ACTTION - IMMPACT XXI - OPIOID SPARING IN PATIENTS WITH ACUTE AND CHRONIC PAIN

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ACTTION

INITIATIVE ON METHODS, MEASUREMENT, AND PAIN ASSESSMENT IN CLINICAL TRIALS

IMMPACT-XXI

Research Design Recommendations for Clinical Trials of Opioid Sparing in Patients with Acute and Chronic Pain

Friday, July 27, 2018
8:16 a.m. to 3:40 p.m.

The Westin City Center
Washington, DC

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:15 a.m.)

DR. DWORKIN: Good morning, everybody, and thank you all for sticking with us for a second day. I just wanted to say a few words of orientation about today.

Today's going to be different from yesterday. The way I think Dennis and I think about this is that the first day generates a lot of ideas, kind of raw material. Everybody gets to say what they think about things. The second day, we try to think of as much more focused, where there's actually something we want to accomplish by the end of today. And what we want to accomplish by 4:00 or so this afternoon -- every once in a while, we end a little bit early, but that's really rare.

What we want to accomplish is to have a kind of scaffolding, enough raw material, enough kind of consensus for Jen Gewandter to draft at least one, maybe two consensus recommendation manuscripts. She will take the lead on it. You will be getting more emails from Jen than you want, because if you

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are willing to and interested in being a co-author of this recommendation's manuscript, you will be invited to be a co-author.

Once Jen has a draft, you'll be asked for your comments and suggestions about the draft of the manuscript, and that will be carried through all the way until when the thing is finally accepted for publication.

That's what we want to accomplish by this afternoon, is have enough for Jen to go home and start writing, one or two manuscripts. The reason I'm saying one or two is there was a sense yesterday that instead of trying to put acute pain and chronic pain into one article, maybe it should be split. And we should have one article about recommendations for clinical trials of opioid sparing and acute pain and one for chronic pain. And I think we'll have a better sense of that by later today.

I think what we want to accomplish today -- and we have two talks, one by Ian Gilron, who's professor of anesthesiology at Queen's

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University and professor of a bunch of other things, but I'm too old to remember all of the titles that Ian told me in the hall a few minutes ago.

So Ian's going to give a talk earlier this morning -- as soon as I sit down -- that's going to focus on and really help us to think about what we want to put together as the scaffolding for acute pain recommendations. And then Mike Rowbotham, who's at Sutter Health in California and also UCSF's Department of Neurology, will give a similar talk for chronic pain for the afternoon.

So this morning, acute pain; this afternoon, chronic pain; and then we all go home around 3:30, 4:00, probably 4:00.

Just one more word I think that evolved after yesterday's discussion. These recommendations, I think at the very highest level, have to start with study objectives. What's the hypothesis that a clinical trial or the clinical trial types that we propose are going to be testing? And that's really how do we think about

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what opioid sparing is?

Obviously, it's not one thing. One thing that became very clear yesterday is that there's lots of ways to think about possible benefits and outcomes of opioid sparing. So there's not just one opioid-sparing study objective. And of course that means there isn't one opioid-sparing clinical trial outcome. The inclusion criteria are going to differ, and then the specific research design, study execution, and analyses are going to differ depending on how we conceptualize the study hypothesis, the study objective.

So something several of us talked about at the end of the day yesterday, is at a minimum this afternoon, we really need a list of the different study objectives -- I think of this synonymously with the hypotheses that are being tested -- study objectives, study questions that could be tested in clinical trials for opioid sparing, however we think it's important to define it, for acute pain, and likewise for chronic pain.

How far we then get beyond study objectives,

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outcomes, inclusion/exclusion criteria into the details, if you will, of study methods, study execution, what do we do about missing data, is going to depend on how fast we move today. I don't know that we're going to get all the way down to details of what do we do about missing data in the clinical trial.

Those weeds probably are beyond what we can accomplish over the next 6 hours. Personally, I'd be quite happy if we get kind of halfway down this list of recommendations, that we succeeded coming up with some consensus for Jen about objectives, hypotheses to be tested, key critical outcomes, and then some ideas, like what Nat put up in one of his early slides yesterday of the kinds of designs that would test that.

So I've said enough. Any questions about our vision for today, any of the things? There are some housekeeping bullets on the slide that I won't repeat. Checkout time is at 12:00. We'll have a break the middle of this morning. As you can see from the agenda, we're planning to start lunch at

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11:30. So that's the day.
Questions, thoughts, comments?
(No response.)
DR. DWORKIN: Well, great. All right. I'm happy to turn it over to Dr. Ian Gilron from Queen's University.
Take it away, Ian.
Presentation - Ian Gilron
DR. GILRON: Thank you, Bob. Thank you, Bob and Dennis and the steering committee for inviting me. I've had some involvement ACTTION an IMMPACT for the past 13, 14 years, and it's been a great learning experience and an honor. I'm an anesthesiologist. I've been designing and conducting analgesic trials for the past 20 years or so and trying to interpret them. Those are my disclosures.
So just a quick recap from yesterday, yesterday I thought was excellent. The talks were very high quality, and I think it's everything we needed. There was a little bit of some insubordination over here, but other than that, it

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was good. As Bob sort of mentioned, it was really about stimulating ideas. And I think a lot of the discussion was really patient centered and clinically oriented. And I think we need to turn the corner here and focus. Really, we're trying to generate recommendations for analgesic clinical trials.
Here's what I took from yesterday and my understanding of the bigger picture of what our goal is for this meeting. Long before widespread recognition of the opioid crisis, I think we've always had a goal, both in acute and chronic pain, of minimizing opioid related adverse drug events. But more recently with the opioid crisis, we also have additional goals of reducing community opioid use, transition to persistent opioid use, and development of new cases of opioid-use disorder.
So how is this relevant to future trials in acute and chronic pain? Well, I think in acute pain, we need to pay more attention to people who already have preexisting chronic pain in opioid use, people with mental health and substance-use

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problems. There's been a growing interest in preventing transition from acute to persistent pain, and that may go in parallel with the development of opioid use.
I really think -- I sent an email to the group early in starting to think about this talk in that the management of acute and subacute pain after hospital discharge in home and community settings I think is a huge clinical gap and also a knowledge gap that we don't know about.
I think most of our discussions yesterday about the opioid crisis in acute pain management was what happens to all these scripts after people go home. And really, a lot of that pain management is unsupervised and we don't know a lot about it. So that's an important issue I think.
So again, I think the narrower focus for today in trials of non-opioid pain treatment interventions is how can we best demonstrate an opioid-sparing effect? Also, it may be an add-on, but the more we talked yesterday, I kind of thought that the changes that are coming on with the opioid

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crisis and widespread efforts to reduce opioid prescribing may affect the landscape of conducting analgesic clinical trials and something else we should be thinking about.
So again, just to really reemphasize this, we're thinking today about clinical trials, so we really have to stay focused on that. So just put a little plug for an excellent review article by John Farrar on clinical trial design just to remind you that we're thinking about trial design and methodology today.
When we think about those different features -- and I usually like to use the PPICO kind of model, the purpose of the trial, the population that we want to study, the intervention, comparator, and the outcomes of interest, so we'll come back to that. We can use any format that we want, but I'm sort of proposing that as a structure to fashion our discussions.
Here's an outline. I want to talk a little bit about opioid use and the concept of rescue analgesia in acute pain trials, and then talk about

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measuring opioid use and opioid effects -- obviously, we had excellent talks yesterday covering that -- and talk a little bit about future directions.

As I speak today, I'm going to pepper my talk with proposed recommendations. I want to start low and go slow. I hope what I think I'm proposing will be kind of motherhood, sort of generic recommendations that hopefully are not contentious. If they are, then, well, we'll get started even earlier, and that will get us thinking about how to move forward.

So for any of you who've never yet been to an ACTTION or an IMMPACT meeting, it's going to be really fun to watch you because you've had a nice sleep and a good breakfast, and you think life is good now. And then at 5 to 4, we're still going to be talking about whether the hyphens should be between "opioid" and "sparing."

(Laughter.)

DR. GILRON: I wanted to talk about opioid use and analgesic trials and start with just a

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little bit of a historical context. A lot of what we know now about pain and analgesic treatment response started from pioneering research by Henry Beecher and others in the 1940's and in the 1950's. And here's an example of the work that was being done then, and in fact, opioid use was kind of a surrogate of pain intensity.

Here's an example of an early open-label study looking at the population distribution. So these are the number of patients -- the dotted line are patients having hysterectomy and the solid line are patients having gastrectomy, and looking at what is the distribution of number of narcotic doses required.

Again, probably something that wouldn't be very popular at any journal at this point in time, but sort of see there seems to be a slight difference, suggesting that maybe pain is greater after a gastrectomy. So a lot of enthusiasm and work ensued, and then maybe about 10 years later, this is the type of work that was being done. We now have an example building on the work done by

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Lasagna and Houde.

Here's an example of a comparative clinical trial looking at to opioids, pentazocine and phenazocine, and looking at pain relief temporal profile after the analgesic administration in two different surgical populations. And here, this is a double-blind, single-dose trial, and the opportunity of seeing some differences in the temporal profile. At least here, it looks like phenazocine has a longer duration of action.

Now, 10 years later, we see that there's some attention to opioid related side effects. Shannon Smith and others in the ACTTION Saber group looked at harms reporting. And you'll notice here, this is the sum total of their safety assessment and reporting in this 1966 trial.

Any comments about the side effects were noted on a separate card on each occasion. That's all it says. And the results, no serious adverse effects were noted. Nausea and vomiting were not noted. I don't know if that means they weren't noted or they weren't --

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(Laughter.)

DR. GILRON: But at least they introduced the concept of opioid related side effects and the importance in starting to recognize.

Around the same time was the concept of opioid rescue in the setting of studying non-opioid intervention. This is a dose-ranging trial. These are actually different cohorts, so it's like a dose-response trial. But I just wanted you to see here, each patient was studied for 1 dose only, and routine analgesic therapy was being prescribed thereafter. So they could get analgesic therapy if they need it. And then at any point, they could be given a further analgesic at any time if they needed satisfactory relief?

I can't even read that from here, but their subsequent pain scores were censored from the analysis. This is maybe one of the earliest descriptions of the last observation carried forward analysis, introducing the concept that rescue analgesia -- first of all, at this point in time, opioid use was widespread enough that it was

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considered standard of care to give opioid therapy for inadequate pain relief, and furthermore, recognizing that this has some challenges in terms of estimating and evaluating analgesic efficacy.

We're getting to the concept of opioid sparing, but I think we need to make sure that we preserve everything we've learned so far about analgesic trials. Then a few decades later, here's individual patient meta-analysis done by Andrew Moore and Henry McQuay, looking at other metrics, the percentage of patients requiring rescue after a single-dose intervention. So this is comparing ibuprofen with rofecoxib.

We can see some differential efficacy compared to placebo between ibuprofen and rofecoxib in terms of the proportion of patients requiring analgesic rescue; and here just to reinforce that data imputation is a serious issue. There is some uncertainty on how to deal with that. We've had many discussions within ACTTION and IMMPACT about this. As we know and we've seen in a lot of different analyses, as soon as someone gets rescue,

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they're not out of the trial, but we don't know what to do with their subsequent data.

Baseline observation carried forward seems to be the most conservative and underestimates the apparent efficacy of the treatment, whereas last observation, it maybe makes things look a little bit better. Again, we don't know; we're imputing data. This is just to introduce the idea that rescue is something that is a challenge for us

A couple of years ago, we published -- I think it was 2016 -- the IMMPACT recommendations on acute pain trial design, so I thought I would put that up and talk about other issues for measuring opioid use, and Brett had discussed a lot of this. Looking at the offset of analgesia in non-opioid intervention and time to first rescue as we talked yesterday, is certainly one possible metric in of itself is a measure of offset of analgesic effect.

Publications that report medium time to rescue need to decide and have some consensus on what's the appropriate dosing interval and regimen. Clearly, the humanitarian and ethical issues of

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managing one's pain in this setting of a clinical trial needs to be incorporated into the science of how we do this.

Just to summarize, acute pain trials of conditions with moderate to severe acute pain are commonly associated with the use of a non-study intervention. It can be opioids and possibly non-opioids. And proper analysis and interpretation of acute pain trials requires careful consideration and control of non-study intervention opioid use and other non-study analgesic treatments.

So I'll give it a try. I'm going to start with my first proposed recommendation regarding analgesic rescue. A trial of an acute pain management intervention should balance between consideration of the ethics of pain under treatment, for example, in the placebo group; and, two, the negative impact of the non-study rescue analgesic treatment on one, the floor effect -- I think Sharon Hertz mentioned this yesterday -- the floor effect and reduced assay sensitivity. If you

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treat pain too effectively in both treatment groups, your ability to demonstrate a difference may be reduced.

Thinking about the analgesic and adverse interactions of the study intervention with your rescue intervention could confound or conflate issues, and also, the potential misattribution of the non-study drug intervention with the study drug intervention. So is the nausea due to the NSAID that you're administering or is it due to the opioid? So again, very motherhood. We're just saying consider these things.

As we've discussed yesterday, the landscape is changing. There's already widespread recognition and changes in practice in perioperative pain medicine in terms of opioid sparing and the concerns about developing chronic opioid use.

I'm adding here, the design of future acute pain trials should consider evolving approaches to minimizing opioid prescribing. For example. as we talked about yesterday, the shifting analgesic pyramid where it's been suggested that opioids go

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on last, and also efforts to have kind of a restrictive opioid regimen in your standard of care protocol.

So if your goal is to demonstrate opioid sparing, we may actually be coming into a practice landscape where you're going to get a floor effect of that because the opioid prescribing is going down. This is really provocative.

So in a couple of months, cannabis is going to be legal in Canada, and I'm not sure how that's going to change everyone's behavior and use. But can or should we consider preexisting concomitant cannabis or other analgesic drug use as an important factor in pain trials? Is it feasible or necessary to exclude cannabis users from analgesic trials? So these are additional things to think about, in all analgesic trials, not necessarily just opioid-sparing trials.

We can start the discussion at any time, so if anyone wants to interrupt with questions in the middle, that's okay, too.

So I'll move on to talking about opioid use.

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And again, historically, patient-controlled analgesia, or PCA, was an important evolution in analgesic trials. In the late '60s or early '70s, a number of groups developed electronic or a computer-controlled apparatus where you have usually an IV, parenteral, a syringe with an opioid like morphine that is connected to the patient's IV tubing.

You have basically an operant response system where you press a button and you get an injection. And for those of you who are not familiar with it, you can set up a lockout interval and a dose.

So each button corresponds to a certain volume of morphine that gets administered. And for people who are a little trigger happy and you don't want to get an overdose, you can actually, somewhere, typically between 5 and 10 minutes, have a lockout interval. And you explain to the patient that they can press all they want for that next 5 minutes. They're not going to get another dose until the machine resets.

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Since these are electronic, they also work as data gathering systems. Here, you can see, for example -- and this is one of the earlier 1971 reports. You can actually keep track of all the times the button was pressed and also look at the cumulative opioid dose of how many successful doses they get.

So not to be cynical, but one of the reasons why opioid consumption is a popular measure in acute pain trials is it's often the best quality data because you just go and get the data from the pump, whereas pain intensity data, you need a nurse, you need the patient to understand. They have to fill out the VAS score and that sort of thing. So this is a very important thing.

What do we do that and how do we use that in trials? One of the earlier efforts to do this by Henry McQuay and others in Oxford was a letter to the editor, to Lancet, in 1980 saying, hey, we can actually use this to be a measure of analgesic effect.

So I'll just quickly show you here on the

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Y-axis, this is the number of administrations of 2 micrograms, a pretty small dose, of fentanyl through a PCA pump in patients, postoperative patients, who had an epidural catheter and got different analgesic drugs through the epidural. It's hard for you to see here, but the first steep curve is patients with postoperative pain pressing the fentanyl pump, and then at point number A, they got a dose of 100 micrograms of fentanyl through the epidural.

So it looks like they got an analgesic effect because their pressing for the PCA IV fentanyl kind of plateaued off for a little while, and then at point b they got a sham, they got a saline injection into the epidural catheter. It didn't seem to do much, so again, we got a steep curve of patients pressing the fentanyl pump to get the short blast of analgesia. And then at point C, there seems to be an elbow there. They got an epidural injection of diamorphine, and it looks like that had a bit of an analgesic effect as their pressing seems to level off.

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That's kind of the early era of what we call PCA analgesimetry using opioid consumption as a measure of analgesic effect. Here we see from the '80s a ketorolac study looking at 2 different doses of ketorolac and looking at cumulative opioid consumption after that, compared to the placebo group. And you see a nice statistical separation between the ketorolac and the placebo groups, looking strictly at opioid consumption.

This is not straightforward. Igor Kissin from Harvard did a really thoughtful and nice discussion review at ANA in 2009, saying that there are limitations -- and we really have to take this with a grain of salt -- in terms of interpreting particularly PCA, where patients are pressing a button for their opioid.

For a lot of reasons, there's a weak correlation between pain intensity and opioid consumption. The effect of the study medication on PCA is something to consider. For example, if the study analgesic is gabapentin, patients are more sedated. They're more sedated. They may not

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necessarily have less pain. So they may not be able to press the button as much due to sedation, and we might be interpreting that as an analgesic effect, maybe inappropriately.

There may be an interference of non-analgesic effects of the opioid that patients are pressing. And patients will self-regulate their own cost benefit or risk-benefit when they press the button. So if they're getting nausea, they might wait a little bit longer before they press the button, and that's not necessarily an analgesic effect. Opioid tolerance could be an issue, and variability in patient training of PCA use.

So on one end of the spectrum, you've got a patient who's sleeping quietly in their room and the nervous mother is pressing the button for them. On the other spectrum, you've got someone who's really good at playing video games, and they're just pressing all the time and really frustrated that they're not getting the opioid dose. So patient training is another issue. Sometimes when

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you look at these data, they look so clean, but the interpretation may not necessarily be that way.

I don't want to go into too much detail, but basically just to say that another problem with interpreting the analgesic efficacy of an intervention by looking at PCA is going to be limited by the fact that patients will titrate themselves down to a certain pain level with the opioid, so you're maybe getting some sort of a floor effect. And how do we interpret a pain intensity reduction with a non-study intervention in the setting of some reduction in PCA, opioid?

There's some confusion there, and there have been some proposals made. One of the earliest ones that I've been aware of was the Silverman integrated analgesic assessment score. Without going into too much detail, basically you take each individual in the trial and you rank order them in terms of what their pain intensity score was compared to the group mean. And you rank order their opioid consumption, and you come up with an integrated score.

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For example, someone with higher pain but lower opioid use would sort of get readjusted compared to the group mean. Another version of this came from Pittsburgh actually in 2013 as a suggestion to separate this out. And I'll show you an example; a sign of low self-esteem. I feel like I have to show some of our own data just to support why I might be up here.

(Laughter.)

DR. DWORKIN: So this is an analgesic trial that we did, comparing the combination of gabapentin and rofecoxib to either single agent in pain after hysterectomy. And this is time after surgery. This was a multidose trial. And here are pain scores, pain evoked by cough in the placebo group, the single-agent groups, and the combination group. And here are the cumulative opioid consumption data over time.

If you look at the opioid scores, it's kind of nice. It sort of addresses the hypothesis we get. Opioid consumption is very high in the placebo group, significantly lower in both single

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agents, and in the combination, it separates out statistically from the single-agent groups. And then we conducted this integrated analgesic assessment score to get even further, to some degree, some further separation by incorporating the level of opioid consumption as well.

I'll just mention also, just looking at appropriate time intervals -- and we'll come back to that -- that correspond to the expected temporal profile of the analgesic drug that you're giving. So we'll come back to that in a moment.

That was addressed -- the 2016 recommendations paper on acute pain really focused on single-dose studies, but there was some recognition that at least these proposals for integrated analgesic assessment have been made, but we really need to do more research to find out what the validity is of doing this compared to -- I mean, to some degree, it's a composite type of scoring system.

Another proposal regarding measures of opioid use in acute pain trials. I think this is

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really motherhood. Acute pain trials in settings where pain is frequently moderate to severe, more than 2 to 3 days in duration, and where opioids are typically used should include context, relevant measures of opioid use. So that could be the number of hydrocodone doses. It could be PCA morphine consumption. So I've tried to stay generic at this point and say context relevant, depending on the acute pain condition.

Then this is maybe a difficult one, but it's kind of a utopian statement, which is measurement of opioid use should ideally span a typical time frame that opioids for that acute pain condition are being administered. So if we're talking about pain after abdominal aortic aneurysm repair, where patients have an epidural, and they're in hospital for 1 to 2 weeks.

Then they go home, and they could be on opioids for another couple of weeks, typically. Then, I'm not sure of the relevance of looking at pain for the first 12 hours. It may tell us something, but if we're really thinking about the

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management of that condition, we should try and think about what the natural history is of the opioid consumption. No one's yelling me down yet.

So moving on with some other things, and this is a little more minutia but some granularity that maybe we should add. Acute pain trials assessing opioid use should preferably, if possible, restrict the non-study opioid to a single opioid chemical entity. For example, just pick one opioid that you're going to use, or at least if you can't do that, then you'll need to use equianalgesic dosing data to consolidate the opioid-use data, and that's going to give you some more uncertainty there. What's the right equivalent if you're using morphine or oxycodone?

This goes to the timing interval. Acute pain trials assessing opioid use should assess opioid use with a temporal resolution that reflects appropriately the expected temporal profile of the intervention. So I'm not talking about what I said here about the natural history of the opioid use. I'm saying if we're looking to track the effects of

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a drug that lasts for 4 to 6 hours, then if you only measure 3-day opioid consumption, you actually may miss the difference that you're looking for.

So you need to think about the non-study intervention and the temporal profile. So you're going to need more temporal resolution for your opioid consumption data tracking.

This is kind of way out there, but it sort of got me thinking. If we do go into the direction of studying more complicated patients who have opioid use disorder, the ones that we said are at highest risk and need the biggest challenge, maybe acute pain trials should somehow consider and incorporate the possibility of non-protocol and/or illicit opioid analgesic use.

So if someone else is taking something, clearly, that's a protocol violation, but we've had entire IMMPACT meetings about how to be aware of that and how to try to mitigate those challenges.

Then not necessarily recommendations but research agenda items, some validation. So maybe we need to do more research on how to integrate

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pain data and come up with the optimal composite score of rescue analgesic use and pain outcome data. And as I said before, doing naturalistic studies and really knowing what is the typical temporal pattern of opioid use on an acute pain condition-specific basis.

Now, we'll move on to talking about opioid effects. And Raj gave a wonderful, I think, really review of this in terms of mechanism, temporal profile, and things like that. And again, this is a review from 2002, so long proceeding the opioid crisis. This has been something that perioperative pain physicians have long been concerned about and trying to work on the various patterns of opioid related adverse effects.

This has gotten its way into analgesic clinical trials, and I think the important thing and the distinction I want to make here is that different method assessments can range anywhere from patient-report types of opioid related symptoms to health provider or clinician kind of non-study personnel data that might come up in

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records, versus specified objective investigator assessed and reported outcome.

Here's an example of a prominent meta-analysis that was reported in 2005 by my Marret and colleagues, showing that NSAIDs reduce opioid consumption by about 25 percent and also reduce nausea and vomiting by about the same amount. So it seems to be a clinically relevant effect.

This was shown in a fairly heterogeneous group of analgesic clinical trials. When you start digging a little deeper, you see that the measure of post-op nausea and vomiting was all put together. Some studies measured vomiting. Some looked at antiemetic use. So there may be a need or a benefit from tightening that up and using validated scales of nausea, for example.

I don't know if Penny's here today, but also patient engagement and finding out what is more important to patients, ongoing nausea where you don't vomit or is vomiting a horrible thing and that sort of thing.

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Here's an example of maybe something, a clinician recorded outcome that's more -- I think time to first bowel movement is kind of objective. And this is something that has been tracked, and here's an example of a systematic review of intravenous lidocaine after abdominal surgery, showing a decreased time to first bowel movement. So this is something that has already been incorporated into multiple analgesic trials such that it has shown up in systematic reviews and meta-analyses.

This is just repeating what we said already, and I would say that acute pain treatment trials that assess opioid use should also assess context-relevant opioid related effects. So it sounds obvious, like the porcupine, Brett, but really, the clinical relevance of a number of milligrams of any opioid is really minimal, I would suggest; and that really we want to look at what the impact is on the patient, so the adverse effect

Acute pain trials assessing opioid use and/or effects should also assess pain intensity.

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I think we've talked about this, in addition to maybe other pain relevant outcomes like quality of recovery, physical emotion function.

I don't know how prescriptive we should be, but I'd say an opioid-sparing study evaluating opioid use and opioid related adverse effects only but not also assessing pain should be discouraged. I don't know. I don't know what Sharon would say about that at FDA. I'm putting it out there anyway.

Acute pain trials assessing opioid effects should, as much as possible, use validated measures. We've already seen some excellent measures that have been developed and used, and we have, I think, a lot of opioid related measures that are in clinical trials that are not necessarily validated. So there may be more work to do, I think, to clean this up a little bit further.

Just as a reminder, I didn't know, again, how prescriptive we wanted to be, so 2003, you've mentioned the domains, and then 2005 got a little

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bit more bold and recommended specific instruments. And I'm not sure whether we want to do and recommend specific scales or scores, but in any case, if we do, I thought I would just put ad classic paper, which I think was used to guide the 2005 IMMPACT paper in terms of the different criteria for outcome measures, and there may be other sets of criteria that are being used now. But looking at the appropriateness of the measure, acceptability, feasibility, interpretability, precision, reliability, validity, and responsiveness.

So we can put that slide up again if we want to have a discussion about specific measures or other issues with that.

I don't know how long things are going, but just some future directions and maybe more research agenda items. I had the pleasure and the honor of working with Dan Carr, Paul Desjardins, and Henrik Kehlet, working on a review article on current methods and challenges for acute pain trials as one article in the ACTTION special issue on clinical

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trials of pain treatments. Once everything is all done, it's going to be all published as a supplement.

Some of the recommendations we had made for future improvements included -- in particular relevant to this talk -- development of trial methods that focus on treating complex patients at the highest risk of severe acute pain. And it's something we talked about a little bit yesterday. And I think to extend that a little bit further, to focus on patients who are at the higher risk of developing new chronic opioid use as well.

I've had some chats with people, and saying that we should do studies in opioid addicts or people with severe depression sounds like the right thing to do and it is the right thing to do, but any of you who conduct analgesic clinical trials know that that would be very challenging. And I think John Markman had put up -- I think it's very telling that the Mark Sullivan study of opioid tapering, that took 3 years to recruit 35 patients, I doubt that that's a group of lazy investigators,

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and I don't think that was the problem. I don't think that's what John was suggesting either.

These are very challenging patients. Probably the dropout rate is going to be high. We already know dropouts lead to uncertainty and we're scratching our heads about imputation. There's a reason why we like to pick clean populations.

So I'll raise the question, at least. Can we feasibly conduct reliable and valid trials that involve patients with preexisting chronic opioid use? That's already been demonstrated in a few analgesic clinical trials. And one example is a Loftus and colleagues in 2010 did a trial of ketamine for pain after a low back surgery in patients that had to be on opioids to be on the trial, and they showed an analgesic effect of ketamine versus placebo in that population.

So that's very important. First of all, it's feasible to do that type of study and also to know what the efficacy of those interventions are in this more challenging population.

Then it gets a little more challenging,

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populations with mental health and substance-use problems; also looking at preventing transition from acute to persistent pain. I think if we had interventions that could reduce that to a very small number, maybe our concerns about chronic opioid use would diminish substantially.

Again, I'll make another plug for something that we really need to learn more about. How really is pain managed in home and community settings after hospital discharge?

So I'm happy for questions, and we can start the discussion soon. But I thought I would just leave up here just some bullet points using the PPICO format as we can have your eyes glazed over it as we have our discussion. So thank you.

(Applause.)

Group Discussion

DR. GILRON: Lee?

DR. SIMON: Simon, Boston. One of the big issues that I don't really get is obviously we're going to need to give people pain killers for acute pain postoperatively, immediately, for that short

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period of time. What is the quality of the studies to understand those that get discharged with the need for opioids versus not the need for opioids?

In the context of the acute pain trial, we want to use the best possible therapeutic intervention to make the patients feel better. It may be that we don't really understand how to use them exactly, but what do we know about that transition period to the outpatient and how that's handled, and whether or not there are other drugs? Are these parallel trials where you do noninferiority versus opioid, versus non-opioid, and how do you measure that? Because these people are going home.

What do you know about that transition period and how that's been studied?

DR. GILRON: Thank you. Our group, we're working with -- one of our senior residents at Queen's is leading a systematic review that we've tried to -- similar challenges that Shannon had, we've tried to look at pain after hospital discharge. And there have been some focused

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articles writing about that.

I don't think anyone -- as far as we can tell -- has conducted a focus research program to look at that very problem. But some opportunities arise.

For example, groups that are looking at interscalene catheters to give local anesthetic, we'll send patients home with them and follow up over the phone. So as you can imagine, you've got an invasive indwelling catheter, so people are going to be watching them very closely. So there have been some placebo-controlled trials in that setting, and that gives us a little bit of information.

That's one issue, getting away from the trial setting and into the real-world setting, that I don't think has been well studied. There's a disconnect, and people have talked about that. We have the acute pain management service in the hospital that's typically -- at least in Canada, it's staffed by anesthesiologists. We use regional anesthesia, a lot of intensive -- Dr. Gan talked a

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lot yesterday -- approaches.

Patterns of hospital discharge have changed a lot over the years, and people will get out fairly quickly, typically, unless there's a reason of -- like a nerve block is something you'll to follow up about nerve injury. I don't know if it's different in the state, but anesthesiologist are not typically involved in a patient's care. It goes to the most responsible physician, which is the surgeon together with the primary care physician.

So I think that's potentially an element of fractured care, and that's why I say that's a clinical gap and a knowledge gap. I don't know if anyone else has --

DR. RAUCK: Well, I was going to comment a little bit, Lee. There are some unintended consequences because I don't think we know a lot about what's happening when they go home. For instance, in North Carolina now, adopting CDC guidelines, the surgeons are only allowed to give a 7-day prescription for opioids.

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So I'm in a chronic pain setting, and we're now seeing patients who are 7 days, 8 days out from a big back surgery or a knee surgery, and they're coming into my clinic to see what are they supposed to do about their pain management. The last thing I need to do is get involved in a perioperative setting there.

I don't know. Are they having pain because they got an infection or they got some other surgical complication? Why am I getting drug into this? That's not the kind of patient I should be seeing in a chronic pain setting or trying to make all these clinical decisions. But that's the realm because of, again, that that's being driven by this opioid crisis and fear of giving these folks opioids, and the push in the U.S. to get them out of the hospital in 2 days, which is probably too early anyway.

So, TJ, I'll let you add to that.

DR. GAN: Rick, I think you really brought up an issue that I think is going to become even more important. And you should be glad in North

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Carolina it's 7 days. New York is 5 days, and you could imagine those patients that are going to end up in my chronic pain clinic about what do I do with that. And this is starting to emerge as a real issue.

My question, Ian, I think one of the challenges that we have here, currently, we do acute pain trials, but we don't really systematically collect the opiate adverse events. Most of the pain trials, almost 99 percent, is collecting this as adverse event reporting. And we all know that adverse event reporting is garbage. I mean, you don't really systematically ask patient of the symptoms. Some people volunteer to say I have these adverse events; other people don't.

So I think, if anything, if the group can come up with some sort of standardized way to collect some of the adverse events -- and I think there are -- we've talked about nausea and vomiting, and again, I have a passing interest in nausea and vomiting. And some of the

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recommendations are pretty specific in terms of collecting symptoms of nausea and vomiting. You collect the incidence, you collect rescue antiemetics.

So there are some fairly well accepted way to collect certain symptoms, but I think that we need to have a system for pain trials to collect these adverse events much more systematically.

DR. GILRON: So I appreciate your comment. I don't necessarily disagree, but I'm not sure if there's consensus, at least in the analgesic trial world, on how to optimally track adverse events. I don't think -- one question is voluntary self-report on one end; how are you feeling, and you may get no response.

I was talking to Lee at breakfast about patients deliberately underreporting side effects because of the potential consequences, to a very prescriptive and itemized question asking about every specific side effect, where that may potentially lead to overreporting of side effects.

So what is clinically relevant and what's

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going to be bothersome to the patient? And it depends on the patient. There are CBO effects. I would suggest that we put that maybe as an agenda item. So I don't know -- I don't know that a trial should have like a specific list at every designated time point of all these different side effects that they're rating. There's potential for rater fatigue. There are a lot of potential issues.

My response would be, maybe we need to have that as a research agenda item, what's the most patient-relevant way of assessing side effects, opioid or otherwise?

John?

DR. FARRAR: Just a quick comment about that, and then to another point. Sorry. John Farrar, University of Pennsylvania. In clinical trials conducted by companies that don't prospectively ask about side effects on purpose because of the reporting requirements of that, in every clinical trial I've been involved in, we asked specifically about side effects. And there's

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clearly a difference in the number of reported. But I think it's better information, and I would strongly recommend that that's where we should be headed.

What I wanted to get at, though, was the issue of when we send people home early, as Richard was saying, they need follow-up. What it brings to mind is that there was an interesting report about the reduction a perinatal deaths of children in the Norwegian countries. And the point made there -- compared to the United States and other theoretically advanced civilizations, theoretical -- is the fact that what they get is daily calls from somebody at the hospital that says, "How are you doing? What's going on? Are you figuring out how to change the diaper? Are you sleeping them on their back or their side?"

At least in the United States, none of that happens. We expect patients to go home and know how to treat their pain and to use the medicines that we spend our lives learning how to use.

So I think that there's a whole issue there

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that is really, really important. But with regards to the conference that we're talking about here, what strikes me is that we need to be very clear about what we're talking about. And what we're talking about here is a procedural process to limit the amount of opioid exposure, and potentially opioid risk, related to what happens when the patient goes home, and how do we train them to use these, and how do we follow up with them? Do we give them 5 pills or 100 pills?

And I would argue that even in those nice graphs that you showed at the beginning with differences in pain and different kinds of procedures, that the variability amongst the people is going to be so broad that if I want to cover everybody, I give them 30 because somebody is going to need 30, and I don't -- Howard was saying it's illegal to torture people for confessions, but we torture our patients all the time. On the other hand, we don't want to give 30 to somebody who's going to use 2.

But that's a procedural process. That's not

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about opioid sparing in the way we were talking about before or the way you presented, with giving NSAIDs or getting other kinds of medicines. And I think if we keep those two things separate in our minds and clearly be very specific about what we're trying to address, this will be a much better place.

Bob, you talked about it maybe being two articles. I am not sure; it might even be three. There's been a lot of discussion about various aspects of this, and I'm not sure they all fit into the same process and wonder what you thought.

DR. GILRON: Yes. I agree with everything you're saying. I think a lot of the issues that you're talking about is how to improve the care of people after they leave the hospital. What I was hearing yesterday from a lot of people was leading to a proposed recommendation that an outcome measure of analgesic trials, acute analgesic trials, should be what is the duration or number of doses required for analgesia as an outcome measure. And the way most acute pain trials are being

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conducted, that's completely not feasible.

So that's kind of one of the reasons why I relegated that to -- well, first of all, research agenda, to know if you're going to do a study in knee arthroplasty, what's the expected duration of pain? Obviously, you're going to have some variability, and what is going to be your standard analgesic protocol in the control group?

So if that's going to be 60 pills of oxycodone, then that's -- and as I say, that landscape is also shifting, so that's going to affect it. But from the perspective of trials, I think we need to just be very focused on that and say we have to learn more about it.

DR. SCRANTON: Rich Scranton from Pacira. For one, on patient reported outcomes, as a sponsor, I have no problem obtaining patient-reported outcomes and discerning that differently than how I assess adverse event reporting, and I've done that for decades. But I think two things. In the acute postoperative period or acute pain experience, I was toying with

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the opioid avoidance -- whatever the definition -- that could be the number of rescues; it could be opioid-free days; it could be time to first rescue; whatever we've come up with as an opioid avoidance that we think is ideal.

But as we're saying, once you go beyond that intense kind of a controlled setting to going home -- and we're talking about persistent use or use outside -- I think then the problem I've been having, that's a different realm for us to measure. And then controlling that prescription and putting it in the protocol, I've not done that yet, to say you're only allowed in this protocol to give 10 oxycodone, and then we're going to kind of see what happens. It's just resistance from surgeons and all of that to kind of put those patients at risk. So that's been part of the problem for us.

But also I would say for us, if you're going to start looking at persistence, then you have to look at patient factors that can predict persistence. And we've been doing that, a DoD registry -- I just talked to Mike Kent last

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night -- where we've actually been looking at 6 months, and we've been measuring PROMIS tools at baseline, and then looking at interventions, and then looking at opioid use patterns over 3, 6 months in a variety of surgical procedures, which is going to help us then determine what we can put into our next trials, what tools will predict persistency that I need to account for in my stratum of studies.

But a lot of this information is just not known, so I'm glad we're having this discussion because I don't know how to design those studies because there's just a dearth of information.

DR. GILRON: Yes. This is exactly what we want, is hands up and red lights. It's 9:15, so I'm going to ask Richard Rauch to come up, and we will continue this. Oh, I'm sorry, and Jen Gewandter.

Mike?

MR. ROWBOTHAM: Mike Rowbotham, Sutter Health and UCSF. As we've gone through some of these talks on acute pain, especially the

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post-surgical outcomes, it seems there's been a lot of discussion in patients who were not on opioids previous to their surgery, but we know, especially for hip and knee arthroplasty, a lot of times this reason for the procedure is because they have intractable chronic pain.

I'm just looking at data, and some of this is your own data, but this is data I got from Eska Osphong [ph], who's published in this area. In Scandinavia, they can get the data out of these databases, and they have studies with up to 9,000 patients. And of the ones who are using opioids preoperatively, at a year, about 20 percent of them are actually using more opioid post-op than they were preoperatively.

I bring it up not because I have an answer but because it's a huge confounder. It's pretty clean and straightforward. If you've got a patient who comes in and they've got an unusual trauma to the joint, and it has to be replaced, and they weren't on any opioids beforehand, those you can really follow very cleanly through different

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electronic health record systems. But for the people who were chronic pain patients and then had a very painful surgery, hard to sort through what to do with them.

DR. RAUCK: I was going to say, even before that [inaudible - off mic].

DR. HERTZ: Actually, I was going to ask another question as part of that. Sharon Hertz. If you're trying to study an analgesic in a particular setting and you're enrolling people who have very different backgrounds getting into that setting, it seems that you're studying a heterogeneous population. That's not necessarily a bad thing, but in terms of assay sensitivity, is that something that we want to risk reducing? Because we now have a mixed bag, we may not even have it fully -- what's the word? It may not be evenly distributed across treatment groups.

So we could get a very spurious response if the two groups respond differently and they're not evenly distributed. So is that the approach? Should it perhaps be two different studies looking

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at both of those populations who both have needs?

DR. RAUCK: Richard Rauck. I'd love to follow up on that, and particularly in the context you're saying, Mike. I hadn't seen, Ian, the breakout of those 4 different kind of subsets.

I might be reading between tea leaves, Sharon, with you, but I heard yesterday, pretty clearly, any trial that sacrifices pain relief isn't going to be looked at that favorably, number one. And number two, our pharma friends, if they went to inflate their data, obviously percent reductions, blah, blah, blah.

So I kind of wonder if we ought not to be more looking at these subsets. I would postulate -- I don't know if the group would agree -- looking at those 4 groups that, Ian, you put forward: preexisting chronic pain patients on opioids; those with mental or substance abuse issues; addressing the community context of opioids and opioid utilization, or things that way; and then I guess the fourth one was that acute to persistent pain.

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Would that even be really more relevant to you guys at the agency if pharma or other people looked at one context of those 4 groups and the impact? Because I would think to you, Raj, and all your stuff you showed yesterday with all the adverse events and where that is epidemiologically, if we don't cover in those 4 subsets, maybe 90 percent of the people at risk in opioid exposure, if you will, or either public health-wise, or acutely, the risk that we see developed -- because to be honest, Mike, in the medical and legal arena that I see, the chronic pain patients who have these procedures are the ones who often get into real trouble in the hospital. They overdose themselves because they're trying to get pain relief, and they end up as medical-legal cases, and blah, blah, blah.

So I just throw that out there. I don't know if people want to respond to some of that.

DR. GILRON: Mike, those are very telling. I don't know that specific data set from Denmark, but it speaks to the issue of persistence of

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chronic pain. So at least when we talk about of transition studies or chronic pain prevention studies, I think it's always important to separate out whether the surgical procedure is being done as an analgesic procedure versus someone who came to the procedure with no pain, and all of a sudden they have a new chronic pain condition.

So 20 percent sounds like the 20 percent of people who continue to have pain after arthroplasty, but I don't know if -- those are just the ones who were on a higher dose. I don't know if they were -- there were other ones who were still --

DR. ROWBOTHAM: For example, you guys know this because you're anesthesiologists. I'm a neurologist. I know at UCSF, for patients who were on pre-op opioids, those are the ones they have special protocols for post-op pain management, where they're very quick to go to ketamine to try and limit the amounts of opioids. These patients require really kind of special handling. So they are at risk for uncontrolled postoperative pain by

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virtue of the fact that they had pre-op pain and opioid use.

DR. GEWANDTER: Can I just interrupt for one second? Since I'm the one that has to write this paper and we don't have that much time for consensus, I wonder if we could bring it back a little bit to what are the objectives and the hypotheses that we're going to be trying to answer? And then that will lead into which population should we be studying, just because I think we don't have that much time.

DR. GILRON: So if we start just looking at this study purpose -- thank you, Jen. That's a good idea.

I think the way Bob and Dennis have phrased this, we've talked about opioid-sparing trials, which was kind of why I asked my question yesterday; should opioid consumption be the primary outcome of this study? Maybe we should start off by talking about a trial where the purpose of the trial is to reduce opioid use. We can start with that.

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DR. DWORKIN: I completely agree. One thing I just want to say is, I love this slide, and I think as far as I'm concerned, I think we could use this PPICO format. but I think both for acute and chronic this afternoon, we're really talking about, at least the way I view it, multiple purposes. There's not one purpose, because I see purpose as study hypothesis.

So I've been making a list of various acute pain study hypotheses, and at the top of my list -- this is not in any kind of sensible order -- Intervention X, and Intervention X could be gabapentin or it could be self-hypnosis, intervention and anything else. Intervention X meaningfully prevents the initiation of opioids in patients undergoing orthopedic surgery.

Now obviously, that would have to be fleshed out, which kinds of orthopedic surgery and what do we mean by meaningfully prevents? But that hypothesis would be that we would be testing in a clinical trial; that we've got an intervention that meaningfully reduces the percentage of patients who

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initiate opioids when they're recovering from surgery.

Now, I don't know if that's a sensible hypothesis. Maybe this group would think that's not a reasonable hypothesis for opioid sparing. But I would personally be thrilled that by the time we have lunch, we had a set of 5 or 6 or 7 hypotheses like that, that the group thought would be meaningful to test in studies of opioid sparing.

So not to beat a dead horse, which I'm often accused of doing, but the second hypothesis on my list is Intervention X -- and again, it could be hypnosis, it could be gabapentin, it be ketorolac -- meaningfully prevents the need for an opioid prescription at discharge; something we talked a lot about yesterday. Maybe the patient doesn't go home with a prescription even though they've had opioids while they've been recovering.

So that's a totally different hypothesis, preventing initiation versus preventing prescription at discharge. I won't read the other hypotheses I jotted down during your talk, Ian, but

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for my purpose, I think this is great. But I just want to emphasize I think there are 5, 6, maybe 8 different hypotheses that we could end up with after this discussion.

Does that make sense?

DR. GILRON: Well, it makes sense to me, but there's a reason why in my talk I started with the evolution of traditional analgesic trial design because the hypotheses that you've just mentioned seem to be aligned with the goals of this meeting, but when I hear that, it sounds like Henrik Kehlet saying we're going to do a trial to see if we can get people home on the day of surgery after their hip. And if you do a trial and you set up your clinical infrastructure, and every one patient expectation to do it, then you will succeed.

So to me, it's just a different way of thinking about hypothesis testing in an analgesic trial design, and I'm not so sure that it's the intervention that's doing it or --

Jim, and then Howard, and then Denham, and Shannon, and then Brett. Jim, let me start with

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you. I'm sorry. We'll get some more input.

DR. RATHMELL: Well, I want to build on that because it's probably on your list already. But I think, Ian, what you pointed out were some really difficult questions that we could address. One is the high-risk population.

DR. GILRON: Jim Rathmell, right?

DR. RATHMELL: Right. Oh, Jim Rathmell, right. Brigham.

So think about the risk of persistent opioid use, so Intervention X reduces persistent opioid use after major surgery, or after major painful hospitalization. If we want to get into the medical realm, you could even do it that way; or Intervention X reduces the risk of persistent opioid use in patients who received their first dose of opioid during a given hospitalization.

Those are the things that really get at the problem to society and the individuals that go on to persistent opioid use and some of which is opioid-use disorder and some of which is chronic pain. The overlap is enormous.

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So that's getting at a testable hypothesis. And it doesn't say it has to be a drug. It could be a new model of care, which would be tremendous. We've got a service that sees people at the day of discharge, and the same people actually see them at 10 days and check up on them, and teach them how to use their medications, and make sure that they're using them appropriately, and refills when appropriate, instead of getting a call or a return to the emergency room. And their outcomes could be decreased emergency room visits and rehospitalization.

So I'm just getting at the idea. Really, we can test a whole lot of different things with one hypothesis.

DR. RAUCK: That's building off of Bob. That's good.

Howard?

DR. FIELDS: Howard Fields, UCSF, a friend of Jim.

(Laughter.)

DR. FIELDS: I'm going to build a little bit

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on what Jim came up with, and I'm going to sound a little cranky.
So the whole point of, it seems to me, looking for opioid sparing is the implicit hypothesis that if you reduce the amount of opioid that you prescribed in hospital and immediately following surgery, you will prevent the development of an opioid-use disorder. Right? That's the hypothesis.
The problem is that's a huge study. If you're going to wind up with 4 or 5 people that have opioid-use disorder out 1,000 or 2,000 patients, that's a completely different kind of study than what we've been talking about up to this point.
DR. RAUCK: That's fair, and I think that something we've got to consider for sure.
Denham? I'm going to take it in the order as I see it.
DR. WARD: Ward, Rochester and Tufts.
As a sole respiratory physiologist in the group of pain specialists here, I just wanted to

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not lose track of the fact that we'd like to reduce the amount of opioids, but we also want to reduce the incidence of respiratory depression both in the immediate postoperative period and the patient that goes home on opioids with sleep apnea and dies in their sleep the first day home.
So rather than just talking about lumping adverse effects, adverse events, safety concerns, safety outcomes as kind of a generic item, I think that risk of going back to the oldest studies that say we didn't see any respiratory depression, if you don't look for it, you aren't going to find it.
So I'd rather say outcomes should always include an explicit measure of respiratory depression while the analgesics are being used, and not just lump respiratory depression into the bucket of adverse outcomes.
DR. GILRON: I'll just quickly follow up on that and maybe build on it, and say when we talk about high-risk populations, we're talking about high risk for pain and opioid use. But maybe we also have to have a bucket of trials to look at

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patients with obstructive sleep apnea after major abdominal surgery who are at high risk for acute toxicity of opioids.
DR. WARD: My criteria for an ambulatory surgery for having A sleep apneic patient is can I send him home without opioids? And if I can send him home without opioids, then I can do it in an ambulatory surgery center. If I can't send him home without opioids, then they have to be hospitalized.
DR. GILRON: As long as the block doesn't wear off at 3 in the morning.
DR. WARD: Absolutely.
DR. GILRON: I think, Howard, to follow up on yours, which I think is really relevant as well, it goes back to Bob's thing. I think you would have to find that population to study rather than look to see if you're really preventing opioid-use disorder. So you probably have to get into that bucket of patients who you identify ahead of time who have an opioid-use disorder or problem, and can you then by opioid sparing in the acute pain -- do

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you either prevent it from becoming worse or can you limit it or affect at all by some Intervention X that doesn't let for recrudescence or whatever.
Shannon, can I jump to Sharon real quick, and then I'll come back to you? I've got you next.
Sharon?
DR. HERTZ: I feel very special.
(Laughter.)
DR. GILRON: No. What would make you think that?
(Laughter.)
DR. HERTZ: They don't jump to me at work.
(Laughter.)
DR. HERTZ: Yes. I think we have to be very careful. We're starting to mix things. So it seems that there's a lot of interest in pursuing opioid reduction for the sake of improved symptoms overall. That's not a bad thing as long as, of course, the new drug doesn't silently destroy your liver, but at least you're not vomiting.
So I think that's one thing, and that may be

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a very useful thing for patients and the healthcare system, is to have people feel better. Then there's this other thing, and that is what happens after patients "should," in air quotes, be better. And that is a combination of what do they need when they get home, but also these other risk factors.

So a person who has no risk factors for opioid-use disorder, who doesn't have chronic pain, who leaves the hospital after a successful whatever, and then has a typical or average course post-op, that's easy-er. But that's a population in which one could explore what is possible with a new drug. Is the new drug able to either reduce in-house symptoms or at least reduce the need for long-term opioid therapy, or even short-term opioid therapy? And that's often the easiest population to study, but that's not necessarily the population of greatest need. So the key is not to stop there.

Then the real societal benefits as well as the patient benefits is to then go on and study other groups: the chronic pain patient who's already coming in for some acute intervention; the

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person with risk factors; and we get a layered thing, a layered set of data, where we can then really understand who benefits from the product or the intervention how clinicians can adopt it in a sensible way.

So I don't think it's an either-or. I see it more as a staged approach to peel the layers away of what the product is and isn't capable of doing.

And one other thing. When we talk about preventing opioid-use disorder, how long do we have to follow someone to sort that out? So that's the other thing; is there an alternative to actually waiting for someone to meet criteria for opioid-use disorder that would predict somebody getting into trouble, which would be more pragmatic to study. And therefore, perhaps companies would be more willing to do it.

DR. RAUCK: Great points. Anybody want to add to it?

Shannon? She's been very patient.

DR. SMITH: So I wish I had gone after or

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before Sharon because now I feel like my comment might not be as accurate. The one thought I was having, though, when you said, Rick, that we should be not wanting to reduce the analgesic effect, is I was thinking a little bit about what Dr. Fields said yesterday about this optimized dosage, and also then what Dr. Gan was saying about trying to look at what patients want.

So trying to come back to figuring out not just are we reducing opioids and maintaining at a certain acceptable level, but are people willing to give up a little bit of pain reduction and not have the side effects? So I just wanted to think about that maybe as a hypothesis or something that we might want to study in, even in acute trials, not just in chronic pain.

DR. GILRON: I agree, Shannon. I was trying to think of that as well. For me, we're not going to change the self-report pain score, but tolerability of pain is different to every person. I might be in the hospital with a 5 or 6, and to what TJ says, I'd rather have that than throwing up

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or whatever it is. But to me, sometimes pain could be thought of as a binary thing, tolerable or intolerable. And whatever tolerable means to me is going to be very different than somebody else.

But I almost think that's more relevant, because I don't want you to cram another pill down my throat to get to a pain score of 3. I'm okay at 5, if that's what I give you, maybe. I don't know. We're all different. Right? And maybe somebody else wants to go to a 2 or 1. I wasn't going to bring that up because I wasn't sure we could solve that or open that whole can of worms.

Sharon, I'm a little curious as to for folks who are trying to design these trials don't know that they can put all those different components into one trial. And I know they cringe when they think they have to do 4 or 5 trials to look at some of these special populations versus something that's more global for them when they're trying to put a package together or trying to look at something that can get into their label.

I don't know if it's relevant to how they

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should think of that or how meaningful is it to you if you're only addressing some of those populations? I know there are folks in the room working on this acute to persistent pain kind of question and some other things, but I don't know if there's any guidance that way for them.

I could see maybe a trial that actually looked at subsets of patients within the trial, or looks at some of that out, or they identify them. I don't know how that is and how the companies would look at if they only had a label that expanded one group of those 4 that Ian put up or something, how that -- I guess that's all new territory for you guys as well.

DR. HERTZ: But right now, we're just getting the patient who has no risk. Right? We're excluding everybody else. So that's what is being used for marketing applications already. On the one hand, yes, it's a burden to do many studies. Again, we're not talking about regulatory issues. We're not talking about what's required or not required; just in terms of understanding what the

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benefit of a drug is.

So right now we're not getting any of those other patients who may be the ones who ultimately benefit most. If you mix them into the same study and then do some analyses, how do you power the study? And then are you going to reduce your ability to even show any effect if you have all kinds of all comers?

But also, from a strategy perspective, it's not necessary to have every piece of information possible about a product in the initial application. It could be done over time. These are, I think, the important questions to ask, and however they get staged premarket, postmarket, all at once, is a separate issue.

DR. GILRON: We're going to try and have coffee at about 9:45 if we can. So how Ajay, and then Brett. And then if you have any other questions, write them down and remember them for after the coffee break.

DR. WASAN: Thank you. I'm Ajay Wasan from the University of Pittsburgh. I think one of the

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areas we're getting hung up on is this difference between the explanatory and the pragmatic trials. And I think it might be helpful in the paper for instance to have a table for recommendations for explanatory and recommendations for pragmatic.

The other key thing related to this, I think, is that the majority of the research in this area in the past three years has actually been pragmatic. It's been looking at prolonged opioid use and looking at changes in patterns of prescribing at discharge. And mostly the interventions have not been single drug. They've been more, not holistic, but comprehensive interventions, whether it's provider education, or whether it's service delivery, whether it's ERAS.

So unlike many of the IMMPACT papers in the past, this paper may actually have a lot more to say about conducting pragmatic studies in this area. So it's something to keep in mind because it's a different mind-set.

DR. STACEY: Brett Stacey, Seattle. I was thinking back to the earlier days of these meetings

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when we're talking about how to improve chronic pain, the analgesic trials, and the idea of adding multiple domains for assessment, So psychosocial function, physical functioning, and sleep. A bunch of other things were suggested as valid measures to look at an analgesic response.

In addition to looking at giving guidance for how to design a trial for opioid sparing, which in reality is a very small minority of acute pain trials -- they have opioid sparing in the title, not that many -- we should say that if you're doing an acute pain trial in a condition in which opioids are commonly used, an assessment of the opioid-sparing effect is appropriate to include, and here are some options for how to do that.

I think that is broader, pushing this out and saying this should be in trials that are considered to be high-quality trials of acute pain, period. And then different guidance for the subset that, really, the design is to focus on opioid sparing.

DR. MADSEN: I'm Torsten Madsen with

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Aptinyx. I guess I struggle a bit with the buckets of definition. There is acute pain, and there is acute settings. There's somebody coming in, in an acute pain setting, with chronic pain disorder, preexisting, and there is a concept around when you are discharged from a hospital, which is also introduced as something relevant to measure.

I think it would be really helpful -- and I find myself supporting Dr. Hertz on having different buckets of concept of patients. Otherwise, it will be too confusing and really too hard to get anything out of. I'm not sure hospital discharge in your Canada clinic is the same as hospital discharge in Illinois where I live right now or, or elsewhere. I'm not sure it's meaningful either from a clinical endpoint point of view, at least as it is right now.

So I think it would be helpful for me to keep that in mind when you go into the clinical study. And also, if there is an operationalizable definition between when acute becomes subacute and when subacute becomes chronic in the setting of

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consequences of perioperative analgesic studies, I think that would be helpful, too.

DR. GILRON: I agree with everything you've said. I tried to get around that by just everywhere I had a recommendation to say "context relevant" or "context sensitive." And I think for the acute pain recommendations paper, we had some definitions. But yes, so there's flare. There's acute or chronic, like of the same type of pain. There's surgical procedure, which causes acute pain in people with chronic pain remote from the surgical procedure.

So we could have a general discussion about that. I don't know if we want to make specific recommendations about each bucket, but I think that's certainly something that we could do that would be worth adding.

So we'll break for half an hour. Thank you.

(Whereupon, at 9:43 a.m., a recess was taken.)

DR. GILRON: Jen, I'm going to let you present some of this.

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DR. GEWANDTER: All right. Thank you for your attention and sitting down so quickly. What we're hoping to accomplish for this paper potentially is a list of potential hypotheses and objectives that could be pursued in an acute pain trial for opioid sparing. I recorded the examples that Bob gave, and I think the two really important things to think about that we hope to cover in the paper are, considering these specific hypotheses and outcomes, what would be the important things to consider in terms of population?

I think the easiest example is Dr. Ward's example where his hypothesis is that Intervention X prevents respiratory depression post-op, and we added and maintain sufficient pain control to all of the hypotheses, so it's more of a well-rounded, optimizing care than just opioid sparing. One inclusion criteria could potentially be they have OSA because they would be at higher risk of respiratory depression.

The other thing that we hope to be able to recommend in the paper is the specific outcomes

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that you would use if you hoping to test these hypotheses. We have two options that we could do right now with the rest of our time. One would be we could take these hypotheses that we already had, and we can kind of flesh out some suggestions for the population and outcome, or we could add to these potential hypotheses that you guys think are important.

I kind of favor the latter at first at least because I think that's where your input is really valuable. And in terms of inclusion and outcome measures, I can work on that, and then you can give feedback in the rounds of feedback, which is a little bit easier for me to do than to come up with what are the most important things to study, which I think is really important to kind of discuss and flesh out.

So that's what we're hoping to do. I can see at least 4 of the ones that are already up here. If you have others --

(Pause.)

DR. GILRON: Go ahead.

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DR. HAYTHORNTHWAITE: Jennifer Haythornthwaite from Johns Hopkins. I'm still not sure we're all in agreement of what opioid sparing means, so I wonder if we shouldn't have at least a 5-minute discussion about that based on yesterday. Because we've been tossing around a lot of different components, and it may be that some components are more important for some ideas than others. But I do worry that we're not in complete agreement on that.

We've obviously included -- I think most of us are in agreement that pain should be part of the concept. I think we're pretty much in agreement that side effects should be part of the concept and that it really -- we've been having discussions on my little row here about kind of the balance that most patients have and how it's so personalized about the amount of pain relief or reduction they want relative to what side effects they're willing to tolerate. And that's especially important for, I think, the acute pain.

When we start talking about chronic pain,

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because we have longer periods of exposure, we have lots of other issues, then the definition of opioid sparing might also cross into opioid-use disorder and other kinds of component parts. I just want to make sure we're in agreement.

DR. RAUCK: I'm a little confused. Are you thinking opioid sparing, how we should set up the trial or opioid sparing as a strict definition of it?

DR. HAYTHORNTHWAITE: This is going to be a paper about opioid sparing, so I think we need to be in an agreement with what we mean by that phrase. And this morning's conversation is about acute pain, so opioid sparing for acute pain may in fact be different than opioid sparing for chronic pain. But I think that we need to make sure we're on the same page for that concept.

DR. GEWANDTER: Do you guys want to answer that question?

DR. HAYTHORNTHWAITE: Well, I just put out --

DR. GEWANDTER: No. I'm talking to the

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person who raised his hand.

DR. HAYTHORNTHWAITE: Sorry.

DR. GEWANDTER: There are two people raising their hands.

DR. SCHOLZ: Just a comment, following up. The hypothesis that you put up emphasized the concept of prevention. I wonder whether that's a bar too high. I think opiate sparing, in my understanding, is already achieved if you can reduce the use of opioids. But prevention, I think prevention includes the concept of maybe preventing pain and entails a different challenge.

MALE VOICE: Who was that?

DR. SCHOLZ: Joachim Scholz, Biogen. Sorry.

DR. GEWANDTER: This is Jen, University of Rochester. I think one of the things we might be having trouble with is I think that opioid sparing can mean different things. Just looking at these 5 hypotheses, it means different things depending on how you set up your trial. So I don't think we need to box ourselves into one meaning. We can talk about that in the paper, that there are a lot

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of different ways to study opioid sparing. There are a lot of different objectives.

So I think that by doing it this way, we're actually addressing that issue directly by saying there's different ways to handle this, and these are the potential ways we could think of that might be most meaningful to handle it.

In reference to your question, I think what you're saying is you don't like the wording of hypothesis, one, because of the word "prevents the initiation of opioids."

Is that what you're saying?

DR. SCHOLZ: Yeah, but it plays into the understanding of opioid sparing. I think opioid sparing entails also reduction of opioid use. It doesn't just set the goal to completely avoid the use of opioids.

DR. GEWANDTER: So I think hypothesis 2 would be addressing that, so prevents the need -- oh no, sorry. So we don't have one yet for decreasing the dosage of opioids. I think that's what you're trying to say. So we can add -- well,

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that's what I'm trying to say. I think we should be adding to these, so that's what we're trying to do now.

DR. GILRON: It's Ian here. I'm going to opportunistically take a chance to say what I think Jennifer is saying could be addressed if we say that -- we had a little bit of discussion about this earlier, that opioid sparing should be, at best, a co-primary outcome, but also, at best, a co-primary study hypothesis.

I think the point is that we always want either pain or opioid related adverse effects together in the study hypothesis, and that might be an issue that I think -- I don't know if you're responding to it or maybe Joachim is also reacting to, is to say preventing opioid prescribing as the study hypotheses. It just sounds like it's missing some clinical relevance if we don't also necessarily tie it to another patient-relevant outcome.

I don't know. In the intro of the paper, we can try to come up with a definition or at least

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elements of what we -- rank order of what's important.

DR. JAMISON: Bob Jamison, Boston. What I've heard is that some acute pain trials could be prohibitive for a number of reasons, one of which is that we don't identify many people who get in trouble with opioids, then that would require a large number. And secondly, that sometimes the intervention is expensive, then you can't do it for everybody.

So I'm wondering if we could have some trials recommending two different hypotheses in the same trial. For instance, can we identify high-risk people? I think we have a lot of data that can identify what is high-risk persons and who gets in trouble.

Then secondly, can we identify ways to keep them compliant? Rob Edwards is going to talk a little bit about this. But we can talk about some of the interventions that help people track their opioid use, including a grant we've just put out looking at blister packs. And every time you use

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an opioid, it monitors when, and where, and how. And that's expensive for everybody, but it would be really targeted and really well used. For some high-risk folks, it would really help manage opioids.

So my point is maybe a trial could have two aims or perhaps two hypotheses, one of which identifies high-risk people; and secondly identify an intervention that might be challenging for everybody to use but could be really targeted to help people be compliant with their opioids.

DR. GILRON: So the first one, the high risk, is that an inclusion criterion or is it -- it's not an hypothesis for the study, it's -- after you got the study done, then you prove the hypothesis, then you could find them, or --

DR. JAMISON: So I guess there's a difference between an aim and a hypothesis. The aim would be to identify -- the aim is can we identify people at high risk for opioid misuse? And I think the answer is we have a lot of markers

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that help identify. And we even talked about, before, a previous history of opioid use or chronic pain, psychosocial factors, or past history of misuse.

So I think we can identify those, and that would be inclusion but also be a hypothesis; are we pretty good at identifying them? And then secondly, are there's some interventions? And there's actually a lot of technology out there that can track opioid use. And some of it's just pretty simple and other is a little bit complicated. But we can track how people use opioids after they leave the hospital.

Rob, do you want to -- did he step out?

DR. EDWARDS: Sure. I can just talk briefly about that. Sorry. Rob Edwards, Brigham and Women's. I see at least three aspects of Bob's nicely informed comment that we should maybe consider for the paper, and one would relate to whether we make recommendations based on inclusion/exclusion criteria and suggest that some trials be performed in high-risk samples because

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that enhances power and assay sensitivity, and that sort of thing.

I think Bob's second crucial point is that we'll likely need to pay a little bit of attention to how opioid use is monitored. We haven't spent a lot of time talking about that, but obviously methods range from patient self-report, to electronic medical records, to urine tox screens, to novel technological methods like a cloud-based assessment of opioid access using these, these blister pack technologies. and that may play into our recommendations as well if we're going to get granular enough that we're going to talk at all about how that opioid assessment is done.

Uh-oh. Have I lost the third point?

DR. JAMISON: It was a good one.

(Laughter.)

DR. EDWARS: It was. It was actually the best one. I saved the best for last, and I knew at that time that I ought not to have done that.

So I agree those are important things to put into the paper to consider at that level. I think

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we'll hang on to those and would want some of the input, but they're good things.

I got a question back here, I think.

DR. FARRAR: John Farrar, University of Pennsylvania. Let me bring something up, and you can decide whether we should put it off to consider after we finish this other conversation. But I'm struck, first of all, by the fact that you forgot control in the first hypothesis there at the end of the sentence, "maintain sufficient pain," which is an interesting concept.

(Laughter.)

DR. FARRAR: But more importantly, I think that phrase raises huge issues with regards to thinking about how we decide whether a patient has sufficient pain control or not. And it becomes even more complicated if you begin to think about patients who either have previous opioid misuse or have chronic pain when they come in to have a surgical procedure done or other things.

At the very least, we need to acknowledge that that's an issue, and I would hope maybe come

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up with some suggestions about how to move forward with that. And I'll just say that a small group of us, ad hoc, got together during the break and talked about this issue of tolerability, pain tolerability, as at least a concept, meaning that there's huge differences in individual processes moving; a patient who just can't stand the constipation and is willing to put up with a lot of pain not to get constipation and so on. But the concept of tolerability, meaning can they get up, and get out of bed, and do the things they have to do.

So I'm not sure that that's the right way, but we need to address that because it's a key piece to this.

DR. GILRON: I agree with you. I think the point was that Bob's initial hypothesis was prevents opiate prescribing. And we said, well, we want pain to be articulated in the hypothesis. So I think it's a language issue. So "maintaining sufficient pain" or "maintaining sufficient pain control," we're not happy with the language, but

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the point is that we want pain to be in there.

DR. FARRAR: I completely agree with that. I guess what I'm getting at is we need to define what we mean by that.

DR. GILRON: And that will come in [inaudible - off mic].

DR. GEWANDTER: Yes. I guess the question is maybe in order to facilitate the discussion, are we happy with these 6 hypotheses or are there any others that people would like to offer up? Lee?

DR. FIELDS: Howard Fields.

DR. SIMON: Simon. Sorry. Howard, go ahead.

DR. FIELDS: Howard Fields, UCSF. For number 3, I would add " Intervention X prevents persistent opioid use and opioid-use disorder," and just add that in. Because persistent opioid use could be because of persistent pain, but what we're really concerned about is people taking more opioid than they need for pain control.

DR. GEWANDTER: I think that my question -- because I was struggling with this as

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well. Sorry. I'm a terrible speller, so this is actually kind of anxiety ridden for me to be typing in front of you.

So would we want it to just be opioid-use disorder? Because, obviously, that's a lot harder to find and measure, potentially. Should we get rid of "persistent opioid use," and should it just be "opioid use disorder?"

DR. FIELDS: I would prefer it to be opioid-use disorder because I think it's like looking for your keys under the light. You want to do the easy study, but then in the end, you haven't really shown anything, in my mind. This whole point is, does it really help patients to reduce their opioid dose? Right?

DR. GEWANDTER: Yes. So maybe at least measure them separately. Because I also think that if you prevent acute pain you might prevent chronic pain. So if your drug does something great to really prevent acute pain, persistent opioid use might be a meaningful outcome as well, but just a very different outcome than opioid-use disorder.

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So separating them I think is a good idea.

Lee, is comment related to his? Because John wants to respond, I think.

DR. SIMON: It's directly related to it.

DR. GEWANDTER: Oka. Lee can go first, and then John.

DR. SIMON: Simon, Boston. I think this one that we're talking about, I can't see the exact number. I think it's 3. This whole issue of this transition, the way it's written, are we talking about just within the hospital postoperatively, or are we talking about postoperatively within the hospital and the transition to the outpatient environment, and how that will be handled?

I think that Bob Dworkin's comments yesterday about, well, isn't opioid sparing not using opioids, not decreasing the amount of opioids we use while maintaining the same or even better pain control?

DR. GEWANDTER: So you're talking about number 3 specifically?

DR. SIMON: Yeah --

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DR. GEWANDTER: I think number 3 is like 3 months later. I don't know. How long does it take to -- I have no idea.

DR. SIMON: Well, that's what I wanted to know, meaning --

DR. GEWANDTER: It's a while later.

DR. SIMON: So it's the transition -- Well then, we have to think about -- it shouldn't just be a while later because then there are the 8 days, or whatever it is, after surgery where people do take opioids sometimes or many times. And then the other question is, then, the 3 months later. So it's two different groups that would need to be looked at.

DR. GEWANDTER: Yes. So I think you're wanting to add another hypothesis.

DR. SIMON: Exactly.

DR. GEWANDTER: Okay.

DR. GILRON: I've got Nat, and then Raj, and then I've got you after that.

DR. KATZ: I just have a question which relates back to Jennifer's point that we haven't

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really defined what we're talking about here with respect to opioid sparing. And I think it's nice when you write a paper to actually indicate to the reader what it is that you're writing about.

So in terms of this concept of opioid sparing, are we taking a dose-centric view of the concept of opioid sparing where any benefit that would accrue to the patient that we want to study is mediated through either reducing or eliminating the need for standard existing opioids?

Or are we including in our definition of opioid sparing, doing interventions that may not even change the dose of opioid at all, but may modify the burden of opioid related adverse effects such as adding an antiemetic to your opioid or something like that?

Or are we even including novel opioids that may intrinsically be less addictive or whatever? What's the boundary of our concept here?

DR. DWORKIN: So I have a question for you and everybody else in the room. This is Bob Dworkin. When we talk about steroid sparing, do we

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talk about sparing just the side effects, of which there are many ugly ones, of steroids, or are we really only talking about the dose? And since a concept like steroid sparing is kind of well known in medicine, would it make sense to just follow whatever it is we mean when we talk about steroid sparing with respect to opioids?

So basically -- and I don't know the answer -- does steroid sparing means sparing the dose of corticosteroids or does it mean keeping the dose the same and also sparing some adverse effects? Do we know? I always thought it was dose, but I could be wrong.

MALE VOICE: It's typically dose.

DR. McNICOL: Ewan McNicol --

DR. DWORKIN: So then, the obvious point I'm making is if steroid sparing in medicine means sparing a dose of corticosteroids, then shouldn't opioid sparing mean preventing, reducing, or discontinuing opioid dosages to be consistent with the rest of medicine?

MALE VOICE: Yes.

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(Laughter.)

DR. GEWANDTER: Ewan's been waiting a while.

MALE VOICE: Yes, sure.

(Laughter.)

DR. McNICOL: I was going to bring up the same point as Jennifer and agree with Nat as well. And clearly, there's some disagreement here. But I think it's important to bring up Nat's original definition and work on that for a short while just to -- it can be a different one for acute versus chronic pain. But unless we have an agreed upon definition to start off with, it's hard to derive hypotheses based on we don't actually know what opioid sparing is.

DR. GEWANDTER: Nat, do you want to give them your slide?

DR. KATZ: Is it not in the computer? I don't know where --

DR. GEWANDTER: This is my computer.

DR. KATZ: Oh. I'd be happy to give them --

DR. RAUCK: While we're waiting for that to

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come up, Raj, I think you had a comment you wanted to make.

DR. RAJA: I just wanted to comment on hypothesis 3 again, that there could be two separate hypotheses, which is based on population that is. One could be the hypotheses prevents persistent opioid-use disorder in opioid-naive patients, or it could be in patients who are quote/unquote "high risk." So the hypothesis changes under those circumstance.

DR. GIBLIN: I wanted to also get back to hypothesis 3. I think it's probably two different hypotheses because you could be preventing chronic pain or you could be preventing pain chronification, or you could be preventing opioid-use disorder. They are two very different things.

DR. MARTEL: Mark Martel, McGill University, Montreal, Canada. I think related to objective or hypothesis 3, something that is missing. So I agree with the importance of assessing opioid-use disorder, but we should keep in mind that an

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opioid-use disorder cannot be assessed using self-report measures; it has to be assessed using a structured clinical interview usually most often done using the SCID.

So that might represent a challenge for researchers. While I think it should remain there, I think what we're missing is an intermediate outcome, which is opioid misuse that can be assessed using, for instance, the COMM, which is not optimal but it can still be used.

For instance, a patient taking more opioids than prescribed. And then we can still keep opioid-use disorder, some patients may escalate in terms of dose and end up meeting criteria for opioid-use disorder. But I think what should really be included as part of hypothesis 3 is prescription opioid misuse, preventing opioid misuse and opioid-use disorder after surgery.

DR. RAUCK: Yeah, good points. In the back. I think that's a good distinction.

DR. EDWARDS: Rob Edwards, Brigham and Women's, now remembering his third point --

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(Laughter.)
DR. EDWARDS: -- which is relevant, happily.
(Laughter.)
DR. EDWARDS: So what I was going to say was, um, a Marco's [ph] suggestion I think is an excellent one, or there will be a point at which -- we may be there -- we need to decide whether opioid sparing can happen without any change in opioid dose because it is perfectly possible to develop an intervention -- we have some already that are empirically supported -- that reduces opioid misuse without actually reducing the amount of opioids that people use.
As we know from ACTTION and other groups, one of the categories of opioid misuse is using opioids to treat non-pain symptoms. So people sometimes use their opioids to treat stress, that sort of thing. So if people are misusing their opioids in that way and we correct or resolve that opioid misuse, they may be using exactly the same amount of opioid they were before, but using it in a perfectly legitimate way, so they're no longer

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misusing. And our intervention will have resolved their opioid misuse without changing their dose at all.
It seems to me an open question, whether we would consider that opioid sparing or not. And that's just an example of, of the central question that I think Bob has posed nicely several times, which is when we're talking about opioid sparing, are we talking about dose? Does it have to be a dose-centric definition or can we have an opioid-sparing effect without actually changing the dose?
DR. RAUCK: I'm sorry, Ian. It seems to me that that's a very valid construct, that you could say a person now takes opioid just as prescribed and you prevented misuse. That's a really valuable societal and individual benefit, probably. But it seems to me, though, if I'm a layperson, I'd be all confused if you say that's actually opioid sparing. Right?
I don't know. Maybe I'm just being too concrete in my thinking of it, but it does seem to

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me like that's a different thing you've done. It's a good thing you've done. It's all laudable and may be part of what we want to put into these papers. We may want to make that distinction. But for me, I don't know. I'd be all confused if you were trying to tell me that that's actually opioid sparing.
So it seemed to me opioid sparing -- and I'm opened, and you guys can tear this all down because I'm not probably the guy that should make the statement anyway. But just hearing it and thinking it through, I would think that opioid sparing does imply some dimunition of dose relative to that in the construct. I don't know.
DR. GILRON: I'm just going to quickly follow that. Ian. We have to talk about Nat's definition here. But there's been work in the palliative care world about giving caffeine to counteract opioid-induced sedation. There's been work on peripheral opioid antagonists to reduce opioid related bowel dysfunction.
So I don't know if we want to throw those

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into the -- I mean, it's a question whether we want to throw those into the bin or not and whether we want to call them opioid sparing. It's semantics.
DR. GEWANDTER: I think Lee's been waiting, and then I can go.
DR. SIMON: Simon, Boston. I'd like to go back because what Bob Dworkin suggested about glucocorticoid sparing is really not applicable here because, in fact, as one of the few rheumatologists in the room, it's a useless concept because, in fact, patient A will have side effects at 3 or 4 or 5 milligrams a day of prednisone. Patient B will only have them at 10 milligrams of prednisone.
Under these circumstances, if you believe that you're decreasing the risk of using glucocorticoids by decreasing the dose, it depends on the individual patient. Similarly, we have the same problem here in trying to translate. Just because people use the terminology doesn't mean it's correct. And part of the problem about this is that we have a need, but what is the need for

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this? What's driving this question?
Is this to allow sponsors to get a leverageable description of a decreased use of a particular product because it is going to benefit the patient? We haven't really asked the patients yet what they really care about in this context. We assume, and we heard something about this yesterday, that it's equianalgesia, is what we're looking for, with less side effects.
So all of that's great and terrific, and Mom and apple pie. The question is, are we trying to develop a system where there will be no opioids used, which then is complicated by the fact that what else are you going to use, and I think that that's why we need to be very careful.
Acute pain, perioperative pain, there's not going to be a lot of things that you're going to want to use in certain circumstances other than opioids. The question is, who needs them afterwards? Who translates into an outpatient environment? Who continues to need them?
Your reference to the hypothesis that if not

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handled correctly, acute pain can lead to chronic pain through brain plasticity, raises some really important questions about what we're trying to do here. So I think that even Nat's excellent thinking about opioid sparing is really inadequate to deal with what we're trying to get a handle on. And that's why the acute pain has to be separated from the chronic pain in this manuscript. It has to be two. And I think we really have to stop here. We can have all the hypotheses in the world, studying anybody. We have to understand what we really want to achieve with, quote/unquote "opioid sparing."
MALE VOICE: Excellent points.
DR. GEWANDTER: So do you want to give any suggestion of what you'd like to achieve with opioid sparing?
DR. SIMON: Sure.
(Laughter.)
DR. SIMON: I think in the context of acute pain, it's not intrahospital use because we don't have anything else. I don't mean to insult the

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people that are developing ketorolac in certain ways, or other people that are developing anti-NGF in other ways. I just mean to suggest that right now, I personally would not want to have a major surgical procedure and be given something that wasn't an opioid, acutely, during that period of time, until it's proven that it works equally and analgesically provided.
So I think that the discussion about in-hospital perioperative treatment of acute pain is different than the transition time and the 3 months after. And that's really I think what we're trying to think about because people shouldn't necessarily have to go home with opioids.
But this is going to require an enormous amount of study of specific patient populations, all of whom have already been listed, those of whom were opioid-use disorder people. Those are people who have been chronic opioid users for other reasons and their opioid experience and how you're going to be able to deal with that patient population.

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So each of those populations has to be studied separately in new drugs or old drugs that can replace the opioids. So the true opioid sparing in the aftermath of surgical procedures is no opioids, not decreased use, not decreased numbers of tablets, but in fact no opioids. That's where to start. And then we can kind of manipulate this after we have analgesics that can actually do that, and then we can prove that through study.
DR. GEWANDTER: Deb?
DR. KATZ: Nat Katz from Boston.
DR. GEWANDTER: Deb was first, and then Nat.
DR. RAUCK: Great. Nat and then Ajay.
DR. KATZ: Oh, excuse me.
DR. RAUCK: Ajay and then Nat.
DR. GEWANDTER: No, Deb was first.
DR. STEINER: Thank you. Deb Steiner from Cambridge. Hi. First of all, I think you raised some amazing points and a lot of points. I don't know if it would be helpful to write them down, but to me, there are a couple of different issues.
There's first this issue of whatever we're

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going to define as opioid sparing. Then you're hitting on something that I think -- I'm going to try this, Joachim -- but we've been discussing a lot in the pain group about what I guess we call the chronification of pain. And that's I think a different topic than what we're discussing today. So maybe that should be put there to discuss this idea of what happens long term. And if we treat acute pain, can we prevent the initiation of chronic pain, which is a super important question.

So maybe it would be helpful if somebody wanted -- I'm not going to volunteer you, Jennifer, but if somebody seriously wanted to try to just make some high-level points. I completely agree with the comments about I think we have acute and we have chronic, and they're going to be different, and just start at a high level about what we should be assessing.

Joachim, I don't know if you want to say anything.

DR. SCHOLZ: Joachim Scholz, Biogen.

DR. STEINER: I try.

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DR. SCHOLZ: So you hit on the concept of disease modification, where there's analgesia, but I think that's not necessarily the topic.

DR. GILRON: Speak up a little bit. I'm sorry.

DR. SCHOLZ: I think that hits on the differentiation between disease modification and chronic pain conditions where there's analgesia. But I think it's beyond the scope of this workshop, a very interesting topic, though.

Maybe I'll just follow up on what Lee said. If you set the goal to avoid the use of opioids entirely, I would hesitate to start a trial because there's a high risk that it fails.

DR. SIMON: No, absolutely. That's because what we have available today.

DR. SCHOLZ: In practical terms, that's not how I would design it, with that hypothesis.

DR. RAUCK: Nat?

DR. KATZ: I think Ajay was first, wasn't he?

DR. WASAN: So just to clarify this

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opioid-use disorder concept before we go into more of the definition, just for everyone, it's divided into mild, moderate, and severe categories. And the mild opioid-use disorder maps on very nicely to the ACTTION definition of opioid misuse.

So just so people know, our group has looked at this, and we actually have a review paper on this issue coming out, so just a way of thinking about it. Some folks outside psychiatry don't think of it that way.

DR. KATZ: So at the risk of oversimplifying things, it seems like if we're going to try to work towards a definition of opioid sparing, there's basically two options I think. One option is to go with the dose reduction option where we're going to define opioid sparing as dose reduction and the potential clinical and societal benefits that derive from it. And then we could mention afterwards that, by the way, there are other ways of reducing opioid adverse events besides reducing the dose like having better opioids, or like adding it antiemetics, or like adding things that reduce

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opioid-use disorder without necessarily modifying the dose, et cetera.

But those are beyond how we're going to consider the concept of opioid sparing for the purpose of this paper, something like that. So I would call that a dose-centric view that could also go on to explain all the different things that were not included and why, especially because a lot of the measures that we would propose for this dose-centric concept, opioid sparing, they'd be the same measures used if you were studying some better opioid or that you thought reduced opioid adverse events or whatever.

So there is a connection there, but I don't have any problem with excluding that from the core definition. The alternative would be more of like a clinical benefit-centric definition, which is more like the one that I had, whereas sort of the center of the definition is reducing the negative impacts of opioids in patients and society, and we can do that through dose reduction, or modifying the pharmacology, or whatever. That's what I went

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with. I think that's an alternative
So I personally don't have a dog in the fight. I think either one would work. If more people are comfortable with the dose-centric one, as long as we have a clear explanation of the connected concepts, I'm fine with that. I just think that we should make a choice.
DR. DWORKIN: There's no reason we need one definition. Why don't we have a dose-centric definition that's consistent with the way sparing is used in other areas of medicine and also have a benefit definition, and then include study, hypotheses, objectives in both of those buckets that are kind of dose sparing and that are benefit enhancing? I mean, that way everything's included.
DR. GEWANDTER: Hanna?
DR. RAUCK: I think those might be relevant in different populations you're studying. Like you said, if it's preventing opioid abuse, that's a whole different thing that may not really require dose reduction if you happen to have something that will prevent the abuse situation, where other times

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a dose-centric approach would seem to make sense, particularly looking at some outcomes that way.
DR. GEWANDTER: I have Hanna and then Brett.
DR. GROL-PROKOPCZYK: So we're probably not wedded right away to having opioid sparing as the key phrase in the title of the paper. It could be called something like recommendations for design of clinical trials to reduce opioid use, opioid adverse effects, and opioid misuse. Like we could present it in that broad way, and thus not be straining the definition of opioid sparing but still be able to cover those other related topics.
DR. GEWANDTER: I think that's a good idea.
Brett's been waiting.
DR. STACEY: Brett Stacey, Seattle. My concern is the absolutism I see in some of these hypotheses; prevents. So how many of you have done a clinical trial for chronic pain where your goal was to prevent chronic back pain? Like prevents. It's like eliminate opioids. Like the only thing that counts is if there's zero opioids? Like really? This is not the way things work. This is

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not absolutism. So it's reductions, improve, reduce. Those are words, not "prevent."
DR. GEWANDTER: So you prefer the wording in number 6.
DR. STACEY: The other thing along those lines, if you look at the patients who are going to fail on that clinical trial, those are the ones that are at risk for dying. Most patients aren't going to have persistent opioid use after surgery. Most patients are going to recover and not have chronic pain. The ones that are more challenging are the ones we want to focus on. And improving is a reasonable objective.
DR. DWORKIN: So let me just respond to the use of the word "prevent." I get your point completely. I guess I've been influenced, in large part, by kind of Merck's shingles vaccine, which was approved by FDA in I think 2005. That cut the risk of shingles by 50 percent, and that was considered prevention.
So the way I was thinking of the word "prevention" is not a kind of absolute reduction to

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zero, but something that meaningfully reduces incidence, like in the case of Zostavax, it reduced it by 50 percent. But the group might decide -- and I don't have any objections to this -- that we wouldn't want to use the word "prevent" because it implies a hundred percent.
DR. RAUCK: Well, it certainly implies that dose zero affected, and you'd be measuring what percentage is dose zero, which it might be difficult or not.
Mike?
DR. ROWBOTHAM: Mike Rowbotham, San Francisco. One thing that hasn't been discussed that much, although I'll talk about it a bit this afternoon, is power calculations. So if you have an outcome like opioid-use disorder -- and I agree that it does require a SCID and skilled interviewer to do it -- you are looking at an uncommon outcome, meaning your sample size has got to increase dramatically.
So what you could do for this is you could focus in on patients who are, let's say, undergoing

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hip or knee arthroplasty or any procedure where they have preexisting pain and are using opioids. Assess them -- which I'm not sure if anybody does this routinely. Assess them pre-op for opioid-misuse or opioid-use disorder. And then you look at your longer-term outcomes 6 months a year for whether or not they've successfully reduced their dose and you've reduced the incidence of really meaningful outcomes, which would be opioid-misuse disorder or opioid-use disorder.

Then since at least based on the data from 9,000 patients, showing maybe 20 percent who were on opioids before actually increase their dose, then you're looking at an outcome that's reasonably frequent, and you could do it in a reasonably sized sample and achievable sample.

DR. GILRON: Yeah. And that follows up on Bob Jamison's suggestion, I think, about how to identify.

DR. RAUCK: Rob? Sorry.

DR. SCHOLZ: Joachim Scholz, Biogen. I think that's

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a different trial from the ones that we have discussed so far. What we have discussed so far was opioid after surgical pain, and my understanding was that we were mainly talking about pharmacological intervention that sets in at the time of surgery, before or immediately after; whereas now we're talking about whether surgery itself can be successful in reducing opioid use.

We heard that in the former setting, we should involve patients who have preoperative pain and are perhaps on opioids. But if you want to test from pharmacological intervention after surgery and measure the reduction of opioid use in response to your intervention, I would rather have a population that is pain free before surgery because otherwise I run into the problem that I have to control for the hospitalization of the patients, the surgery, and the interventions that I actually want to measure. So I think those are two separate questions.

DR. RAUCK: I agree. To Mike, I think if you just took an overall population and tried to

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look for preventing opioid-use disorder, your sample size is enormous. We do know there's a fair number of patients who come for surgery who already have an opioid use disorder, and can you affect their postoperative care because you're right, a lot of them end up on increased opioids. We see them back in the pain clinic. You can't ever get them back down because of the way they're treated acutely, and this, that, and the other. And there could be a whole set of things, that you might show that Intervention X is different than not Intervention X in that group of patients who have been preselected. I could see studying that group a lot easier than the other group.

Raj, and then TJ.

DR. RAJA: Just a comment that I think you're looking at acute pain trials, and all the hypotheses seem to be focusing on surgery. Given the suggestion that there are patients who may have acute pain, get hospitalized, and may even have a higher risk than those who have had surgery, I think that group should not be omitted or ignored.

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DR. RAUCK: Excellent point. Yeah. A motor vehicle accident and there's blunt trauma. There are all kinds of people we see that way. Yeah, that's great to think about.

TJ?

DR. GAN: TJ Gan, Stony Brook, New York. I've heard all the discussion about this opioid sparing, and in fact it's one of the reasons we are here, and it's in the title of the meeting here. Now, if we are going to sort of ignore opioid sparing for convenience and also because we couldn't reach consensus, perhaps we should then make a point that opioid sparing should not be used if we can't even make a definition of opioid sparing.

DR. RAUCK: So your proposal?

DR. RAJA: Well, I'm just saying that if we are going to write a paper on opioid sparing, I agree with Nat, that we need to define it. If we can't define it, then perhaps that is not the term to be used because it would still be used widely, unless a group like this is saying, well, that is

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not a good term to use.
DR. GILRON: To be fair -- and I maybe like the people with more white hair. But my understanding is that terminology emerged from PCA opioid acute pain trials and really was a dose-centric approach. And if we're not going to take a dose-centric approach -- I thought you wanted opioid sparing. So when Hanna said that, I thought -- I think I'd be okay with not using opioid sparing because Nat's definition, although the title is defining opioid sparing, it goes beyond that.
I don't know. Should we vote?
DR. GEWANDTER: Does anyone have a strong objection to not using the term "opioid sparing"?
DR. DWORKIN: Well, I do.
(Laughter.)
DR. DWORKIN: It seems to me that for a day and a half, we've sort of made the assumption that there are circumstances where some reduction or prevention of opioid dosage, or number of pills, or prescriptions at discharge would be of potential

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value. And the potential values that we've talked about are decreased risk of OUD, decreased risk of overdose, decreased risk of a bad syndrome of side effects.
So we're assuming that there's some relationship between dosage and various sorts of adverse outcomes. It sounds to me like there aren't great data in support of that assumption, but I think that's the assumption underlying much of our discussion, is that there are dosage, bad outcome relationships, and there are circumstances where you assume that a reduction, sparing of dosage, will potentially improve outcomes.
DR. GEWANDTER: Sharon wants to make a comment, and then Kurt I think.
DR. HERTZ: So the group can decide that the term is not informative or useful, but it's still going to get used. So it might be better to try and create some general concepts associated with it that could help coordinate the use out in the community. It could be that even if it's something as broad as opioid sparing can be applied in many

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settings and doesn't necessarily reflect the same activity in each, and then go into the different things.
DR. GILRON: So just to follow that, maybe we can have separate terms. So we could have opioid side effects sparing, opioid dose sparing, and opioid-use disorders sparing or a benefit definition. I think that's the bifurcation that Nat was talking about, dose-centric sparing versus a benefit definition of things.
Yeah, Jim?
DR. RATHMELL: So can you put Nat's definition backup? It's a place to start. It's really good. It's pretty comprehensive, at least for acute pain. And then we start just by saying outright, we're not sure that dose reduction is the only way to get favorable outcomes associated with opioid use. Just acknowledge that up front, the link between using opioids in the postoperative period in reasonable doses and bad things happening in the long term hasn't been established, so we acknowledge that. But opioid sparing is an

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approach that we're going to try and test to see if that's indeed true.
DR. GILRON: Right, maybe one way. There may be other ways, but it may be a way to look at it.
DR. KROENKE: Yeah. First of all, looking at this definition again, I like it, even if it's modified. My own personal opinion is I would not reject the term "opioid sparing" unless we have a good reason to reject it. I think all of the things they said about revised titles where we expanded, reduce opiates, reducing side effects, reduce misuse, those could all be part of the events we're trying to prevent.
So I'd favor retaining "opiate sparing" because it's a simple term that we could define. I think most of that's going to be -- and I also favor a dose-centric approach because if you use that, those who read zero are the same as no opiates. So you can have your cake and eat it too by having a dose-centric approach, but it's not absolutely like none. This has a dose-centric

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approach in this definition.
The only other comment I'd make is with acute pain, I think that's obvious. But there are only a few settings you can study it in. One is in a post-surgical or hospitalized setting and another is the emergency room because acute pain trying to study in other settings -- and the third is dental practice where it's come up, post-dental procedures. And that's where the research has been done about what can we do instead of opiates.
The final thing I'd say is this question about it seems like there are two covariates that are important at baseline before you do any intervention. And then you can use inclusion criteria as a stratifying variable. And it seems the two variables that have come up repeatedly is, does the person have preceding opioid use and does the person have preceding chronic pain of some degree? Both of those can be measured, and then it can be decided are those exclusion criteria, or do you focus on separate trials, or do you stratify them and adjust for them, but some studies haven't.

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I would say the one problem with saying I would exclude people from trials that already have pain, that would take out all orthopedic surgery. So everybody who goes to orthopedic common surgeries like hip arthroplasty and knee arthroplasty and others are only going because they have pain that requires surgery. So it depends on the procedure.
DR. RAUCK: Some of those orthopods, the patients are on opioids are not. They may all have pain, but those --
DR. KROENKE: That's what I'm saying. Those are the two important variables. What is the presence of pain prior to whatever intervention you're going to do and what is the use of opiates prior to intervention? And then you just decide, do I do separate trials or do I stratify, or adjust.
DR. RAUCK: Right. Bob?
DR. DWORKIN: So there are only 15 minutes left before lunch, so I'm just kind of curious, how many people -- show of hands -- like this

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definition?
(Hands raised.)
DR. DWORKIN: All right. Let's move on to the next topic.
DR. SANDBRINK: What's needed, but I think, based on this definition, do some wordsmithing.
DR. DWORKIN: So we can wordsmith it, absolutely, decide whether opioid sparing is hyphenated or not.
(Laughter.)
DR. DWORKIN: But I think you guys now have 15 minutes to talk about something else. We've endorsed the Katz definition.
DR. SANDBRINK: One comment briefly about this definition, and I'm sorry.
DR. RAUCK: Say who you are first.
DR. SANDBRINK: Oh, yeah. Sandbrink, Washington D.C. VA. The specification here is that the intention is to reduce the adverse effect of opioids on patients. I don't think that has to be part of the definition here. The definition is with the opiate sparing. You could argue, maybe in

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a following sentence, the goal for this approach is, or the intention of it is, but the definition doesn't require why you're actually doing it. And you could ask them about harm's reduction for the society. You could talk about harm's reduction in many ways. But I fear that the definition would be more clean if you take that section, these two words out. Just a consideration.
(Pause.)
DR. SANDBRINK: There are many reasons for that. There could be cost. It could be the stakeholders -- the state may have mandates on it. There may be limitations. There may be stigma. There are many, many reasons for that, and certainly on just the adverse effect of opioids on patients.
DR. GILRON: So just to clarify, you're saying that you endorse what's on the screen, but you want to get rid of adverse effects on patients? Is that correct?
DR. SANDBRINK: I fear that that is not the definition of opiate sparing. That's the intention

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to do so.
DR. GILRON: No, no, no. We're making --
DR. SANDBRINK: Yes, otherwise, I endorse it absolutely.
DR. GILRON: No, no. I just want to be clear what you're suggesting we remove.
DR. SANDBRINK: I would remove the "to reduce the adverse effects of opioids on patients." That's not part of the definition --
DR. GILRON: I think a lot of us specifically want that in there. I hear what you're saying but I don't think that's the definition that we want to use.
Bob?
DR. DWORKIN: Could you read what it would be without? Because I don't see what it would be without that phrase.
DR. SANDBRINK: Or the implementation of an intervention that decreases the opioid dose by tapering it off completely modifies the pharmacokinetic profile or modifies pharmacogenomic properties while maintaining or enhancing pain

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control. The rationale for this may be to reduce harm on the patient, on society, to avoid the use of opioids in somebody maybe who has contraindications.
It's certainly much larger than the adverse effect or maybe you should say harms on society. But you're including a goal for something that you identify as a process. Right? What is the definition for opioid sparing?
DR. DWORKIN: Friedhelm, how about you type that out for Jen, and we'll put it on the screen and look at it first thing after lunch? I think some of us are visual and need to see it.
DR. RAUCK: Thanks, Mike, and then Raj.
DR. ROWBOTHAM: Mike Rowbotham. I think just to quickly put my two cents worth in on the definition, you would just take the word "adverse effect" and just put in "harmful effects." And then you would include at the end "modifying pharmacodynamic properties and the incidence of opioid-misuse disorder, opioid-use disorder, and overdose."

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DR. RAUCK: So just really change "adverse" to "harmful," reduce the harmful effects.
DR. ROWBOTHAM: Yeah, and you just add those other ones that are --
DR. FARRAR: But wouldn't you want that as a separate concept, Mike?
DR. ROWBOTHAM: Yes, that's the rationale.
DR. FARRAR: Right. So the first statement is harm. We need a word in there. I agree completely, Bob. Adverse effects suggests nausea, vomiting, respiratory depression. And what we also mean, though, is the development of opioid-use disorder, and that's not evident. But I think limiting it to those two in the definition will limit us because there may be people who have other views of what the opioids do that are bad. I don't think we should restrict the opioid-sparing definition to that, but have then a second sentence that basically says, the reason we want to do this is to reduce adverse events, reduce respiratory depression, improve pain control, and reduce opioid-use disorder, or something like that.

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DR. GEWANDTER: In the back?
DR. J. BROWN: Jeremy Brown from NIH. I just wanted to save a few words. But why is it the implementation? Why doesn't it start with an intervention to reduce? That way you get rid of a few words.
DR. GEWANDTER: I think we can wordsmith it later. I can send it out, and you guys can feel free to comment on how it's been wordsmithed But thank you for those suggestions. That's helpful.
How much time do we have left?
DR. RAUCK: Raja had a comment. I left him.
DR. GEWANDTER: Oh, sorry.
DR. RAJA: I think the only comment is a definition, sometimes wordsmithing it can take months. I'm involved in a project, and therefore I think what you suggested, sending this draft definition and having people input probably is a better way of doing this because there are a number of options for doing this.
DR. RAUCK: You're trying to beat the rush hour traffic home to Baltimore?

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(Laughter.)
DR. RAUCK: Nat?
DR. KATZ: I have a proposed modification of my own definition that I think might --
DR. RAUCK: Does this have to be seconded and then voted on?
DR. KATZ: Of course, and thirded. And I think it's short enough that I could just read it out loud without walking up there and showing it. I think it takes into account a lot of people's comments. Ready?
"An intervention" -- thank you, Jeremy -- "An intervention to reduce the use of opioids and attendant harms while maintaining or enhancing pain control."
DR. KROENKE: And then you can define the other things in subsequent sentences.
(Crosstalk.)
DR. WASAN: [Inaudible - off mic] -- we need to get away from just thinking about -- [inaudible - off mic].
DR. KATZ: Maybe that's close enough to

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circulate that for further comment.
DR. RAUCK: Yep, circulate around.
Cole, did you have a comment?
DR. C. BROWN: Cole Brown, Innocall. Not really to the definition in general, and I see that you guys are trying to move past the definition, so maybe it will help transition.
I think it's going back to the concept of OUD, and I think Jim kind of mentioned it. I think when we're thinking in the realm of acute pain trials from a practical aspect, thinking about OUD as an actual outcome in those studies become problematic for a couple of reasons.
We've listed a sample size perspective from a duration perspective. If I'm going to develop a drug that I think is going to help patients in the first 72 hours, to still be monitoring patients 6 and 12 months down the line and doing some kind of questionnaire during that interval I think becomes problematic.
So I'm just wondering if we're all okay with using the reduction opioid usage or the adverse

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events as a surrogate outcome for the theoretical reduction in opioid-use disorder because it becomes really problematic and difficult to actually assess OUD in an acute pain trial.
DR. RAUCK: Valid things to think about for sure. I don't know if we'll tackle all of that right now, but they're good things certainly to discuss and put it into the record that way.
Jen, it looks like we made progress on the definition. Do you want to go back, or Bob, before lunch and try to look at these hypotheses a little more, or do you want to just go ahead and think about lunch now?
DR. DWORKIN: So you want to add to it or delete [inaudible - off mic].
DR. GEWANDTER: Hanna, do you have a comment?
DR. GROL-PROKOPCZYK: I mean, very minor, but we saw yesterday that duration of use seems to predict misuse more than dosage, and I didn't see a hypothesis referring to duration directly.
DR. GEWANDTER: Thank you.

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DR. RAUCK: TJ?
DR. GAN: I just want to caution about the difference between acute and chronic trials because I think, from what I heard and based on the evidence, the number of people who then go on to use acute in the long term for an acute trial is really not the majority. As we saw yesterday, that Raj put up, between less than 1 percent. And if we are going to focus on that, it's a wrong thing to focus in the acute pain, a chronic pain maybe. So I still think that in the acute pain trials. Chronic pain maybe.
So I still think that in the acute setting, what the patients hate to experience, those are things I think we need to think more about in the acute setting than just sort of looking at the opioid-disuse disorder.
DR. RAUCK: Before I get to John. And maybe I got my head around it wrong. I think what I heard Sharon say, which I liked, was -- you're right -- you need the global studies that are looking more -- just sort of the bigger picture

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questions. But it does seem relevant to me to look at these subsets because the subsets, embedded in them are some of the real high-risk populations, whether it's those who go on to persistent pain, those with chronic pain before surgeries, and then some of the other issues that Ian's put up.

So I don't think those are going to be the defining things of a therapy or an intervention as I see it, but I see those special populations as, one, most of those seem like they could be studied, which is relevant. I've been in too many trials of great trial designs that could never be studied, really, or populations found, but could be identified and may have meaning even if they're not the overarching reason you would at the therapy, or the intervention, or --

DR. GAN: I agree with you with a Subgroup, but I think you are talking about in general. Let's be real, an everyday trial, we're not -- those subsets I think it's important, I agree, but it may not be the population.

DR. RAUCK: For me in a chronic pain

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world -- and obviously companies are interested in this, of trying to prevent persistent pain, the old adage that 10 percent of the patients who get acute back pain go on to develop chronic pain, but they use 90 percent of the resources and expenses of it. So it's relevant if you can prevent that 10 percent, that that's a meaningful thing that way.

John, you had a comment.

DR. FARRAR: Along those lines specifically, I think we need to keep in mind that as a community, the pain community is being lambasted for the overuse of opioid in the setting of -- I mean, take, for example, third-molar extractions and going home with 30 Percocet. I don't know how to fit -- because the development of OUD is clearly rare enough, that it's going to be very hard to study. Maybe we can go back and do it in databases and so on.

But it seems to me that if we don't at least address that in some way, there's going to be a large pushback on the fact that we're not at least mentioning the very important societal component of

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this, which is that although it's rare, there clearly are young people who got 30 Percocet, and are now addicted, and might not have been if they hadn't had that process. I don't know how to do that, but I do think leaving it out completely is going to be problematic.

DR. GEWANDTER: Okay. So I think what you're saying is that interventions targeted at proper prescribing practices are interesting, and making that an objective of some of the trials, not just like adding this drug, would be interesting for the paper.

Okay. Thank you. Yes? Sorry. I don't know your name.

MS. WENTWORTH: Hi. Kerry Wentworth, Flexion.

Nat, going back to your revised definition, you just have "dose reduction." In that definition, would you presume avoidance also equals dose reduction?

DR. KATZ: Well, I included reducing to zero as part of reduction, but if people feel like it

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would be more clear to state that explicitly, then we could say "or complete cessation," which is what I had in my original definition, but I was responding to people's desire for simplification.

MS. WENTWORTH: From the sponsor's side, I think that kind of clarification, even if it exists in another definition, could be useful.

DR. SMITH: I just want to follow up on that. This is Shannon Smith. Are you saying avoidance or are you saying reduction to zero? Because I think those are two separate things, like not going on it at all or --

MS. WENTWORTH: Exactly. They could be definitely two separate things.

DR. SMITH: Okay.

MS. WENTWORTH: But could they still fall under opioid sparing?

DR. STEINER: But Nat, are we not going to get into this same issue that came up yesterday? Like what's going to be like a meaningful reduction in opioid use?

MALE VOICE: Maybe.

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(Laughter.)
DR. GILRON: So maybe we'll just take a final question before lunch or maybe just go for lunch.
DR. RAUCK: It looks to me like everybody's ready for lunch.
(Applause.)
(Whereupon, at 11:30 a.m., a lunch recess was taken.)

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A F T E R N O O N S E S S I O N
(12:20 p.m.)
Presentation - Michael Rowbotham
DR. ROWBOTHAM: Thank you, everybody. I can tell it's the last lecture of the day, so Bob told me I could talk about whatever I felt like.
I can see already that not only did I forget the hyphen, but a "Z" got added at the end --
(Laughter.)
DR. ROWBOTHAM: -- which I'm blaming Valorie for. She put a Z in there.
Anyway, I'm going to talk about the chronic pain issues and research designs and methods. My current position, I'm Sutter Health's chief research officer, which means that I oversee all their clinical trials, basic science, large-scale epidemiology at the data coordinating center. And I'm chagrined to say that we have zip, nada, nothing organized in the chronic pain area.
So I won't tell you anything about Sutter Health's chronic pain research program because there isn't one. But it is a large health system.

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It's the eighth largest in the country, 3 million patients, 26 hospitals, and it's actually the world's largest installation of Epic, the electronic health record, which I will talk about a little bit.
(Murmurs from audience.)
DR. ROWBOTHAM: Oooh. Yeah, I know. Oooh, the evil empire.
(Laughter.)
DR. ROWBOTHAM: I still see some patients occasionally at the Pain Management Center, and it allows me to keep my UCSF designation.
What does opioid sparing mean? We've talked about that to great extent, and it seems like we're getting our way towards a definition, so I won't go into this anymore. What I want to talk a little bit -- one of the speakers yesterday said there really weren't addiction medicine speakers as part of the group. Well, I actually am -- in my previous lifetime before I went into neurology, I had extensive experience in addiction medicine because I was the medical director for the

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methadone programs for substance abuse at SF General Hospital. And this was in the very beginning of the AIDS era. So we had a lot of more traditional injection drug users, and then a lot of patients who were polydrug abusers, young gay men, early stages of AIDS. It was a very complicated period.
So I learned about that before I started working with Howard as a fellow at the end of my residency. So my first experience was as a visiting medical student in Chiang Mai, Thailand at McCormick Hospital, which was run by the Seventh Day Adventists. It's the only place I could find, besides a hospital in the Ivory Coast, that would actually take an American medical student in those days.
So there, as you may know, a really high-grade heroin was available in northern Thailand for next to nothing. There would be travelers living, getting very strung out on just the purest of the pure injection opioids. And then they'd get caught, and they would be deported. And

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they were given the option of checking themselves into the hospital and going through an opioid detox before the Thai border authorities threw them out, never to return.

So there was a very simple protocol that the hospital had. It was a manacle on the ankle with a chain to the bed and some colored liquid that had methadone in it at first in decreasing amounts. And they would go through withdrawal, really pretty severe withdrawal despite this, and we had 100 percent success.

(Laughter.)

DR. ROWBOTHAM: So I can tell you that that works. It does work.

The other is, at the methadone clinic, there were gradual rules changes. When I first was there, they had had some patients who had been up to 120 milligrams of methadone a day, but they had set a limit already by that point of 85 milligrams. And then there was another dose reduction to 45 milligrams a day that we were supposed to be implementing. That's potentially hazardous to your

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health. I got death threats. And I had on one occasion, one of the counselors who was an ex-addict himself, put himself between me and one of the clients who was ready to take me out with a knife in the midst of doing all this. so involuntary tapers can work, but they're difficult.

The other was that the worst thing that could happen to one of the long-term methadone maintenance patients was for them to come into an inheritance. So they would suddenly get some money. It would be completely setting their pants on fire. They just had to go out and use it, and they would just disappear from the program. And depending on the amount of money they'd inherited, they would be back looking horrible, having spent all the money. So the lesson there is it's very hard to get people to go down on their own doses, but when the circumstances change, they can go up very, very quickly. So down so slow, up is fast.

The other thing is this is a study that is really pretty obscure, 2003 study. And it was a UK study. They were looking at patients who reported

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stopping their opioids at some point. This is partly related to the stigma of being on chronic opioids. The families think of them as an addict. They think of themselves as an addict by being on these. When I talk to my patients about this, it's not infrequent that they test to see do I still need to take this every day? Can I reduce my dose? Can I get off of it?

So this study, they looked at patients who had basically done this. Of this 104 in this group, 59 actually stopped permanently. And it was due to fear of addiction in 10 percent, various adverse events in another group or that they just really wasn't working for their pain. But this is unsanctioned, unsupervised withdrawal. And the corollary with this to the methadone maintenance program and diversion is that if you look at the street value of opioids, if you're trying to sell a bottle of methadone from a methadone clinic, it's not worth very much because you can dilute it. And it's pink colored, and you have to put a fair amount of water in it before it's really obviously

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different from the usual stuff that you get dispensed.

So as a result, because it can be adulterated like that, it's just not worth as much as if you had the brand name Dolophine tablets from a pharmacy. So prescription opioids are really the gold standard. If you can get those, that's the best.

So we would have occasional patients in the methadone clinic who had figured out how to beat the system. And the way you beat the system is you taper yourself down on your opioid, so you sell the extra liquid. You maybe have some withdrawal symptoms, but you put up with it because you can live on that.

The most clever was a woman who'd had pancreatitis because she was also an alcoholic and had convinced her surgeon, just across the street at the main part of SF General, to give her prescriptions for methadone. So she was getting liquid methadone from our clinic and methadone tablets from a surgeon at the hospital. That's the

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trifecta, right? You can't lose if you've got that situation. She sells the Dolophine tablets for a lot of money and she drinks her methadone. Her urines come out perfect; her urine testing, because oral, it's all the same. So this phenomena of patients manipulating their own doses, it can really go both ways.

The other is, especially now, as opioids have kind of moved down the chart to being really last resort, 3rd. 4th, 5th-line therapy, this slide, which I've shown and cited in papers about clinical trial ethics and who gets recruited is really relevant for this. This is a long-term study of newly diagnosed epilepsy patients. It's an old study. It's published in 2000, and they had 470.

With the first antiepileptic drug, 47 percent became seizure free. So of those who still had uncontrolled seizures, they tried a second monotherapy, and they got another 13 percent seizure free. Then when you went to the third antiepileptic, now they only got an additional

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1 percent seizure free, and you ended up with still more than a third with uncontrolled seizures.

So the point is that as you keep trying treatments and they fail, you're getting a more and more select group. They're less representative of the general pain population that's untreated. And where this relates to trial ethics is if there's lots of approved therapies, why would you give somebody something that is in phase 2A that's completely unproven for their particular condition when you haven't actually exhausted the regular therapies? But of course by only testing those people, you're picking the most refractory population, the ones like this that are still having uncontrolled seizures despite dual therapy and multiple single-drug trials.

So the other thing that was interesting about this study was that old drugs versus new drugs really didn't make any difference. This is the follow-on study where they got up to a thousand subjects and really had all the newer antiepileptic drugs that had been introduced. And, really, all

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that it did was it got the failure rate from 36 percent to 32 percent.

These are kind of sobering thoughts about who it is that we're seeing in our clinics. And I'm reminded of the very nice videos that John Markman showed yesterday of these kind of opioid refugees. These are unusual problems that he was showing us in terms of their diagnosis. It's just not something that you're going to see every day.

I wanted to turn a little bit to devices because we've been talking about drugs but not really so much about devices. And devices are really potentially a very interesting option in their various permutations for opioid sparing.

Let's say the device has a direct pain relieving effect that's so good that you don't need to even initiate opioids. So that's obviously opioid sparing. Let's say the device plus opioids gets equivalent pain relief at a lower opioid dose than opioids alone. So again, it's either synergistic or it has a direct pain relieving effect.

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Going down the list, it could make it possible to taper down to a lower dose or even completely discontinue in patients already on opioids. One example would be patients using clonidine as an assist to opioid taper. Oral clonidine doesn't really have any analgesic effect; you really need to give it intraspinally, but it does help reduce withdrawal symptoms and helps people get through a taper.

Another possibility is you have a device that makes it possible to receive opioids still, but in a form that's less prone to abuse, mostly because you just control it better. So this doesn't require direct pain relief or synergy. It could be something like transdermal absorption where it's much harder to cut your dose in half and sell the other half of it. But it could be something like intraspinal or some kind of an ambulatory PCA.

The examples I list here are spinal cord stim, deep brain stim, any spinal drug delivery system, and devices that would deliver drugs that

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might relief craving and other behaviors associated with addiction.

The other would be what about preventing opioid-use disorder by devices that monitor patients. So again, it's not really sparing, but it prevents unsanctioned dose escalation and all the risks associated with that, which are the things that we're really concerned about here. We're concerned about patients having opioid-misuse disorder, opioid-use disorder, accidental or intentional overdose, et cetera, et cetera, and a device could help there. It could also be tamper proof so that people can't exceed the limits that they're allowed to use even though they're ambulatory.

Now, you would need a monitoring system because there are lots of different opioids out there. So the patient could be taking sanctioned methadone but also injecting fentanyl. And unless you were really doing sensitive urine testing, you wouldn't really pick that up. The other is specialized pill bottles that monitor when the pill

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bottle is opened and every capsule that's taken.

What about apps? Apps are big in the addiction world as ways for people to manage their symptoms. There's a company called Pear Therapeutics that has an app that kind of functions like a digital friend or an AA support member, or a family member. It delivers messages of support to reduce craving and enhance unsanctioned opioid use.

The MIT Media Arts and Sciences program have some very clever stuff that they're developing to just do behavioral modification in general. So things like sending signals or otherwise changing the valence of particular situations, it turns out that you just release an odor at a particular time, you can change people's mood and how they're feeling about something really quite rapidly.

Then you can do other things like aversive conditioning where you pair drug use some kind of negative beliefs, so that when the patient is feeling the need to use, they're also getting these aversive thoughts about it that help keep them from doing that. So these would all accomplish the goal

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of opioid sparing.

So let's get into some of the trial design issues. Historical controls, they're really not useful, especially right now. I think there's agreement here that the landscape for chronic pain opioid prescribing has changed dramatically in the past 5 years, and we were already seeing it in some of the graphs that were shown yesterday that the peak prescribing has already hit and has passed, so we really can't use data from 5 or 6 years ago. It's really going to need to be generated prospectively.

Then as we saw in the talks today and yesterday, chronicity of opioid use is associated with opioid-use disorder, but the dose has kind of a tenuous relationship with risk. And even though some of these data sets are fairly large, they haven't successfully settled the question.

Then from looking at the data that's been shown at this meeting about surgery in patients who are opioid naive, and developing opioid problems or just chronic opioid use, there's a long and

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variable gap sometimes between when those occur. So since now prescribers are giving a lot less and often tending to rely on academic pain programs, where you're kind of in a bubble protected from the predations of the Drug Enforcement Agency and your state narcotics control boards, prescribers in the community are feeling very, very intense pressure coming from all sorts of different directions to discourage them from prescribing. So the doses are lower, and that's maybe partially due to availability of drugs like buprenorphine, but obviously that's only a small part of the equation.

I think prescribers have responded to the educational programs. They do have a better sense for who's a high-risk patient. This has probably paradoxically pushed some patients who were using prescription opioids that they were getting from their physician or one of their friends' or relatives' physicians and now are on the street market to get their needs met, and of course suffering the consequences for that. So really, it's only a prospective study that can really

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settle these questions.
So we've talked a lot about randomized control trials, and if we're looking for something like reducing the amount of opioids being taken each day or specific adverse effects, the trial length really dramatically changes both the costs and the feasibility of doing the study. So if we're looking at opioid use a month post-op, a piece of cake, easy. Lots of people have done those studies.
Three months, feasible, getting a little more difficult, especially if you're trying to recruit a chronic pain population in the first place. And if you're going for 6 months or longer, then it starts getting really hard. Patients don't want to be in a study that long and they drop out. So dropout rates for opioid studies I think are probably higher than just about any other therapeutic area, and they're 40 to 50 percent in a lot of the studies.
If your goal is to reduce the incidence of opioid-use disorder or something even more

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uncommon, like deaths from opioid overdose, which as we saw yesterday -- and if I remember the numbers correctly, it was like 64,000 a year in the country. So that's, fortunately, a very rare outcome. And from what we also saw from the slides yesterday, patients who were really using substantial amounts of opioids, at a year after surgery, it's on the order of about 1 percent or so.
So that's a rare outcome. And that means that if you want to impact that rare outcome, you need an enormous study. You don't need hundreds of patients. You need thousands of patients, probably tens of thousands of patients to show a change in that parameter. So suggesting things like patients who are already on opioids and seeing who increases versus decreases, something with 19, 20 percent likelihood, that's an outcome that you can look for in a traditional clinical trial. But once the outcome you're looking to change starts dropping down 2, 3, 1 percent, then you're just not going to do that in a randomized controlled trial unless you

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really have enormous amounts of money to spend on it.
Doing the power analysis, the power calculations, we really need to have a clear idea as to what is the outcome measure, how likely is that outcome, and that's going to tell you how many people you're going to need to recruit. The more you skew your study population towards really high-risk patients -- so that would be patients with a prior history of substance abuse or active ongoing alcohol abuse or something like that, or especially for opioids; use of stimulants and amphetamines really skews the risks upward towards opioid misuse -- that would make it much easier to show the impact of your intervention.
But of course, those are really hard patients to find and recruit. They're just not cooperative. So you can do a case control design, and for devices, that works reasonably well, but it just depends on how easy it is to get the device off label. And I'll talk a little bit about cohort designs as a form of a pragmatic trial.

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The other thing is, for prospective randomized-controlled trials, everything, start to finish, there are only two words you need to know, and they're both in the pirate dictionary because they start with R. That's recruitment, retention. That's all you need to know. So high OUD risk patients, hard to recruit, hard to retain. They're usually left out of studies. And dropouts -- and I'll show you some data on this -- you can just figure they're failures. People may tell you, give you all sorts of reasons like their cat got sick or their aunt died across the country, but generally, people drop out of a clinical trial, especially of opioids, because they just don't like what they're getting. It's not working for them in one way or another.
This is an old study now. This was a NIH funded study of levorphanol, which we picked because nobody had ever heard of it, even though it's a very good, very potent opioid that you can get literally from a chemical supply house encapsulated. This was a study where the treatment

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period was around 8 weeks, followed by a taper period.

This really mimic clinical practice in that the patients got to choose how many capsules they took. They could go up or down, depending on side effects, so their job was to find the optimum balance between relief and side effects. So it wasn't like a traditional trial phase 2 where you get slotted into a particular dosage group. The only randomization was whether or not you got itty-bitty capsules with a levorphanol in them or very little levorphanol in them.

When you looked at the data, we had 81 subjects all with verified neuropathic pain. We started with 81. And even though this was a very patient friendly protocol, only 59 completed. Fifteen of the drops are due to adverse events. Agitation was noteworthy in the higher strength group. And what we found was when really looking individually at all the dropouts, in the lead up to their time of dropping out, you could see they were falling behind the rest of their dose cohort, or

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their capsule strength cohort, in getting less relief and experiencing more side effects. So they were on the road to failure, and then they just dropped out.

Even though we saw significant differences in the pain relief scores, there was really no difference in relief ratings. And that makes me worry a little bit about some of these complicated composite measures because if somebody's only experiencing a limited set of symptoms and you're looking at multiple symptoms as part of your outcome, it just takes away some of the sensitivity.

The other was that the actual daily dose that people took was widely variable. We saw a very significant difference in the number of capsules patients took, depending on which capsule strength group they were assigned to. But when you actually calculated that back into milligrams of levorphanol, people titrated themselves to really very different levels.

The last couple of slides are really on

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pragmatic trials. So we're lucky here. I've got Ajay and I've got Ian, that we wrote this paper together about pragmatic trials, which are called really effectiveness trials. They're really in-practice studies, and they've been applied only, to a very limited extent, in the pain area. But they have some advantages, and I want to spend some time talking about that.

Patients stay in their usual care situation. They don't have to go to a specialized program in order to participate in this study. What that does is -- as we all know, those of us who've done clinical trials and have run clinical trial centers is, patients love it because they get so much TLC. They come in. The study coordinators are so nice to them. They call them up. They're really concerned about how they're doing. And of course, they're very concerned that they bring back their medication and do all the pill counts.

So it's a very kind of supportive and high-touch, high-contact environment. So it's not surprising at all that people's pain scores go down

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a lot, even if they're really not getting anything other than placebo.

When you just keep them in their usual care situation, you kind of wash out a little bit of that, and you get the outcomes from review of the electronic health record. So correlations are straightforward enough, but proof of causation is difficult, and you have to design the trial in a particular way in order to actually test various options against each other. So the data collection is really all important.

As we saw yesterday, when John showed his very nice screenshot of the Epic trying to prescribe buprenorphine, EHR use is just awful. Anybody who doesn't know it, Epic is a billing system. I hope nobody's here from Epic, but when I heard the sort of moans and groans, I kind of get the feeling, no.

(Laughter.)

DR. ROWBOTHAM: It's a billing system. It makes sure that when you see the patient, that you capture what you did. It gets categorized as to

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what level of intensity the encounter is, and the bill goes out, and the clinic or hospital collects their money, and they're all happy. And as John also said, you never look at your patients again. You're looking at the screen the whole time.

So when I see patients, I'm really lucky. And that's really why when I see patients, I do it in a teaching program -- and I would never try and do it in a solo practice -- is because I've got a resident or fellow who's already talked to the patient, filled out most of the electronic health record, is busily typing away while I'm sitting in a chair with nothing, maybe a piece of paper, just asking questions and poking them, and doing sensory testing and all that other kind of fun stuff. And I don't even look at the screen until after the encounter is over. It's great. It's even better than the old days when I would have to type up or dictate my report.

So if you're a resident or fellow, they're incredibly fast typists. I'm just really amazed, and they are really good because they spend all

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their time typing and not a whole lot of time looking at the patients.

As I mentioned, Sutter Health has the world's largest installation of Epic. Does that get us anywhere with Epic in terms of getting them to make their platform more user friendly, especially in the pain area? No. It doesn't do anything.

We also have in the Bay area and other parts of the country this thing called CareEverywhere. So if a patient comes in, and I'm looking to see who they've seen since I last saw them, I can see their records. I'm at UCF. I can see their Sutter records. I can see their Kaiser records. I can see anyone else who's in our region to see what kind of encounters that they've had. I don't get as much detail, but at least I can know.

But not everybody has Epic. Not everybody has the same electronic health record platform. So in the cancer area, oncologists are all in private practice. They're not using Epic when they see the cancer patients in the clinic. A patient gets

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admitted to the hospital, we've got Epic. We've got a thing called Beacon for doing standardized chemotherapy orders.

But it's an incredible amount of labor to correlate the outpatient private practice docs' records and correlate it with what's happening in Epic because those systems, they just don't talk to each other at all. And if you've tried to do data analysis in electronic health records, you know that little misspellings of difficult-to-spell last names like Rowbotham, just really trip it up. Or if you do last name first, you don't see all the other ones where it's first name last. So they just require a lot of special care.

You can get questionnaires in. Our dementia clinic has the MoCA online in there. And you can get it filled out, and you can get it into the electronic record. We scan a lot of our research questionnaires into there, but that doesn't mean you can easily get it back out again into a database that you could do work with. So they're hard.

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They have some other weird features, and I would suggest if you have any interest in this, read this book. It's a few years old now by Robert Wachter on The Digital Doctor, which is really the history of how electronic health records so quickly got into all the hospitals. And that was this meaningful use thing and all the Obama shovel-ready project money that came along with the economic downturn, the great recession in 2008-2009.

So there are ways of directly testing hypotheses within a pragmatic trial. Using things like cluster randomized designs is just one example. Your randomization, instead of a clinical trial, it's not at the level of the patient. It's at a different level. It's at a group level. So you randomize at the level of the physician, or the practice location, or the country, or the state. It can be anything you want. You just need to make sure that your randomization gives you groups that are comparable to each other.

For example, in California, you wouldn't want to do political opinion polls in San Francisco

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and have your comparison group be down in the Central Valley, because they're pretty different in terms of how they look at things. You can't compare one against the other.

So instead what you could do is you could maybe compare San Francisco to Berkeley, God forbid, because those are sort of reasonably similar on the political spectrum, and medically it's the same thing. So you really have to dive pretty deep into the healthcare system to make sure that you're comparing practices, facilities, locations, hospital size, whatever, that are reasonably comparable.

We heard from Jim here and some others that even within a clinic, the practice style of the individual physicians can be dramatically different. One doctor may say, "Hey. Opioids? Sky is the limit." The other one's like, "No, I don't prescribe opioids, but I'll do an epidural on you tomorrow morning." They're just really different in terms of how they approach things.

So there's a lot of potential for

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confounders, but the advantages are that you can recruit very large numbers of patients. And if you're doing things like just where you have access to a particular treatment style, then you don't even necessarily need consent.

So let's say a new device has come out, like some whizzbang new MRI scanner that's ultra sensitive. And you roll it out in San Francisco, let's say in Sutter Health. We roll it out in San Francisco and Los Banos, down in the Central Valley, and those are the only places. We could do a study comparing what you get out of the scanner in those two locations, and then we could pick a bunch of other Sutter sites as our comparators. And we could do it prospectively and thoughtfully, and see what the impact is. And that essentially could function as a cluster randomized trial.

So there's a lot of potential here, but it just takes a lot of thought and a lot of planning to make sure you get all the confounders out, and you really know who you're looking at.

The other is, what about some of the outcome

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measures? As I mentioned, you can build them into the electronic record, and things like telemedicine and sensors would help a lot.

There's a very interesting meeting that happens every year in San Jose at the Computer History Museum called the Precision Medicine World Conference. It's heavily oriented towards neurosciences and especially oncology because it's so much in the area of biomarkers. But a lot of it are people who believe in what they call the quantified self. And that's basically where you just measure yourself on everything all the time, and all that gets uploaded into the Cloud, and it can be analyzed.

So by doing things like telemedicine or censored technology in a system where there's common electronic records platforms, you could actually be collecting a lot of data from patients just as they go about their daily activities. You collect the data. You crunch all the numbers, and you can come up with correlations about -- or information about different ways of approaching

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pain. And it could be anything. It could be devices. It could be behavioral. It could be drugs. It could be anything that we want to come up with, but it can be done in this kind of design, and you can get large numbers of patients if you have enough cooperating healthcare programs. It could be national and international.

So there's potential here. It's not been done that much in the pain area, but we do have our friends from NIH here involved with the initiatives around opioid-sparing studies.

I think that's my last slide. It is my last slide. So I'll take questions or we can go on into the planning part.

(Applause.)

DR. ROWBOTHAM: Ian?

DR. GILRON: Thanks, Mike. That was very interesting and great talk.

Something that I think may be a trial design feature, I want to ask you how important you think it is. It has to do with opioid-dose titration. I think it might be important because maybe in

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clinical practice, in primary care, that may be happening in an unsupervised fashion. And because tolerance to opioid related side effects can develop, people can end up on higher, higher doses if the opportunity is there. And at some point, the realization is not made that there really isn't analgesic efficacy there.

So I guess I wanted to ask you what was your experience in your trial? We've done a couple of opioid trials where it's really more looking at side effects and pain relief as a guide to making the decision, do we do the next up-step of dose titration.

So I guess the question is, do you think that the method of opioid-dose titration in trials is important in optimizing dosing?

DR. ROWBOTHAM: Well, I think with telemedicine, making it easier to stay in touch with patients in studies, if that was introduced -- it's not really used, but it's there; it's available -- you can track them more closely. What we did in the levorphanol study was we started

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with very low doses. They had to come back every week at the beginning.

So even if they took their entire week's worth of pills, they wouldn't end up in the hospital. And then as they went along, they kind of got a little more rope each time. And we just gave them parameters that they needed to stay in, and then the coordinators stayed in touch close touch with the patients in order to get around that.

Now, of course if you had an electronic pill bottle, or you had an ambulatory PCA, or some other kind of thing, not only could you lock the device -- the device locks out, but you also get instantaneous feedback. The flashing red siren goes off in the study center saying, Mr. Jones is trying to force open the pill bottle with a crowbar and succeeded, and is now taking an entire week's worth of pills. You could get that kind of remote sensing, and then you could provide instantaneous feedback on, don't take that extra dose, or feedback on managing, it really could be automated

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to do that.

DR. JAMISON: Good talk and good thoughts. You alluded to the fact that opioid therapy is a moving target, and then you can start trials, opioid-induced hyperalgesia, where you can't recruit enough people on high-dose opioids, or you set a target. You have a certain opioid dose, and then you just can't get anybody.

So take your best guess. If we're going to come up with some design looking at something that we could start and then 10 years later, it's not appropriate or unfair, how much is this a challenge going forward?

DR. ROWBOTHAM: Well, that's why I keep coming back to this more in-practice trial rather than randomized-controlled trials because in that situation, you don't even necessarily need to do much to recruit. The patients are already there. It's really more what they have access to or if you institute a special program. And then as part of the consent to go into that program, they consent to have their data collected.

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So it's not the same as doing the kind of studies where you recruiting patients with high-dose opioids and then maybe trying some intervention to see if there's opioid-induced hyperalgesia or not because you're not necessarily doing an experimental intervention. You're just offering people different menus.

Basically, Howard and I walked up 14th street. Well, we walked like 8 blocks before we found a place that we felt like going into, so we had all those choices along the way. It's the same thing. In these cluster randomized designs, you could have 3 or 4 different interventions, and you just roll that intervention out. Because we're not talking about doing experimental treatment here. We're just talking about what techniques are going to give us the best outcomes? How are we going to reduce the harms of opioids and get some clue about how to roll back the severe harms?

We're not talking about the kind of studies -- and I have one that I slogged away at for years to try and recruit patients, where the

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intervention just requires a very specialized patient group, as you just mentioned now and we've heard some talks, that are just nearly impossible to recruit for.

Hope that answers the question.

DR. FARRAR: Interested in your thoughts on the randomized withdrawal structure, especially in the setting where maybe what we're trying to do is to overall reduce the amount of opioids that are chronic pain patients take. When I was seeing patients with chronic pain, I once a year would say let's try and taper down a little bit.

Doing that in a blinded way, even in an N of 1 kind of structure, or actually setting up a randomized withdrawal trial of some sort sounds like a reasonable way to go with the caveat that how you do the withdrawal is clearly a key feature of those. And I wondered what you or others might think about that.

DR. ROWBOTHAM: Well, I think maybe Jennifer and Bob may want to change seats because he may want to tell you about his experience trying to

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recruit for this. I assume you're not talking about EERW type studies for experimental therapeutics because there, that's a little bit different.

But I think if you try -- as soon as you talk to a patient -- because I tried this. I tried to do these studies. And as soon as you say one of the arms is going to withdraw your opioid, it's game over. I mean, it's just like, no. I maybe would think about a study that would increase my dose --

(Laughter.)

DR. ROWBOTHAM: -- but randomized decreasing dose, that's going to be hard.

So that's just a difficult task to accomplish. We essentially have accomplished it as a society by just putting intense pressure on physicians to just not prescribe anymore, creating this whole class of opioid refugees that are in the various clinics, mostly academic clinics around the country. So I think that it's hard to get people to voluntarily sign up.

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I actually proposed a study that was going to use -- and I'm so glad it didn't get funded. Anyone heard of UROD, ultra rapid opioid detoxification? It's basically how the rock stars make it to the next gig when they get too strung out.

Basically, you put the person under general anesthesia. You flush them out with naloxone. You have them under anesthesia. You keep their blood pressure stable and all the other things that the anesthesiologists in the room are so good at. And then you see what happens afterwards. You could put them on naltrexone at the end so they really perhaps couldn't relapse.

Fortunately, that study wasn't funded, so I didn't have to actually do it. But it would be hard to recruit patients. It would be a very special patient. And I'm going to have to look at the one that Howard cited yesterday from Stanford because I think the only way you get a recruitment rate of people wanting to taper is you've got an access line with a very big funnel of all the

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opioid users so that those few people that are actually highly motivated and are actively looking to taper get to you.

DR. FARRAR: If I could follow up with one other point. There's an interesting historical example of this, which is when Brompton's solution originally came out, he prescribed it as 1 teaspoon 4 times a day, and then he just adjusted the dose based on how the patient reported. So the patient never actually knew what dose they were on. I always thought that was a really intriguing idea. I don't know how to implement that in clinical practice or in a clinical study, but it just was an interesting idea.

MALE VOICE: You need a team of lawyers.

(Laughter.)

DR. ROWBOTHAM: Richard?

DR. RAUCK: Yeah, Mike. Richard Rauck. I think things have changed with patients in our chronic clinics. We're a pretty busy clinic ourselves. Patients are much more receptive now to structured approaches. They actually are getting

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the message, and some of this is being driven home by their spouses. Husbands or wives say I don't like you taking this. Some of them say I don't like the stigma I get every time I go to the drugstore, and they call me this or that or I'm a daily.

So it's interesting that a reasonable number now -- and I think you could put in place, is what I'm trying to say to you, some of this. In our clinic, we bought this whole-body cryo machine. I don't know if it does anything. Maybe it's placebo, but you sort of say, maybe you can come down on your opioids if you do this, or we put in 400 stimulators last year to your point on devices.

I think the confounder for me, as a clinician of 32 years, is I still think I do a very poor job of knowing which patients have opioid-use disorders. When you're just seeing them month after month, or every 2 or 3 months in the clinic, they can disguise that situation so well. And that's a different group of patients than the ones who are motivated or say, "Hey, I'm tired of this.

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All of a sudden I do realize the risk to me with these higher doses," and blah, blah, blah.

So if we're going to study them, they're kind of different groups, I think with probably very different outcomes and things. But as we see them in the clinic, they're not always easy to separate out those two very different groups of people.

DR. ROWBOTHAM: Yeah. I think actually the comment that Howard made yesterday on dose optimization is a good way of putting it because it's not pejorative; it's a neutral term. And I used to say to patients -- because there'd be these long discussions -- and this is a long time ago; it doesn't really come up so much anymore -- about whether or not to try opioids. And I would tell them -- because there would be all these mystical things associated with them. And it's like, "Everybody's conspiring to keep me away from these," which just makes them even more interested in trying them.

So I would tell them, I said, "I can make

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you better with opioids, and I can make you even better than that by then taking them away," because then they were demystified. It's like, "Oh, it's just a pill." It makes me a little bit better, and then it wears off, and then I really feel crummy, and my spouse says I'm irritable now or unpredictable. And they're sort of like, "Okay, well I tried that. Maybe it's not so great," and then they're, willing to go down or go off altogether.

DR. RAUCK: Although I would say -- Richard Rauck again -- the corollary to that is -- at least in my population and is maybe not that educated -- all they see is they miss a dose, and the first sign of withdrawal is their pain increases. So then they're very myopic to say I took a dose and it helped my pain, really helping the mini withdrawal. And no matter how much I talked to them about that, that that's not really helping your pain, that you're just keeping yourself out of a withdrawal scenario, they don't understand that. And I can understand why, because

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they took the dose and the pain got better.

So that sometimes, it seems so simple to us, but it's so hard for them to rationalize that.

DR. ROWBOTHAM: Well, that's one of the problems with doing migraine studies. And Howard knows this, from Neil Raskin, is that people take their migraine pill after the migraines already peaked. So of course they feel better because they were going to get better anyway. They were already on that part of the curve.

Ajay?

DR. WASAN: I was going to say -- this is Ajay Wasan from Pittsburgh. There are a variety of studies going on now using more explanatory models with adjuncts to opioids. It could be medications. It could be psychosocial interventions. One example, is Jin Ren Mao [ph] has a nice trial, a mass general one, adding duloxetine to see if you can reduce opioids, or Beth Darnall in Stanford has a big trial from PCORI on psychosocial interventions in conjunction with tapering opioids.

So I think we definitely need to mention

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that in the paper about the explanatory trials that have -- it may not be a mandatory taper, but it may be an option for patients, that they get this adjunct, and then if they notice some benefit, they have the option of very slowly going down like 10 percent per month. So that would be the opioid sparing. And there are a number of these things funded, so we should definitely say something about it.

DR. ROWBOTHAM: Yeah. It would be a good way of evaluating buprenorphine a little bit more, too.

Howard?

DR. FIELDS: Howard Fields, USCSF. Can I ask Sharon Hertz a question? Are you answering questions today?

Apparently, there are several companies out there that are working on developing selective reversible kappa opioid antagonists. In theory, if you look at rodent research, part of the dysphoria of withdrawal is due to dynorphins acting at the kappa receptor. So there's some evidence that the

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dysphoria, the aversion of withdrawal, can be blocked by kappa antagonism, which is maybe why buprenorphine is more effective than a pure opioid when you're trying to taper people.

So the question I had for the FDA is, are there any INDs out there for kappa antagonists?

DR. HERTZ: I can't even begin to answer that.

(Laughter.)

DR. FIELDS: That in itself -- that's an answer.

DR. HERTZ: My suggestion is you check clinicaltrials.gov.

DR. ROWBOTHAM: Does anybody have a computer here?

DR. GILRON: Bob, should we go on to the next part?

DR. DWORKIN: I just set Jen up with a computer. [Inaudible - off mic]. Let's take a 10 or 15-minute break and then resume.

DR. GILRON: Okay. Thank you.

DR. DWORKIN: We' going to take a 10-minute

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coffee/bathroom break and resume for the panel at like 5 after 2.

(Whereupon, at 1:52 p.m., a recess was taken.)

Group Discussion

DR. GEWANDTER: So now we're going to talk about chronic pain. At the break, Bob and I were talking. I think what we want to think about for this part of the discussion, if we're keeping with this theme of what hypotheses are we looking at, or do we think it might particularly important, I think our first question is, which of the -- sorry, I have to find it again -- which of the hypotheses that we came up with for the acute setting are applicable to the chronic setting? Then Bob came up with a couple, and I came up with a couple of extras, that it might be specific to the chronic space, and maybe we could also talk about other ideas that you guys have.

Let me open this one. So we can talk about if we think that -- there's a couple. One of these is at discharge, like that's not going to be

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applicable to the acute pain. I think obviously the one that talks about at discharge doesn't apply, but maybe you can comment on if you think that there are any others that really don't apply in the chronic setting. I think that would be the easiest. So I'll give you a couple minutes to read the first slide.

DR. KATZ: May I ask a question about your question?

DR. GEWANDTER: Yes, you may.

DR. KATZ: Would it be helpful to draw a distinction between chronic pain studies on patients who are not currently on opioids versus chronic pain studies in patients who are currently on opioids?

DR. GEWANDTER: Yeah, I think so.

DR. RAJA: Raj again. It looks like except for 5, all of your hypotheses have surgery in some form there.

DR. GEWANDTER: Have what? Surgery?

DR. RAJA: Surgery.

DR. GEWANDTER: Oh, right, yes. Sorry.

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That's true. They do have surgery in there, but let's forget about surgery. So for the first one, Intervention X, meaningfully prevents the initiation of opioids in chronic pain patients. Sorry. I didn't retype them. But let's just pretend that these are substitute chronic pain patients for surgery, people with surgery.

That would potentially obviously be a possibility. If someone comes to the clinic, and they've tried NSAIDs, and they've tried all these other things, one option might be to give them an opioid, but you could randomize them to an opioid or your experimental drug and see if they're able to avoid having opioids.

Yes?

DR. SCHOLZ: Joachim Scholz, still from Biogen. I think that would also be applicable to the acute pain because surgery is not the only situation where people are receiving opioids. It's the example that we have discussed because it's relatively straightforward to design a trial around it. I mean, there are other interventions or

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indications for which people receive opioids.

DR. GEWANDTER: So I think your point -- if I can just make sure I understand -- is that when we talk about these hypotheses in the paper, we should avoid saying "with surgery" and just say with whatever acute pain condition.

DR. SCHOLZ: It's one example, and it's the most frequently studied. It's easy to think about other situations where people receive opioids, otherwise we put the blame on the surgeons.

DR. GEWANDTER: Yes?

DR. RATHMELL: Jim Rathmell from Brigham. I know what you're trying to do is take the acute texts and mold it toward chronic. So I'm going to talk out loud for a minute and think about the two contexts that are really common in the chronic pain world. One is the decision, when all else has failed, whether or not to initiate chronic opioid therapy and how to choose patients who will do well. So that's one big context where we want to generate some hypotheses.

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The other is the patient who comes on opioids, persistent opioid use, for whatever reason, and they're referred for appropriateness. So the other hypotheses is how do we determine who's appropriate and who and how to Wean and taper opioids. So those are the two big contexts where the hypotheses will come in. And I think maybe if we start there, then we can fit them into the acute pain.

DR. GEWANDTER: I think that the second scenario might fit in a little bit better with the newer hypotheses that weren't in the acute pain setting thing that we came up with. So I'm not sure if -- I think one thing that you brought up that we are not addressing here is the issue of how do you choose who should be in those studies. I think maybe if we could establish first what the hypotheses would be that we would be testing, then maybe once we finished that, we can discuss how do you choose who are the appropriate people to be putting in those kinds of trials, if that's okay.

DR. FARRAR: I understand that maybe all of

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these, if we substitute chronic pain for surgery, have some applicability. The thing that clearly distinguishes the chronic pain environs is that a lot of the patients we see are folks already on opioid. So I think one of the questions that I would pose and interested in feedback is whether we would need some hypotheses that would relate to getting people off, or treating pain in a different way that would allow them to reduce the amount of opioid they're on or to --

Now, I do have to say that most of the chronic pain patients who are reasonably treated for their chronic pain on opioids are not the problem. So I will voice a bias, which is that reducing the amount of opioid they're on might be useful if they're on a high dose because of the endocrinopathies and the other things that we know about. But if they're on a low dose, it's not clear that opioid sparing is necessarily beneficial. Even in that setting, it's clearly something we need to think about.

DR. GEWANDTER: So I think maybe we can skip

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a little bit -- and I think it seems like people really want to talk about this, so let's talk about it. So for inclusion for these studies -- I think these three hypotheses that I have up here now are related to what you guys are talking about, where someone's on opioids and you're trying to either lower their dose, get them off, or number 3 is to prevent them from escalating their dose.

So I guess the question is maybe we should talk a little bit about who are those people. Are they people that are having function problems because of their opioids? Are they people who are on just a numerically high dose that we don't think is good? Who do you think should be included? Two different people have brought that up. That's an important thing to talk about.

DR. WASAN: To follow up on John's comment, I'll maybe have slightly different language here related to optimizing opioid care, to add that in, which may include some reduction in certain situations, might include keeping the same dose and doing more rigorous monitoring, all kinds of

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things. It might be the lowest effective dose, all sorts of things, because I think that would help a lot and tie together a lot more different study designs with the same goal of improved opioid care.

DR. GEWANDTER: Ajay, if I can just try to see what you're saying. So you're saying maybe just tweaking the language a little bit. Instead of saying "withdrawal" or "dose reduction" to be using the language of optimizing instead.

DR. WASAN: Yeah, and that may mean a whole variety of things, optimizing opioid care. So technically it's a little different than your definition of opioid sparing, but that seems to me a bigger overarching umbrella concept that would include more designs and promote a whole variety of higher improved standards or any kind of opioid research, and also include that concept of opioid sparing if you want to be that specific in the hypothesis.

So, yes. It's a long answer.

DR. GEWANDTER: What? Make it bigger?

DR. RAJA: [Inaudible - off mic].

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DR. GEWANDTER: Thank you.

DR. WASAN: Yeah. So there's dose optimization, but there's also care optimization. Those are related kind of ideas. It's a whole variety of things, just like taking care of a diabetic, prescribing insulin, there's a whole variety of things you do that are associated with good care.

DR. GEWANDTER: I think part of that would be what is Intervention X, right? So Intervention X can either be a new drug or it can be some kind of care optimization scenario where you're trying to have a multimodal intervention that changes some other things to allow you to decrease -- to optimize your dose of opioids. So I think maybe we're getting a little bit in the weeds. We recognize that there are all sorts of different ways that these interventions can be not just a drug. I think we recognize that.

DR. JAMISON: Just clarification. So we're not talking about how to taper opioids, and we're not talking about how to identify opioid misuse

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requiring tapering.

DR. GEWANDTER: I think those are the two questions. One is how to identify the people that should be included, and one is how to actually do it. So I think in this paper, we could get into it a little bit, like what kind of inclusion should we be using and who's most at need to be in these types of studies. But I think in terms of how to taper, that would be potentially up to the investigator to decide what's the intervention? So a certain tapering strategy would be an intervention that you would be testing, or part of the intervention with whatever else, whatever drug you are doing.

You guys can feel free to disagree if you think that we can be prescriptive about how to taper, but I'm not the person who would be making that decision for sure.

DR. ROWBOTHAM: I think it might be -- if I could make a suggestion, to start out with a blank slide because we're looking at such a different situation, patients with chronic pain as opposed to

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acute pain where you have more control.
The reason I spent so much time on the pragmatic trials is we actually have this going on already. We've got two regulators in the room. We had Sharon and a former regulator, Lee. When government sets a policy or the FDA approves a drug, they will have the sponsor come and make a presentation. The sponsor's statisticians will be there. The FDA statisticians will be there. They will battle it out. It's quite entertaining. And then there'll be a decision as to what will be the labeling for that drug. That makes a big difference.
Likewise, when the government imposes new policies and rolls those out, you are essentially doing a natural experiment. So the whole idea with the pragmatic trials in the cluster randomized design is you essentially roll out different practice styles either based on changes in a hospital or a clinic's formulary, its guidelines for how something is going to be managed; or what types of treatment patients will have access to;

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or you design a special care program, and that's just the way that everybody does it after that.
For example, hospitals have very rigorous criteria for how certain things are managed postoperatively, so there's no confusion; that people know what to do. I think what we can do here is talk a bit about what things would we like to see evaluated prospectively in terms of changing the way that we manage patients.
Simple examples could be things like everybody who comes in with acute pain, see somebody to have an assessment for opioid-misuse and opioid-use disorder; or every time they go to get a new prescription, there are certain questions that are asked. These can be really, really simple things. The can be pharmacologic, they can be device, they can be just practice styles. It can be all sorts of different things.
So I just wanted to demystify the pragmatic trials. It's really just you roll something out at different places, and then you look and see what the effect is. So it can be even simpler than

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that. One hospital has one different type of opioid on its formulary and the other one has a different one on its formulary. And then you just decide what it is that you want to be looking at some time point. There's no consent needed as long as you're doing things that are within standard of medical, appropriate standards of medical care. And then you can see what kinds of very simple interventions make a difference; unless we're here to try and design the next trial of a new drug or device, which we could be, but that's sort of a different -- that's just a different approach.
DR. GEWANDTER: Raj?
DR. RAJA: I think central to what we are trying to achieve here may be a hypothesis that Intervention X -- it could be single or a combination of interventions -- prevents the development of opioid use disorder or misuse, abuse, or related events in patients in chronic pain on opioids.
What we are trying to see is, is there an intervention that will prevent a patient who may be

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on opioids developing a misuse or abuse disorder. So maybe that's a hypothesis worth putting in.
DR. DWORKIN: Mike, I take your point, but I'm still stuck on the more classic randomized control trial. So just thinking off the top of my head, let's say we take patients with muscular skeletal, low back pain that are on somewhere between 100 and 200 milligrams, stably on 100 to 200 milligrams of morphine equivalents.
Given what Richard was saying about the patients he's seeing in his clinic, it seems to me we should be able to get them to agree to a trial of the following sort, that they're going to be randomized to one of 3 groups, continued on their stable dose of 100 to 200 morphine equivalent, a double-blind NSAID APAP kind of placebo but not really -- and may be better than placebo given the recent studies; and the third group is new compound that is thought to be potentially opioid sparing. The two groups that get either NSAID APAP or new compound, we taper them down to 50 percent of the dose that they came in with.

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I'm just kind of blowing off the top of my head here. We have two hypotheses that we test. One is that there's noninferiority of new compound to maintaining this initial dose and that pain goes up in the NSAID APAP group, which we kind of think as a surrogate for placebo.

Now, that's a kind of standard, randomized-controlled trial where we're testing a putative opioid-sparing compound against a kind of placebo versus maintaining the dose that's at a level that, at least in the state of Washington, is considered too high.

Is that not something anyone would ever want to do? Because to me, if someone would fund it, and I had a compound, it seems like an interesting clinical trial, or am I kind of barking up the wrong tree?

DR. ROWBOTHAM: No, I wouldn't say that. It's just that we're kind of coming at the issue from different directions.

DR. DWORKIN: No, that's right. No. What I just proposed is different than a pragmatic trial,

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and they answer very different questions. I'm thinking of having some -- and it doesn't have to be a new compound as some of us talked about at the break. I'm very interested in triple reuptake inhibitors, so I would love to do the study I just described with the third group being a triple reuptake inhibitor that I would hypothesize, allows the musculoskeletal patients to come down to 50 percent of their dose while maintaining pain control, which we talked about this morning.

So I don't know that anyone's going to do that trial, but I would be a little disappointed, personally, if our article didn't lay out those kinds of hypotheses and designs.

DR. HAYTHORNTHWAITE: Sorry. I was just having a sidebar. Never mind.

DR. RAUCK: I'll add a little bit. I think there's some truth to what Mike was trying to say, is that those patients under that design paradigm, a lot of them are tempted [indiscernible]. The fallout dropout rate is huge because the people who perceive -- if compound Y or whatever isn't that

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good or not quite as good, they come in. And once you start that wean thing and they know it, it really can fall apart the trial.

So that is part of it. They might be motivated first, and maybe that's okay; you'll find that out. I'm trying to think. Let's say anti-nerve growth factor was the compound that you're willing to look at. So if it has enough efficacy, it could be the perfect one, then maybe it's okay that the others fall out, and the ones in the third group will get anti-nerve growth, and it's great, and they do really well, and they wean right down, and that's your end game if it's potent enough.

So I could see that, but Mike's Point is also right. We've been part of that trial trying to enroll patients who were going to sign up to voluntarily wean off, and it was not a good decision to try to find those people and all the efforts we spent. So I'm kind of mixed on this. You're right. I think describing that as an option makes sense, but I don't know that it's going to

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work in all scenarios.

DR. DWORKIN: Richard, because of your experience, I didn't have a discontinuation group. It was tapered down to 50 percent. We'd want to have double-blinded Lomotil or some mildly constipating agent, so the patients didn't immediately realize they were in the group tapered off. And I'm tapering down to 2 active drugs, I guess either a triple reuptake inhibitor or an anti-NGF. And then a kind of pseudo but maybe not very placebo of NSAID plus APAP. It's a very different design than the one that just ended.

I don't know that anyone's ever going to do it, but it would be cool to at least say this is the kind of thing that someone could do if they had a compound that they thought was potentially opioid sparing.

DR. WASAN: I think that also points out the strengths or weaknesses of explanatory and pragmatic are the same question. Right? Because in that explanatory version, you still have significant placebo effects, of course, and placebo

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is really an active comparator for all of the endogenous analgesic systems that activates. That could always be criticized. You can never answer that aspect of it and what you kind of described on top of all the retention issues.

So you can take that same hypothesis and say you could test it better in a pragmatic concept. I mean, either one. You could make your argument both ways.

DR. DWORKIN: Ajay, I don't think you're right because there's no triple re-uptake inhibitor that Mike can test at Sutter, with the possible exception of a combination of Wellbutrin and an SSRI, but that's a little bit crazy. If I've got a triple re-uptake inhibitor or Ken has an anti-NGF, we just can't test that in a pragmatic trial.

DR. WASAN: Right, for a new compound, yes.

DR. DWORKIN: Exactly.

DR. WASAN: I was thinking in the scenario of recycling some old compound, which you suggested.

MALE VOICE: So again, thinking about I have

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a compound, let's say, hypothetically, in my pipeline for chronic pain. What you just said is probably what I'm going to need to do in order to have that entertaining adcom experience, as I would say is not necessarily entertaining, but to have that discussion about approval.

Is 50 percent -- so you just threw out a number. If that's what I show with no difference in functional or those patients who were on that higher dose of opioids were functioning fine, and all I showed is I reduced it by 50 percent, function didn't change, patient said I'm not any better than it was before; my pain's not any worse, is that going to be sufficient?

DR. DWORKIN: I'll stop talking, but I think the question you just asked is a great question, and my prediction is going to be the very most difficult section of what Jen is going to write. So you're right. I threw out 50 percent, but is that meaningful? Maybe we don't care whether they're on 160 of morphine equivalent versus 80, or maybe we do. In Washington, we do, but in New

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York, maybe not so much.

DR. GEWANDTER: Deb has a question.

DR. STEINER: Well, it's sort of a question, but yeah. Deb Steiner, Cambridge, still. What sponsors are going to do, we have, or Biogen has, Vixotrigine, Nav 1.7 blocker. Let's say they want to investigate whether there could potentially be opioid-sparing effects of some sort. From their vantage point -- I don't know that we're going to get to the granularity, but is it -- and it's a very similar question?

What's the key? Is it that the tolerability -- you can taper the opioids. You can figure out the design exactly how you want to do it. But is it that you want to see that you're improving the things related to the opioid side effects, that discussion yesterday. Is it the pain intensity? Is it the functional outcomes? Is it everything?

So I think there is really going to need to be some guidance on -- there could be primary and secondary endpoints. Maybe secondary endpoints

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could lead to labeling. It's a lot to undertake for people who are going into this and interested in it because I think there's a lot of commitment from sponsors working in pain to try to come up with novel analgesics, which are not opioids.

So it's just the challenge of what should the key be because it can't be everything. And then, obviously, all this, well, everybody would love to do that dreaded -- the percent reduction. I just think there's so much, I'm not sure, again, whether that's the detail or whether there's a high level to start with. I'm done.

DR. ROWBOTHAM: Let me just comment, and then maybe I'll just stop talking about pragmatic trials. If you're talking about things that could become standard of care or postmarketing studies, then this is the way to evaluate the impact of something in large, large, large numbers of people so that you can look at uncommon outcomes and see if there's an impact.

So we heard a little bit yesterday about how cannabinoids have been legalized in some states,

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but not all. And so we're already in the midst of it's not a pragmatic trial because it wasn't done prospectively with thoughtfulness as to what you were -- or at least not that I know of -- what kinds of parameters they're going to be looking at. But you have this natural experiment going on where Colorado and now California and other states are legalizing marijuana, or cannabinoids, and we're going to see what the impact is.

So all the pragmatic trial does is you think about it in advance, and you set up the way of measuring the outcomes that you want to look at before you impose the policy change, the practice style change, the formulary change, all those other things that you're going to impose. And the beauty of them is they're low cost per subject. And depending on what you're doing, you don't necessarily need to get individual subject consent.

Nobody's really -- Congress or the state legislatures voted on the cannabinoids, and yes, we're in a democracy. But everybody who's trying marijuana now as a result of living in Colorado,

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they're not having to sign a consent form necessarily to enter into a study. So that's really the difference. We're talking about premarketing versus marketing or practice style issues.

DR. GEWANDTER: I think Deb and then Roy have a comment.

DR. STEINER: Sorry. I just thought of one more thing. What would you do in this situation where you have a new analgesic, and you may not be 100 percent sure about whether there are any effect when you stop the medication or taper it, and you also don't know if there are any potential interactions with the medication?

How is somebody going to weave in that type of thing to the type of study that a sponsor might consider? I just think it takes everything that we've been talking about and just makes it even that much more challenging because then you're talking about the side effects, and you're randomizing people, and giving Lomotil for potential side effects of the opioids, and what are

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the side effects of the drug that you're using? It just seems challenging.

DR. FREEMAN: So the challenge over here is one of -- Roy Freeman, Boston. The challenge is one of endpoints. I see every endpoint as having substantial flaws. Bob's endpoint of opioid reduction, 50, 20, 90, 80 I think is really appealing to your congressmen. There are less drugs out there in the community, but what it actually really means in terms of -- your term, this meaningful prevention I think is almost impossible to ascertain.

So that's the one, the opioid crisis endpoint, 50 percent less opioids out in the community. It would be a wonderful headline, but I'm not sure that it really means anything.

There's the adverse event endpoint, which I think on paper sounds like a pretty reasonable endpoint. But as has come up once or twice, which do you prefer, nausea or constipation, vomiting or -- and how do you weight that endpoint? Is it going to be to use Deb's multicomponent composite

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endpoint? Do you get patients together to decide whether they prefer constipation, which will get 1 point versus lots of vomiting, which will get 3 points? It's really difficult I think to operationalize but perhaps worthwhile the effort. That to me is an appealing endpoint.

Then there's function, and I think we have good measures of function, and I think we can use that. To me, that's possibly the most appealing endpoint. And then there's the hard endpoint, death. And usually death is very straightforward in a clinical trial. You're either dead or you're not.

But here it's actually really tricky because one of the more interesting talks I thought was by the pulmonary guy. I'm sorry, I forget your name. And he raised the issue that there are actually several ways of dying. You can die from a voluntary overdose, suicide; you can die by a mistaken overdose, too much opioids, not enough of a 50 percent reduction; or you can die from too much pain, and pain results in respiratory

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depression.
So it becomes really complicated. You're withdrawing opioids, you're causing more pain, and that may result in your hard endpoint death, or you're leaving patients on too much opioids, and they're overdosing unintentionally, and there's your hard endpoint death.
So this is a long way around to maybe saying, well, maybe Michael, you have a point with the pragmatic clinical trial. Patients will vote with their feet. We don't really know how to operationalize each one of these 4 endpoints, but patients will know. And we'll come to a conclusion, yes, with Bob's triple re-uptake inhibitor or whatever we're doing, the one that's available on the market. Patients prefer this or that. But we won't -- and here's my problem with pragmatic trials, and I really am a fan, is that you come to the end of a pragmatic trial and you say, well, what did we really learn over here? You just lack of granularity that Bob's randomized, placebo-controlled trial gives.

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DR. STACEY: Brett Stacey, Seattle. So I am entertained by thinking about the Steve Passik headline title I read, that I showed from 2007 about dose doesn't really matter because I've heard people repeatedly tell me dose doesn't matter, yet show me the study where it shows that higher doses are associated with less mortality or more function. They're not. Right?
So do you associate function, death risk, adverse effects, the higher the dose, the more of those who have? The data we don't have is that if you reduce someone's dose, they slide down that scale, and they now assume the risk at that lower level. But no one can show me some big study that shows higher doses are better for survivability, for adverse effects, for function in general for opioids.
So lower doses are safer. Everything we could look at would say that. We don't have data that says reducing is better and that's what the idea of a clinical trial, is to say two things. One is what interventions allow us to get to lower

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dose? And if we do get to a lower dose, is it safer? Am I missing something with this? I know we talk about, oh, it's for congressmen and other people, but why is it not for people?
DR. ROWBOTHAM: I'm thinking through just the last couple of comments. One thing that's come up in some of our previous IMMPACT meetings about the problems in pain clinical trials, which is the placebo effect and I think in a more general sense, study power issues and recruitment difficulties. One of the advantages of doing in-practice studies is it gets you to large scale quickly, and you can look at, without having to do all the work of recruitment, just how malleable, just how much change can be induced in certain outcomes as a way of framing your studies.
So let's say -- and we've actually already done some of this experiment. If you said 10 years ago, or 12 years ago, gee, what would happen if we got morphine equivalent doses down by 50 or 80 percent, and you proposed it as a study, well, one, nobody would sign up for it. And if they did, it

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would just take you forever to recruit enough subjects, and you'd have other issues.
Instead, the insurance companies and the legislators did it for us. They said, "Guess what? We're not going along with this anymore." And now we can look at how much overdose deaths and other kinds of severe outcomes have changed as a result of that kind of experiment that's been imposed on us.
So there are some framing questions that can be answered by that without having the power issues and the placebo effect issues in the classic randomized trial. I mean, clearly, that's the way -- if you really want to prove very specific hypothesis, that's the only way you can do it is by a properly randomized-controlled trial.
I'm just thinking more about the larger societal issues and how to compare non-opioids with opioids, behavioral interventions, all the different kinds of things, is by having an agreed upon set of definitions and outcome measures, and then see what happens when they get rolled out in

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different places and what impact they have.
DR. STEINER: Hi. It's Deb Steiner, Cambridge. I was thinking about what we're discussing. First of all, hopefully we're doing this mostly for the patients -- I think we are -- and my experience in any of the trials that I've done, when we get feedback, we do patient ad boards [ph], is they want functional endpoints. That's what appeals to them. We do cognitive debriefing. They're not going to care about reduction in opioid use.
We have so much discussion internally in companies about using functional endpoints, and can we get regulatory acceptance. I won't exactly put Sharon on the spot, but maybe this is an opportunity because maybe this is a situation that really caters to using functional endpoints. And to me, functional endpoints actually would include the side effects that we're talking about because they actually don't make good functioning very pleasant or always possible.
I think some of the other

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things -- especially the more I'm thinking about what one would do as a company and trying to have this beneficial to be able t study for a drug, I don't see that it's going to work too easily. So anyway, just a thought.
DR. RAUCK: It seems to me that both of these have a lot of value as I sit now and think about them.
Mike, to your point, we could take a North Carolina point exactly when the legislature passed some of the laws you're talking about and following CDC guidelines, and in our clinic where we saw 48,000 patients last year, it'd be really intriguing. And that's something NIH would fund, a drug company doesn't care about.
We could come in and, look, how did it change practice, and then to Brett's point, did it change any pain relief? Did it really make a difference or not? They might have functioned just as well. How did it go, and look at that. I think, Bob, yours are classic, we still have to do for explanatory purposes, and the drug companies

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and all those folks have got to have that.
I did want to answer one thing to you, Deb. I would go with you all day long to adcom meeting if you show 50 percent opioid reduction with your new intervention or drug, with your Nav 1.7. I think that's a completely relevant endpoint. I can't think that our agency in today's environment, where we're trying to decrease opioid exposures and opioid pills, wouldn't be clinically relevant and meaningful.
DR. STEINER: I agree that it is. I'm thinking -- I guess I'm trying to balance multiple factors, so I completely agree. I'm just trying to think of how to put it into practice.
DR. RAUCK: I think Bob's thing is the way you would look at it. I think you could do that in a clinical trial, I think. But, boy, it is a high hurdle. I mean, you do have to have an effective analgesic. It just can't be a -- it's got to be better than an Advil or ibuprofen.
MALE VOICE: Can I make a comment to Bob's design?

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DR. HERTZ: So are you saying that if the population went on average from 10 milligrams per day to 5 milligrams per day, that 50 percent reduction should be assumed to be clinically relevant? It's a question..
DR. RAUCK: Yeah, that's fair question. I wish I had those patients in the clinic.
(Laughter.)
DR. DWORKIN: Sharon, I will answer your question. That's why I said starting with patients who are between 100 and 200. I didn't say starting with patients on 20 or 40. I said we'll enroll patients, musculoskeletal low back pain, stably on somewhere between 100 and 200 mean morphine for exactly your reason.
DR. STEINER: Are those going to likely be the patients who are going to respond as well to the -- for a variety of reasons, to the novel analgesic?
DR. DWORKIN: Well, we don't know.
DR. STEINER: I know.
DR. DWORKIN: That's why we do the clinical

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trial.
So Ken's going to put his anti-NGF into the trial, and I'm going to put my triple re-uptake inhibitor, and we'll let you know in 2 years which of those drugs allows taper down to 50 percent.
DR. STEIN: Is that 2 years from concept development?
(Laughter.)
DR. KROENKE: Just a comment on pragmatic trials and clarification. There are several types of pragmatic trials. Some of what you discussed in its largest sense are not even trials. They're using quasi-experimental, pre- and post-policy changes. So whether' that's a pre, post, or a large cohort with a secular, it's useful. But then other pragmatic trials might take clinics or healthcare systems and randomize some hospitals to one policy or intervention and one not. So that's more aligned with large pragmatic trials.
Then there are effectiveness trials, which takes a smaller number of people, which is usually what we've done, 250 or 300, and randomizes them to

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a complex design, which is usually care management, optimizing things versus usual care or something like that. All of them are in the range of pragmatic as opposed -- because they don't have blinding, they have broader inclusion criteria. You don't use specialized providers. You use the providers that are there.
That being said, one limitation, the more you get into the real world and saying you're not going to consent, the problem is we have very few of the measures we want in the electronic records. If I was being a pragmatic trial in diabetes, everybody gets A1cs. If I was doing it in a blood pressure, everybody's got it.
Many electronic record systems don't routinely have patient -- even measures incorporated, much less function, much less adverse events. About all you'll be able to get is, has drug prescribing changed? Are we using less opiates or more? And are we having less diagnosable OUD by ICD, and are we having less opioid related deaths?

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So I think that's a good design for looking at the really bad outcomes, ranging from opioid related mortality, which is the worst; opioid-use disorder, which is intermediate; and persistent opiate use in dose if we believe that's important. I think a pragmatic design using large record systems, thousands and thousands, would be good for answering those more serious, less common events. If we're interested in saying -- but it gives us no idea about patient outcomes, or that patients have better pain control, less adverse events.
So I think we need designs -- the large thing you described would be good for those uncommon, easy to diagnose events out of electronic records probably before the ones that are going to require measurement of pain control, adverse events, have we optimized the regimen, and are probably going to require patient enrollment and consent probably at the level of hundreds of patients, but not thousands. And that could be pragmatic designs and not efficacy designs where you have placebos. So I just wanted to clarify.

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MALE VOICE: Thank you for that.
DR. WASAN: I would just add one thing to that. I guess number one, I think our recommendations can be aspirational because, for instance, Epic is actually getting better at being able to capture patient-reported outcomes at every visit, and some systems are trying to use that enhance functionality of Epic as an example for how to do that.
Then secondly, I think that the chronic pain section is another opportunity to revisit this need maybe for some different measures such as the tolerability, idea of tolerability measure to develop. The chronic pain session would be a good place to mention that need because that can be a good global summary measure that may help us answer some of these questions.
DR. GEWANDTER: I'm sorry. Are you responding to him? I'm sorry, I don't know your name,, but he's been waiting.
DR. VERBURG: Ken Verburg from Pfizer.
Bob, I think you're taking the hard road on

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your triple re-uptake inhibitor. The first point I would say is it's a very difficult. Unless you already have evidence in your pocket that your treatment is effective or as effective, most patients -- in fact, most investigators won't take a patient off something, no matter whether it's appropriate or not. It's pretty hard.

So you need that foundational evidence, and so you try to gather that in a forward manner, randomized-controlled trial. The difficulty nowadays, of course, is trying to randomize to an active control that includes an opioid. IRBs are not looking too kindly on 4 to 6 months of continuous opioid therapy in patients that are either naive to opioid therapy in the first place. You've actually confounded the problem potentially.

But if your therapy is 50 percent as effective as safe opioid therapy and you want to test that in some fashion, I think it's a twofold process, which is a randomized-controlled trial with some estimate of what of what your efficacy is relative to what standard of care of opioids is,

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and then you go into the database phenomena to see how much combination therapy is used; is it lower over the course of time.

I mean, that's the way that I would think about it. So I wouldn't spend a lot of time, a lot of pages of the manuscript on trying to use the randomized withdrawal or lower dose effect. I just think it's too doggone difficult. I'm not sure who would go after that.

DR. DWORKIN: This is fascinating, Ken. I would hypothesize and think it was worth testing that -- forget about the triple re-uptake inhibitor -- that tanezumab would make it possible for patients with musculoskeletal low back pain, who were between 100 and 200-milligram morphine equivalents, to cut their dose in half. I think that's reasonable.

Do you think we don't think that's reasonable? I'd be surprised if you didn't think that was a reasonable hypothesis.

DR. VERBURG: Well, ideally what you'd like to have is an agent that's as fully effective. So

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the trials that go on now are actually patients that have failed opioid therapy, found it to be not as effective. They can't tolerate it or they don't want to take it. So you're into a patient population, which has gone through that process for one reason or another.

If the drug is effective in that population -- you've sort of surmised yourself -- I think I have a sufficient body of evidence to say that it's a pretty useful therapeutic maybe in standard practice, but then you actually evaluate it in terms of its effectiveness actually in the practice conditions. If it's as effective as an opioid or 50 percent as effective, you want to see how that manifests itself in practice care.

I don't want to try to prove that in a randomized-controlled trial. I just think it's too difficult, given all the boundaries now around what's appropriate opioid use or not. That's just my notion on this.

DR. GEWANDTER: Actually, Ian had a question, and Raj, and then Brett.

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DR. GILRON: Sorry, Bob, just to play devil's advocate. We go through. This consensus paper gets published in January of 2019, and it inspires people to design a clinical trial of tanezumab or something. So that gets funded and ready to start in June of 2020. No, no, best case scenario.

What do you think about the feasibility of recruiting to a trial, I don't know, 50, 100 patients who are on a 100 to 200-milligram equivalents morphine with low back pain? I'm being devil's advocate in terms of this kind of study hypothesis and trial design, and asking that in, let's say, June of 2020, what's going to be the number of patients, first of all, on that dose at that point in time, and should we be inspiring that kind of a study?

DR. DWORKIN: I have to defer to Brett and Richard and others who see patients. My guess would be that even in another year or two, they're going to be plenty of patients with musculoskeletal, non-specific low back pain on 100

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to 200 morphine equivalents. But if I'm wrong, I certainly agree with you. We'd be proposing a clinical trial that nobody could do because the patients aren't out there.

DR. KATZ: I can provide a sort of answer to that question, I think. Nat Katz. So people are probably aware that there are 10 pharmaceutical companies or so, plus or minus, that have gotten together to do a large clinical trial on opioid-induced hyperalgesia, where the entry requirement was essentially that you're on roughly that amount of opioid, and then you would get tested for hyperalgesia. You get randomized to either stay on your opioid or come off your opioid.

We did a lot of work with patients in advance of that trial to try to figure out what would entice you to enroll in a trial like. A lot of work was done to try to figure out how to get this done. And over a year and a half, the sponsor spent certainly over a million dollars just in patient recruitment costs, and they reached out to something like 6 million individuals in a variety

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of different channels. And with all that aggressive effort, in a year and a half, I think they're randomized 19 maybe.

DR. DWORKIN: Nat, I want to respectfully disagree. That's a very different trial. You were telling patients that you were going to, on a double-blind basis, bring them down to zero. My trial -- actually, I think it's Ken's trial, but I'll call it my trial -- is you're telling patients you're going to reduce their dose by -- either keep them on the same dose or reduce their dose by half with a double-blinded drug that we hypothesize is going to allow a 50 percent dose reduction.

I want to participate in my trial. I might not have wanted to participate in your trial.

DR. KATZ: That's why I said it was kind of a partial answer, so maybe you'll double the recruitment rate or maybe even triple it.

(Laughter.)

MALE VOICE: [Inaudible - off mic]

(Laughter.)

DR. STACEY: I want to say one more thing

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about your trial. This is Brett.

DR. DWORKIN: And then I'll tell you about another trial that you can all hate. I'm going for two trial designs that everybody hates.

DR. STACEY: With your new analgesic drugs that are coming to market, when you test them in your ideal subject population, perfectly screened, exactly what you want, what's the NNT? What's the numbers needed to treat to get a significant clinical response?

DR. VERBURG: Your response definition is 50 percent reduction. It's 1 in 15, 1 in 25.

DR. STACEY: Yeah. So that's going to be really challenging when you get to your chronic, high-dose opioid patients and start tapering them down where most of them are going to fit. And there's going to be a little subset that succeed. So this is challenging with that when it comes to actually conducting it. It's not like a regular study where we're just adding something on. If you don't work, oh well, it doesn't work.

We're adding and taking at the same time,

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and adding something that has a half chance of not being anything. And if it is something, it may be a completion, but often it's going to be a dropped pass. So it's going to cause a lot of clinical study disruption.

DR. GEWANDTER: Raj has been waiting, and then back there, too.

DR. RAJA: I thought Ian would say this, but this has been somewhat looked at in this New England Journal article, which was using drug X, using drug Y, which is an opioid, and the combination. In that, you showed that the combination reduced opioid effect -- I mean, reduced the opioid dose. However, at least within that sample size, you were not able to show a difference in the adverse effect profile.

So I think this is a crossover design, a kind of a trial that has been done in the past. Maybe you can comment a little bit more on that.

DR. GILRON: Well, the thought did go through my mind, and it reminds me back to what Mitchell Max wrote like in the mid '90s in an ISP

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supplement, talking about combining opioids with other drugs. So they've been talking about this for a while.

I didn't think of an opioid-plus drug X combination trial as an opioid-sparing trial. And it comes back to what I was asking about in the morning, which is, that wasn't the purpose of the trial. The purpose of the trial was can we get better analgesic efficacy without worsening side effect profile.

So it ends up being a demonstration of opioid sparing, and the bonus, we can argue whether it's clinically relevant, was that we got lower pain intensity scores with the combination without the worsening side effect profile, which is -- it's kind of the -- you're proposing I guess an add-on design because they're already on the opioid, which is fine. But your endpoint, I believe, is opioid-dose reduction without making anything else worse.

Is that correct? So it's a different goal, but it looks the same.

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DR. SCHOLZ: In light of the discussions that we have, I think the hurdles for opioid reduction as a primary outcome measure are really high. We do not have validated assumptions about what is meaningful. There's some uncertainty which adverse effects would be the target that we should seek or whether composite measures are better than single measures.

So I think it's more realistic to look at trial designs that have analgesia as a primary outcome measure and then opioid reduction, and you can define that as you like, as a secondary outcome measure. It would also be easier to calculate sample size, efficacy, and so forth, simply from a design perspective.

DR. DWORKIN: Mike, can I ask you a question? I know you've thought a tremendous amount about tolerance, and outside of the preclinical realm, what evidence do we have in people that opioid tolerance occurs? Now everybody, I guess, thinks it occurs because patients increase their doses over time to

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apparently maintain the same level of analgesia.

So I'm really changing the subject here. Is another possible type of opioid sparing a drug that prevents or reduces up-titration? Jen and I were talking about this at the break. Wouldn't that be sparing if Richard takes a patient who has failed everything and decides he wants to try not very much oxycodone, let's say 40 milligrams a day, and we now put that patient on agent X -- I'm not going to use examples anymore -- and agent X versus placebo actually prevents the need to titrate up the 40 milligrams of oxycodone versus placebo? Those patients creep up over 6 months.

So would that be another kind of opioid sparing that we haven't talked about, the prevention or the decrease of apparent tolerance over time?

DR. ROWBOTHAM: Well, I would think so just because you end up at lower doses.

DR. DWORKIN: Has anyone done --

DR. ROWBOTHAM: If we're considering that as being one of the ways of measuring opioid sparing,

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that you'd just end up on a lower dose, assuming that the pain control is identical.

DR. DWORKIN: Exactly.

DR. WASAN: Well, one of the things it makes me think about is that upper titration is not necessarily the norm anymore, especially with all the ceilings and limits. Going beyond 90 is something that's unusual now. It's a strawman in a way to say that we have a natural history, is that it's going to be up-titrated when it may not necessarily because it's really so provider dependent as a standard practice.

DR. DWORKIN: To go back to Brett's point, Brett would rather -- his patient is on 40, then 90. So even within that below 100 realm, one could imagine that 40th day of oxycodone is preferable to the 90th day of oxycodone.

DR. WASAN: You could, but the data for that, the differences between low and moderate dosing right up to 50, and then 50 to 90 for instance, is very little in terms of what are the incremental benefits, while in theory, yeah, there

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are incremental benefits, and we could make the case that there are some incremental benefits.
Mark Jensen liked to say at these meetings, "Is the juice worth the squeeze?" He always liked to say that. So that would be the issue, which is it's a fairly rigorous design, an investment, to see if we can get someone on an average of 40 milligrams of morphine versus 75 for instance.
DR. GEWANDTER: Are you responding to his question? Because there are other people first? Are you responding to his comment?
DR. RAUCK: No.
DR. GEWANDTER: Okay. Jennifer first, and then you can go.
DR. HAYTHORNTHWAITE: I'm sitting here thinking about this and the struggle of what are some of the events that lead somebody who is on chronic opioid therapy to escalate their dose. And we know that some sort of an acute injury or surgery is a precipitating event, so what about thinking about those circumstances?
So somebody who has a chronic pain

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condition, we've already identified them as being a risk group for the acute pain studies that is a delicate one. Why not think about that for the chronic pain kind of opioid-sparing discussion, that we think about what are the key events, one of which is going in for a surgical procedure where they then have to be dosed at much higher levels to compensate for the fact that they're already on chronic dosing, and are there some clinical trials that would be very useful in reducing how much they have to take while they're in the hospital and during their recuperative period that might land them in a place within 3 months that they're actually back to baseline or even lower?
So you've got a kind of a manageable period of time that's kind of feasible, but you're really trying to interrupt and event that normally would create the escalation that we've seen historically.
DR. RAUCK: Nat, I was really proud. I think we were the high-end roller in that study you talked about. We had 2 --
(Laughter.)

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DR. RAUCK: -- in 2 years. And that was the study we were talking about, so that was an impossible study.
I was trying to reflect. There are some things that are different in our populations. For instance, ketamine that we do for CRPS patients, it's my colleague's opinion, strong opinion, James North, that those people only do well if you get them off opioids first. And you might say they'll do better anyway, but that's not been our experience necessarily. They wean off, they hurt a lot. And James' premise on that is to get the NMDA effect of ketamine, you have to be off opioids before you're going to see that benefit.
So we still put 2 or 3 people in these in-house, long-term infusions with ketamine, meaning that those patients are willing to come completely off their opioids to do that. So why is that? I think it's because they've read about ketamine. They really have this visceral feeling that it's going to really help them. They want to be helped. And then probably they trust their

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clinicians. If a clinician can go in and really look them in the eye -- and they kind of know when we're kind of bullshitting them or not. They kind of know when we're saying, "Why don't you come into this trial? I don't know what it's going to do," because you've got to sell these trials.
The other population of patients now, for us, intrathecal pump patients. We won't put in pumps and start opioids unless they come off all their systemic opioids. I believe a little bit in micro-dosing with opioids. I think it's a dead-end street when you have them on systemic. So those people who are motivated, who really want the pump, they'll come off their opioid.
So I think, Ken, a little bit to your thing with, say, anti-nerve growth, we've done all your tanezumab studies I think from the early, early days. There is something where I could go into the patient, really look him in the eye, and say, "This looks like a really great analgesic," because you've got to sell these people on the trials if you're a clinical site. That's part of it. They

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trust us
But I think you could go in there and say, "Look. What I know about this is if you're off the opioid, it'll be better for you. You'll get a better response." Maybe we know that and maybe we don't, but that's what the trial is. That's an easier sell. Maybe it's more meaningful; maybe it's not. Maybe it's a whole different question you're trying to answer there. I don't know. But I do think this idea of getting off opioids, and how you look at that, and opioid sparing can be done under different constructs in the idea of a clinical trial.
DR. ROWBOTHAM: If I could maybe focus the discussion a little bit on what outcomes should we prioritize. So we heard a little bit about how you can always get an A1c on a patient with diabetes and the blood pressure because that's in the chart, always. So what are the things that we should be pushing on to improve, that would really help us do any kind of trial that you would want to be able to see to know how patients with pain respond?

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Would you want to see -- I'll just throw out an example, probably one of the hardest ones -- a psychologist administered or otherwise administered screening tool for opioid misuse or opioid-use disorder in everybody on opioids? That it just becomes like measuring pain or blood pressure.
What are the priorities of things that you would want to be able to have when, let's say, you're screening charts to see who you might want to invite into a clinical trial? Because right now we have these kind of random insertions of pain ratings from the ER, or whatever, in the medical record that are really useless, but we don't have any of the more precise assessments. We don't really have the tools other than going through a lot of different databases to see who's getting opioids and how regularly they're filling their prescriptions, other than kind of self-report and looking at what's in the chart.
So what are the priority items that we would want to try and advocate for as being routinely available that would help us design trials to look

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at opioid sparing?
DR. HAYTHORNTHWAITE: I think urine tox screens, especially as cannabis starts to grow and kind of become much more prevalent. I think we've just got to understand that better. And I don't think it will be a rule out the way it might have been in the past, although maybe it should be.
DR. ROWBOTHAM: So you're not advocating for an opioid-specific tox screen, but a broad based --
DR. HAYTHORNTHWAITE: A broad based, yeah, street drugs. We need to know if somebody's using cocaine.
DR. ROWBOTHAM: Right. So that would be something that you would want to see --
DR. HAYTHORNTHWAITE: Intermittent.
DR. ROWBOTHAM: -- excuse the word "imposed," in the healthcare system, that you get that routinely.
DR. HAYTHORNTHWAITE: I don't think you need it for every visit, but I think you need it irregularly.

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DR. ROWBOTHAM: I'm not disagreeing with you at all. Actually, one of the things that happened when I was running the methadone clinic was we started screening for things other than opioids. Man, that was Pandora's box.
(Laughter.)
DR. ROWBOTHAM: It's like, oh my God, they're using that, and that, and that, and that. But that's a good one.
Any other ones?
DR. WASAN: PDMP data. That's becoming available now, so you can actually see what the patient filled. That's important because a lot of these states need to actually be pushed. And Pennsylvania is the case. You need to push the state to actually make that PDMP data available for research, and also to get it embedded in your EMR. Then opioid adherence checklists, there's the short version that Bob and Rob have developed. Those things are standard ways of looking at adherence.
DR. STACEY: We do have the embedded PDMP in our EHR, which is great. You just hit the button,

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and there it is. But I would think if we're really doing a clinical trial setting, we would want measures of anxiety, depression, sleep, some estimate of function. I mean, these are basic things, but you can have questionnaires that are pretty darn short that address those things, that are done routinely.

MALE VOICE: [Inaudible - off mic].

DR. KROENKE: Just to modify what I said a little bit before -- and maybe it was -- I can't recall whether it was Ian who said some healthcare systems are now routinely incorporating patient-reported outcomes in their health records. For some, it's PROMIS. For some, it's other things like grief depression screens or pain screens.

So without stating the obvious, obviously you want pain measures as an outcome. And if you're going to do large studies and pragmatic measures, you could decide to use it in healthcare systems that have routinely recorded at least some minimalistic patient-reported outcomes of which pain and depression tend to be the most common.

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Then you could link it to prescribing. So as prescribing changed, people who have reduced opiates, or have less lower doses or higher doses, you could then track those outcomes. So another way is do that kind of trial in systems that are all routinely capturing that.

DR. ROWBOTHAM: Right. So if I could expand on that and transition into another field, now, for the targeted therapy oncology trials, you really need to have your patient's tumor fully characterized through mutational analysis, sent to Foundation Medicine or some other one. That's a little bit what I'm trying to get at, even though we don't have those kind of markers for pain. But those are the things that, let's say a sponsor came to us and said, I'm interested in doing a trial with these characteristics for our new compound. Tell me how many patients in your clinic or your health system has all this information.

So that gets to what you're talking about with A1c, because if you're trying to do a diabetes trial and you're saying, well, you're looking at

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random glucoses, that's the hard way to do it, whereas if you just look in the electronic chart and say, well, we have a thousand patients who still have A1cs over 8, then bingo, you're just like ready to roll to get ready to start enrolling.

So that what I'm trying to get at here. What are the data points? What potential outcome measures would we want to have accessible to us so that we could characterize our patient populations quickly as preparatory to more focused studies?

Did that capture your comment?

DR. KROENKE: Well, I was thinking actually outcomes in studies. Now, if you're looking at it to identify potential subjects for studies, if a large healthcare system like Kaiser or Cleveland Clinic, as Mayo Clinic -- a number of healthcare systems have started incorporation -- you could say give me all of the people with ICD codes of musculoskeletal pain or low back pain who have 2 consecutive pain scores on PROMIS or other pain scores at a certain threshold. Then you'd say, we got 2000 people like that.

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So we have a sufficient population of persistent pain. That would be the A1c equivalent. You could also, if you did a pragmatic trial, look at the relationship of those scores in patients with those conditions in relation to prescribing changes.

DR. ROWBOTHAM: Right. That's the key point that you made, really, really key point, which is you get a single measure that is relatively unchanging, like mutational analysis of the tumor -- If there's a driver mutation, they tend not to go away -- versus serial measurements, which are a study in and of themselves, potentially, if you're doing correlations, but are even better at prep to research because you can start looking at the dynamics and characterize the population even much more precisely by having serial measures.

Is that what --

DR. KROENKE: And some of those systems that are incorporating this also have a few other brief measures, like the PROMIS 10 or some physical function, which have items on sleep and fatigue and

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anxiety. So what I'm saying is you could do those kinds of studies in systems that had that stuff routinely captured in electronic records, and there are systems like that with thousands of patients found.

DR. VERBURG: Maybe some prior use of analgesic medications would be helpful. Some of these pain scores are taken with certain type of therapy, and then the therapy is adjusted, and of course more proximal to the point that you're trying to identify the patient, and you'll find out that that pain score is particularly relevant. Maybe that's taken care of with serial. But I think some sense of what the medication history and experience has been would be very useful.

DR. ROWBOTHAM: So that's something where -- Ian was bringing up, and I think you did, too -- but certain systems are -- or Brett, you brought it up -- automatically checking the pharmacy databases in terms of filled prescriptions. So that's an advance, to have that routinely available, and of course for opioids, but

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also, really, all the medications would help because it's impossible to get that out of patients when you ask them. They just give you the vaguest answers compared to actually looking and say, well gee, they've had 12 filled prescriptions in the last 18 months.

DR. GEWANDTER: So that's really helpful maybe for things we might be able to consider for inclusion criteria. But I'm wondering if we could maybe circle back to what we might want to actually be the outcome domains we're going to recommend in relation to the actual opioid-sparing endpoints. I think we talked about a lot of different things, obviously, like dose. We talked about AEs. either separately or as one syndrome. We talked about function.

So for the paper, do we want to list these as all possibles? Do we want to prioritize them? Do we want to make any comments about that?

DR. ROWBOTHAM: Well, I think for sure, function, the function scales. But also if we really want to get at the more uncommon outpoints,

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especially opioid-use disorder, some screening that has some validity, as simple as possible because we've got Jennifer here, but there aren't 10,000 Jennifers to spread around the country to make sure every patient gets screened for some of these different disorders. So some things along the codes related to drug misuse and addiction, if we could get those in the chart, and especially serially for that one.

DR. DWORKIN: I guess I'm thinking back to Richard's question about -- actually, everybody's question about is 50 percent reduction clinically meaningful? So I guess I would think we'd want to make sure the trial included whatever measures might answer the question of whether the sparing is actually clinically meaningful or whether it doesn't make a difference whether a patient's on 40 or 80 a day of oxycodone.

I don't know what those measures. Clearly, function, mood, but that would be to me critical, that the trial has within it some way of getting at the clinical importance of whatever the sparing is.

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DR. SCRANTON: This is Richard. I was intrigued by what you said, Richard. Some patients were willing to go down to zero, and they must have suffered some to get there, to then be put on something that they perceived a benefit. So what is that patient-reported trade-off that they are willing to do? That's what I want to be able to measure, because maybe it is going from 10 to 5 or 10 to zero or 100 to 50. It may not matter, but if I could capture that motivation.

DR. RAUCK: Yeah. No, that's right. It surprised me, and I think it is a carrot, that they think there's something that can help them more. I think what's changed a little bit is the stigma of opioids for a lot of these patients is really weighing in on them more and more. So a lot of them we see don't want to be on the drug as much that way.

We do help them. We give them a lot of alpha-2 drugs and things to help with the withdrawal as they come down. Everybody tolerates it differently. They're motivated. And Nat's

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right. In the other trial where all it was, was, hey, here's a the trial where you either continue on your opioid or you're going to be weaned off, and maybe you will be better when you come off, which happens. I mean, we've always seen that. But try to talk them into that, you've got to have something else. I think they're savvy enough. These patients, like I said, somehow, body language or something, we convinced to them whether we really think it may be worth coming off it.

DR. GEWANDTER: So maybe what you're saying is for research agenda, actually asking patients what they're hoping for when they come off their opioids or what they're expecting might be a good research agenda.

DR. ROWBOTHAM: Question way in the back.

DR. SANDBRINK: Sandbrink, Washington, D.C. VA. In the VA system, we've taken a lot of patients down. And I think nowadays, the communication and the discussion with the patient has gotten much, much easier. So your experience from a few years back is not necessarily what it is

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nowadays because patients realize that there is an opioid crisis, and they perceive it more of something that could potentially affect them as well. They get much more input by their families and caregivers who are concerned about these opioid medications that this patient has.

So the discussions with the patients have gotten, at least in our setting, somewhat more easier. And maybe that's easier, in part because our healthcare system in the VA, everybody talks with the patients now in the same language. The primary cares and the pain specialties, we do have the same approach as we express caution about opioids, and we ask our patients how motivated they are.

A few years back, I think the common notion was that no patient really wants to come off. And often nowadays still that is the assumption that providers have, "Oh, my patients don't want to come off." But when you actually ask them, there's actually quite a bit of motivation to reduce the dosage out there. I think we have to ask all these

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patients now -- not a few years back and take what it was a few years ago, but we have to ask them now about where are you in this continuum of being motivated to come off and of change.

DR. CRAIG: Hi. It's Kevin Craig from GW Pharmaceuticals. I've been listening with interest to this idea of what patients will go through to get off the opioids, to get onto a new treatment. And I think in clinical practice, that's fascinating. My concern about that in a trial -- and it's probably something that ought to be studied -- is that really ramps up the expectancy. And with expectancy comes placebo response.

So getting a sense of if someone's gone through 2 weeks of withdrawal to get onto a trial, I wonder what that would be like in terms of the placebo effects as well.

DR. RAUCK: So I think that's fair. That probably is true for sure that you might have that. But there's one big advantage to doing it that way, is you can do that before you randomize so you

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don't have the dropouts. So if they don't make it or they can't come off, while you're not supposed to do that, anticipating coming into the trial, you can still do it before you randomize them. So it does help you in dealing with that part of it.

DR. ROWBOTHAM: Actually, that's another good point, though, in terms of outcome measures that we should be capturing more routinely. For example, there's a lot of anesthesiologists in this room, so I assume the sum total of epidural steroid injections is probably pretty high.

Do you guys look at whether or not the patient reduces their opioid dose in the month after the epidural? They don't.

DR. RAUCK: It's whether they pay their bill.

(Laughter.)

DR. ROWBOTHAM: Yeah, exactly. That's right.

But that's an important point because we do a lot of interventions, and we don't tell the

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patients, okay, you just had the intervention. Now, I want you to cut your opioid dose in half immediately. In clinical trials, I'm just curious, we've talked at some of these meetings about rescue medication use, especially when the rescue medication is a low potency opioid, but we're really not capturing that data just in routine practice where we're all the time introducing things, where we're really not checking to see, okay, the person responded to the triple uptake inhibitor or combination to effect the same. Did they then start spontaneously reducing their opioid? Yes or no?

We don't really have that information, and I don't think we necessarily get it in the clinical trials, especially the compounds that are in phase 2 because you may be excluding people on opioids or they're on really low doses of opioids and not necessarily likely to go off.

DR. GEWANDTER: So I think we've got probably enough to start a draft of a paper. So unless anyone has anything they really want to

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bring up or air now, maybe we could end a little early. It's getting late. And obviously, if you have any other ideas that you want to send to me before the first draft is drafted, you can feel free to do that. You can find my email on the Rochester webpage, or you can ask Valorie. She knows my email.

So unless anyone else has any burning things they'd like to bring up, maybe we should end here.

(No response.)

Adjournment

DR. GEWANDTER: Okay. Thank you all for your participation.

(Applause.)

(Whereupon, at 3:40 p.m., the meeting was adjourned.)

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