAP, CPAP, and LMA.

15 put LMA in without positive-pressure ventilation.

18 airway obstruction, they're trying to breathe, I'm

DR. ROBACK: Right, right, no, I see.

DR. WARD: I'm just going to do an LMA, and

19 not going to do positive-pressure ventilation.

DR. ROBACK: Oh, without.

11 over, positive-pressure ventilation. Yes.

Jan	ety Outcomes in Frocedural Sedation		November 19, 2010
	Page 205		Page 207
1	DR. ROBACK: Yes.	1	of worry such that quality improvement systems
2	DR. WARD: Continue breathing.	2	should pay attention to it.
3	DR. GAN: Anything that would fit into that	3	DR. BHATT: I just had a question on your
4	middle column there, LMA, tracheal intubation,	4	next slide about the three sentinel outcomes. I
5	maybe common aspiration.	5	realize that you've got the outcomes and the
6	DR. KARAN: The same way I wouldn't consider	6	interventions there, and most of them are
7	CPAP or BiPAP necessary positive-pressure	7	interventions, but you do have a couple of outcomes
8	ventilation. It's just support. It'd be in a	8	like pulmonary aspiration and neurologic deficit.
9	different category, and maybe that would just be	9	So it looks to me like you guys were looking
10	kind of in the same area as an oral airway or a	10	for a home for those serious events, but it
11	nasal airway.	11	doesn't you're not looking it doesn't map
12	DR. GREEN: Yes. I mean this is not a final	12	well to a suspected etiology because it would be a
13	version, so we're wide open to suggestions.	13	suspected etiology for a grave intervention.
14	DR. CARLSON: So are you looking at	14	So is there a benefit?
15	intermediate as sort of precursor events,	15	DR. GREEN: Yeah. At first, we tried to
16	significant precursor events, and sentinel events	16	construct this entirely out of interventions.
17	as actually having patient harm? Is there any	17	DR. BHATT: Yes.
18	correlation in that, or is this harm issue, true	18	DR. GREEN: But yet, then as a failsafe
19	harm, or a precursor of where you prevent harm in	19	there's certain things that obviously are going to
20	this sort of taxonomy at all?	20	need scrutiny even. You can imagine a very rare
21	DR. ROBACK: Rob, can you go back to the	21	scenario where someone just didn't intervene, and
22	other one, please? I'll just bring it up again.	22	this is to make sure that all of those are
	Page 206		Page 208
_	Page 206	_	Page 208
1	So there's our formal definition. The		captured.
2	So there's our formal definition. The sentinel event is life-threatening, whereas the	2	captured. DR. GAN: In a way, they almost need to be,
2 3	So there's our formal definition. The sentinel event is life-threatening, whereas the intermediate one serious enough to endanger if not	2 3	captured. DR. GAN: In a way, they almost need to be, in my mind, separated because, for example, one
2 3 4	So there's our formal definition. The sentinel event is life-threatening, whereas the intermediate one serious enough to endanger if not promptly managed?	2 3 4	captured. DR. GAN: In a way, they almost need to be, in my mind, separated because, for example, one intervention following pulmonary aspiration is
2 3 4 5	So there's our formal definition. The sentinel event is life-threatening, whereas the intermediate one serious enough to endanger if not promptly managed? DR. CARLSON: So in harm taxonomy, you might	2 3 4 5	captured. DR. GAN: In a way, they almost need to be, in my mind, separated because, for example, one intervention following pulmonary aspiration is intubation.
2 3 4 5 6	So there's our formal definition. The sentinel event is life-threatening, whereas the intermediate one serious enough to endanger if not promptly managed? DR. CARLSON: So in harm taxonomy, you might have temporary harm, but it would be fleeting in	2 3 4 5 6	captured. DR. GAN: In a way, they almost need to be, in my mind, separated because, for example, one intervention following pulmonary aspiration is intubation. DR. GREEN: In that case, two boxes would be
2 3 4 5 6 7	So there's our formal definition. The sentinel event is life-threatening, whereas the intermediate one serious enough to endanger if not promptly managed? DR. CARLSON: So in harm taxonomy, you might have temporary harm, but it would be fleeting in the sense of intubation, you don't expect to be	2 3 4 5 6 7	captured. DR. GAN: In a way, they almost need to be, in my mind, separated because, for example, one intervention following pulmonary aspiration is intubation. DR. GREEN: In that case, two boxes would be checked there.
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	Page 209		Page 211
1	for the sedation event, and it's just part of what	1	DR. RIKER: How do you currently within this
	you do. It should take less than a minute.	2	tool look at apnea, a respiratory rate of 4, or a
3	DR. BERKENBOSCH: I actually kind of like		heart rate of 40, or a blood pressure of 72, when
4	the idea of keeping them both in the same column,		no intervention is performed versus if it is?
	even though one is an intervention, one is an event		Because one of the things we wrestled with is these
	or an occurrence, because I think you we can		isolated vital signs that may or may not be
	argue about which one should be in the intermediate		clinically significant, and you may have already
	versus sentinel.		solved the problem.
9	But the idea here is that you're capturing	9	DR. ROBACK: Well, that is the crux of it,
10	data that I think we all believe is probably really	10	isn't it? I mean you've hit the nail on the head.
11	important to capture in a way that is simple. And	11	Rob, if you could bring up the other one again, and
12	when you get to the point of entering it into the	12	if you could go over to apnea on the far right
13	database and analyzing it, you can tease out which	13	corner column.
14	were the events and which were the interventions	14	We really considered that in order for apnea
15	very easily, just by the way you code the	15	to be meaningful, it would have to be enough
16	electronic database. So I don't have a problem	16	respiratory depression and hesitation in
17	with that.	17	ventilatory effort that you needed to do something.
18	I think it's more I think we're getting	18	DR. WARD: And they're checking apnea
19	hung up in the definitions a little bit and almost	19	without having necessarily checked any of the other
20	getting a little bit lost in the forest for the	20	boxes, the way that's defined. You could just
21	trees kind of deal, where what we really want to do	21	DR. BHATT: That's respiratory depression.
22	is get a tool that's going to capture the events of	22	DR. WARD: For respiratory depression.
			Dece 040
	Page 210		
	Page 210		Page 212
	interest, and do it in a way that's simplistic,	1	DR. ROBACK: Well, but it does say, without
2	interest, and do it in a way that's simplistic, doable at the bedside so that if you are doing a	2	DR. ROBACK: Well, but it does say, without positive-pressure ventilation. So you'd have at
2 3	interest, and do it in a way that's simplistic, doable at the bedside so that if you are doing a clinical research project in multiple different	2 3	DR. ROBACK: Well, but it does say, without positive-pressure ventilation. So you'd have at least that to be considered apnea.
2 3 4	interest, and do it in a way that's simplistic, doable at the bedside so that if you are doing a clinical research project in multiple different areas, you've got the universally acceptable tool	2 3 4	DR. ROBACK: Well, but it does say, without positive-pressure ventilation. So you'd have at least that to be considered apnea. DR. WARD: Just without positive-pressure
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2 3 4 5 6	interest, and do it in a way that's simplistic, doable at the bedside so that if you are doing a clinical research project in multiple different areas, you've got the universally acceptable tool that is easily doable by the principal investigator, as well as the other sedation	2 3 4 5 6	DR. ROBACK: Well, but it does say, without positive-pressure ventilation. So you'd have at least that to be considered apnea. DR. WARD: Just without positive-pressure ventilation so DR. ROBACK: No. It responds to brief
2 3 4 5 6 7	interest, and do it in a way that's simplistic, doable at the bedside so that if you are doing a clinical research project in multiple different areas, you've got the universally acceptable tool that is easily doable by the principal investigator, as well as the other sedation providers who may not be as invested in the	2 3 4 5 6 7	DR. ROBACK: Well, but it does say, without positive-pressure ventilation. So you'd have at least that to be considered apnea. DR. WARD: Just without positive-pressure ventilation so DR. ROBACK: No. It responds to brief (Crosstalk.)
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1	this paradoxical response, do we know what I	1	they said, you know, I know there's a certain
	mean is that clear enough for people to say what?		incidence of it. This kid did. Or this
3	DR. ROBACK: So that's on the green one.		patient I'm a pediatrician and we always to talk
4	Rob, if you could go back to the		to kids. Sorry.
5	DR. GREEN: Yes, there are definitions that	5	DR. GREEN: The things in the etiology only
	you hover to see.		apply if there's something in the intermediate or
7	DR. ROBACK: Yes. The paradoxical response		sentinel column. So in this case, the paradoxical
8	is on the research tool, right?		response would only apply if there were patient
9	DR. GREEN: Yeah.		family dissatisfied or hospitalization or
10	DR. ROBACK: Go down. There you go. So if		escalation of care. If it were less than that, it
11	you could hover over "paradoxical response." Right	11	wouldn't be tracked on this.
	there. Thanks, Steve. So that's how we defined	12	DR. ROBACK: So you would expect that if
13	it, unanticipated restlessness or agitation in	13	they had a paradoxical response that someone would
14	response to sedatives.	14	be dissatisfied and that sub-optimal sedation
15	DR. GREEN: So if this were embedded in your	15	quality would be realized.
16	electronic medical record, you could quickly hover	16	DR. GREEN: If it were of sufficient
17	over and reference definitions.	17	magnitude. Mike, you've had your hand up the
18	DR. GAN: How is that different from the one	18	longest.
19	below?	19	DR. IRWIN: Go back to the airway a bit,
20	DR. ROBACK: Unpleasant recovery, agitation?	20	because maybe you should have upper airway
	Well this is in response to the in a sedative	21	obstruction should be in there, rather than
22	drug, what you expect to occur as the drug was	22	even maybe it's much more common, say, than
	Page 214		Page 216
	Page 214		Page 216
	given, whereas the unpleasant recovery action is		laryngospasm. And simple maneuvers such as
2	given, whereas the unpleasant recovery action is during recovery.	2	laryngospasm. And simple maneuvers such as obstruction
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1	lift or something like that, it wouldn't be	1	form not just for kids, right? So I think airway	
	considered an intermediate outcome.		obstruction is a much more general term than	
3	DR. IRWIN: But you wouldn't be able to put		laryngospasm would be.	
4	it in the suspected etiology. There's nothing to	4	DR. ROBACK: So I think our committee felt	
	take for that.	5	like if it was partial airway obstruction, that it	
6	DR. ROBACK: So you're proposing that we put		should be managed by one of these interventions	
7	partial airway obstruction here.		here. Although you didn't mention using the LMA	
8			without positive pressure as one way of doing it	
9	the commonest airway incident whenever you	9	that we hadn't considered.	
10	DR. ROBACK: But I guess we put it in the	10	DR. KARAN: I wonder also differentiating	
11	secondary tool because it's one of those things	11	between invasive and non-invasive ventilation, in	
	that falls into the category that this is just good		which case LMA and tracheal intubation would be in	
	sedation care. You gave the guy a jaw thrust. I	13	one category, and applying a mask with just some	
14	mean, that's what we do. And we're trying to		CPAP or BiPAP would be in another category.	
	really think about outcomes and interventions that	15	If I'm using an LMA for sedation, and it's	
	are out of the ordinary or are more meaningful. We	16	unplanned, I would think that's a little bit more	
	would capture it's still important to identify		severe not in the ED but for sedation than	
18	partial airway obstruction and the jaw thrust you	18	just applying a mask and apply some BiPAP or CPAP	
19	provided, but that would be in the secondary tool.		for it.	
20	DR. CARLSON: As suspected, etiology, it's	20	DR. BERKENBOSCH: So that begs the question	
21	not as I mean, it does seem in the sense that	21	to me, and maybe a show of hands, how many people	
22	apnea and obstruction sort of fit together for	22	would call placing an LMA invasive ventilation?	
	Page 218		Page 220	
1	Page 218 better checking. We did positive-pressure	1	Page 220 (Show of hands.)	
	-	1 2		
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2 3	better checking. We did positive-pressure ventilation, check mark, obstruction. Or is that	2	(Show of hands.) DR. BERKENBOSCH: How many would not?	
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1	clinical trials question, because I think you've	1	recurrent apnea that were clinically important, at
2	put a lot of work in a great QI tool. I	2	some point you would give a reversal agent if
3	particularly like that it's connected to MedDRA,	3	applicable, or you would convert it to tracheal
4	because I understand all these terminologies map to	4	intubation.
5	MedDRA terminology, which is important for the FDA.	5	I think just one concept from a research
6	This is a question for the group whether	6	angle, obviously sentinel outcomes are going to be
7	it's a show of hands or whatever. How useful is	7	rare enough that they can never be your primary
8	this tool if you were and I'm assuming we're	8	outcome. But what you could say say it was a
9	talking about a late phase 3 or phase 4 study if	9	trial of propofol versus another propofol-like drug
10	you were just putting a late phase 3/phase 4 study	10	with a large trial, your main safety outcome could
11	together, and you'd have to have some sort of	11	these airway breathing things. Either a composite
12	sedation score, some efficacy score, maybe OAAS or	12	endpoint of positive-pressure ventilation, reversal
13	some of the other scores we've had, and the only	13	agent, tracheal intubation, neuromuscular blockade,
14	other data you collected was this TROOPS data,	14	or pulmonary aspiration, comparing that between the
15	would that be adequate for a late phase 3/phase 4	15	frequency of those.
16	multi-institutional because I think one of the	16	DR. ROBACK: Frank?
17	advantages of this is the ability to collect the	17	DR. DEXTER: Yes, I'm struggling with that,
18	data online with a website in a multi-	18	because let's suppose that different people are
19	institutional.	19	going to intervene at a different level of
20	Is this a useful tool for that?	20	saturation. Then unless it is specified in the
21	DR. DAHAN: Well, what I wonder is suppose	21	study what hypotension you're going to treat and
22	this happens once during the case, and you tick it	22	how you're going to treat it, what level of low
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1	off? But now suppose it happens recurrently? How	1	saturation you're going to treat, or
2	do you cope with that, when you're doing your so	2	hypoventilation you're going to treat, I don't
3	you changed your for instance, you change your	3	follow necessarily that that would be sufficient.
4	propofol dosing, but still the patient has an	4	As long as it's designated, sure, and prespecified.
5	apneic event. You need to fill in several forms	5	Then you have a randomized trial because now it's
6	now.	6	between the groups.
7	DR. ROBACK: Well, we do have the at the	7	Similarly, in terms of being sufficient, I
8	bottom there's the "other," and I guess we could	8	think that the continuous measure of vital signs is
9	specifically note that if you have recurrence of	9	a logical endpoint in addition to the intervention,
10	any of these adverse events, you could record it in	10	so you can understand why did the clinician do the
11	the "other" category. It's an important point,	11	interventions that they did. What information data
12	because clearly if you're doing bag-valve mask for	12	did they have?
13	5 seconds or 10 seconds or 30 seconds, that's one	13	DR. GREEN: Yes, again this is intended to
14	thing. But if you're doing it repeatedly over the	14	be clinically oriented for what people are doing in
1		1	

13 5 sec 14 thing. But if you're doing it repeatedly over the 15 course of 10 minutes, that's a much different

16 encounter. 17 DR. DAHAN: For clinical purposes, this is 18 great, but for research purposes, it's very

19 restricted in the sense that things might happen,

20 things might change, especially patients that do

21 extremely poorly.

22 DR. GREEN: Yes, I think if there were

22 regular [indiscernible] practice, if I were to do, A Matter of Record

20 specific number.

15 actual practice. For research, it would be great

16 to have an endpoint like this, but underneath it to 17 have all that data, to know when they intervene. I

18 don't think you're going to get people to agree on

19 that they're going to give positive pressure at any

DR. DEXTER: So I would say that even in

Min-U-Script®

21

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1	for example, is have a large amount of anesthesia	1	that you can I think things balance out in the
	information management system data like we have, we		end. People act more uniformly for these
3	see these data all the time, and it isn't possible,	3	significant things.
4	because we can do study after study we've done	4	But one comment I wanted to make, Steve,
5	showing that people will treat based on different	5	about what you're saying about making a composite
6	vital signs. Some people treat and others will	6	outcome. It will be different in different
7	treat, and we don't know that that's better or	7	populations, but if you were to power an ED study
8	worse; it's different.	8	based on those amount of outcomes, you will need a
9	If we were to have a similar scale for	9	million children because we don't the frequency
10	general anesthesia or something like that, we would	10	of these events is very, very [indiscernible].
11	still say what does that mean necessarily? You	11	So I would say that, I think in a healthy
12	combine it with the vital signs. Then you can	12	population of children that you're sedating, you
13	understand, at least describe quantitatively what	13	are going to need the other part of your tool as
14	the drug is doing.	14	your primary.
15	DR. GREEN: But yet it's more than vital	15	DR. GREEN: Yes, very true. When I said
16	signs that determine when you're going to	16	that statement, I was thinking of an adult propofol
17	intervene. It's looking at the patient and	17	style thing. But for ketamine and for other
18	multiple number of factors. I think Maala was	18	things, that wouldn't work.
19	first.	19	Jenifer, you've had your hand up.
20	DR. BHATT: I just wanted to comment about	20	DR. LIGHTDALE: I'm going to use the dreaded
	that. I think that it's true, people will		aviation analogy. I'm actually coming around to
22	intervene for different things. But I think if	22	the concept that maybe it's okay to go with the
	Page 226		Page 228
1	Page 226 you're looking at intermediate or sentinel	1	Page 228 fact that this is going to be a perception of
	-		-
2	you're looking at intermediate or sentinel	2	fact that this is going to be a perception of
2	you're looking at intermediate or sentinel outcomes, I think that people will be more uniform	2 3	fact that this is going to be a perception of whether or not an adverse event happened. That's
2 3 4 5	you're looking at intermediate or sentinel outcomes, I think that people will be more uniform in terms of when they intervene. We had six different centers with probably over 200 providers providing us not 200	2 3 4	fact that this is going to be a perception of whether or not an adverse event happened. That's okay. You know, we should get that. If people think something bad happened, just why do they think it happened?
2 3 4 5 6	you're looking at intermediate or sentinel outcomes, I think that people will be more uniform in terms of when they intervene. We had six different centers with probably over 200 providers providing us not 200 providers. That's probably an exaggeration. A lot	2 3 4	fact that this is going to be a perception of whether or not an adverse event happened. That's okay. You know, we should get that. If people think something bad happened, just why do they
2 3 4 5 6 7	you're looking at intermediate or sentinel outcomes, I think that people will be more uniform in terms of when they intervene. We had six different centers with probably over 200 providers providing us not 200 providers. That's probably an exaggeration. A lot of providers. It made no sense just providing	2 3 4 5 6 7	fact that this is going to be a perception of whether or not an adverse event happened. That's okay. You know, we should get that. If people think something bad happened, just why do they think it happened? As long as we have a black box, those actually are collecting [indiscernible]. I think
2 3 4 5 6 7 8	you're looking at intermediate or sentinel outcomes, I think that people will be more uniform in terms of when they intervene. We had six different centers with probably over 200 providers providing us not 200 providers. That's probably an exaggeration. A lot of providers. It made no sense just providing sedation and still our rate of serious	2 3 4 5 6 7 8	fact that this is going to be a perception of whether or not an adverse event happened. That's okay. You know, we should get that. If people think something bad happened, just why do they think it happened? As long as we have a black box, those actually are collecting [indiscernible]. I think the clinical trials have to collect that data, and
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	Page 229		Page 231
1	us as we were preparing this. And you know, the	1	maybe you could go ahead and show that. So we got
	World SIVA tool has all that information in the		the minor outcome/intervention. So the tool
	beginning, and that would have to continue to be,		includes that.
	because like you said, how sick the patient is,	4	Is this now a sufficient tool? Because
	their age, the procedure, what drugs you're using,	_	we're talking about writing this paper, and I'm
	all those things matter.	6	going to make a statement here that we should use
7	DR. WARD: So I guess I'll get back to the		MedDRA. I think that's kind of mandated. But then
	question that I kind of want to get a concept		I'm going to say that there's this thing out there
	from I think it's a great QI tool that you've		that is very useful because it's online, multi-
	got started. It has very attractive features on		institutional. And again, I'm going to say
	being online, Web-based, if I'm designing a		something about it's a great QI tool, and it is or
	multicenter clinical trial. Clearly, as you just		is not a sufficient tool for clinical trials.
	pointed out, I've got to get some demographic data	13	DR. SESSLER: Well, I think many of us had
	collected for the clinical trial that would have to	14	said that you probably should have continuous
15	get that this doesn't go with.	15	monitoring for key things. You should have some
16	But given that I get the demographic data,	16	sort of black box. But as usual, it's context
17	but I probably don't have the black box the data	17	dependent. There is a role for pragmatic trials.
18	if I'm doing a multicenter clinical trial that's	18	Pragmatic trials are usually extremely large but
19	altogether different.	19	simple, and you make up for the simplicity with
20	Would it be acceptable for this to be the	20	very, very large numbers.
21	sufficient measure of outcomes in a multicenter,	21	But in a typical clinical trial, I don't see
22	late phase clinical trial? Because it's got some	22	much excuse for not continuously recording key
	Dare 200		Page 232
	Page 230		
	attractive features, but it was designed as a QI	1	things, key measures of at least ventilation.
2	attractive features, but it was designed as a QI database, not a clinical trial.	2	things, key measures of at least ventilation. DR. CARLSON: I think as you write this up,
2 3	attractive features, but it was designed as a QI database, not a clinical trial. DR. GREEN: I think it covers major	2 3	things, key measures of at least ventilation. DR. CARLSON: I think as you write this up, we have a pragmatic tool that may have some
2 3 4	attractive features, but it was designed as a QI database, not a clinical trial. DR. GREEN: I think it covers major outcomes, but as Maala pointed out, you couldn't	2 3 4	things, key measures of at least ventilation. DR. CARLSON: I think as you write this up, we have a pragmatic tool that may have some weaknesses, but it can be tweaked to fit a need.
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1	DR. DEXTER: I'll try one more time. I	1	procedures with the drug, to some extent.
2	don't understand how it's sufficient. If you were	2	DR. BHATT: So we can adjust for that in the
	to say that you specified in a study how people are	3	analysis.
	going to use the vital sign data and respond, no	4	
	problem. I totally understand that not necessarily	5	the thing. You can adjust it for the analysis,
	having all the vital sign data for all the	6	
7	thousands of patients.	7	
8	But I know that as a statistically oriented	8	information to know what the person in the
و	reviewer, if I were to have a study where they say	9	operating room, or the procedural location was
10	essentially, we have a multicenter and there are	10	responding to.
11	two particular drugs and one drug has more airway	11	DR. ROBACK: But is it practical or possible
12	interventions, without knowing how people are using	12	to say, all right, if the patient has apnea for
13	the drugs or what it is that they're seeing, and	13	3 seconds, or their pulse ox goes down to 78,
	whether or not it's homogeneous you've got to		that's when you can do positive pressure. I mean,
	show that there's homogeneity of treatment among	15	clinicians are going to do what they're going to
	the centers.	16	do. And I guess that's the challenge. And finding
17	If you don't know whether or not it's due to	17	a way to in instances where you have the ability
18	the drug or whether it's due to different practices		to capture all of the continuous physiologic data,
	among the centers, I don't understand what would	19	and then coupling that to the interventions that
20	you do at the end of your study if have	20	were performed
21	heterogeneity among the centers? I think that in	21	DR. DEXTER: If that's what clinicians are
22	that circumstance, you'd be left with a failed	22	going to do, that's why you have continuous sensor
	Page 234		Page 236
1	trial.	1	data to study how the clinicians respond in the
2	But of course there's going to be	2	real world to the drug, so to speak.
3	heterogeneity among centers, potentially if it's a	3	DR. RIKER: So this is designed to get rid
4	new drug. If it's an old, established drug, I can	4	of those insignificant events that nobody cares
5	understand why it would be homogeneous. But like	5	about, and to focus on the clinically significant
6	when propofol first came out, I know that as a	6	interventions that everyone would agree are
7	resident, people would say, give more, give more to	7	significant. And I think what everybody's saying
8	stop patients from moving like say. That's my	8	here is by itself, this isn't enough for what we're
9	concern in terms of it being a new drug.	9	talking about, and we need both.
10	DR. WARD: If the demographic data and the	10	We need all of this you know, how often
11	use data dose, things like that were	11	was there an apnea of X-duration, maybe with or
12	collected in addition this is the outcome	12	without any intervention, or an airway obstruction
	tool you've clearly got to have a demographic,	13	and you did a jaw thrust and you're done?
	site-specific stratification, demographic data,	14	
15	dose data, in addition to this.	15	included, but they really want this as well, so
16	DR. BHATT: So what you're trying to get at	16	
	is that the different techniques, sedation	17	
18	techniques that are different, at each of these	18	
19	5	19	5
20	DR. DEXTER: They're going to be entirely	20	6
	different how people are going to see certain		need both. This is a perfect quality instrument.
22	airway they're going to be doing different	22	But if you're doing research, you have a higher bar

Dai	ety outcomes in Frocedural Sedation		
	Page 237		Page 239
1	to meet. Research has to be done in a way that you	1	DR. SESSLER: And that's exactly what I mean
2	would not do clinical practice, and in a way that	2	by sensitivity, is that if you're looking for
3	you don't evaluate quality. You really need to	3	anything that's relatively rare, you need a very
4	measure the things that you think matter.	4	large sample size. If you're looking for things
5	I'm also worried about sensitivity, because	5	that are common, you don't.
6	I think when you presented this yesterday, you said	6	If you have 10 times as many desaturations
7	that adverse events were actually quite rare. You	7	as interventions, you can detect potentially
8	could possibly end up with false negatives if you	8	important differences between two different
9	don't have a very large trial here, in a way that	9	treatments with continuous monitoring in a way that
10	you would not with continuous data, where you would	10	you never would just by tracking clinician
11	see things.	11	interventions. Recognizing that clinical
12	DR. GREEN: Yes. I don't think any here is	12	interventions are important; they're measuring
13	disagreeing with the optimal nature of having this	13	something different. I'm absolutely not saying
14	continuous data if you have it available. The	14	ignore that. I'm saying you need to do both.
15	question is large trials	15	DR. GAN: So you expect people to know what
16	DR. SESSLER: Well, I don't think if you	16	2 standard deviation from normal it is?
17	have it available is an excuse, frankly. I	17	DR. ROBACK: Well, we put this because
18	appreciate that you don't often have electronic	18	that's the American Heart definition for children.
19	records set up in the places where you're doing	19	Again, what we care about is did someone think the
20	sedation. But if you're doing research, you have a	20	blood pressure was low enough for them to receive
21	different bar to meet. It's easy enough now to	21	bolus IV, isotonic crystallite? Did they think
22	plug a USB disk into almost anything, download it,	22	that the heart rate was low enough that they
	Page 238		Page 240
1	hook up a computer. This is not technically	1	started chest compressions?
2	complicated. So whether or not it's available, if	2	I mean those are the things and again,
3	you're doing research, you have to do high-quality	3	we're not going to get the continuous data, the
4	work, and that includes continuous monitoring.	4	drop where there's no intervention performed. But
5	DR. GAN: How do you define this blood	5	I guess we assume that if their heart rate went
6	pressure change?	6	down and nobody did anything, and they woke up and
7	DR. GREEN: Can you bring up the other one	7	they were fine, that it didn't much matter. But it
8	please, Rob? And then go under hypertension.	8	does matter if you're comparing two drugs in a
9	DR. WARD: And then while he's doing that,	9	•
10	when you're doing continuous when you say	10	Yes, Maala?
1			
	continuous morning, that's in order to connect to	11	DR. BHATT: Can I ask you a question just on
	continuous morning, that's in order to connect to the intervention, correct, Dan?	11 12	DR. BHATT: Can I ask you a question just on the continuous data monitoring? If you collect all
12 13	continuous morning, that's in order to connect to the intervention, correct, Dan? So if you're doing continuous monitoring,	11 12 13	DR. BHATT: Can I ask you a question just on the continuous data monitoring? If you collect all this information and you're looking at this as
12 13 14	continuous morning, that's in order to connect to the intervention, correct, Dan? So if you're doing continuous monitoring, you can back and say, okay, that was just	11 12 13 14	DR. BHATT: Can I ask you a question just on the continuous data monitoring? If you collect all this information and you're looking at this as separate from the patient, how do you separate new
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1	written. But as part of clinical trials, when I	1	or electrical conversion. It's going to be a rare
2	say experience doing that, I haven't found	2	event, but I think it's probably worth putting into
3	that at least pharmaceutical companies have	3	the tool.
4	wanted us to filter, because one of the whole	4	DR. ROBACK: Intermediate or sentinel?
5	challenges has been is whether or not that rare	5	DR. BERKENBOSCH: That would probably be
	aberrant event, it was actually an artifact or not	6	sentinel. You could argue SBT, that's
7	an artifact.	7	hemodynamically stable and gets a dose, but then it
8	My experience has been that oftentimes the		might not be sentinel. But I also think it's not
9	clinicians cannot necessarily determine whether or		uncommon for those of us who use dexmedetomidine a
	not it was an artifact or not. Sometimes it's		lot to give a little bit of atropine or
	completely obvious in terms of you just change the		glycopyrrolate for bradycardia, and I don't see
	transducer and you can make a note or something		that as something that's being captured. But yet,
	like that. But there have been several situations		that's an intervention that's probably worth
	where people thought it was an artifact, and it		capturing. So medical intervention for
	wasn't an artifact, with new devices.		bradycardia. We've got the fluids for hypotension,
16	DR. ROBACK: Jenifer?		but
17	DR. LIGHTDALE: I'm also going to say you	17	(a)
	still need the human person to say whether or not	18	
	something went wrong. And I'm actually going to	19	
	come back to Joe's comment yesterday about IV		want to I'm not sure a lot of people would think
	infiltration, that he has put that as something		of atropine or glycopyrrolate as a vasoactive drug.
	that he's noticed everybody complains about it.	21	
22	that he's holiced everybody complains about it.	22	
	Page 242		Page 244
1	Page 242 The truth is we wouldn't know if there was	1	Page 244 thing? I thought it caused hypertension. I don't
			, i i i i i i i i i i i i i i i i i i i
2	The truth is we wouldn't know if there was		thing? I thought it caused hypertension. I don't use the drug myself.
2 3	The truth is we wouldn't know if there was constantly IV infiltrations unless we let people	2	thing? I thought it caused hypertension. I don't use the drug myself. DR. BERKENBOSCH: We give it occasionally.
2 3 4	The truth is we wouldn't know if there was constantly IV infiltrations unless we let people write that down, like drug X that keeps sclerosing	2 3	thing? I thought it caused hypertension. I don't use the drug myself. DR. BERKENBOSCH: We give it occasionally. DR. GREEN: Is it necessary?
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	Page 245		Page 247
1	So before you kind of leave this, is there	1	monitored.
	any other Susan?	2	DR. SESSLER: Yes. It may not be available
3	DR. KARAN: I have a practical question.	3	to clinicians. I believe we often blind our
4	Again, understanding the importance of the	4	monitoring.
5	continuous monitoring, I'm just wondering, let's	5	DR. KOCHMAN: This is not an unusual
6	just say we're evaluating a drug that we're going	6	circumstance. I was on a DSMB, and I can't get
7	to be using for mild sedation, and it's not	7	into the details of it, but that's the way that
8	clinically relevant to do continuous monitoring,	8	this DSMB for an anesthesia device worked. We had
9	then would you propose for a study like this that	9	all of the data collected. The clinicians made
10	you would do it in kind of a blind way to capture	10	whatever response they made, blind to the data, and
11	it, but allow the clinical course to happen so	11	then we adjunctively went back and crossed the
12	you're actually capturing what an interventionist	12	events with the data. Then we also looked at the
13	or what a proceduralist would be doing when you're	13	data to see if there were corresponding events.
14	giving the sedation drug?	14	So that's not unusual. I think it's a
15	Would it bias the study? If you're doing	15	reasonable model.
	continuous monitoring, it's now right now a	16	DR. SESSLER: We often do our studies that
	standard of care to do continuous monitoring for a		way.
	mild or moderate sedative.	18	DR. CARLSON: I mean, I agree with all this
19	DR. SESSLER: Okay. Continuous monitoring		and this is the best way of doing it, we probably
	is absolutely not the standard of care, and I'm not		should go that way. But this is a huge
	proposing it as a standard of care. I am proposing		infrastructure cost of how we get this. So you're
22	it for most studies, because we're doing] we're	22	talking about isolate OR suites where you're doing
	Page 246		Page 248
1	Page 246 doing mild to	1	
1	-		Page 248 this, where the data is available, that infrastructure is there
2	doing mild to		this, where the data is available, that
2	doing mild to DR. KARAN: Has it been continuous	2	this, where the data is available, that infrastructure is there
2 3 4	doing mild to DR. KARAN: Has it been continuous collecting versus continuous monitoring?	2 3 4	this, where the data is available, that infrastructure is there DR. SESSLER: No, no
2 3 4 5	doing mild to DR. KARAN: Has it been continuous collecting versus continuous monitoring? DR. DEXTER: I would like to see that before	2 3 4 5	this, where the data is available, that infrastructure is there DR. SESSLER: No, no DR. CARLSON: but we're talking about
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1	continuous, what do you actually mean by	1	But if you're just capturing data, even if
2	continuous? It could mean that you set a blood	2	it is dichotomous, it will be a step up beyond just
3	pressure every 2 minutes or 3 minutes, right, in	3	having the tool, but still not getting to point
4	the standard way, and then you collect all these	4	where we are in the state where we have the
5	data. You may not [indiscernible] versus, in	5	continuous thing.
6	extreme, putting a line [indiscernible] to do a	6	So in large RCTs with many centers, it's
7	continuous.	7	probably going to be difficult at investigator-
8	DR. WARD: Let's define data, whether it's	8	initiated study to have
9	continuous. This is a tool that doesn't have any	9	DR. WARD: No, I understand what you're
10	associated data with it. I don't have a vital	10	saying, but for what we have up there, vital sign
11	signs record with it.	11	abnormalities are defined as changes greater than
12	DR. GAN: We need to define what continuous	12	25 percent of baseline and 2 standard deviations.
13	means.	13	I think as a PI in that study, unless I had that
14	DR. WARD: You can have a whole discussion	14	data to look at, I wouldn't trust that out in the
15	on what continuous means. Right now, I kind of	15	hundreds of places that there was enough
16	want to focus on this is a tool by itself,	16	consistency of the investigator to have checked
17	without any with the demographic data. You've	17	that hypotension, exactly having met that vital
18	clearly got to have the patient level demographic	18	signs criteria.
19	data with it. But you don't have any measurements	19	DR. PRATIK: But the thresholds can be made
20	of the data, continuous or discontinuous, or	20	easier when you're not trying to call them adverse
21	whatever the sample rate happens to be, which these	21	events. So if you just say anything less than 90
22	clinical interventions outcomes are based on.	22	systolic, I want you to report. Okay, and you're
	Page 250		Page 252
1	So I'd like to get a vote. Would this be an	1	not calling them adverse events. You're just
2	appropriate sufficient tool in that situation for a		saying two groups
	phase 3 trial?	3	DR. WARD: I'm using this tool.
4	DR. RIKER: Without continuous data.	4	DR. PRATIK: Yes.
5	DR. WARD: Without the physiological	5	DR. WARD: I'm not redesigning the tool.
6	data not talking about the sample rate. Maybe	6	I'm using this. If we redesign the tool, then
	it's continuous, maybe it's once every minute,		we're back to collecting data for a clinical trial.
	maybe once every five minutes. But this is a tool		I don't see anybody saying that this is a
	that by itself doesn't have any physiological data		sufficient tool
	connected to it. It only has it's an	10	DR. PRATIK: In its present form.
	intervention outcome collection tool.	11	DR. WARD: in its present form for a
	Great for QI.	12	phase 3 trial. Phase 4, postmarketing survey, now
13	DR. SESSLER: This is like measuring the		you've got the drug is in use, you want to do
14	frequency of car crashes with two different cars		some postmarketing. You put out there, use this
	without recording the speed.		tool and we're going to put it into a central
16	DR. WARD: It is. That's not a bad	16	
17	DR. PRATIK: Middle ground, if you cannot		tool for that?
	get to this discussion about continuous, having	18	DR. RIKER: Phase 4?
	thresholds over here without calling them adverse	19	DR. WARD: Phase 4. For phase 4.
	events, you get caught up with thresholds because	20	(Hands raised.)
	you start calling them whether they're adverse of	21	DR. WARD: Possibly? So a little bit
	not.		possibly sufficient.
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1	Maala?	1	To use the car wreck analogy, well, I don't
2	DR. DAHAN: Still too static in my opinion.		know the speed, but I know there's a scratch on the
3	DR. WARD: So no consensus that this would	3	
	necessarily be a monitoring phase 4, postmarketing		think that's a big deal, versus the one where it's
	survey.	5	
6	DR. DEXTER: With hypotension listed as	6	to that, the physiologic numbers, that's a
	hypotension or relative to an unspecified standard,		different level of scrutiny, and is that required
	which you can't know for different patients,		for a phase 4 trial?
	then because knowing a baseline depends on the	9	DR. WARD: Well, that's where the
	frequency of monitoring by definition. Without		question I mean, I think we've already decided
	specifying the frequency of monitoring, then it		it is required for a phase 3 trial. But what I'm
	would not be interpretable in terms of the		sort of hearing that there's not much enthusiasm
	hypotension.		for this as a tool for a phase 4.
14	It might be good for screening purposes, for	14	Yes?
	quality purposes. But as part of a phase 4 trial,	15	DR. ROCA: I just want to make a quick
	it wouldn't be interpretable at the end. If you		comment. As you consider whether it would be
	were to say, for example, a mean blood pressure of		useful for phase 4, keep in mind that sometimes a
	65 or something like that, when monitored every	18	phase 4, depending on what you're looking at, and
	2 minutes, then I think that that would be quite	19	depending on how circumscribed the phase 3 trials
	reasonable in that circumstance.		were that garnered approval, phase 4 may actually
20	DR. ROBACK: Maala?		may be opening to a whole completely new patient
22	DR. BHATT: So I just had a question for		population, where you really don't have information
		22	
	Page 254		Page 256
1	-	1	
	Mark and Steve I guess, given the compensation,		in the phase 3 trials that would apply to those.
2	Mark and Steve I guess, given the compensation, people seem uncomfortable with the brevity of this	2	in the phase 3 trials that would apply to those. So you may actually have to consider a
2 3	Mark and Steve I guess, given the compensation, people seem uncomfortable with the brevity of this tool, which is I think what makes it powerful for a	2 3	in the phase 3 trials that would apply to those. So you may actually have to consider a phase 4 trial to be needing as much data as the
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Sa	ery Outcomes in Frocedural Sedation	10000	, , , ,
	Page 257		Page 259
1	there that sort of says how many corners have had	1 too literally. But if the statement in some form	ı
2	an automobile accident? We don't know much about	2 appeared in the paper, I want to know whether	er it
3	it, but we know that street corner has an issue for	3 would be a yes or a no. You would like that	
4	it.	4 statement to be in the paper, or you would no	t like
5	So I'm not saying it's not useful data in a	5 that statement to be in the paper. Again, not	
6	clinical trial, but designing a clinical trial in	6 those exact words.	
7	which this is sufficient as the primary outcome	7 DR. DEXTER: When it says, "for many	
8	measure, doesn't seem like it's useful for that.	8 outcomes for severity and length of time data	
9	DR. GREEN: Yes. You know, I think in	9 should be collected," the thing would be, as D	an
10	clinical practice and in research, there is an	Lo has talked about, it's really sort of an integral.	
11	incredible diversity of these outcomes and what I	L1 In other words, because when you say severi	
	would consider an unacceptable diversity that	L2 problem is that if you use the let's take puls	-
	prevents us from doing any meaningful comparisons.	L3 oximetry. If you use the nadir measurement,	
	The whole reason why we took on this project in the	L4 very subject to artifact.	
	first place is to try and come up with something	DR. WARD: So you're down on this one	here.
	that was better than total chaos.	L6 DR. DEXTER: Yes.	
17	DR. WARD: Oh, absolutely.	DR. WARD: We're going to go through the	nem in
18	DR. GREEN: So admittedly, not everybody is	L8 sequence, but that's okay. We'll take it out of	
19	going to agree on something like that. So this is	L9 sequence. We'll start with this statement.	
	just a humble attempt.	DR. DEXTER: I think that it isn't the	
21	DR. WARD: And this may be a platform,	severity, because inherently, that's the nadir	
22	because it is going to be a Web-based platform with	22 which is very poor statistical properties, and it	's
	Page 258		Page 260
1		1 highly sensitive to the sampling rate, and that	-
	Page 258 a database behind it, it may be a platform that will have TROOP 2 that will be designed as a	 highly sensitive to the sampling rate, and that will differ among pulse oximeters, for example 	-
2	a database behind it, it may be a platform that		-
2 3	a database behind it, it may be a platform that will have TROOP 2 that will be designed as a	2 will differ among pulse oximeters, for example	-
2 3	a database behind it, it may be a platform that will have TROOP 2 that will be designed as a clinical trial platform, because I think it has a	2 will differ among pulse oximeters, for example3 based upon the averaging.	2,
2 3 4 5	a database behind it, it may be a platform that will have TROOP 2 that will be designed as a clinical trial platform, because I think it has a lot of advantages for that.	 2 will differ among pulse oximeters, for example 3 based upon the averaging. 4 In the same way, the length of time data 	e, tors,
2 3 4 5 6	a database behind it, it may be a platform that will have TROOP 2 that will be designed as a clinical trial platform, because I think it has a lot of advantages for that. DR. GAN: Let's say, for example, if you	 2 will differ among pulse oximeters, for example 3 based upon the averaging. 4 In the same way, the length of time data 5 will also differ markedly among different monit 	e, tors, s, if you
2 3 4 5 6 7	a database behind it, it may be a platform that will have TROOP 2 that will be designed as a clinical trial platform, because I think it has a lot of advantages for that. DR. GAN: Let's say, for example, if you want to recommend this, let's say you recommend for	 2 will differ among pulse oximeters, for example 3 based upon the averaging. 4 In the same way, the length of time data 5 will also differ markedly among different moni 6 even connected to the same patient, whereas 	e, tors, s, if you , a
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1	don't actually say it.	1	Breath-to-breath data, for example, is by
2	DR. WARD: I don't actually say that, and	2	definition discontinuous because it's only measured
3	that could be an oversight	3	on a breath-to-breath-to-breath.
4	AUDIENCE MEMBER: You won't forget.	4	DR. DEXTER: From the perspective of a
5	DR. WARD: Yes, that may be an oversight. I	5	early let's say phase 1/3 trials, something like
6	wrote it down or it may be intentional. I'll have	6	that, 5-minute increments is a very long period of
7	to decide which it's going to be. You have to	7	time, I mean, if you're giving the bolus of a drug
8	define continuous though, Dan.	8	or something like that. So initially, you're going
9	DR. GAN: How do you even define it?	9	to do it more frequently once you've learned the
10	DR. WARD: Yes, that's why it isn't there.	10	nature of responsiveness and the timing.
11	Defining continuous is a difficult situation.	11	DR. WARD: So all those caveats would be
12	DR. DEXTER: Defining continuous, I don't	12	incorporated as I write the paper. So take the
13	perceive it as being particularly challenging	13	statement as a so let's start at the beginning.
14	because it depends on the time course of	14	I want to hear a vote here.
15	physiological change when you're talking about	15	The scope of our recommendations include
16	measuring something in nanoseconds or longer	16	phase 1 to 4 clinical trials? Yes?
17	periods of time. So you look at the time course of	17	(Show of hands.)
18	events, and sample at a rate that's comparable to	18	DR. WARD: Anybody say no?
19	what is going on.	19	DR. SESSLER: What are the recommendations?
20	DR. WARD: But it is sampled, following	20	DR. WARD: We haven't gotten there yet.
21	continuous	21	(Laughter.)
22	DR. DEXTER: Concerning that pulse oximeter,	22	DR. WARD: But we are excluding phase 1
	Page 262		Page 264
1	what you're getting is averaged over a certain		
-		1	trials
2			trials. DR. SESSLER: Shouldn't that be the last
	number of seconds anyway, and so forth. There's	2	DR. SESSLER: Shouldn't that be the last
3	number of seconds anyway, and so forth. There's never a reason to be sampling at a rate that	2	DR. SESSLER: Shouldn't that be the last question?
3 4	number of seconds anyway, and so forth. There's never a reason to be sampling at a rate that exceeds the average end period, so to speak, of	2 3	DR. SESSLER: Shouldn't that be the last question? DR. WARD: Yeah, it might be.
3 4	number of seconds anyway, and so forth. There's never a reason to be sampling at a rate that	2 3 4 5	DR. SESSLER: Shouldn't that be the last question?
3 4 5 6	number of seconds anyway, and so forth. There's never a reason to be sampling at a rate that exceeds the average end period, so to speak, of your device.	2 3 4 5 6	DR. SESSLER: Shouldn't that be the last question? DR. WARD: Yeah, it might be. The physiologic profile of a new
3 4 5 6	number of seconds anyway, and so forth. There's never a reason to be sampling at a rate that exceeds the average end period, so to speak, of your device. DR KARAN: Blood pressure measurement,	2 3 4 5 6 7	DR. SESSLER: Shouldn't that be the last question? DR. WARD: Yeah, it might be. The physiologic profile of a new compound some of these are motherhood and apple
3 4 5 6 7 8	number of seconds anyway, and so forth. There's never a reason to be sampling at a rate that exceeds the average end period, so to speak, of your device. DR KARAN: Blood pressure measurement, that's not arterial?	2 3 4 5 6 7 8	DR. SESSLER: Shouldn't that be the last question? DR. WARD: Yeah, it might be. The physiologic profile of a new compound some of these are motherhood and apple pie, I understand a new compound, well
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1	modification? So phase 1 and phase 2.	1 DR. WARD: Okay.
2	This one I think we've already discussed.	2 DR. GAN: But your intention is to collect
3	MedDRA is probably useful to classify, but TROOPS	3 similar outcomes so that you can make comparisons,
	is not a sufficient classification system.	4 right? I think that is what that meant.
5	Everybody say yes? Hands up?	5 DR. WARD: That's what I meant by that,
6	(Show of hands.)	6 right.
7	DR. WARD: Okay. Data should be collected	7 DR. GAN: Motherhood and apple pie, sure.
8	in ways that facilitate pooling from meta-analysis?	8 Who wouldn't agree to that?
	Yes?	9 DR. SESSLER: I think it's meaningless.
10	DR. SESSLER: What does that mean?	10 (Laughter.)
11	DR. WARD: I think we heard some of that	11 DR. GAN: The second one is meaningless
12	from our statistical discussion yesterday.	12 DR. DEXTER: If the point is that you should
13	DR. DEXTER: I think that I kind of agree	13 use standardized measures of efficacy and
14	with Dan's question. I think if you collect data	14 standardized measures of adverse events.
	as part of phase 1 through phase 4 studies, you're	15 DR. GAN: That's exactly
	collecting all the data. So I'm not quite	16 DR. DEXTER: My recommendation would be to
17	following what, as part of clinical studies, that	17 say that.
	means. If you're collecting all the data, how is	18 DR. GAN: Exactly. That's exactly what it
	that different than facilitating pooling for	19 says.
	meta-analysis?	20 (Crosstalk.)
21	DR. LIGHTDALE: Sedation studies are	21 DR. DEXTER: Just say that.
22	routinely confused I mean, outcomes are	22 DR. DWORKIN: [Inaudible - off mic].
	Page 266	Page 268
1	Page 266 different across sedation studies, and makes it	Page 268 1 DR. SESSLER: A general rule of practice is
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2 3	different across sedation studies, and makes it very difficult [inaudible off mic].	DR. SESSLER: A general rule of practice is 2 say what you mean.
2 3 4	different across sedation studies, and makes it very difficult [inaudible off mic]. DR. SESSLER: Right. Okay. So what you do	 DR. SESSLER: A general rule of practice is say what you mean. DR. WARD: I sat down, and in 15 minutes
2 3 4 5	different across sedation studies, and makes it very difficult [inaudible off mic]. DR. SESSLER: Right. Okay. So what you do when you do a meta-analysis is you try to find a	 DR. SESSLER: A general rule of practice is say what you mean. DR. WARD: I sat down, and in 15 minutes with my handwritten notes over the meeting, so
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1	notes to put these down. That's why I'm putting	1 If clinical intervention is used as an
2	these up here, for you guys to help clarify for me	2 outcome, it should be procedure specific in a
3	to say what I mean. And your names are going to be	3 well-defined criteria for intervention initiation.
4	on the paper, so you guys get to say what you mean,	4 That's Dan's example of the nasal prongs, endoscopy
5	too.	5 versus nasal prongs in an MRI, that if you're going
6	All right. So we talked about this one	6 to have an intervention that you're collecting, you
7	already, with the caveats that we talked about. I	7 can't just say we collected data when nasal prongs
8	think we've heard that a lot, that you have to	8 were put on to the patient if your study is
9	classify both severity and length.	9 heterogeneous in the kinds of situations that it
10	DR. GOZAL: Maybe we should "precise" after	10 was in.
11		11 We're okay with that? Again, these are
12	DR. WARD: Yeah, intervention to correct it?	12 concept statements. These won't be sentences in
13	DR. GOZAL: Yeah.	13 the paper; might be.
14	DR. WARD: Those are both things that would	14 A clinical intervention scale would be
15	be collected in order to decide when an	15 useful, but we need to be shown they're reliable
16	intervention was made, would have to be based on	16 and valid.
17	both. And we've been talking about that quite a	DR. DEXTER: I don't think you need to have
18	bit. The relationship or lack thereof between	18 "valid" because it's very unlikely that people I
19	adverse events and adverse clinical outcomes should	19 mean, I know it's like apple pie. It sounds great,
20	be defined as much as possible.	20 except it's not like people are going to be doing
21	These kind of papers have a lot of	21 clinical interventions likely that are invalid. I
22	motherhood and apple pie kind of statements in it.	22 think validity is pretty clear, but reliability
	Page 270	Page 272
	And that's not bad because these statements kind of	1 will be the challenge.
2	And that's not bad because these statements kind of are made to each other, but they don't end up in a	 will be the challenge. DR. WARD: It's easy to show face validity
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1	for intervention, or describe the events relating	1 second point is taking in account the third.
	to the intervention that was performed, because	2 DR. WARD: Or the third taking in account
	people aren't going to stick to criteria all the	3 the second.
	time. But there has to be at least some further	4 DR. DEXTER: Yeah. The other issue is when
5	characterization of the events surrounding the data	5 you say "measurement instrument," it's not clear
	or surrounding the intervention.	6 whether in instrument you mean like a instrument
7		7 like a scale, or you mean an instrument like a
8		8 physical device, like the pulse oximeter.
9	of an idea of why the intervention occurred.	9 DR. WARD: Could be other one, or both. It
10		10 includes both was the concept I think, as a general
11	much there's a lot of overlap between these.	11 idea.
	This was a concept that I liked when it came up.	12 DR. DEXTER: Doesn't the second one
	It's useful to consider the measuring instrument	13 incorporate the third, and you can just kind of not
	and the relevance instrument separately.	14 worry about the third?
15	DR. DEXTER: What is relevance instrument?	15 DR. WARD: The third's a concept, and the
16	DR. WARD: Well, it sort of goes	16 second is a particular device, a scale, 1 to 5.
17	back again, not to overuse Dan's example,	17 No. I think the second is incorporated by the
	putting nasal prongs on a patient could be	18 third as a general concept.
	something that you're measuring, or additional	19 DR. DEXTER: So for example, how about
	supplemental oxygen could be something that you're	20 instead of getting a word, a "clinical intervention
	measuring. It's not particularly relevant in some	21 scale," just say a "clinical intervention," or
	procedural sedations, and very relevant in other	22 "measurement of the clinical intervention."
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1	procedural sedations.	1 DR. WARD: Okay. I'm not wordsmithing
2	So understanding that you might be maybe	2 these. These are just concepts. We'll argue about
3	measuring a bunch of things, but then you've got to	3 the wordsmithing once I send the paper around. But
4	make a decision about what you measured is a the	4 I'm trying to find out what concepts; am I going to
5	desaturation for 5 seconds to 90 percent, you	5 set somebody off if I include the concept in it or
6	measured it because you've got a lot of data coming	6 if I don't include the concept in it.
7	in. Then you can make a decision that your	7 The cause of an AE should be separated by a
8	screening tool, it then decides whether that	8 drug, disease, procedure, provider. That's the
9	measurement becomes a relevant outcome. So	9 context, and that's come up.
10	separating the concept of your measurement tool and	10 Mark?
11	your relevance tool.	11 DR. WEISS: I would consider also putting
12	DR. GAN: So more like context sensitive.	12 the word "site" as well, because I do believe it
13	DR. WARD: Context sensitive, procedure	13 may not be politically correct, but I do believe
14	sensitive, patient sensitive.	14 that the site where we do these procedures directly
15	DR. DWORKIN: Don't you want a stronger word	15 influences, sometimes, either the rate of which we
16	than "useful"? Isn't it important or imperative?	16 have an adverse effect, or our ability to respond
17	Useful is a pretty weak word, given what you just	17 to the adverse effect. So I would include the word
18	said.	18 "site" in that as well.
19	DR. DEXTER: Since you have the previous	19 DR. WARD: Yeah. No, I agree. I think
	statement that a clinical intervention scale would	20 doing something out in the boonies, you have a
21		
	need to be reliable, I'm wondering, because of	21 lower instance of intervention than doing it down
	need to be reliable, I'm wondering, because of exactly the point of useful, whether or not the	

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1	around. So, yes, site is good. Thank you.	1	DR. SESSLER: By the time you get to phase
2	Other? Rather than call for votes in every		3, and you're trying to make a broad statement, and
3	one of them, I'm just going to kind of go through		if it's successful, the drug will get approved, and
	these, and let's hear objections or agreement.		it will go out and be used in many contexts, not
5			just the one you studied, then it's probably
6	through without someone picking at it. It got		appropriate to include a broad range.
	through.	7	
8	DR. WARD: I've been known to wear people	8	clinical trials in sedation, efficacy gets shown
9	out, too.	9	pretty quickly. If something's not going to
10	Where are we? Decreasing major	10	progress beyond a phase 1 trial, it really doesn't
11	sophistication can be used as the compound	11	work. So we're really talking a phase 3 now as
12	progresses from phase 1 to 3. We've talked about	12	opposed to other compounds, where we're still not
13	that, although we're sort of coming into the	13	sure what the efficacy is in a larger population.
14	consensus that even phase 4 trials probably require	14	We're only more worried about are there going to be
15	a higher level of measurement than would normally	15	too many adverse events that show up.
16	be done clinically. There's no reason to say we	16	This is a different kind of climate. We're
17	can just collect the usual clinical data in	17	all aware of this clinical trial paradigm in a
18	certainly in a phase 3 and a phase 4, but I	18	diabetic or in a hypertensive drug in which you
19	probably don't need to put all the RespiTrace and	19	don't expect a lot of adverse events. And for
20	everything else as we get more and more patients as	20	diabetic drugs, we've worked out ways to look at
21	the study's progressing.	21	them, but we're still not sure how effective it's
22	DR. KARAN: If your phase 4 trial involves	22	going to be.
	Page 278		Page 280
1	-	1	
	OSA patients, or your phase 3 trial didn't, then	1	When we moved dexmedetomidine from a phase 1
2	OSA patients, or your phase 3 trial didn't, then you might want to use something else	2	When we moved dexmedetomidine from a phase 1 to a phase 2, we were pretty sure that it worked as
2 3	OSA patients, or your phase 3 trial didn't, then you might want to use something else DR. WARD: That was a point you made, that	2 3	When we moved dexmedetomidine from a phase 1 to a phase 2, we were pretty sure that it worked as a sedative. We weren't sure whether its
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	Page 281		Page 283
1	useful.	1	be able to select one versus another. That's my
2	DR. WUNSCH: Should there be something to	2	impression, but I'll take other views. Ron's
3	differentiate between non-standard monitors that	3	shaking his head.
4	are non-invasive versus invasive in terms of how	4	DR. LITMAN: No, we don't. Jerry has, as he
5	much we would suggest people consider using them?	5	talked about, the only published delirium score,
6	I think there's a huge risk profile that goes as	6	but very few people use it.
7	soon as there's any invasive monitoring that gets	7	DR. WARD: But it could be used in a
8	added.	8	clinical trial.
9	DR. WARD: What does everybody think? I	9	DR. LITMAN: When it's easy [indiscernible],
10	think I'm more worried about accuracy rather than	10	he could use.
11	invasiveness. I think getting inaccurate data out	11	DR. WARD: Yeah.
	there in a clinical trial has a negative purpose.	12	DR. CONWAY: Is it really a safety outcome,
	I think invasiveness adds another ethical issue on		then? And it's in the rate/goal [ph]. Like
14	top of it, but whatever the group		rate/goal is specifically in an efficacy paper.
15	DR. SESSLER: I agree. The issue doesn't		I'm not sure that delirium is a safety outcome.
	seem to be invasive or not; it seems to be	16	DR. WARD: I'm sorry. What?
	accuracy. And the burden is on the investigator to	17	AUDIENCE MEMBER: It could be insofar as it
	justify any methods used, and the reviewers will		might delay the discharge home.
	look closely at anything that's not standard.	19	DR. WARD: Yeah.
20	DR. BERKENBOSCH: And you would	20	
	appropriately describe the limitations of whatever		definitely a safety issue. I actually saw a case
22	non-standard monitoring you choose to incorporate	22	where a woman was placed on delirium, got on to the
	5		
	Page 282		Page 284
1	Page 282 into your trial.	1	Page 284 roof of the hospital, and jumped off the roof of
1	-		
2	into your trial.		roof of the hospital, and jumped off the roof of the hospital. So that's pretty pretty serious
2 3	into your trial. DR. SESSLER: Exactly. This is just generic	2	roof of the hospital, and jumped off the roof of the hospital. So that's pretty pretty serious (Laughter.)
2 3 4 5	into your trial. DR. SESSLER: Exactly. This is just generic methods. We used some methods, and it's validated as follows, and here are the limitations. And then if they're real limitations, you put a paragraph in	2 3 4	roof of the hospital, and jumped off the roof of the hospital. So that's pretty pretty serious (Laughter.) DR. IRWIN: This was in Los Angeles, actually.
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1	advaraa avant	1	your paper. Frank, looked whether the actient has
	adverse event.		your paper, Frank, looked whether the patient has
2	DR. WARD: Right. Patient recall may be useful but will need		been told they're going to have recall versus not
3	-		told whether they're going to have recall makes a
	to be defined in relation to expectations.		difference, whether it's unpleasant or unexpected
	Unexpected?		or not.
6	DR. RIKER: This is a morass. In the ICU,	6	So it's a morass, but I think if you're
	unpleasant recall occurs more frequently in the		doing a clinical trial, you can define some of the
	deeply sedated patient than it does in the lightly		parameters that you want to look at. I guess what
	sedated patient. And the issue is they're so		I'm saying there is that it needs to be defined in
	deeply sedated, they establish no real memories,		relation to the expectations. You just can't ask
	and all they have are delusions and hallucinations.		did you remember anything, and if they say yes,
12	So that's in the ICU, and I don't know how		that's an adverse outcome. It's not that simple.
	long that has to be present to be even applicable	13	Finally, the difficulty in relaying the
	to a shorter-term procedure. But we saw yesterday		occurrence of biomarkers in phase 3 clinical trials
	that with ketamine, emergence delirium, or		to rare SAE mandates postmarketing studies and data
	hallucinations is 10 percent. So those patients		collection. I mean, that gets back to the
17	5 5		midazolam story originally. We don't really know
	happened. So this gets really tough.		what a CO2 response curve for example, or even a
19	DR. WARD: Yeah. And maybe it's a morass		saturation during a sedation, means as far as how
	that we don't want have into.		often you're going to get a respiratory arrest when
21	DR. RIKER: Or it needs to be a more		you're using it in thousands of patients.
22	sophisticated assessment.	22	Any other ones people want to add?
	Dogo 286		D 000
	Page 286		Page 288
1	DR. CARLSON: I agree with that, but I think	1	Page 288 DR. GAN: Is it important to assess when the
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2	DR. CARLSON: I agree with that, but I think	2	DR. GAN: Is it important to assess when the
2 3	DR. CARLSON: I agree with that, but I think in the sense of a lot of things, we need to measure	2 3	DR. GAN: Is it important to assess when the patient gets back to baseline? As we are now more
2 3 4	DR. CARLSON: I agree with that, but I think in the sense of a lot of things, we need to measure it, and then decide later how to apply it, because	2 3 4	DR. GAN: Is it important to assess when the patient gets back to baseline? As we are now more patient centered again, this is not something we
2 3 4	DR. CARLSON: I agree with that, but I think in the sense of a lot of things, we need to measure it, and then decide later how to apply it, because not measuring I think recall and sedation is an	2 3 4	DR. GAN: Is it important to assess when the patient gets back to baseline? As we are now more patient centered again, this is not something we have in the past collected, but I just wonder
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Jui	ery outcomes in Frocedural Sedución	1	,
	Page 289		Page 291
1	following after	1	use if you have a sedation drug, it's probably
2	DR. WARD: That would be I think a	2	not going to be used in isolation. So if you
3	neurological outcome	3	didn't do a phase 3 trial at the beginning of the
4	DR. GAN: Right.	4	midazolam, making sure you combine it with an
5	DR. WARD: but that's not kind of		opioid that's why I think it's going to be used,
6	returning to I mean, that's different than kind		so good point.
	of when are you ready to be discharged.	7	
8	DR. GAN: Not so much discharged; when you	8	DR. ROBACK: As I'm thinking more about
9	get back to what your senses because sometimes	و	continuous physiologic data and our recommendation
	people, they say I had this procedure, but it takes		that this is really required, I think we need to
	me two or three days to get back to normal.		add that further work is really needed to really
12	DR. WARD: If you ever used Innovar I'm		understand or to define what these numbers mean,
13	old enough to		because right now, there is really no consensus,
14	DR. GAN: Oh, yeah.		and there's no that this number means one thing,
15	DR. WARD: have used droperidol and		and that number means another thing. And we're
	fentanyl when I was a resident, and you will have		going to have to develop those as we go forward to
	several days before patients say that they're back		make this data really be meaningful.
	to normal.	18	DR. WARD: Well, I think what Dan's point
19	So yeah, point taken. I thought you meant		has been is that you can then connect it to the
20	more you're ready for discharge.	20	
21	DR. GAN: No. This one is more longer term.	21	itself probably is not going to be meaningful
22	DR. WARD: And I think that came up when we		unless you connect it to the clinical intervention.
	Page 290		Page 292
1		1	
	Page 290 talked about longer term follow-up, the 1 week to 1 month kind of follow-up for neurological changes.		But vice versa, the clinical intervention may not
	talked about longer term follow-up, the 1 week to 1	2	But vice versa, the clinical intervention may not be meaningful if you can't connect it to
2	talked about longer term follow-up, the 1 week to 1 month kind of follow-up for neurological changes.	2 3	But vice versa, the clinical intervention may not
2 3 4	talked about longer term follow-up, the 1 week to 1 month kind of follow-up for neurological changes. Jenifer, then Hannah.	2 3	But vice versa, the clinical intervention may not be meaningful if you can't connect it to physiological data. So that's a good point to be able to make there.
2 3 4 5	talked about longer term follow-up, the 1 week to 1 month kind of follow-up for neurological changes. Jenifer, then Hannah. DR. LIGHTDALE: Just very quickly, I think	2 3 4 5	But vice versa, the clinical intervention may not be meaningful if you can't connect it to physiological data. So that's a good point to be able to make there.
2 3 4 5 6	talked about longer term follow-up, the 1 week to 1 month kind of follow-up for neurological changes. Jenifer, then Hannah. DR. LIGHTDALE: Just very quickly, I think certainly safety, if you're not ready to drive, we	2 3 4 5	But vice versa, the clinical intervention may not be meaningful if you can't connect it to physiological data. So that's a good point to be able to make there. Other comments from the panel or the
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