

*ACTION - IMPACT XXI - OPIOID SPARING IN
PATIENTS WITH ACUTE AND CHRONIC PAIN*

July 27, 2018

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1 ACTTION

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5 INITIATIVE ON METHODS, MEASUREMENT, AND PAIN

6 ASSESSMENT IN CLINICAL TRIALS

7

8 IMPACT-XXI

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11 Research Design Recommendations for

12 Clinical Trials of Opioid Sparing in

13 Patients with Acute and Chronic Pain

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16 Friday, July 27, 2018

17 8:16 a.m. to 3:40 p.m.

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20 The Westin City Center

21 Washington, DC

22

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4 chronic pain opioid sparing trial

5 research designs, methods, and

6 study execution

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8 Group Discussion: Recommendations for 40

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1 PROCEEDINGS

2 (8:15 a.m.)

3 DR. DWORKIN: Good morning, everybody, and

4 thank you all for sticking with us for a second

5 day. I just wanted to say a few words of

6 orientation about today.

7 Today's going to be different from

8 yesterday. The way I think Dennis and I think

9 about this is that the first day generates a lot of

10 ideas, kind of raw material. Everybody gets to say

11 what they think about things. The second day, we

12 try to think of as much more focused, where there's

13 actually something we want to accomplish by the end

14 of today. And what we want to accomplish by 4:00

15 or so this afternoon -- every once in a while, we

16 end a little bit early, but that's really rare.

17 What we want to accomplish is to have a kind

18 of scaffolding, enough raw material, enough kind of

19 consensus for Jen Gewandter to draft at least one,

20 maybe two consensus recommendation manuscripts.

21 She will take the lead on it. You will be getting

22 more emails from Jen than you want, because if you

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1 are willing to and interested in being a co-author
2 of this recommendation's manuscript, you will be
3 invited to be a co-author.
4 Once Jen has a draft, you'll be asked for
5 your comments and suggestions about the draft of
6 the manuscript, and that will be carried through
7 all the way until when the thing is finally
8 accepted for publication.
9 That's what we want to accomplish by this
10 afternoon, is have enough for Jen to go home and
11 start writing, one or two manuscripts. The reason
12 I'm saying one or two is there was a sense
13 yesterday that instead of trying to put acute pain
14 and chronic pain into one article, maybe it should
15 be split. And we should have one article about
16 recommendations for clinical trials of opioid
17 sparing and acute pain and one for chronic pain.
18 And I think we'll have a better sense of that by
19 later today.
20 I think what we want to accomplish
21 today -- and we have two talks, one by Ian Gilron,
22 who's professor of anesthesiology at Queen's

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1 University and professor of a bunch of other
2 things, but I'm too old to remember all of the
3 titles that Ian told me in the hall a few minutes
4 ago.
5 So Ian's going to give a talk earlier this
6 morning -- as soon as I sit down -- that's going to
7 focus on and really help us to think about what we
8 want to put together as the scaffolding for acute
9 pain recommendations. And then Mike Rowbotham,
10 who's at Sutter Health in California and also
11 UCSF's Department of Neurology, will give a similar
12 talk for chronic pain for the afternoon.
13 So this morning, acute pain; this afternoon,
14 chronic pain; and then we all go home around 3:30,
15 4:00, probably 4:00.
16 Just one more word I think that evolved
17 after yesterday's discussion. These
18 recommendations, I think at the very highest level,
19 have to start with study objectives. What's the
20 hypothesis that a clinical trial or the clinical
21 trial types that we propose are going to be
22 testing? And that's really how do we think about

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1 what opioid sparing is?
2 Obviously, it's not one thing. One thing
3 that became very clear yesterday is that there's
4 lots of ways to think about possible benefits and
5 outcomes of opioid sparing. So there's not just
6 one opioid-sparing study objective. And of course
7 that means there isn't one opioid-sparing clinical
8 trial outcome. The inclusion criteria are going to
9 differ, and then the specific research design,
10 study execution, and analyses are going to differ
11 depending on how we conceptualize the study
12 hypothesis, the study objective.
13 So something several of us talked about at
14 the end of the day yesterday, is at a minimum this
15 afternoon, we really need a list of the different
16 study objectives -- I think of this synonymously
17 with the hypotheses that are being tested -- study
18 objectives, study questions that could be tested in
19 clinical trials for opioid sparing, however we
20 think it's important to define it, for acute pain,
21 and likewise for chronic pain.
22 How far we then get beyond study objectives,

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1 outcomes, inclusion/exclusion criteria into the
2 details, if you will, of study methods, study
3 execution, what do we do about missing data, is
4 going to depend on how fast we move today. I don't
5 know that we're going to get all the way down to
6 details of what do we do about missing data in the
7 clinical trial.
8 Those weeds probably are beyond what we can
9 accomplish over the next 6 hours. Personally, I'd
10 be quite happy if we get kind of halfway down this
11 list of recommendations, that we succeeded coming
12 up with some consensus for Jen about objectives,
13 hypotheses to be tested, key critical outcomes, and
14 then some ideas, like what Nat put up in one of his
15 early slides yesterday of the kinds of designs that
16 would test that.
17 So I've said enough. Any questions about
18 our vision for today, any of the things? There are
19 some housekeeping bullets on the slide that I won't
20 repeat. Checkout time is at 12:00. We'll have a
21 break the middle of this morning. As you can see
22 from the agenda, we're planning to start lunch at

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1 11:30. So that's the day.
 2 Questions, thoughts, comments?
 3 (No response.)
 4 DR. DWORKIN: Well, great. All right. I'm
 5 happy to turn it over to Dr. Ian Gilron from
 6 Queen's University.
 7 Take it away, Ian.
 8 Presentation - Ian Gilron
 9 DR. GILRON: Thank you, Bob. Thank you, Bob
 10 and Dennis and the steering committee for inviting
 11 me. I've had some involvement ACTTION an IMPACT
 12 for the past 13, 14 years, and it's been a great
 13 learning experience and an honor. I'm an
 14 anesthesiologist. I've been designing and
 15 conducting analgesic trials for the past 20 years
 16 or so and trying to interpret them. Those are my
 17 disclosures.
 18 So just a quick recap from yesterday,
 19 yesterday I thought was excellent. The talks were
 20 very high quality, and I think it's everything we
 21 needed. There was a little bit of some
 22 insubordination over here, but other than that, it

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

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

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

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1 measuring opioid use and opioid
 2 effects -- obviously, we had excellent talks
 3 yesterday covering that -- and talk a little bit
 4 about future directions.
 5 As I speak today, I'm going to pepper my
 6 talk with proposed recommendations. I want to
 7 start low and go slow. I hope what I think I'm
 8 proposing will be kind of motherhood, sort of
 9 generic recommendations that hopefully are not
 10 contentious. If they are, then, well, we'll get
 11 started even earlier, and that will get us thinking
 12 about how to move forward.
 13 So for any of you who've never yet been to
 14 an ACTTION or an IMPACT meeting, it's going to be
 15 really fun to watch you because you've had a nice
 16 sleep and a good breakfast, and you think life is
 17 good now. And then at 5 to 4, we're still going to
 18 be talking about whether the hyphens should be
 19 between "opioid" and "sparing."
 20 (Laughter.)
 21 DR. GILRON: I wanted to talk about opioid
 22 use and analgesic trials and start with just a

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1 little bit of a historical context. A lot of what
 2 we know now about pain and analgesic treatment
 3 response started from pioneering research by Henry
 4 Beecher and others in the 1940's and in the 1950's.
 5 And here's an example of the work that was being
 6 done then, and in fact, opioid use was kind of a
 7 surrogate of pain intensity.
 8 Here's an example of an early open-label
 9 study looking at the population distribution. So
 10 these are the number of patients -- the dotted line
 11 are patients having hysterectomy and the solid line
 12 are patients having gastrectomy, and looking at
 13 what is the distribution of number of narcotic
 14 doses required.
 15 Again, probably something that wouldn't be
 16 very popular at any journal at this point in time,
 17 but sort of see there seems to be a slight
 18 difference, suggesting that maybe pain is greater
 19 after a gastrectomy. So a lot of enthusiasm and
 20 work ensued, and then maybe about 10 years later,
 21 this is the type of work that was being done. We
 22 now have an example building on the work done by

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1 Lasagna and Houde.
 2 Here's an example of a comparative clinical
 3 trial looking at to opioids, pentazocine and
 4 phenazocine, and looking at pain relief temporal
 5 profile after the analgesic administration in two
 6 different surgical populations. And here, this is
 7 a double-blind, single-dose trial, and the
 8 opportunity of seeing some differences in the
 9 temporal profile. At least here, it looks like
 10 phenazocine has a longer duration of action.
 11 Now, 10 years later, we see that there's
 12 some attention to opioid related side effects.
 13 Shannon Smith and others in the ACTTION Saber group
 14 looked at harms reporting. And you'll notice here,
 15 this is the sum total of their safety assessment
 16 and reporting in this 1966 trial.
 17 Any comments about the side effects were
 18 noted on a separate card on each occasion. That's
 19 all it says. And the results, no serious adverse
 20 effects were noted. Nausea and vomiting were not
 21 noted. I don't know if that means they weren't
 22 noted or they weren't --

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1 (Laughter.)
 2 DR. GILRON: But at least they introduced
 3 the concept of opioid related side effects and the
 4 importance in starting to recognize.
 5 Around the same time was the concept of
 6 opioid rescue in the setting of studying non-opioid
 7 intervention. This is a dose-ranging trial. These
 8 are actually different cohorts, so it's like a
 9 dose-response trial. But I just wanted you to see
 10 here, each patient was studied for 1 dose only, and
 11 routine analgesic therapy was being prescribed
 12 thereafter. So they could get analgesic therapy if
 13 they need it. And then at any point, they could be
 14 given a further analgesic at any time if they
 15 needed satisfactory relief?
 16 I can't even read that from here, but their
 17 subsequent pain scores were censored from the
 18 analysis. This is maybe one of the earliest
 19 descriptions of the last observation carried
 20 forward analysis, introducing the concept that
 21 rescue analgesia -- first of all, at this point in
 22 time, opioid use was widespread enough that it was

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1 considered standard of care to give opioid therapy
 2 for inadequate pain relief, and furthermore,
 3 recognizing that this has some challenges in terms
 4 of estimating and evaluating analgesic efficacy.
 5 We're getting to the concept of opioid
 6 sparing, but I think we need to make sure that we
 7 preserve everything we've learned so far about
 8 analgesic trials. Then a few decades later, here's
 9 individual patient meta-analysis done by Andrew
 10 Moore and Henry McQuay, looking at other metrics,
 11 the percentage of patients requiring rescue after a
 12 single-dose intervention. So this is comparing
 13 ibuprofen with rofecoxib.
 14 We can see some differential efficacy
 15 compared to placebo between ibuprofen and rofecoxib
 16 in terms of the proportion of patients requiring
 17 analgesic rescue; and here just to reinforce that
 18 data imputation is a serious issue. There is some
 19 uncertainty on how to deal with that. We've had
 20 many discussions within ACTTION and IMPACT about
 21 this. As we know and we've seen in a lot of
 22 different analyses, as soon as someone gets rescue,

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1 they're not out of the trial, but we don't know
 2 what to do with their subsequent data.
 3 Baseline observation carried forward seems
 4 to be the most conservative and underestimates the
 5 apparent efficacy of the treatment, whereas last
 6 observation, it maybe makes things look a little
 7 bit better. Again, we don't know; we're imputing
 8 data. This is just to introduce the idea that
 9 rescue is something that is a challenge for us
 10 A couple of years ago, we published -- I
 11 think it was 2016 -- the IMPACT recommendations on
 12 acute pain trial design, so I thought I would put
 13 that up and talk about other issues for measuring
 14 opioid use, and Brett had discussed a lot of this.
 15 Looking at the offset of analgesia in non-opioid
 16 intervention and time to first rescue as we talked
 17 yesterday, is certainly one possible metric in of
 18 itself is a measure of offset of analgesic effect.
 19 Publications that report medium time to
 20 rescue need to decide and have some consensus on
 21 what's the appropriate dosing interval and regimen.
 22 Clearly, the humanitarian and ethical issues of

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1 managing one's pain in this setting of a clinical
 2 trial needs to be incorporated into the science of
 3 how we do this.
 4 Just to summarize, acute pain trials of
 5 conditions with moderate to severe acute pain are
 6 commonly associated with the use of a non-study
 7 intervention. It can be opioids and possibly
 8 non-opioids. And proper analysis and
 9 interpretation of acute pain trials requires
 10 careful consideration and control of non-study
 11 intervention opioid use and other non-study
 12 analgesic treatments.
 13 So I'll give it a try. I'm going to start
 14 with my first proposed recommendation regarding
 15 analgesic rescue. A trial of an acute pain
 16 management intervention should balance between
 17 consideration of the ethics of pain under
 18 treatment, for example, in the placebo group; and,
 19 two, the negative impact of the non-study rescue
 20 analgesic treatment on one, the floor effect -- I
 21 think Sharon Hertz mentioned this yesterday -- the
 22 floor effect and reduced assay sensitivity. If you

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1 treat pain too effectively in both treatment
 2 groups, your ability to demonstrate a difference
 3 may be reduced.
 4 Thinking about the analgesic and adverse
 5 interactions of the study intervention with your
 6 rescue intervention could confound or conflate
 7 issues, and also, the potential misattribution of
 8 the non-study drug intervention with the study drug
 9 intervention. So is the nausea due to the NSAID
 10 that you're administering or is it due to the
 11 opioid? So again, very motherhood. We're just
 12 saying consider these things.
 13 As we've discussed yesterday, the landscape
 14 is changing. There's already widespread recognition
 15 and changes in practice in perioperative pain
 16 medicine in terms of opioid sparing and the
 17 concerns about developing chronic opioid use.
 18 I'm adding here, the design of future acute
 19 pain trials should consider evolving approaches to
 20 minimizing opioid prescribing. For example. as we
 21 talked about yesterday, the shifting analgesic
 22 pyramid where it's been suggested that opioids go

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1 on last, and also efforts to have kind of a
 2 restrictive opioid regimen in your standard of care
 3 protocol.
 4 So if your goal is to demonstrate opioid
 5 sparing, we may actually be coming into a practice
 6 landscape where you're going to get a floor effect
 7 of that because the opioid prescribing is going
 8 down. This is really provocative.
 9 So in a couple of months, cannabis is going
 10 to be legal in Canada, and I'm not sure how that's
 11 going to change everyone's behavior and use. But
 12 can or should we consider preexisting concomitant
 13 cannabis or other analgesic drug use as an
 14 important factor in pain trials? Is it feasible or
 15 necessary to exclude cannabis users from analgesic
 16 trials? So these are additional things to think
 17 about, in all analgesic trials, not necessarily
 18 just opioid-sparing trials.
 19 We can start the discussion at any time, so
 20 if anyone wants to interrupt with questions in the
 21 middle, that's okay, too.
 22 So I'll move on to talking about opioid use.

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1 And again, historically, patient-controlled
 2 analgesia, or PCA, was an important evolution in
 3 analgesic trials. In the late '60s or early '70s,
 4 a number of groups developed electronic or a
 5 computer-controlled apparatus where you have
 6 usually an IV, parenteral, a syringe with an opioid
 7 like morphine that is connected to the patient's IV
 8 tubing.
 9 You have basically an operant response
 10 system where you press a button and you get an
 11 injection. And for those of you who are not
 12 familiar with it, you can set up a lockout interval
 13 and a dose.
 14 So each button corresponds to a certain
 15 volume of morphine that gets administered. And for
 16 people who are a little trigger happy and you don't
 17 want to get an overdose, you can actually,
 18 somewhere, typically between 5 and 10 minutes, have
 19 a lockout interval. And you explain to the patient
 20 that they can press all they want for that next
 21 5 minutes. They're not going to get another dose
 22 until the machine resets.

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1 Since these are electronic, they also work
 2 as data gathering systems. Here, you can see, for
 3 example -- and this is one of the earlier 1971
 4 reports. You can actually keep track of all the
 5 times the button was pressed and also look at the
 6 cumulative opioid dose of how many successful doses
 7 they get.
 8 So not to be cynical, but one of the reasons
 9 why opioid consumption is a popular measure in
 10 acute pain trials is it's often the best quality
 11 data because you just go and get the data from the
 12 pump, whereas pain intensity data, you need a
 13 nurse, you need the patient to understand. They
 14 have to fill out the VAS score and that sort of
 15 thing. So this is a very important thing.
 16 What do we do that and how do we use that in
 17 trials? One of the earlier efforts to do this by
 18 Henry McQuay and others in Oxford was a letter to
 19 the editor, to Lancet, in 1980 saying, hey, we can
 20 actually use this to be a measure of analgesic
 21 effect.
 22 So I'll just quickly show you here on the

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1 Y-axis, this is the number of administrations of
 2 2 micrograms, a pretty small dose, of fentanyl
 3 through a PCA pump in patients, postoperative
 4 patients, who had an epidural catheter and got
 5 different analgesic drugs through the epidural.
 6 It's hard for you to see here, but the first steep
 7 curve is patients with postoperative pain pressing
 8 the fentanyl pump, and then at point number A, they
 9 got a dose of 100 micrograms of fentanyl through
 10 the epidural.
 11 So it looks like they got an analgesic
 12 effect because their pressing for the PCA IV
 13 fentanyl kind of plateaued off for a little while,
 14 and then at point b they got a sham, they got a
 15 saline injection into the epidural catheter. It
 16 didn't seem to do much, so again, we got a steep
 17 curve of patients pressing the fentanyl pump to get
 18 the short blast of analgesia. And then at point C,
 19 there seems to be an elbow there. They got an
 20 epidural injection of diamorphine, and it looks
 21 like that had a bit of an analgesic effect as their
 22 pressing seems to level off.

1 That's kind of the early era of what we call
2 PCA analgesimetry using opioid consumption as a
3 measure of analgesic effect. Here we see from the
4 '80s a ketorolac study looking at 2 different doses
5 of ketorolac and looking at cumulative opioid
6 consumption after that, compared to the placebo
7 group. And you see a nice statistical separation
8 between the ketorolac and the placebo groups,
9 looking strictly at opioid consumption.

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

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

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

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

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

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

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

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

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

9 (Laughter.)

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

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

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1 agents, and in the combination, it separates out
2 statistically from the single-agent groups. And
3 then we conducted this integrated analgesic
4 assessment score to get even further, to some
5 degree, some further separation by incorporating
6 the level of opioid consumption as well.
7 I'll just mention also, just looking at
8 appropriate time intervals -- and we'll come back
9 to that -- that correspond to the expected temporal
10 profile of the analgesic drug that you're giving.
11 So we'll come back to that in a moment.
12 That was addressed -- the 2016
13 recommendations paper on acute pain really focused
14 on single-dose studies, but there was some
15 recognition that at least these proposals for
16 integrated analgesic assessment have been made, but
17 we really need to do more research to find out what
18 the validity is of doing this compared to -- I
19 mean, to some degree, it's a composite type of
20 scoring system.
21 Another proposal regarding measures of
22 opioid use in acute pain trials. I think this is

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1 really motherhood. Acute pain trials in settings
2 where pain is frequently moderate to severe, more
3 than 2 to 3 days in duration, and where opioids are
4 typically used should include context, relevant
5 measures of opioid use. So that could be the
6 number of hydrocodone doses. It could be PCA
7 morphine consumption. So I've tried to stay
8 generic at this point and say context relevant,
9 depending on the acute pain condition.
10 Then this is maybe a difficult one, but it's
11 kind of a utopian statement, which is measurement
12 of opioid use should ideally span a typical time
13 frame that opioids for that acute pain condition
14 are being administered. So if we're talking about
15 pain after abdominal aortic aneurysm repair, where
16 patients have an epidural, and they're in hospital
17 for 1 to 2 weeks.
18 Then they go home, and they could be on
19 opioids for another couple of weeks, typically.
20 Then, I'm not sure of the relevance of looking at
21 pain for the first 12 hours. It may tell us
22 something, but if we're really thinking about the

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1 management of that condition, we should try and
2 think about what the natural history is of the
3 opioid consumption. No one's yelling me down yet.
4 So moving on with some other things, and
5 this is a little more minutia but some granularity
6 that maybe we should add. Acute pain trials
7 assessing opioid use should preferably, if
8 possible, restrict the non-study opioid to a single
9 opioid chemical entity. For example, just pick one
10 opioid that you're going to use, or at least if you
11 can't do that, then you'll need to use
12 equianalgesic dosing data to consolidate the
13 opioid-use data, and that's going to give you some
14 more uncertainty there. What's the right
15 equivalent if you're using morphine or oxycodone?
16 This goes to the timing interval. Acute
17 pain trials assessing opioid use should assess
18 opioid use with a temporal resolution that reflects
19 appropriately the expected temporal profile of the
20 intervention. So I'm not talking about what I said
21 here about the natural history of the opioid use.
22 I'm saying if we're looking to track the effects of

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1 a drug that lasts for 4 to 6 hours, then if you
2 only measure 3-day opioid consumption, you actually
3 may miss the difference that you're looking for.
4 So you need to think about the non-study
5 intervention and the temporal profile. So you're
6 going to need more temporal resolution for your
7 opioid consumption data tracking.
8 This is kind of way out there, but it sort
9 of got me thinking. If we do go into the direction
10 of studying more complicated patients who have
11 opioid use disorder, the ones that we said are at
12 highest risk and need the biggest challenge, maybe
13 acute pain trials should somehow consider and
14 incorporate the possibility of non-protocol and/or
15 illicit opioid analgesic use.
16 So if someone else is taking something,
17 clearly, that's a protocol violation, but we've had
18 entire IMPACT meetings about how to be aware of
19 that and how to try to mitigate those challenges.
20 Then not necessarily recommendations but
21 research agenda items, some validation. So maybe
22 we need to do more research on how to integrate

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

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

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

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1 records, versus specified objective investigator
2 assessed and reported outcome.

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

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

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

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

12 This is just repeating what we said already,
13 and I would say that acute pain treatment trials
14 that assess opioid use should also assess
15 context-relevant opioid related effects. So it
16 sounds obvious, like the porcupine, Brett, but
17 really, the clinical relevance of a number of
18 milligrams of any opioid is really minimal, I would
19 suggest; and that really we want to look at what
20 the impact is on the patient, so the adverse effect
21 Acute pain trials assessing opioid use
22 and/or effects should also assess pain intensity.

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

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

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

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

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1 bit more bold and recommended specific instruments.
 2 And I'm not sure whether we want to do and
 3 recommend specific scales or scores, but in any
 4 case, if we do, I thought I would just put ad
 5 classic paper, which I think was used to guide the
 6 2005 IMMPACT paper in terms of the different
 7 criteria for outcome measures, and there may be
 8 other sets of criteria that are being used now.
 9 But looking at the appropriateness of the measure,
 10 acceptability, feasibility, interpretability,
 11 precision, reliability, validity, and
 12 responsiveness.
 13 So we can put that slide up again if we want
 14 to have a discussion about specific measures or
 15 other issues with that.
 16 I don't know how long things are going, but
 17 just some future directions and maybe more research
 18 agenda items. I had the pleasure and the honor of
 19 working with Dan Carr, Paul Desjardins, and Henrik
 20 Kehlet, working on a review article on current
 21 methods and challenges for acute pain trials as one
 22 article in the ACTTION special issue on clinical

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1 trials of pain treatments. Once everything is all
 2 done, it's going to be all published as a
 3 supplement.
 4 Some of the recommendations we had made for
 5 future improvements included -- in particular
 6 relevant to this talk -- development of trial
 7 methods that focus on treating complex patients at
 8 the highest risk of severe acute pain. And it's
 9 something we talked about a little bit yesterday.
 10 And I think to extend that a little bit further, to
 11 focus on patients who are at the higher risk of
 12 developing new chronic opioid use as well.
 13 I've had some chats with people, and saying
 14 that we should do studies in opioid addicts or
 15 people with severe depression sounds like the right
 16 thing to do and it is the right thing to do, but
 17 any of you who conduct analgesic clinical trials
 18 know that that would be very challenging. And I
 19 think John Markman had put up -- I think it's very
 20 telling that the Mark Sullivan study of opioid
 21 tapering, that took 3 years to recruit 35 patients,
 22 I doubt that that's a group of lazy investigators,

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1 and I don't think that was the problem. I don't
 2 think that's what John was suggesting either.
 3 These are very challenging patients.
 4 Probably the dropout rate is going to be high. We
 5 already know dropouts lead to uncertainty and we're
 6 scratching our heads about imputation. There's a
 7 reason why we like to pick clean populations.
 8 So I'll raise the question, at least. Can
 9 we feasibly conduct reliable and valid trials that
 10 involve patients with preexisting chronic opioid
 11 use? That's already been demonstrated in a few
 12 analgesic clinical trials. And one example is a
 13 Loftus and colleagues in 2010 did a trial of
 14 ketamine for pain after a low back surgery in
 15 patients that had to be on opioids to be on the
 16 trial, and they showed an analgesic effect of
 17 ketamine versus placebo in that population.
 18 So that's very important. First of all,
 19 it's feasible to do that type of study and also to
 20 know what the efficacy of those interventions are
 21 in this more challenging population.
 22 Then it gets a little more challenging,

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1 populations with mental health and substance-use
 2 problems; also looking at preventing transition
 3 from acute to persistent pain. I think if we had
 4 interventions that could reduce that to a very
 5 small number, maybe our concerns about chronic
 6 opioid use would diminish substantially.
 7 Again, I'll make another plug for something
 8 that we really need to learn more about. How
 9 really is pain managed in home and community
 10 settings after hospital discharge?
 11 So I'm happy for questions, and we can start
 12 the discussion soon. But I thought I would just
 13 leave up here just some bullet points using the
 14 PPICO format as we can have your eyes glazed over
 15 it as we have our discussion. So thank you.
 16 (Applause.)
 17 Group Discussion
 18 DR. GILRON: Lee?
 19 DR. SIMON: Simon, Boston. One of the big
 20 issues that I don't really get is obviously we're
 21 going to need to give people pain killers for acute
 22 pain postoperatively, immediately, for that short

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1 period of time. What is the quality of the studies
2 to understand those that get discharged with the
3 need for opioids versus not the need for opioids?
4 In the context of the acute pain trial, we
5 want to use the best possible therapeutic
6 intervention to make the patients feel better. It
7 may be that we don't really understand how to use
8 them exactly, but what do we know about that
9 transition period to the outpatient and how that's
10 handled, and whether or not there are other drugs?
11 Are these parallel trials where you do
12 noninferiority versus opioid, versus non-opioid,
13 and how do you measure that? Because these people
14 are going home.
15 What do you know about that transition
16 period and how that's been studied?
17 DR. GILRON: Thank you. Our group, we're
18 working with -- one of our senior residents at
19 Queen's is leading a systematic review that we've
20 tried to -- similar challenges that Shannon had,
21 we've tried to look at pain after hospital
22 discharge. And there have been some focused

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1 articles writing about that.
2 I don't think anyone -- as far as we can
3 tell -- has conducted a focus research program to
4 look at that very problem. But some opportunities
5 arise.
6 For example, groups that are looking at
7 interscalene catheters to give local anesthetic,
8 we'll send patients home with them and follow up
9 over the phone. So as you can imagine, you've got
10 an invasive indwelling catheter, so people are
11 going to be watching them very closely. So there
12 have been some placebo-controlled trials in that
13 setting, and that gives us a little bit of
14 information.
15 That's one issue, getting away from the
16 trial setting and into the real-world setting, that
17 I don't think has been well studied. There's a
18 disconnect, and people have talked about that. We
19 have the acute pain management service in the
20 hospital that's typically -- at least in Canada,
21 it's staffed by anesthesiologists. We use regional
22 anesthesia, a lot of intensive -- Dr. Gan talked a

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1 lot yesterday -- approaches.
2 Patterns of hospital discharge have changed
3 a lot over the years, and people will get out
4 fairly quickly, typically, unless there's a reason
5 of -- like a nerve block is something you'll to
6 follow up about nerve injury. I don't know if it's
7 different in the state, but anesthesiologist are
8 not typically involved in a patient's care. It
9 goes to the most responsible physician, which is
10 the surgeon together with the primary care
11 physician.
12 So I think that's potentially an element of
13 fractured care, and that's why I say that's a
14 clinical gap and a knowledge gap. I don't know if
15 anyone else has --
16 DR. RAUCK: Well, I was going to comment a
17 little bit, Lee. There are some unintended
18 consequences because I don't think we know a lot
19 about what's happening when they go home. For
20 instance, in North Carolina now, adopting CDC
21 guidelines, the surgeons are only allowed to give a
22 7-day prescription for opioids.

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1 So I'm in a chronic pain setting, and we're
2 now seeing patients who are 7 days, 8 days out from
3 a big back surgery or a knee surgery, and they're
4 coming into my clinic to see what are they supposed
5 to do about their pain management. The last thing
6 I need to do is get involved in a perioperative
7 setting there.
8 I don't know. Are they having pain because
9 they got an infection or they got some other
10 surgical complication? Why am I getting drug into
11 this? That's not the kind of patient I should be
12 seeing in a chronic pain setting or trying to make
13 all these clinical decisions. But that's the realm
14 because of, again, that that's being driven by this
15 opioid crisis and fear of giving these folks
16 opioids, and the push in the U.S. to get them out
17 of the hospital in 2 days, which is probably too
18 early anyway.
19 So, TJ, I'll let you add to that.
20 DR. GAN: Rick, I think you really brought
21 up an issue that I think is going to become even
22 more important. And you should be glad in North

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

6 My question, Ian, I think one of the
 7 challenges that we have here, currently, we do
 8 acute pain trials, but we don't really
 9 systematically collect the opiate adverse events.

10 Most of the pain trials, almost 99 percent, is
 11 collecting this as adverse event reporting. And
 12 we all know that adverse event reporting is
 13 garbage. I mean, you don't really systematically
 14 ask patient of the symptoms. Some people volunteer
 15 to say I have these adverse events; other people
 16 don't.

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

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

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

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

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

22 So what is clinically relevant and what's

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

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

14 John?

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

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

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

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

22 So I think that there's a whole issue there

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1 that is really, really important. But with regards
 2 to the conference that we're talking about here,
 3 what strikes me is that we need to be very clear
 4 about what we're talking about. And what we're
 5 talking about here is a procedural process to limit
 6 the amount of opioid exposure, and potentially
 7 opioid risk, related to what happens when the
 8 patient goes home, and how do we train them to use
 9 these, and how do we follow up with them? Do we
 10 give them 5 pills or 100 pills?
 11 And I would argue that even in those nice
 12 graphs that you showed at the beginning with
 13 differences in pain and different kinds of
 14 procedures, that the variability amongst the people
 15 is going to be so broad that if I want to cover
 16 everybody, I give them 30 because somebody is going
 17 to need 30, and I don't -- Howard was saying it's
 18 illegal to torture people for confessions, but we
 19 torture our patients all the time. On the other
 20 hand, we don't want to give 30 to somebody who's
 21 going to use 2.
 22 But that's a procedural process. That's not

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1 about opioid sparing in the way we were talking
 2 about before or the way you presented, with giving
 3 NSAIDs or getting other kinds of medicines. And I
 4 think if we keep those two things separate in our
 5 minds and clearly be very specific about what we're
 6 trying to address, this will be a much better
 7 place.
 8 Bob, you talked about it maybe being two
 9 articles. I am not sure; it might even be three.
 10 There's been a lot of discussion about various
 11 aspects of this, and I'm not sure they all fit into
 12 the same process and wonder what you thought.
 13 DR. GILRON: Yes. I agree with everything
 14 you're saying. I think a lot of the issues that
 15 you're talking about is how to improve the care of
 16 people after they leave the hospital. What I was
 17 hearing yesterday from a lot of people was leading
 18 to a proposed recommendation that an outcome
 19 measure of analgesic trials, acute analgesic
 20 trials, should be what is the duration or number of
 21 doses required for analgesia as an outcome measure.
 22 And the way most acute pain trials are being

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1 conducted, that's completely not feasible.
 2 So that's kind of one of the reasons why I
 3 relegated that to -- well, first of all, research
 4 agenda, to know if you're going to do a study in
 5 knee arthroplasty, what's the expected duration of
 6 pain? Obviously, you're going to have some
 7 variability, and what is going to be your standard
 8 analgesic protocol in the control group?
 9 So if that's going to be 60 pills of
 10 oxycodone, then that's -- and as I say, that
 11 landscape is also shifting, so that's going to
 12 affect it. But from the perspective of trials, I
 13 think we need to just be very focused on that and
 14 say we have to learn more about it.
 15 DR. SCRANTON: Rich Scranton from Pacira.
 16 For one, on patient reported outcomes, as a
 17 sponsor, I have no problem obtaining
 18 patient-reported outcomes and discerning that
 19 differently than how I assess adverse event
 20 reporting, and I've done that for decades. But I
 21 think two things. In the acute postoperative
 22 period or acute pain experience, I was toying with

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1 the opioid avoidance -- whatever the
 2 definition -- that could be the number of rescues;
 3 it could be opioid-free days; it could be time to
 4 first rescue; whatever we've come up with as an
 5 opioid avoidance that we think is ideal.
 6 But as we're saying, once you go beyond that
 7 intense kind of a controlled setting to going
 8 home -- and we're talking about persistent use or
 9 use outside -- I think then the problem I've been
 10 having, that's a different realm for us to measure.
 11 And then controlling that prescription and putting
 12 it in the protocol, I've not done that yet, to say
 13 you're only allowed in this protocol to give 10
 14 oxycodone, and then we're going to kind of see what
 15 happens. It's just resistance from surgeons and
 16 all of that to kind of put those patients at risk.
 17 So that's been part of the problem for us.
 18 But also I would say for us, if you're going
 19 to start looking at persistence, then you have to
 20 look at patient factors that can predict
 21 persistence. And we've been doing that, a DoD
 22 registry -- I just talked to Mike Kent last

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1 night -- where we've actually been looking at
 2 6 months, and we've been measuring PROMIS tools at
 3 baseline, and then looking at interventions, and
 4 then looking at opioid use patterns over 3,
 5 6 months in a variety of surgical procedures, which
 6 is going to help us then determine what we can put
 7 into our next trials, what tools will predict
 8 persistency that I need to account for in my
 9 stratum of studies.

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

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

19 Mike?

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

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

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

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

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

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

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

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

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1 at both of those populations who both have needs?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 initiate opioids when they're recovering from
 2 surgery.
 3 Now, I don't know if that's a sensible
 4 hypothesis. Maybe this group would think that's
 5 not a reasonable hypothesis for opioid sparing.
 6 But I would personally be thrilled that by the time
 7 we have lunch, we had a set of 5 or 6 or 7
 8 hypotheses like that, that the group thought would
 9 be meaningful to test in studies of opioid sparing.
 10 So not to beat a dead horse, which I'm often
 11 accused of doing, but the second hypothesis on my
 12 list is Intervention X -- and again, it could be
 13 hypnosis, it could be gabapentin, it be
 14 ketorolac -- meaningfully prevents the need for an
 15 opioid prescription at discharge; something we
 16 talked a lot about yesterday. Maybe the patient
 17 doesn't go home with a prescription even though
 18 they've had opioids while they've been recovering.
 19 So that's a totally different hypothesis,
 20 preventing initiation versus preventing
 21 prescription at discharge. I won't read the other
 22 hypotheses I jotted down during your talk, Ian, but

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1 for my purpose, I think this is great. But I just
 2 want to emphasize I think there are 5, 6, maybe 8
 3 different hypotheses that we could end up with
 4 after this discussion.
 5 Does that make sense?
 6 DR. GILRON: Well, it makes sense to me, but
 7 there's a reason why in my talk I started with the
 8 evolution of traditional analgesic trial design
 9 because the hypotheses that you've just mentioned
 10 seem to be aligned with the goals of this meeting,
 11 but when I hear that, it sounds like Henrik Kehlet
 12 saying we're going to do a trial to see if we can
 13 get people home on the day of surgery after their
 14 hip. And if you do a trial and you set up your
 15 clinical infrastructure, and every one patient
 16 expectation to do it, then you will succeed.
 17 So to me, it's just a different way of
 18 thinking about hypothesis testing in an analgesic
 19 trial design, and I'm not so sure that it's the
 20 intervention that's doing it or --
 21 Jim, and then Howard, and then Denham, and
 22 Shannon, and then Brett. Jim, let me start with

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1 you. I'm sorry. We'll get some more input.
 2 DR. RATHMELL: Well, I want to build on that
 3 because it's probably on your list already. But I
 4 think, Ian, what you pointed out were some really
 5 difficult questions that we could address. One is
 6 the high-risk population.
 7 DR. GILRON: Jim Rathmell, right?
 8 DR. RATHMELL: Right. Oh, Jim Rathmell,
 9 right. Brigham.
 10 So think about the risk of persistent opioid
 11 use, so Intervention X reduces persistent opioid
 12 use after major surgery, or after major painful
 13 hospitalization. If we want to get into the
 14 medical realm, you could even do it that way; or
 15 Intervention X reduces the risk of persistent
 16 opioid use in patients who received their first
 17 dose of opioid during a given hospitalization.
 18 Those are the things that really get at the
 19 problem to society and the individuals that go on
 20 to persistent opioid use and some of which is
 21 opioid-use disorder and some of which is chronic
 22 pain. The overlap is enormous.

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1 So that's getting at a testable hypothesis.
 2 And it doesn't say it has to be a drug. It could
 3 be a new model of care, which would be tremendous.
 4 We've got a service that sees people at the day of
 5 discharge, and the same people actually see them at
 6 10 days and check up on them, and teach them how to
 7 use their medications, and make sure that they're
 8 using them appropriately, and refills when
 9 appropriate, instead of getting a call or a return
 10 to the emergency room. And their outcomes could be
 11 decreased emergency room visits and
 12 rehospitalization.
 13 So I'm just getting at the idea. Really, we
 14 can test a whole lot of different things with one
 15 hypothesis.
 16 DR. RAUCK: That's building off of Bob.
 17 That's good.
 18 Howard?
 19 DR. FIELDS: Howard Fields, UCSF, a friend
 20 of Jim.
 21 (Laughter.)
 22 DR. FIELDS: I'm going to build a little bit

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

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

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

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

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1 a very useful thing for patients and the healthcare
 2 system, is to have people feel better. Then
 3 there's this other thing, and that is what happens
 4 after patients "should," in air quotes, be better.
 5 And that is a combination of what do they need when
 6 they get home, but also these other risk factors.
 7 So a person who has no risk factors for
 8 opioid-use disorder, who doesn't have chronic pain,
 9 who leaves the hospital after a successful
 10 whatever, and then has a typical or average course
 11 post-op, that's easy-er. But that's a population
 12 in which one could explore what is possible with a
 13 new drug. Is the new drug able to either reduce
 14 in-house symptoms or at least reduce the need for
 15 long-term opioid therapy, or even short-term opioid
 16 therapy? And that's often the easiest population
 17 to study, but that's not necessarily the population
 18 of greatest need. So the key is not to stop there.
 19 Then the real societal benefits as well as
 20 the patient benefits is to then go on and study
 21 other groups: the chronic pain patient who's
 22 already coming in for some acute intervention; the

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1 person with risk factors; and we get a layered
 2 thing, a layered set of data, where we can then
 3 really understand who benefits from the product or
 4 the intervention how clinicians can adopt it in a
 5 sensible way.
 6 So I don't think it's an either-or. I see
 7 it more as a staged approach to peel the layers
 8 away of what the product is and isn't capable of
 9 doing.
 10 And one other thing. When we talk about
 11 preventing opioid-use disorder, how long do we have
 12 to follow someone to sort that out? So that's the
 13 other thing; is there an alternative to actually
 14 waiting for someone to meet criteria for opioid-use
 15 disorder that would predict somebody getting into
 16 trouble, which would be more pragmatic to study.
 17 And therefore, perhaps companies would be more
 18 willing to do it.
 19 DR. RAUCK: Great points. Anybody want to
 20 add to it?
 21 Shannon? She's been very patient.
 22 DR. SMITH: So I wish I had gone after or

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1 before Sharon because now I feel like my comment
 2 might not be as accurate. The one thought I was
 3 having, though, when you said, Rick, that we should
 4 be not wanting to reduce the analgesic effect, is I
 5 was thinking a little bit about what Dr. Fields
 6 said yesterday about this optimized dosage, and
 7 also then what Dr. Gan was saying about trying to
 8 look at what patients want.
 9 So trying to come back to figuring out not
 10 just are we reducing opioids and maintaining at a
 11 certain acceptable level, but are people willing to
 12 give up a little bit of pain reduction and not have
 13 the side effects? So I just wanted to think about
 14 that maybe as a hypothesis or something that we
 15 might want to study in, even in acute trials, not
 16 just in chronic pain.
 17 DR. GILRON: I agree, Shannon. I was trying
 18 to think of that as well. For me, we're not going
 19 to change the self-report pain score, but
 20 tolerability of pain is different to every person.
 21 I might be in the hospital with a 5 or 6, and to
 22 what TJ says, I'd rather have that than throwing up

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1 or whatever it is. But to me, sometimes pain could
 2 be thought of as a binary thing, tolerable or
 3 intolerable. And whatever tolerable means to me is
 4 going to be very different than somebody else.
 5 But I almost think that's more relevant,
 6 because I don't want you to cram another pill down
 7 my throat to get to a pain score of 3. I'm okay at
 8 5, if that's what I give you, maybe. I don't know.
 9 We're all different. Right? And maybe somebody
 10 else wants to go to a 2 or 1. I wasn't going to
 11 bring that up because I wasn't sure we could solve
 12 that or open that whole can of worms.
 13 Sharon, I'm a little curious as to for folks
 14 who are trying to design these trials don't know
 15 that they can put all those different components
 16 into one trial. And I know they cringe when they
 17 think they have to do 4 or 5 trials to look at some
 18 of these special populations versus something
 19 that's more global for them when they're trying to
 20 put a package together or trying to look at
 21 something that can get into their label.
 22 I don't know if it's relevant to how they

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1 should think of that or how meaningful is it to you
 2 if you're only addressing some of those
 3 populations? I know there are folks in the room
 4 working on this acute to persistent pain kind of
 5 question and some other things, but I don't know if
 6 there's any guidance that way for them.
 7 I could see maybe a trial that actually
 8 looked at subsets of patients within the trial, or
 9 looks at some of that out, or they identify them.
 10 I don't know how that is and how the companies
 11 would look at if they only had a label that
 12 expanded one group of those 4 that lan put up or
 13 something, how that -- I guess that's all new
 14 territory for you guys as well.
 15 DR. HERTZ: But right now, we're just
 16 getting the patient who has no risk. Right? We're
 17 excluding everybody else. So that's what is being
 18 used for marketing applications already. On the
 19 one hand, yes, it's a burden to do many studies.
 20 Again, we're not talking about regulatory issues.
 21 We're not talking about what's required or not
 22 required; just in terms of understanding what the

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1 benefit of a drug is.
 2 So right now we're not getting any of those
 3 other patients who may be the ones who ultimately
 4 benefit most. If you mix them into the same study
 5 and then do some analyses, how do you power the
 6 study? And then are you going to reduce your
 7 ability to even show any effect if you have all
 8 kinds of all comers?
 9 But also, from a strategy perspective, it's
 10 not necessary to have every piece of information
 11 possible about a product in the initial
 12 application. It could be done over time. These
 13 are, I think, the important questions to ask, and
 14 however they get staged premarket, postmarket, all
 15 at once, is a separate issue.
 16 DR. GILRON: We're going to try and have
 17 coffee at about 9:45 if we can. So how Ajay, and
 18 then Brett. And then if you have any other
 19 questions, write them down and remember them for
 20 after the coffee break.
 21 DR. WASAN: Thank you. I'm Ajay Wasan from
 22 the University of Pittsburgh. I think one of the

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1 areas we're getting hung up on is this difference
 2 between the explanatory and the pragmatic trials.
 3 And I think it might be helpful in the paper for
 4 instance to have a table for recommendations for
 5 explanatory and recommendations for pragmatic.
 6 The other key thing related to this, I
 7 think, is that the majority of the research in this
 8 area in the past three years has actually been
 9 pragmatic. It's been looking at prolonged opioid
 10 use and looking at changes in patterns of
 11 prescribing at discharge. And mostly the
 12 interventions have not been single drug. They've
 13 been more, not holistic, but comprehensive
 14 interventions, whether it's provider education, or
 15 whether it's service delivery, whether it's ERAS.
 16 So unlike many of the IMPACT papers in the
 17 past, this paper may actually have a lot more to
 18 say about conducting pragmatic studies in this
 19 area. So it's something to keep in mind because
 20 it's a different mind-set.
 21 DR. STACEY: Brett Stacey, Seattle. I was
 22 thinking back to the earlier days of these meetings

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1 when we're talking about how to improve chronic
 2 pain, the analgesic trials, and the idea of adding
 3 multiple domains for assessment, So psychosocial
 4 function, physical functioning, and sleep. A bunch
 5 of other things were suggested as valid measures to
 6 look at an analgesic response.
 7 In addition to looking at giving guidance
 8 for how to design a trial for opioid sparing, which
 9 in reality is a very small minority of acute pain
 10 trials -- they have opioid sparing in the title,
 11 not that many -- we should say that if you're doing
 12 an acute pain trial in a condition in which opioids
 13 are commonly used, an assessment of the
 14 opioid-sparing effect is appropriate to include,
 15 and here are some options for how to do that.
 16 I think that is broader, pushing this out
 17 and saying this should be in trials that are
 18 considered to be high-quality trials of acute pain,
 19 period. And then different guidance for the subset
 20 that, really, the design is to focus on opioid
 21 sparing.
 22 DR. MADSEN: I'm Torsten Madsen with

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1 Aptinyx. I guess I struggle a bit with the buckets
2 of definition. There is acute pain, and there is
3 acute settings. There's somebody coming in, in an
4 acute pain setting, with chronic pain disorder,
5 preexisting, and there is a concept around when you
6 are discharged from a hospital, which is also
7 introduced as something relevant to measure.
8 I think it would be really helpful -- and I
9 find myself supporting Dr. Hertz on having
10 different buckets of concept of patients.
11 Otherwise, it will be too confusing and really too
12 hard to get anything out of. I'm not sure hospital
13 discharge in your Canada clinic is the same as
14 hospital discharge in Illinois where I live right
15 now or, or elsewhere. I'm not sure it's meaningful
16 either from a clinical endpoint point of view, at
17 least as it is right now.
18 So I think it would be helpful for me to
19 keep that in mind when you go into the clinical
20 study. And also, if there is an operationalizable
21 definition between when acute becomes subacute and
22 when subacute becomes chronic in the setting of

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1 consequences of perioperative analgesic studies, I
2 think that would be helpful, too.
3 DR. GILRON: I agree with everything you've
4 said. I tried to get around that by just
5 everywhere I had a recommendation to say "context
6 relevant" or "context sensitive." And I think for
7 the acute pain recommendations paper, we had some
8 definitions. But yes, so there's flare. There's
9 acute or chronic, like of the same type of pain.
10 There's surgical procedure, which causes acute pain
11 in people with chronic pain remote from the
12 surgical procedure.
13 So we could have a general discussion about
14 that. I don't know if we want to make specific
15 recommendations about each bucket, but I think
16 that's certainly something that we could do that
17 would be worth adding.
18 So we'll break for half an hour. Thank you.
19 (Whereupon, at 9:43 a.m., a recess was
20 taken.)
21 DR. GILRON: Jen, I'm going to let you
22 present some of this.

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1 DR. GEWANDTER: All right. Thank you for
2 your attention and sitting down so quickly. What
3 we're hoping to accomplish for this paper
4 potentially is a list of potential hypotheses and
5 objectives that could be pursued in an acute pain
6 trial for opioid sparing. I recorded the examples
7 that Bob gave, and I think the two really important
8 things to think about that we hope to cover in the
9 paper are, considering these specific hypotheses
10 and outcomes, what would be the important things to
11 consider in terms of population?
12 I think the easiest example is Dr. Ward's
13 example where his hypothesis is that Intervention X
14 prevents respiratory depression post-op, and we
15 added and maintain sufficient pain control to all
16 of the hypotheses, so it's more of a well-rounded,
17 optimizing care than just opioid sparing. One
18 inclusion criteria could potentially be they have
19 OSA because they would be at higher risk of
20 respiratory depression.
21 The other thing that we hope to be able to
22 recommend in the paper is the specific outcomes

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1 that you would use if you hoping to test these
2 hypotheses. We have two options that we could do
3 right now with the rest of our time. One would be
4 we could take these hypotheses that we already had,
5 and we can kind of flesh out some suggestions for
6 the population and outcome, or we could add to
7 these potential hypotheses that you guys think are
8 important.
9 I kind of favor the latter at first at
10 least because I think that's where your input is
11 really valuable. And in terms of inclusion and
12 outcome measures, I can work on that, and then you
13 can give feedback in the rounds of feedback, which
14 is a little bit easier for me to do than to come up
15 with what are the most important things to study,
16 which I think is really important to kind of
17 discuss and flesh out.
18 So that's what we're hoping to do. I can
19 see at least 4 of the ones that are already up
20 here. If you have others --
21 (Pause.)
22 DR. GILRON: Go ahead.

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1 DR. HAYTHORNTHWAITE: Jennifer
 2 Haythornthwaite from Johns Hopkins. I'm still not
 3 sure we're all in agreement of what opioid sparing
 4 means, so I wonder if we shouldn't have at least a
 5 5-minute discussion about that based on yesterday.
 6 Because we've been tossing around a lot of
 7 different components, and it may be that some
 8 components are more important for some ideas than
 9 others. But I do worry that we're not in complete
 10 agreement on that.
 11 We've obviously included -- I think most of
 12 us are in agreement that pain should be part of the
 13 concept. I think we're pretty much in agreement
 14 that side effects should be part of the concept and
 15 that it really -- we've been having discussions on
 16 my little row here about kind of the balance that
 17 most patients have and how it's so personalized
 18 about the amount of pain relief or reduction they
 19 want relative to what side effects they're willing
 20 to tolerate. And that's especially important for,
 21 I think, the acute pain.
 22 When we start talking about chronic pain,

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1 because we have longer periods of exposure, we have
 2 lots of other issues, then the definition of opioid
 3 sparing might also cross into opioid-use disorder
 4 and other kinds of component parts. I just want to
 5 make sure we're in agreement.
 6 DR. RAUCK: I'm a little confused. Are you
 7 thinking opioid sparing, how we should set up the
 8 trial or opioid sparing as a strict definition of
 9 it?
 10 DR. HAYTHORNTHWAITE: This is going to be a
 11 paper about opioid sparing, so I think we need to
 12 be in an agreement with what we mean by that
 13 phrase. And this morning's conversation is about
 14 acute pain, so opioid sparing for acute pain may in
 15 fact be different than opioid sparing for chronic
 16 pain. But I think that we need to make sure we're
 17 on the same page for that concept.
 18 DR. GEWANDTER: Do you guys want to answer
 19 that question?
 20 DR. HAYTHORNTHWAITE: Well, I just put
 21 out --
 22 DR. GEWANDTER: No. I'm talking to the

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1 person who raised his hand.
 2 DR. HAYTHORNTHWAITE: Sorry.
 3 DR. GEWANDTER: There are two people raising
 4 their hands.
 5 DR. SCHOLZ: Just a comment, following up.
 6 The hypothesis that you put up emphasized the
 7 concept of prevention. I wonder whether that's a
 8 bar too high. I think opiate sparing, in my
 9 understanding, is already achieved if you can
 10 reduce the use of opioids. But prevention, I think
 11 prevention includes the concept of maybe preventing
 12 pain and entails a different challenge.
 13 MALE VOICE: Who was that?
 14 DR. SCHOLZ: Joachim Scholz, Biogen. Sorry.
 15 DR. GEWANDTER: This is Jen, University of
 16 Rochester. I think one of the things we might be
 17 having trouble with is I think that opioid sparing
 18 can mean different things. Just looking at these 5
 19 hypotheses, it means different things depending on
 20 how you set up your trial. So I don't think we
 21 need to box ourselves into one meaning. We can
 22 talk about that in the paper, that there are a lot

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1 of different ways to study opioid sparing. There
 2 are a lot of different objectives.
 3 So I think that by doing it this way, we're
 4 actually addressing that issue directly by saying
 5 there's different ways to handle this, and these
 6 are the potential ways we could think of that might
 7 be most meaningful to handle it.
 8 In reference to your question, I think what
 9 you're saying is you don't like the wording of
 10 hypothesis, one, because of the word "prevents the
 11 initiation of opioids."
 12 Is that what you're saying?
 13 DR. SCHOLZ: Yeah, but it plays into the
 14 understanding of opioid sparing. I think opioid
 15 sparing entails also reduction of opioid use. It
 16 doesn't just set the goal to completely avoid the
 17 use of opioids.
 18 DR. GEWANDTER: So I think hypothesis 2
 19 would be addressing that, so prevents the
 20 need -- oh no, sorry. So we don't have one yet for
 21 decreasing the dosage of opioids. I think that's
 22 what you're trying to say. So we can add -- well,

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1 that's what I'm trying to say. I think we should
 2 be adding to these, so that's what we're trying to
 3 do now.
 4 DR. GILRON: It's Ian here. I'm going to
 5 opportunistically take a chance to say what I think
 6 Jennifer is saying could be addressed if we say
 7 that -- we had a little bit of discussion about
 8 this earlier, that opioid sparing should be, at
 9 best, a co-primary outcome, but also, at best, a
 10 co-primary study hypothesis.
 11 I think the point is that we always want
 12 either pain or opioid related adverse effects
 13 together in the study hypothesis, and that might be
 14 an issue that I think -- I don't know if you're
 15 responding to it or maybe Joachim is also reacting
 16 to, is to say preventing opioid prescribing as the
 17 study hypotheses. It just sounds like it's missing
 18 some clinical relevance if we don't also
 19 necessarily tie it to another patient-relevant
 20 outcome.
 21 I don't know. In the intro of the paper, we
 22 can try to come up with a definition or at least

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1 elements of what we -- rank order of what's
 2 important.
 3 DR. JAMISON: Bob Jamison, Boston. What
 4 I've heard is that some acute pain trials could be
 5 prohibitive for a number of reasons, one of which
 6 is that we don't identify many people who get in
 7 trouble with opioids, then that would require a
 8 large number. And secondly, that sometimes the
 9 intervention is expensive, then you can't do it for
 10 everybody.
 11 So I'm wondering if we could have some
 12 trials recommending two different hypotheses in the
 13 same trial. For instance, can we identify
 14 high-risk people? I think we have a lot of data
 15 that can identify what is high-risk persons and who
 16 gets in trouble.
 17 Then secondly, can we identify ways to keep
 18 them compliant? Rob Edwards is going to talk a
 19 little bit about this. But we can talk about some
 20 of the interventions that help people track their
 21 opioid use, including a grant we've just put out
 22 looking at blister packs. And every time you use

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1 an opioid, it monitors when, and where, and how.
 2 And that's expensive for everybody, but it would be
 3 really targeted and really well used. For some
 4 high-risk folks, it would really help manage
 5 opioids.
 6 So my point is maybe a trial could have two
 7 aims or perhaps two hypotheses, one of which
 8 identifies high-risk people; and secondly identify
 9 an intervention that might be challenging for
 10 everybody to use but could be really targeted to
 11 help people be compliant with their opioids.
 12 DR. GILRON: So the first one, the high
 13 risk, is that an inclusion criterion or is
 14 it -- it's not an hypothesis for the study,
 15 it's -- after you got the study done, then you
 16 prove the hypothesis, then you could find them,
 17 or --
 18 DR. JAMISON: So I guess there's a
 19 difference between an aim and a hypothesis. The
 20 aim would be to identify -- the aim is can we
 21 identify people at high risk for opioid misuse?
 22 And I think the answer is we have a lot of markers

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1 that help identify. And we even talked about,
 2 before, a previous history of opioid use or chronic
 3 pain, psychosocial factors, or past history of
 4 misuse.
 5 So I think we can identify those, and that
 6 would be inclusion but also be a hypothesis; are we
 7 pretty good at identifying them? And then
 8 secondly, are there's some interventions? And
 9 there's actually a lot of technology out there that
 10 can track opioid use. And some of it's just pretty
 11 simple and other is a little bit complicated. But
 12 we can track how people use opioids after they
 13 leave the hospital.
 14 Rob, do you want to -- did he step out?
 15 DR. EDWARDS: Sure. I can just talk briefly
 16 about that. Sorry. Rob Edwards, Brigham and
 17 Women's. I see at least three aspects of Bob's
 18 nicely informed comment that we should maybe
 19 consider for the paper, and one would relate to
 20 whether we make recommendations based on
 21 inclusion/exclusion criteria and suggest that some
 22 trials be performed in high-risk samples because

1 that enhances power and assay sensitivity, and that
 2 sort of thing.
 3 I think Bob's second crucial point is that
 4 we'll likely need to pay a little bit of attention
 5 to how opioid use is monitored. We haven't spent a
 6 lot of time talking about that, but obviously
 7 methods range from patient self-report, to
 8 electronic medical records, to urine tox screens,
 9 to novel technological methods like a cloud-based
 10 assessment of opioid access using these, these
 11 blister pack technologies. and that may play into
 12 our recommendations as well if we're going to get
 13 granular enough that we're going to talk at all
 14 about how that opioid assessment is done.
 15 Uh-oh. Have I lost the third point?
 16 DR. JAMISON: It was a good one.
 17 (Laughter.)
 18 DR. EDWARDS: It was. It was actually the
 19 best one. I saved the best for last, and I knew at
 20 that time that I ought not to have done that.
 21 So I agree those are important things to put
 22 into the paper to consider at that level. I think

1 up with some suggestions about how to move forward
 2 with that. And I'll just say that a small group of
 3 us, ad hoc, got together during the break and
 4 talked about this issue of tolerability, pain
 5 tolerability, as at least a concept, meaning that
 6 there's huge differences in individual processes
 7 moving; a patient who just can't stand the
 8 constipation and is willing to put up with a lot of
 9 pain not to get constipation and so on. But the
 10 concept of tolerability, meaning can they get up,
 11 and get out of bed, and do the things they have to
 12 do.
 13 So I'm not sure that that's the right way,
 14 but we need to address that because it's a key
 15 piece to this.
 16 DR. GILRON: I agree with you. I think the
 17 point was that Bob's initial hypothesis was
 18 prevents opiate prescribing. And we said, well, we
 19 want pain to be articulated in the hypothesis. So
 20 I think it's a language issue. So "maintaining
 21 sufficient pain" or "maintaining sufficient pain
 22 control," we're not happy with the language, but

1 we'll hang on to those and would want some of the
 2 input, but they're good things.
 3 I got a question back here, I think.
 4 DR. FARRAR: John Farrar, University of
 5 Pennsylvania. Let me bring something up, and you
 6 can decide whether we should put it off to consider
 7 after we finish this other conversation. But I'm
 8 struck, first of all, by the fact that you forgot
 9 control in the first hypothesis there at the end of
 10 the sentence, "maintain sufficient pain," which is
 11 an interesting concept.
 12 (Laughter.)
 13 DR. FARRAR: But more importantly, I think
 14 that phrase raises huge issues with regards to
 15 thinking about how we decide whether a patient has
 16 sufficient pain control or not. And it becomes
 17 even more complicated if you begin to think about
 18 patients who either have previous opioid misuse or
 19 have chronic pain when they come in to have a
 20 surgical procedure done or other things.
 21 At the very least, we need to acknowledge
 22 that that's an issue, and I would hope maybe come

1 the point is that we want pain to be in there.
 2 DR. FARRAR: I completely agree with that.
 3 I guess what I'm getting at is we need to define
 4 what we mean by that.
 5 DR. GILRON: And that will come in
 6 [inaudible - off mic].
 7 DR. GEWANDTER: Yes. I guess the question
 8 is maybe in order to facilitate the discussion, are
 9 we happy with these 6 hypotheses or are there any
 10 others that people would like to offer up? Lee?
 11 DR. FIELDS: Howard Fields.
 12 DR. SIMON: Simon. Sorry. Howard, go
 13 ahead.
 14 DR. FIELDS: Howard Fields, UCSF. For
 15 number 3, I would add " Intervention X prevents
 16 persistent opioid use and opioid-use disorder," and
 17 just add that in. Because persistent opioid use
 18 could be because of persistent pain, but what we're
 19 really concerned about is people taking more opioid
 20 than they need for pain control.
 21 DR. GEWANDTER: I think that my
 22 question -- because I was struggling with this as

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1 well. Sorry. I'm a terrible speller, so this is
 2 actually kind of anxiety ridden for me to be typing
 3 in front of you.
 4 So would we want it to just be opioid-use
 5 disorder? Because, obviously, that's a lot harder
 6 to find and measure, potentially. Should we get
 7 rid of "persistent opioid use," and should it just
 8 be "opioid use disorder?"
 9 DR. FIELDS: I would prefer it to be
 10 opioid-use disorder because I think it's like
 11 looking for your keys under the light. You want to
 12 do the easy study, but then in the end, you haven't
 13 really shown anything, in my mind. This whole
 14 point is, does it really help patients to reduce
 15 their opioid dose? Right?
 16 DR. GEWANDTER: Yes. So maybe at least
 17 measure them separately. Because I also think that
 18 if you prevent acute pain you might prevent chronic
 19 pain. So if your drug does something great to
 20 really prevent acute pain, persistent opioid use
 21 might be a meaningful outcome as well, but just a
 22 very different outcome than opioid-use disorder.

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1 So separating them I think is a good idea.
 2 Lee, is comment related to his? Because
 3 John wants to respond, I think.
 4 DR. SIMON: It's directly related to it.
 5 DR. GEWANDTER: Oka. Lee can go first, and
 6 then John.
 7 DR. SIMON: Simon, Boston. I think this one
 8 that we're talking about, I can't see the exact
 9 number. I think it's 3. This whole issue of this
 10 transition, the way it's written, are we talking
 11 about just within the hospital postoperatively, or
 12 are we talking about postoperatively within the
 13 hospital and the transition to the outpatient
 14 environment, and how that will be handled?
 15 I think that Bob Dworkin's comments
 16 yesterday about, well, isn't opioid sparing not
 17 using opioids, not decreasing the amount of opioids
 18 we use while maintaining the same or even better
 19 pain control?
 20 DR. GEWANDTER: So you're talking about
 21 number 3 specifically?
 22 DR. SIMON: Yeah --

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1 DR. GEWANDTER: I think number 3 is like
 2 3 months later. I don't know. How long does it
 3 take to -- I have no idea.
 4 DR. SIMON: Well, that's what I wanted to
 5 know, meaning --
 6 DR. GEWANDTER: It's a while later.
 7 DR. SIMON: So it's the transition -- Well
 8 then, we have to think about -- it shouldn't just
 9 be a while later because then there are the 8 days,
 10 or whatever it is, after surgery where people do
 11 take opioids sometimes or many times. And then the
 12 other question is, then, the 3 months later. So
 13 it's two different groups that would need to be
 14 looked at.
 15 DR. GEWANDTER: Yes. So I think you're
 16 wanting to add another hypothesis.
 17 DR. SIMON: Exactly.
 18 DR. GEWANDTER: Okay.
 19 DR. GILRON: I've got Nat, and then Raj, and
 20 then I've got you after that.
 21 DR. KATZ: I just have a question which
 22 relates back to Jennifer's point that we haven't

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1 really defined what we're talking about here with
 2 respect to opioid sparing. And I think it's nice
 3 when you write a paper to actually indicate to the
 4 reader what it is that you're writing about.
 5 So in terms of this concept of opioid
 6 sparing, are we taking a dose-centric view of the
 7 concept of opioid sparing where any benefit that
 8 would accrue to the patient that we want to study
 9 is mediated through either reducing or eliminating
 10 the need for standard existing opioids?
 11 Or are we including in our definition of
 12 opioid sparing, doing interventions that may not
 13 even change the dose of opioid at all, but may
 14 modify the burden of opioid related adverse effects
 15 such as adding an antiemetic to your opioid or
 16 something like that?
 17 Or are we even including novel opioids that
 18 may intrinsically be less addictive or whatever?
 19 What's the boundary of our concept here?
 20 DR. DWORKIN: So I have a question for you
 21 and everybody else in the room. This is Bob
 22 Dworkin. When we talk about steroid sparing, do we

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1 talk about sparing just the side effects, of which
 2 there are many ugly ones, of steroids, or are we
 3 really only talking about the dose? And since a
 4 concept like steroid sparing is kind of well known
 5 in medicine, would it make sense to just follow
 6 whatever it is we mean when we talk about steroid
 7 sparing with respect to opioids?
 8 So basically -- and I don't know the
 9 answer -- does steroid sparing means sparing the
 10 dose of corticosteroids or does it mean keeping the
 11 dose the same and also sparing some adverse
 12 effects? Do we know? I always thought it was
 13 dose, but I could be wrong.
 14 MALE VOICE: It's typically dose.
 15 DR. McNICOL: Ewan McNicol --
 16 DR. DWORKIN: So then, the obvious point I'm
 17 making is if steroid sparing in medicine means
 18 sparing a dose of corticosteroids, then shouldn't
 19 opioid sparing mean preventing, reducing, or
 20 discontinuing opioid dosages to be consistent with
 21 the rest of medicine?
 22 MALE VOICE: Yes.

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1 (Laughter.)
 2 DR. GEWANDTER: Ewan's been waiting a while.
 3 MALE VOICE: Yes, sure.
 4 (Laughter.)
 5 DR. McNICOL: I was going to bring up the
 6 same point as Jennifer and agree with Nat as well.
 7 And clearly, there's some disagreement here. But I
 8 think it's important to bring up Nat's original
 9 definition and work on that for a short while just
 10 to -- it can be a different one for acute versus
 11 chronic pain. But unless we have an agreed upon
 12 definition to start off with, it's hard to derive
 13 hypotheses based on we don't actually know what
 14 opioid sparing is.
 15 DR. GEWANDTER: Nat, do you want to give
 16 them your slide?
 17 DR. KATZ: Is it not in the computer? I
 18 don't know where --
 19 DR. GEWANDTER: This is my computer.
 20 DR. KATZ: Oh. I'd be happy to give
 21 them --
 22 DR. RAUCK: While we're waiting for that to

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1 come up, Raj, I think you had a comment you wanted
 2 to make.
 3 DR. RAJA: I just wanted to comment on
 4 hypothesis 3 again, that there could be two
 5 separate hypotheses, which is based on population
 6 that is. One could be the hypotheses prevents
 7 persistent opioid-use disorder in opioid-naive
 8 patients, or it could be in patients who are
 9 quote/unquote "high risk." So the hypothesis
 10 changes under those circumstance.
 11 DR. GIBLIN: I wanted to also get back to
 12 hypothesis 3. I think it's probably two different
 13 hypotheses because you could be preventing chronic
 14 pain or you could be preventing pain
 15 chronification, or you could be preventing
 16 opioid-use disorder. They are two very different
 17 things.
 18 DR. MARTEL: Mark Martel, McGill University,
 19 Montreal, Canada. I think related to objective or
 20 hypothesis 3, something that is missing. So I
 21 agree with the importance of assessing opioid-use
 22 disorder, but we should keep in mind that an

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1 opioid-use disorder cannot be assessed using
 2 self-report measures; it has to be assessed using a
 3 structured clinical interview usually most often
 4 done using the SCID.
 5 So that might represent a challenge for
 6 researchers. While I think it should remain there,
 7 I think what we're missing is an intermediate
 8 outcome, which is opioid misuse that can be
 9 assessed using, for instance, the COMM, which is
 10 not optimal but it can still be used.
 11 For instance, a patient taking more opioids
 12 than prescribed. And then we can still keep
 13 opioid-use disorder, some patients may escalate in
 14 terms of dose and end up meeting criteria for
 15 opioid-use disorder. But I think what should
 16 really be included as part of hypothesis 3 is
 17 prescription opioid misuse, preventing opioid
 18 misuse and opioid-use disorder after surgery.
 19 DR. RAUCK: Yeah, good points. In the back.
 20 I think that's a good distinction.
 21 DR. EDWARDS: Rob Edwards, Brigham and
 22 Women's, now remembering his third point --

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

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

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

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

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

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

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1 people that are developing ketorolac in certain
2 ways, or other people that are developing anti-NGF
3 in other ways. I just mean to suggest that right
4 now, I personally would not want to have a major
5 surgical procedure and be given something that
6 wasn't an opioid, acutely, during that period of
7 time, until it's proven that it works equally and
8 analgesically provided.
9 So I think that the discussion about
10 in-hospital perioperative treatment of acute pain
11 is different than the transition time and the
12 3 months after. And that's really I think what
13 we're trying to think about because people
14 shouldn't necessarily have to go home with opioids.
15 But this is going to require an enormous
16 amount of study of specific patient populations,
17 all of whom have already been listed, those of whom
18 were opioid-use disorder people. Those are people
19 who have been chronic opioid users for other
20 reasons and their opioid experience and how you're
21 going to be able to deal with that patient
22 population.

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

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1 going to define as opioid sparing. Then you're
 2 hitting on something that I think -- I'm going to
 3 try this, Joachim -- but we've been discussing a
 4 lot in the pain group about what I guess we call
 5 the chronification of pain. And that's I think a
 6 different topic than what we're discussing today.
 7 So maybe that should be put there to discuss this
 8 idea of what happens long term. And if we treat
 9 acute pain, can we prevent the initiation of
 10 chronic pain, which is a super important question.
 11 So maybe it would be helpful if somebody
 12 wanted -- I'm not going to volunteer you, Jennifer,
 13 but if somebody seriously wanted to try to just
 14 make some high-level points. I completely agree
 15 with the comments about I think we have acute and
 16 we have chronic, and they're going to be different,
 17 and just start at a high level about what we should
 18 be assessing.
 19 Joachim, I don't know if you want to say
 20 anything.
 21 DR. SCHOLZ: Joachim Scholz, Biogen.
 22 DR. STEINER: I try.

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1 DR. SCHOLZ: So you hit on the concept of
 2 disease modification, where there's analgesia, but
 3 I think that's not necessarily the topic.
 4 DR. GILRON: Speak up a little bit. I'm
 5 sorry.
 6 DR. SCHOLZ: I think that hits on the
 7 differentiation between disease modification and
 8 chronic pain conditions where there's analgesia.
 9 But I think it's beyond the scope of this workshop,
 10 a very interesting topic, though.
 11 Maybe I'll just follow up on what Lee said.
 12 If you set the goal to avoid the use of opioids
 13 entirely, I would hesitate to start a trial because
 14 there's a high risk that it fails.
 15 DR. SIMON: No, absolutely. That's because
 16 what we have available today.
 17 DR. SCHOLZ: In practical terms, that's not
 18 how I would design it, with that hypothesis.
 19 DR. RAUCK: Nat?
 20 DR. KATZ: I think Ajay was first, wasn't
 21 he?
 22 DR. WASAN: So just to clarify this

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1 opioid-use disorder concept before we go into more
 2 of the definition, just for everyone, it's divided
 3 into mild, moderate, and severe categories. And
 4 the mild opioid-use disorder maps on very nicely to
 5 the ACTTION definition of opioid misuse.
 6 So just so people know, our group has looked
 7 at this, and we actually have a review paper on
 8 this issue coming out, so just a way of thinking
 9 about it. Some folks outside psychiatry don't
 10 think of it that way.
 11 DR. KATZ: So at the risk of oversimplifying
 12 things, it seems like if we're going to try to work
 13 towards a definition of opioid sparing, there's
 14 basically two options I think. One option is to go
 15 with the dose reduction option where we're going to
 16 define opioid sparing as dose reduction and the
 17 potential clinical and societal benefits that
 18 derive from it. And then we could mention
 19 afterwards that, by the way, there are other ways
 20 of reducing opioid adverse events besides reducing
 21 the dose like having better opioids, or like adding
 22 it antiemetics, or like adding things that reduce

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1 opioid-use disorder without necessarily modifying
 2 the dose, et cetera.
 3 But those are beyond how we're going to
 4 consider the concept of opioid sparing for the
 5 purpose of this paper, something like that. So I
 6 would call that a dose-centric view that could also
 7 go on to explain all the different things that were
 8 not included and why, especially because a lot of
 9 the measures that we would propose for this
 10 dose-centric concept, opioid sparing,
 11 they'd be the same measures used if you were
 12 studying some better opioid or that you thought
 13 reduced opioid adverse events or whatever.
 14 So there is a connection there, but I don't
 15 have any problem with excluding that from the core
 16 definition. The alternative would be more of like
 17 a clinical benefit-centric definition, which is
 18 more like the one that I had, whereas sort of the
 19 center of the definition is reducing the negative
 20 impacts of opioids in patients and society, and we
 21 can do that through dose reduction, or modifying
 22 the pharmacology, or whatever. That's what I went

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

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

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

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

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1 hip or knee arthroplasty or any procedure where
2 they have preexisting pain and are using opioids.
3 Assess them -- which I'm not sure if anybody does
4 this routinely. Assess them pre-op for
5 opioid-misuse or opioid-use disorder. And then you
6 look at your longer-term outcomes 6 months a year
7 for whether or not they've successfully reduced
8 their dose and you've reduced the incidence of
9 really meaningful outcomes, which would be
10 opioid-misuse disorder or opioid-use disorder.
11 Then since at least based on the data from
12 9,000 patients, showing maybe 20 percent who were
13 on opioids before actually increase their dose,
14 then you're looking at an outcome that's reasonably
15 frequent, and you could do it in a reasonably sized
16 sample and achievable sample.
17 DR. GILRON: Yeah. And that follows up on
18 Bob Jamison's suggestion, I think, about how to
19 identify.
20 DR. RAUCK: Rob? Sorry.
21 DR. SCHOLZ: Joachim Scholz, Biogen. I
22 think that's

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1 a different trial from the ones that we have
2 discussed so far. What we have discussed so far
3 was opioid after surgical pain, and my
4 understanding was that we were mainly talking about
5 pharmacological intervention that sets in at the
6 time of surgery, before or immediately after;
7 whereas now we're talking about whether surgery
8 itself can be successful in reducing opioid use.
9 We heard that in the former setting, we
10 should involve patients who have preoperative pain
11 and are perhaps on opioids. But if you want to
12 test from pharmacological intervention after
13 surgery and measure the reduction of opioid use in
14 response to your intervention, I would rather have
15 a population that is pain free before surgery
16 because otherwise I run into the problem that I
17 have to control for the hospitalization of the
18 patients, the surgery, and the interventions that I
19 actually want to measure. So I think those are two
20 separate questions.
21 DR. RAUCK: I agree. To Mike, I think if
22 you just took an overall population and tried to

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1 look for preventing opioid-use disorder, your
2 sample size is enormous. We do know there's a fair
3 number of patients who come for surgery who already
4 have an opioid use disorder, and can you affect
5 their postoperative care because you're right, a
6 lot of them end up on increased opioids. We see
7 them back in the pain clinic. You can't ever get
8 them back down because of the way they're treated
9 acutely, and this, that, and the other. And there
10 could be a whole set of things, that you might show
11 that Intervention X is different than not
12 Intervention X in that group of patients who have
13 been preselected. I could see studying that group
14 a lot easier than the other group.
15 Raj, and then TJ.
16 DR. RAJA: Just a comment that I think
17 you're looking at acute pain trials, and all the
18 hypotheses seem to be focusing on surgery. Given
19 the suggestion that there are patients who may have
20 acute pain, get hospitalized, and may even have a
21 higher risk than those who have had surgery, I
22 think that group should not be omitted or ignored.

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1 DR. RAUCK: Excellent point. Yeah. A motor
2 vehicle accident and there's blunt trauma. There
3 are all kinds of people we see that way. Yeah,
4 that's great to think about.
5 TJ?
6 DR. GAN: TJ Gan, Stony Brook, New York.
7 I've heard all the discussion about this opioid
8 sparing, and in fact it's one of the reasons we are
9 here, and it's in the title of the meeting here.
10 Now, if we are going to sort of ignore opioid
11 sparing for convenience and also because we
12 couldn't reach consensus, perhaps we should then
13 make a point that opioid sparing should not be used
14 if we can't even make a definition of opioid
15 sparing.
16 DR. RAUCK: So your proposal?
17 DR. RAJA: Well, I'm just saying that if we
18 are going to write a paper on opioid sparing, I
19 agree with Nat, that we need to define it. If we
20 can't define it, then perhaps that is not the term
21 to be used because it would still be used widely,
22 unless a group like this is saying, well, that is

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

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

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

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

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

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

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1 definition?
 2 (Hands raised.)
 3 DR. DWORKIN: All right. Let's move on to
 4 the next topic.
 5 DR. SANDBRINK: What's needed, but I think,
 6 based on this definition, do some wordsmithing.
 7 DR. DWORKIN: So we can wordsmith it,
 8 absolutely, decide whether opioid sparing is
 9 hyphenated or not.
 10 (Laughter.)
 11 DR. DWORKIN: But I think you guys now have
 12 15 minutes to talk about something else. We've
 13 endorsed the Katz definition.
 14 DR. SANDBRINK: One comment briefly about
 15 this definition, and I'm sorry.
 16 DR. RAUCK: Say who you are first.
 17 DR. SANDBRINK: Oh, yeah. Sandbrink,
 18 Washington D.C. VA. The specification here is that
 19 the intention is to reduce the adverse effect of
 20 opioids on patients. I don't think that has to be
 21 part of the definition here. The definition is
 22 with the opiate sparing. You could argue, maybe in

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

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

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

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

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

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

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

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

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

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1 questions. But it does seem relevant to me to look
 2 at these subsets because the subsets, embedded in
 3 them are some of the real high-risk populations,
 4 whether it's those who go on to persistent pain,
 5 those with chronic pain before surgeries, and then
 6 some of the other issues that Ian's put up.
 7 So I don't think those are going to be the
 8 defining things of a therapy or an intervention as
 9 I see it, but I see those special populations as,
 10 one, most of those seem like they could be studied,
 11 which is relevant. I've been in too many trials of
 12 great trial designs that could never be studied,
 13 really, or populations found, but could be
 14 identified and may have meaning even if they're not
 15 the overarching reason you would at the therapy, or
 16 the intervention, or --
 17 DR. GAN: I agree with you with a Subgroup,
 18 but I think you are talking about in general.
 19 Let's be real, an everyday trial, we're
 20 not -- those subsets I think it's important, I
 21 agree, but it may not be the population.
 22 DR. RAUCK: For me in a chronic pain

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1 world -- and obviously companies are interested in
 2 this, of trying to prevent persistent pain, the old
 3 adage that 10 percent of the patients who get acute
 4 back pain go on to develop chronic pain, but they
 5 use 90 percent of the resources and expenses of it.
 6 So it's relevant if you can prevent that 10
 7 percent, that that's a meaningful thing that way.
 8 John, you had a comment.
 9 DR. FARRAR: Along those lines specifically,
 10 I think we need to keep in mind that as a
 11 community, the pain community is being lambasted
 12 for the overuse of opioid in the setting of -- I
 13 mean, take, for example, third-molar extractions
 14 and going home with 30 Percocet. I don't know how
 15 to fit -- because the development of OUD is clearly
 16 rare enough, that it's going to be very hard to
 17 study. Maybe we can go back and do it in databases
 18 and so on.
 19 But it seems to me that if we don't at least
 20 address that in some way, there's going to be a
 21 large pushback on the fact that we're not at least
 22 mentioning the very important societal component of

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1 this, which is that although it's rare, there
 2 clearly are young people who got 30 Percocet, and
 3 are now addicted, and might not have been if they
 4 hadn't had that process. I don't know how to do
 5 that, but I do think leaving it out completely is
 6 going to be problematic.
 7 DR. GEWANDTER: Okay. So I think what
 8 you're saying is that interventions targeted at
 9 proper prescribing practices are interesting, and
 10 making that an objective of some of the trials, not
 11 just like adding this drug, would be interesting
 12 for the paper.
 13 Okay. Thank you. Yes? Sorry. I don't
 14 know your name.
 15 MS. WENTWORTH: Hi. Kerry Wentworth,
 16 Flexion.
 17 Nat, going back to your revised definition,
 18 you just have "dose reduction." In that
 19 definition, would you presume avoidance also equals
 20 dose reduction?
 21 DR. KATZ: Well, I included reducing to zero
 22 as part of reduction, but if people feel like it

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1 would be more clear to state that explicitly, then
 2 we could say "or complete cessation," which is what
 3 I had in my original definition, but I was
 4 responding to people's desire for simplification.
 5 MS. WENTWORTH: From the sponsor's side, I
 6 think that kind of clarification, even if it exists
 7 in another definition, could be useful.
 8 DR. SMITH: I just want to follow up on
 9 that. This is Shannon Smith. Are you saying
 10 avoidance or are you saying reduction to zero?
 11 Because I think those are two separate things, like
 12 not going on it at all or --
 13 MS. WENTWORTH: Exactly. They could be
 14 definitely two separate things.
 15 DR. SMITH: Okay.
 16 MS. WENTWORTH: But could they still fall
 17 under opioid sparing?
 18 DR. STEINER: But Nat, are we not going to
 19 get into this same issue that came up yesterday?
 20 Like what's going to be like a meaningful reduction
 21 in opioid use?
 22 MALE VOICE: Maybe.

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1 (Laughter.)
 2 DR. GILRON: So maybe we'll just take a
 3 final question before lunch or maybe just go for
 4 lunch.
 5 DR. RAUCK: It looks to me like everybody's
 6 ready for lunch.
 7 (Applause.)
 8 (Whereupon, at 11:30 a.m., a lunch recess
 9 was taken.)
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1 It's the eighth largest in the country, 3 million
 2 patients, 26 hospitals, and it's actually the
 3 world's largest installation of Epic, the
 4 electronic health record, which I will talk about a
 5 little bit.
 6 (Murmurs from audience.)
 7 DR. ROWBOTHAM: Oooh. Yeah, I know. Oooh,
 8 the evil empire.
 9 (Laughter.)
 10 DR. ROWBOTHAM: I still see some patients
 11 occasionally at the Pain Management Center, and it
 12 allows me to keep my UCSF designation.
 13 What does opioid sparing mean? We've talked
 14 about that to great extent, and it seems like we're
 15 getting our way towards a definition, so I won't go
 16 into this anymore. What I want to talk a little
 17 bit -- one of the speakers yesterday said there
 18 really weren't addiction medicine speakers as part
 19 of the group. Well, I actually am -- in my
 20 previous lifetime before I went into neurology, I
 21 had extensive experience in addiction medicine
 22 because I was the medical director for the

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1 AFTERNOON SESSION
 2 (12:20 p.m.)
 3 Presentation - Michael Rowbotham
 4 DR. ROWBOTHAM: Thank you, everybody. I can
 5 tell it's the last lecture of the day, so Bob told
 6 me I could talk about whatever I felt like.
 7 I can see already that not only did I forget
 8 the hyphen, but a "Z" got added at the end --
 9 (Laughter.)
 10 DR. ROWBOTHAM: -- which I'm blaming Valorie
 11 for. She put a Z in there.
 12 Anyway, I'm going to talk about the chronic
 13 pain issues and research designs and methods. My
 14 current position, I'm Sutter Health's chief
 15 research officer, which means that I oversee all
 16 their clinical trials, basic science, large-scale
 17 epidemiology at the data coordinating center. And
 18 I'm chagrined to say that we have zip, nada,
 19 nothing organized in the chronic pain area.
 20 So I won't tell you anything about Sutter
 21 Health's chronic pain research program because
 22 there isn't one. But it is a large health system.

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

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

5 So there was a very simple protocol that the
 6 hospital had. It was a manacle on the ankle with a
 7 chain to the bed and some colored liquid that had
 8 methadone in it at first in decreasing amounts.

9 And they would go through withdrawal, really pretty
 10 severe withdrawal despite this, and we had 100
 11 percent success.

12 (Laughter.)

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

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

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

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

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

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

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

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1 different from the usual stuff that you get
 2 dispensed.

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

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

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

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

8 The other is, especially now, as opioids
 9 have kind of moved down the chart to being really
 10 last resort, 3rd, 4th, 5th-line therapy, this
 11 slide, which I've shown and cited in papers about
 12 clinical trial ethics and who gets recruited is
 13 really relevant for this. This is a long-term
 14 study of newly diagnosed epilepsy patients. It's
 15 an old study. It's published in 2000, and they had
 16 470.

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

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

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

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

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

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

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

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

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

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

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

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1 might relief craving and other behaviors associated
2 with addiction.
3 The other would be what about preventing
4 opioid-use disorder by devices that monitor
5 patients. So again, it's not really sparing, but
6 it prevents unsanctioned dose escalation and all
7 the risks associated with that, which are the
8 things that we're really concerned about here.
9 We're concerned about patients having opioid-misuse
10 disorder, opioid-use disorder, accidental or
11 intentional overdose, et cetera, et cetera, and a
12 device could help there. It could also be tamper
13 proof so that people can't exceed the limits that
14 they're allowed to use even though they're
15 ambulatory.
16 Now, you would need a monitoring system
17 because there are lots of different opioids out
18 there. So the patient could be taking sanctioned
19 methadone but also injecting fentanyl. And unless
20 you were really doing sensitive urine testing, you
21 wouldn't really pick that up. The other is
22 specialized pill bottles that monitor when the pill

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1 bottle is opened and every capsule that's taken.
2 What about apps? Apps are big in the
3 addiction world as ways for people to manage their
4 symptoms. There's a company called Pear
5 Therapeutics that has an app that kind of functions
6 like a digital friend or an AA support member, or a
7 family member. It delivers messages of support to
8 reduce craving and enhance unsanctioned opioid use.
9 The MIT Media Arts and Sciences program have
10 some very clever stuff that they're developing to
11 just do behavioral modification in general. So
12 things like sending signals or otherwise changing
13 the valence of particular situations, it turns out
14 that you just release an odor at a particular time,
15 you can change people's mood and how they're
16 feeling about something really quite rapidly.
17 Then you can do other things like aversive
18 conditioning where you pair drug use some kind of
19 negative beliefs, so that when the patient is
20 feeling the need to use, they're also getting these
21 aversive thoughts about it that help keep them from
22 doing that. So these would all accomplish the goal

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1 of opioid sparing.
2 So let's get into some of the trial design
3 issues. Historical controls, they're really not
4 useful, especially right now. I think there's
5 agreement here that the landscape for chronic pain
6 opioid prescribing has changed dramatically in the
7 past 5 years, and we were already seeing it in some
8 of the graphs that were shown yesterday that the
9 peak prescribing has already hit and has passed, so
10 we really can't use data from 5 or 6 years ago.
11 It's really going to need to be generated
12 prospectively.
13 Then as we saw in the talks today and
14 yesterday, chronicity of opioid use is associated
15 with opioid-use disorder, but the dose has kind of
16 a tenuous relationship with risk. And even though
17 some of these data sets are fairly large, they
18 haven't successfully settled the question.
19 Then from looking at the data that's been
20 shown at this meeting about surgery in patients who
21 are opioid naive, and developing opioid problems or
22 just chronic opioid use, there's a long and

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1 variable gap sometimes between when those occur.
2 So since now prescribers are giving a lot less and
3 often tending to rely on academic pain programs,
4 where you're kind of in a bubble protected from the
5 predations of the Drug Enforcement Agency and your
6 state narcotics control boards, prescribers in the
7 community are feeling very, very intense pressure
8 coming from all sorts of different directions to
9 discourage them from prescribing. So the doses are
10 lower, and that's maybe partially due to
11 availability of drugs like buprenorphine, but
12 obviously that's only a small part of the equation.
13 I think prescribers have responded to the
14 educational programs. They do have a better sense
15 for who's a high-risk patient. This has probably
16 paradoxically pushed some patients who were using
17 prescription opioids that they were getting from
18 their physician or one of their friends' or
19 relatives' physicians and now are on the street
20 market to get their needs met, and of course
21 suffering the consequences for that. So really,
22 it's only a prospective study that can really

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

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

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

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

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1 period was around 8 weeks, followed by a taper
 2 period.
 3 This really mimic clinical practice in that
 4 the patients got to choose how many capsules they
 5 took. They could go up or down, depending on side
 6 effects, so their job was to find the optimum
 7 balance between relief and side effects. So it
 8 wasn't like a traditional trial phase 2 where you
 9 get slotted into a particular dosage group. The
 10 only randomization was whether or not you got itty-
 11 bitty capsules with a levorphanol in them or very
 12 little levorphanol in them.
 13 When you looked at the data, we had 81
 14 subjects all with verified neuropathic pain. We
 15 started with 81. And even though this was a very
 16 patient friendly protocol, only 59 completed.
 17 Fifteen of the drops are due to adverse events.
 18 Agitation was noteworthy in the higher strength
 19 group. And what we found was when really looking
 20 individually at all the dropouts, in the lead up to
 21 their time of dropping out, you could see they were
 22 falling behind the rest of their dose cohort, or

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1 their capsule strength cohort, in getting less
 2 relief and experiencing more side effects. So they
 3 were on the road to failure, and then they just
 4 dropped out.
 5 Even though we saw significant differences
 6 in the pain relief scores, there was really no
 7 difference in relief ratings. And that makes me
 8 worry a little bit about some of these complicated
 9 composite measures because if somebody's only
 10 experiencing a limited set of symptoms and you're
 11 looking at multiple symptoms as part of your
 12 outcome, it just takes away some of the
 13 sensitivity.
 14 The other was that the actual daily dose
 15 that people took was widely variable. We saw a
 16 very significant difference in the number of
 17 capsules patients took, depending on which capsule
 18 strength group they were assigned to. But when you
 19 actually calculated that back into milligrams of
 20 levorphanol, people titrated themselves to really
 21 very different levels.
 22 The last couple of slides are really on

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1 pragmatic trials. So we're lucky here. I've got
 2 Ajay and I've got Ian, that we wrote this paper
 3 together about pragmatic trials, which are called
 4 really effectiveness trials. They're really
 5 in-practice studies, and they've been applied only,
 6 to a very limited extent, in the pain area. But
 7 they have some advantages, and I want to spend some
 8 time talking about that.
 9 Patients stay in their usual care situation.
 10 They don't have to go to a specialized program in
 11 order to participate in this study. What that does
 12 is -- as we all know, those of us who've done
 13 clinical trials and have run clinical trial centers
 14 is, patients love it because they get so much TLC.
 15 They come in. The study coordinators are so nice
 16 to them. They call them up. They're really
 17 concerned about how they're doing. And of course,
 18 they're very concerned that they bring back their
 19 medication and do all the pill counts.
 20 So it's a very kind of supportive and
 21 high-touch, high-contact environment. So it's not
 22 surprising at all that people's pain scores go down

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1 a lot, even if they're really not getting anything
 2 other than placebo.
 3 When you just keep them in their usual care
 4 situation, you kind of wash out a little bit of
 5 that, and you get the outcomes from review of the
 6 electronic health record. So correlations are
 7 straightforward enough, but proof of causation is
 8 difficult, and you have to design the trial in a
 9 particular way in order to actually test various
 10 options against each other. So the data collection
 11 is really all important.
 12 As we saw yesterday, when John showed his
 13 very nice screenshot of the Epic trying to
 14 prescribe buprenorphine, EHR use is just awful.
 15 Anybody who doesn't know it, Epic is a billing
 16 system. I hope nobody's here from Epic, but when I
 17 heard the sort of moans and groans, I kind of get
 18 the feeling, no.
 19 (Laughter.)
 20 DR. ROWBOTHAM: It's a billing system. It
 21 makes sure that when you see the patient, that you
 22 capture what you did. It gets categorized as to

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1 what level of intensity the encounter is, and the
2 bill goes out, and the clinic or hospital collects
3 their money, and they're all happy. And as John
4 also said, you never look at your patients again.
5 You're looking at the screen the whole time.
6 So when I see patients, I'm really lucky.
7 And that's really why when I see patients, I do it
8 in a teaching program -- and I would never try and
9 do it in a solo practice -- is because I've got a
10 resident or fellow who's already talked to the
11 patient, filled out most of the electronic health
12 record, is busily typing away while I'm sitting in
13 a chair with nothing, maybe a piece of paper, just
14 asking questions and poking them, and doing sensory
15 testing and all that other kind of fun stuff. And
16 I don't even look at the screen until after the
17 encounter is over. It's great. It's even better
18 than the old days when I would have to type up or
19 dictate my report.
20 So if you're a resident or fellow, they're
21 incredibly fast typists. I'm just really amazed,
22 and they are really good because they spend all

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1 their time typing and not a whole lot of time
2 looking at the patients.
3 As I mentioned, Sutter Health has the
4 world's largest installation of Epic. Does that
5 get us anywhere with Epic in terms of getting them
6 to make their platform more user friendly,
7 especially in the pain area? No. It doesn't do
8 anything.
9 We also have in the Bay area and other parts
10 of the country this thing called CareEverywhere.
11 So if a patient comes in, and I'm looking to see
12 who they've seen since I last saw them, I can see
13 their records. I'm at UCF. I can see their Sutter
14 records. I can see their Kaiser records. I can
15 see anyone else who's in our region to see what
16 kind of encounters that they've had. I don't get
17 as much detail, but at least I can know.
18 But not everybody has Epic. Not everybody
19 has the same electronic health record platform. So
20 in the cancer area, oncologists are all in private
21 practice. They're not using Epic when they see the
22 cancer patients in the clinic. A patient gets

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1 admitted to the hospital, we've got Epic. We've
2 got a thing called Beacon for doing standardized
3 chemotherapy orders.
4 But it's an incredible amount of labor to
5 correlate the outpatient private practice docs'
6 records and correlate it with what's happening in
7 Epic because those systems, they just don't talk to
8 each other at all. And if you've tried to do data
9 analysis in electronic health records, you know
10 that little misspellings of difficult-to-spell last
11 names like Rowbotham, just really trip it up. Or
12 if you do last name first, you don't see all the
13 other ones where it's first name last. So they
14 just require a lot of special care.
15 You can get questionnaires in. Our dementia
16 clinic has the MoCA online in there. And you can
17 get it filled out, and you can get it into the
18 electronic record. We scan a lot of our research
19 questionnaires into there, but that doesn't mean
20 you can easily get it back out again into a
21 database that you could do work with. So they're
22 hard.

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1 They have some other weird features, and I
2 would suggest if you have any interest in this,
3 read this book. It's a few years old now by Robert
4 Wachter on The Digital Doctor, which is really the
5 history of how electronic health records so quickly
6 got into all the hospitals. And that was this
7 meaningful use thing and all the Obama shovel-ready
8 project money that came along with the economic
9 downturn, the great recession in 2008-2009.
10 So there are ways of directly testing
11 hypotheses within a pragmatic trial. Using things
12 like cluster randomized designs is just one
13 example. Your randomization, instead of a clinical
14 trial, it's not at the level of the patient. It's
15 at a different level. It's at a group level. So
16 you randomize at the level of the physician, or the
17 practice location, or the country, or the state.
18 It can be anything you want. You just need to make
19 sure that your randomization gives you groups that
20 are comparable to each other.
21 For example, in California, you wouldn't
22 want to do political opinion polls in San Francisco

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1 and have your comparison group be down in the
 2 Central Valley, because they're pretty different in
 3 terms of how they look at things. You can't
 4 compare one against the other.
 5 So instead what you could do is you could
 6 maybe compare San Francisco to Berkeley, God
 7 forbid, because those are sort of reasonably
 8 similar on the political spectrum, and medically
 9 it's the same thing. So you really have to dive
 10 pretty deep into the healthcare system to make sure
 11 that you're comparing practices, facilities,
 12 locations, hospital size, whatever, that are
 13 reasonably comparable.
 14 We heard from Jim here and some others that
 15 even within a clinic, the practice style of the
 16 individual physicians can be dramatically
 17 different. One doctor may say, "Hey. Opioids? Sky
 18 is the limit." The other one's like, "No, I don't
 19 prescribe opioids, but I'll do an epidural on you
 20 tomorrow morning." They're just really different
 21 in terms of how they approach things.
 22 So there's a lot of potential for

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1 confounders, but the advantages are that you can
 2 recruit very large numbers of patients. And if
 3 you're doing things like just where you have access
 4 to a particular treatment style, then you don't
 5 even necessarily need consent.
 6 So let's say a new device has come out, like
 7 some whizzbang new MRI scanner that's ultra
 8 sensitive. And you roll it out in San Francisco,
 9 let's say in Sutter Health. We roll it out in San
 10 Francisco and Los Banos, down in the Central
 11 Valley, and those are the only places. We could do
 12 a study comparing what you get out of the scanner
 13 in those two locations, and then we could pick a
 14 bunch of other Sutter sites as our comparators.
 15 And we could do it prospectively and thoughtfully,
 16 and see what the impact is. And that essentially
 17 could function as a cluster randomized trial.
 18 So there's a lot of potential here, but it
 19 just takes a lot of thought and a lot of planning
 20 to make sure you get all the confounders out, and
 21 you really know who you're looking at.
 22 The other is, what about some of the outcome

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1 measures? As I mentioned, you can build them into
 2 the electronic record, and things like telemedicine
 3 and sensors would help a lot.
 4 There's a very interesting meeting that
 5 happens every year in San Jose at the Computer
 6 History Museum called the Precision Medicine World
 7 Conference. It's heavily oriented towards
 8 neurosciences and especially oncology because it's
 9 so much in the area of biomarkers. But a lot of it
 10 are people who believe in what they call the
 11 quantified self. And that's basically where you
 12 just measure yourself on everything all the time,
 13 and all that gets uploaded into the Cloud, and it
 14 can be analyzed.
 15 So by doing things like telemedicine or
 16 censored technology in a system where there's
 17 common electronic records platforms, you could
 18 actually be collecting a lot of data from patients
 19 just as they go about their daily activities. You
 20 collect the data. You crunch all the numbers, and
 21 you can come up with correlations about -- or
 22 information about different ways of approaching

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1 pain. And it could be anything. It could be
 2 devices. It could be behavioral. It could be
 3 drugs. It could be anything that we want to come
 4 up with, but it can be done in this kind of design,
 5 and you can get large numbers of patients if you
 6 have enough cooperating healthcare programs. It
 7 could be national and international.
 8 So there's potential here. It's not been
 9 done that much in the pain area, but we do have our
 10 friends from NIH here involved with the initiatives
 11 around opioid-sparing studies.
 12 I think that's my last slide. It is my last
 13 slide. So I'll take questions or we can go on into
 14 the planning part.
 15 (Applause.)
 16 DR. ROWBOTHAM: Ian?
 17 DR. GILRON: Thanks, Mike. That was very
 18 interesting and great talk.
 19 Something that I think may be a trial design
 20 feature, I want to ask you how important you think
 21 it is. It has to do with opioid-dose titration. I
 22 think it might be important because maybe in

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1 clinical practice, in primary care, that may be
 2 happening in an unsupervised fashion. And because
 3 tolerance to opioid related side effects can
 4 develop, people can end up on higher, higher doses
 5 if the opportunity is there. And at some point,
 6 the realization is not made that there really isn't
 7 analgesic efficacy there.
 8 So I guess I wanted to ask you what was your
 9 experience in your trial? We've done a couple of
 10 opioid trials where it's really more looking at
 11 side effects and pain relief as a guide to making
 12 the decision, do we do the next up-step of dose
 13 titration.
 14 So I guess the question is, do you think
 15 that the method of opioid-dose titration in trials
 16 is important in optimizing dosing?
 17 DR. ROWBOTHAM: Well, I think with
 18 telemedicine, making it easier to stay in touch
 19 with patients in studies, if that was
 20 introduced -- it's not really used, but it's there;
 21 it's available -- you can track them more closely.
 22 What we did in the levorphanol study was we started

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1 with very low doses. They had to come back every
 2 week at the beginning.
 3 So even if they took their entire week's
 4 worth of pills, they wouldn't end up in the
 5 hospital. And then as they went along, they kind
 6 of got a little more rope each time. And we just
 7 gave them parameters that they needed to stay in,
 8 and then the coordinators stayed in touch close
 9 touch with the patients in order to get around
 10 that.
 11 Now, of course if you had an electronic pill
 12 bottle, or you had an ambulatory PCA, or some other
 13 kind of thing, not only could you lock the
 14 device -- the device locks out, but you also get
 15 instantaneous feedback. The flashing red siren
 16 goes off in the study center saying, Mr. Jones is
 17 trying to force open the pill bottle with a crowbar
 18 and succeeded, and is now taking an entire week's
 19 worth of pills. You could get that kind of remote
 20 sensing, and then you could provide instantaneous
 21 feedback on, don't take that extra dose, or
 22 feedback on managing, it really could be automated

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1 to do that.
 2 DR. JAMISON: Good talk and good thoughts.
 3 You alluded to the fact that opioid therapy is a
 4 moving target, and then you can start trials,
 5 opioid-induced hyperalgesia, where you can't
 6 recruit enough people on high-dose opioids, or you
 7 set a target. You have a certain opioid dose, and
 8 then you just can't get anybody.
 9 So take your best guess. If we're going to
 10 come up with some design looking at something that
 11 we could start and then 10 years later, it's not
 12 appropriate or unfair, how much is this a challenge
 13 going forward?
 14 DR. ROWBOTHAM: Well, that's why I keep
 15 coming back to this more in-practice trial rather
 16 than randomized-controlled trials because in that
 17 situation, you don't even necessarily need to do
 18 much to recruit. The patients are already there.
 19 It's really more what they have access to or if you
 20 institute a special program. And then as part of
 21 the consent to go into that program, they consent
 22 to have their data collected.

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1 So it's not the same as doing the kind of
 2 studies where you recruiting patients with
 3 high-dose opioids and then maybe trying some
 4 intervention to see if there's opioid-induced
 5 hyperalgesia or not because you're not necessarily
 6 doing an experimental intervention. You're just
 7 offering people different menus.
 8 Basically, Howard and I walked up 14th
 9 street. Well, we walked like 8 blocks before we
 10 found a place that we felt like going into, so we
 11 had all those choices along the way. It's the same
 12 thing. In these cluster randomized designs, you
 13 could have 3 or 4 different interventions, and you
 14 just roll that intervention out. Because we're not
 15 talking about doing experimental treatment here.
 16 We're just talking about what techniques are going
 17 to give us the best outcomes? How are we going to
 18 reduce the harms of opioids and get some clue about
 19 how to roll back the severe harms?
 20 We're not talking about the kind of
 21 studies -- and I have one that I slogged away at
 22 for years to try and recruit patients, where the

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1 intervention just requires a very specialized
 2 patient group, as you just mentioned now and we've
 3 heard some talks, that are just nearly impossible
 4 to recruit for.
 5 Hope that answers the question.
 6 DR. FARRAR: Interested in your thoughts on
 7 the randomized withdrawal structure, especially in
 8 the setting where maybe what we're trying to do is
 9 to overall reduce the amount of opioids that are
 10 chronic pain patients take. When I was seeing
 11 patients with chronic pain, I once a year would say
 12 let's try and taper down a little bit.
 13 Doing that in a blinded way, even in an N of
 14 1 kind of structure, or actually setting up a
 15 randomized withdrawal trial of some sort sounds
 16 like a reasonable way to go with the caveat that
 17 how you do the withdrawal is clearly a key feature
 18 of those. And I wondered what you or others might
 19 think about that.
 20 DR. ROWBOTHAM: Well, I think maybe Jennifer
 21 and Bob may want to change seats because he may
 22 want to tell you about his experience trying to

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1 recruit for this. I assume you're not talking
 2 about EERW type studies for experimental
 3 therapeutics because there, that's a little bit
 4 different.
 5 But I think if you try -- as soon as you
 6 talk to a patient -- because I tried this. I tried
 7 to do these studies. And as soon as you say one of
 8 the arms is going to withdraw your opioid, it's
 9 game over. I mean, it's just like, no. I maybe
 10 would think about a study that would increase my
 11 dose --
 12 (Laughter.)
 13 DR. ROWBOTHAM: -- but randomized decreasing
 14 dose, that's going to be hard.
 15 So that's just a difficult task to
 16 accomplish. We essentially have accomplished it as
 17 a society by just putting intense pressure on
 18 physicians to just not prescribe anymore, creating
 19 this whole class of opioid refugees that are in the
 20 various clinics, mostly academic clinics around the
 21 country. So I think that it's hard to get people
 22 to voluntarily sign up.

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1 I actually proposed a study that was going
 2 to use -- and I'm so glad it didn't get funded.
 3 Anyone heard of UROD, ultra rapid opioid
 4 detoxification? It's basically how the rock stars
 5 make it to the next gig when they get too strung
 6 out.
 7 Basically, you put the person under general
 8 anesthesia. You flush them out with naloxone. You
 9 have them under anesthesia. You keep their blood
 10 pressure stable and all the other things that the
 11 anesthesiologists in the room are so good at. And
 12 then you see what happens afterwards. You could
 13 put them on naltrexone at the end so they really
 14 perhaps couldn't relapse.
 15 Fortunately, that study wasn't funded, so I
 16 didn't have to actually do it. But it would be
 17 hard to recruit patients. It would be a very
 18 special patient. And I'm going to have to look at
 19 the one that Howard cited yesterday from Stanford
 20 because I think the only way you get a recruitment
 21 rate of people wanting to taper is you've got an
 22 access line with a very big funnel of all the

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1 opioid users so that those few people that are
 2 actually highly motivated and are actively looking
 3 to taper get to you.
 4 DR. FARRAR: If I could follow up with one
 5 other point. There's an interesting historical
 6 example of this, which is when Brompton's solution
 7 originally came out, he prescribed it as 1 teaspoon
 8 4 times a day, and then he just adjusted the dose
 9 based on how the patient reported. So the patient
 10 never actually knew what dose they were on. I
 11 always thought that was a really intriguing idea.
 12 I don't know how to implement that in clinical
 13 practice or in a clinical study, but it just was an
 14 interesting idea.
 15 MALE VOICE: You need a team of lawyers.
 16 (Laughter.)
 17 DR. ROWBOTHAM: Richard?
 18 DR. RAUCK: Yeah, Mike. Richard Rauck. I
 19 think things have changed with patients in our
 20 chronic clinics. We're a pretty busy clinic
 21 ourselves. Patients are much more receptive now to
 22 structured approaches. They actually are getting

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

7 So it's interesting that a reasonable number
 8 now -- and I think you could put in place, is what
 9 I'm trying to say to you, some of this. In our
 10 clinic, we bought this whole-body cryo machine. I
 11 don't know if it does anything. Maybe it's
 12 placebo, but you sort of say, maybe you can come
 13 down on your opioids if you do this, or we put in
 14 400 stimulators last year to your point on devices.

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

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

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

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

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

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

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

1 they took the dose and the pain got better.

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

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

11 Ajay?

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

22 So I think we definitely need to mention

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

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

13 Howard?

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

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

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

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

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

9 (Laughter.)

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

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

14 DR. ROWBOTHAM: Does anybody have a computer
 15 here?

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

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

21 DR. GILRON: Okay. Thank you.

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

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

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

5 Group Discussion

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

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

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

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

10 DR. GEWANDTER: Yes, you may.

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

16 DR. GEWANDTER: Yeah, I think so.

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

20 DR. GEWANDTER: Have what? Surgery?

21 DR. RAJA: Surgery.

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

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1 That's true. They do have surgery in there, but
 2 let's forget about surgery. So for the first one,
 3 Intervention X, meaningfully prevents the
 4 initiation of opioids in chronic pain patients.
 5 Sorry. I didn't retype them. But let's just
 6 pretend that these are substitute chronic pain
 7 patients for surgery, people with surgery.
 8 That would potentially obviously be a
 9 possibility. If someone comes to the clinic, and
 10 they've tried NSAIDs, and they've tried all these
 11 other things, one option might be to give them an
 12 opioid, but you could randomize them to an opioid
 13 or your experimental drug and see if they're able
 14 to avoid having opioids.
 15 Yes?
 16 DR. SCHOLZ: Joachim Scholz, still from
 17 Biogen. I think that would also be applicable to
 18 the acute pain because surgery is not the only
 19 situation where people are receiving opioids. It's
 20 the example that we have discussed because it's
 21 relatively straightforward to design a trial around
 22 it. I mean, there are other interventions or

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1 indications for which people receive opioids.
 2 DR. GEWANDTER: So I think your point -- if
 3 I can just make sure I understand -- is that when
 4 we talk about these hypotheses in the paper, we
 5 should avoid saying "with surgery" and just say
 6 with whatever acute pain condition.
 7 DR. SCHOLZ: It's one example, and it's the
 8 most
 9 frequently studied. It's easy to think about other
 10 situations where people receive opioids, otherwise
 11 we put the blame on the surgeons.
 12 DR. GEWANDTER: Yes?
 13 DR. RATHMELL: Jim Rathmell from Brigham. I
 14 know what you're trying to do is take the acute
 15 texts and mold it toward chronic. So I'm going to
 16 talk out loud for a minute and think about the two
 17 contexts that are really common in the chronic pain
 18 world. One is the decision, when all else has
 19 failed, whether or not to initiate chronic opioid
 20 therapy and how to choose patients who will do
 21 well. So that's one big context where we want to
 22 generate some hypotheses.

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1 The other is the patient who comes on
 2 opioids, persistent opioid use, for whatever
 3 reason, and they're referred for appropriateness.
 4 So the other hypotheses is how do we determine
 5 who's appropriate and who and how to Wean and taper
 6 opioids. So those are the two big contexts where
 7 the hypotheses will come in. And I think maybe if
 8 we start there, then we can fit them into
 9 the acute pain.
 10 DR. GEWANDTER: I think that the second
 11 scenario might fit in a little bit better with the
 12 newer hypotheses that weren't in the acute pain
 13 setting thing that we came up with. So I'm not
 14 sure if -- I think one thing that you brought up
 15 that we are not addressing here is the issue of how
 16 do you choose who should be in those studies. I
 17 think maybe if we could establish first what the
 18 hypotheses would be that we would be testing, then
 19 maybe once we finished that, we can discuss how do
 20 you choose who are the appropriate people to be
 21 putting in those kinds of trials, if that's okay.
 22 DR. FARRAR: I understand that maybe all of

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1 these, if we substitute chronic pain for surgery,
 2 have some applicability. The thing that clearly
 3 distinguishes the chronic pain environs is that a
 4 lot of the patients we see are folks already on
 5 opioid. So I think one of the questions that I
 6 would pose and interested in feedback is whether we
 7 would need some hypotheses that would relate to
 8 getting people off, or treating pain in a different
 9 way that would allow them to reduce the amount of
 10 opioid they're on or to --
 11 Now, I do have to say that most of the
 12 chronic pain patients who are reasonably treated
 13 for their chronic pain on opioids are not the
 14 problem. So I will voice a bias, which is that
 15 reducing the amount of opioid they're on might be
 16 useful if they're on a high dose because of the
 17 endocrinopathies and the other things that we know
 18 about. But if they're on a low dose, it's not
 19 clear that opioid sparing is necessarily
 20 beneficial. Even in that setting, it's clearly
 21 something we need to think about.
 22 DR. GEWANDTER: So I think maybe we can skip

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1 a little bit -- and I think it seems like people
 2 really want to talk about this, so let's talk about
 3 it. So for inclusion for these studies -- I think
 4 these three hypotheses that I have up here now are
 5 related to what you guys are talking about, where
 6 someone's on opioids and you're trying to either
 7 lower their dose, get them off, or number 3 is to
 8 prevent them from escalating their dose.
 9 So I guess the question is maybe we should
 10 talk a little bit about who are those people. Are
 11 they people that are having function problems
 12 because of their opioids? Are they people who are
 13 on just a numerically high dose that we don't think
 14 is good? Who do you think should be included? Two
 15 different people have brought that up. That's an
 16 important thing to talk about.
 17 DR. WASAN: To follow up on John's comment,
 18 I'll maybe have slightly different language here
 19 related to optimizing opioid care, to add that in,
 20 which may include some reduction in certain
 21 situations, might include keeping the same dose and
 22 doing more rigorous monitoring, all kinds of

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1 things. It might be the lowest effective dose, all
 2 sorts of things, because I think that would help a
 3 lot and tie together a lot more different study
 4 designs with the same goal of improved opioid care.
 5 DR. GEWANDTER: Ajay, if I can just try to
 6 see what you're saying. So you're saying maybe
 7 just tweaking the language a little bit. Instead
 8 of saying "withdrawal" or "dose reduction" to be
 9 using the language of optimizing instead.
 10 DR. WASAN: Yeah, and that may mean a whole
 11 variety of things, optimizing opioid care. So
 12 technically it's a little different than your
 13 definition of opioid sparing, but that seems to me
 14 a bigger overarching umbrella concept that would
 15 include more designs and promote a whole variety of
 16 higher improved standards or any kind of opioid
 17 research, and also include that concept of opioid
 18 sparing if you want to be that specific in the
 19 hypothesis.
 20 So, yes. It's a long answer.
 21 DR. GEWANDTER: What? Make it bigger?
 22 DR. RAJA: [Inaudible - off mic].

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1 DR. GEWANDTER: Thank you.
 2 DR. WASAN: Yeah. So there's dose
 3 optimization, but there's also care optimization.
 4 Those are related kind of ideas. It's a whole
 5 variety of things, just like taking care of a
 6 diabetic, prescribing insulin, there's a whole
 7 variety of things you do that are associated with
 8 good care.
 9 DR. GEWANDTER: I think part of that would
 10 be what is Intervention X, right? So
 11 Intervention X can either be a new drug or it can
 12 be some kind of care optimization scenario where
 13 you're trying to have a multimodal intervention
 14 that changes some other things to allow you to
 15 decrease -- to optimize your dose of opioids. So I
 16 think maybe we're getting a little bit in the
 17 weeds. We recognize that there are all sorts of
 18 different ways that these interventions can be not
 19 just a drug. I think we recognize that.
 20 DR. JAMISON: Just clarification. So we're
 21 not talking about how to taper opioids, and we're
 22 not talking about how to identify opioid misuse

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1 requiring tapering.
 2 DR. GEWANDTER: I think those are the two
 3 questions. One is how to identify the people that
 4 should be included, and one is how to actually do
 5 it. So I think in this paper, we could get into it
 6 a little bit, like what kind of inclusion should we
 7 be using and who's most at need to be in these
 8 types of studies. But I think in terms of how to
 9 taper, that would be potentially up to the
 10 investigator to decide what's the intervention? So
 11 a certain tapering strategy would be an
 12 intervention that you would be testing, or part of
 13 the intervention with whatever else, whatever drug
 14 you are doing.
 15 You guys can feel free to disagree if you
 16 think that we can be prescriptive about how to
 17 taper, but I'm not the person who would be making
 18 that decision for sure.
 19 DR. ROWBOTHAM: I think it might be -- if I
 20 could make a suggestion, to start out with a blank
 21 slide because we're looking at such a different
 22 situation, patients with chronic pain as opposed to

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

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

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

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1 on opioids developing a misuse or abuse disorder.
 2 So maybe that's a hypothesis worth putting in.
 3 DR. DWORKIN: Mike, I take your point, but
 4 I'm still stuck on the more classic randomized
 5 control trial. So just thinking off the top of my
 6 head, let's say we take patients with muscular
 7 skeletal, low back pain that are on somewhere
 8 between 100 and 200 milligrams, stably on 100 to
 9 200 milligrams of morphine equivalents.
 10 Given what Richard was saying about the
 11 patients he's seeing in his clinic, it seems to me
 12 we should be able to get them to agree to a trial
 13 of the following sort, that they're going to be
 14 randomized to one of 3 groups, continued on their
 15 stable dose of 100 to 200 morphine equivalent, a
 16 double-blind NSAID APAP kind of placebo but not
 17 really -- and may be better than placebo given the
 18 recent studies; and the third group is new compound
 19 that is thought to be potentially opioid sparing.
 20 The two groups that get either NSAID APAP or new
 21 compound, we taper them down to 50 percent of the
 22 dose that they came in with.

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1 I'm just kind of blowing off the top of my
 2 head here. We have two hypotheses that we test.
 3 One is that there's noninferiority of new compound
 4 to maintaining this initial dose and that pain goes
 5 up in the NSAID APAP group, which we kind of think
 6 as a surrogate for placebo.
 7 Now, that's a kind of standard,
 8 randomized-controlled trial where we're testing a
 9 putative opioid-sparing compound against a kind of
 10 placebo versus maintaining the dose that's at a
 11 level that, at least in the state of Washington, is
 12 considered too high.
 13 Is that not something anyone would ever want
 14 to do? Because to me, if someone would fund it,
 15 and I had a compound, it seems like an interesting
 16 clinical trial, or am I kind of barking up the
 17 wrong tree?
 18 DR. ROWBOTHAM: No, I wouldn't say that.
 19 It's just that we're kind of coming at the issue
 20 from different directions.
 21 DR. DWORKIN: No, that's right. No. What I
 22 just proposed is different than a pragmatic trial,

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1 and they answer very different questions. I'm
 2 thinking of having some -- and it doesn't have to
 3 be a new compound as some of us talked about at the
 4 break. I'm very interested in triple reuptake
 5 inhibitors, so I would love to do the study I just
 6 described with the third group being a triple
 7 reuptake inhibitor that I would hypothesize, allows
 8 the musculoskeletal patients to come down to 50
 9 percent of their dose while maintaining pain
 10 control, which we talked about this morning.
 11 So I don't know that anyone's going to do
 12 that trial, but I would be a little disappointed,
 13 personally, if our article didn't lay out those
 14 kinds of hypotheses and designs.
 15 DR. HAYTHORNTHTWAITE: Sorry. I was just
 16 having a sidebar. Never mind.
 17 DR. RAUCK: I'll add a little bit. I think
 18 there's some truth to what Mike was trying to say,
 19 is that those patients under that design paradigm,
 20 a lot of them are tempted [indiscernible]. The
 21 fallout dropout rate is huge because the people who
 22 perceive -- if compound Y or whatever isn't that

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1 good or not quite as good, they come in. And once
 2 you start that wean thing and they know it, it
 3 really can fall apart the trial.
 4 So that is part of it. They might be
 5 motivated first, and maybe that's okay; you'll find
 6 that out. I'm trying to think. Let's say
 7 anti-nerve growth factor was the compound that
 8 you're willing to look at. So if it has enough
 9 efficacy, it could be the perfect one, then maybe
 10 it's okay that the others fall out, and the ones in
 11 the third group will get anti-nerve growth, and
 12 it's great, and they do really well, and they wean
 13 right down, and that's your end game if it's potent
 14 enough.
 15 So I could see that, but Mike's Point is
 16 also right. We've been part of that trial trying
 17 to enroll patients who were going to sign up to
 18 voluntarily wean off, and it was not a good
 19 decision to try to find those people and all the
 20 efforts we spent. So I'm kind of mixed on this.
 21 You're right. I think describing that as an option
 22 makes sense, but I don't know that it's going to

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1 work in all scenarios.
 2 DR. DWORKIN: Richard, because of your
 3 experience, I didn't have a discontinuation group.
 4 It was tapered down to 50 percent. We'd want to
 5 have double-blinded Lomotil or some mildly
 6 constipating agent, so the patients didn't
 7 immediately realize they were in the group tapered
 8 off. And I'm tapering down to 2 active drugs, I
 9 guess either a triple reuptake inhibitor or an
 10 anti-NGF. And then a kind of pseudo but maybe not
 11 very placebo of NSAID plus APAP. It's a very
 12 different design than the one that just ended.
 13 I don't know that anyone's ever going to do
 14 it, but it would be cool to at least say this is
 15 the kind of thing that someone could do if they had
 16 a compound that they thought was potentially opioid
 17 sparing.
 18 DR. WASAN: I think that also points out the
 19 strengths or weaknesses of explanatory and
 20 pragmatic are the same question. Right? Because
 21 in that explanatory version, you still have
 22 significant placebo effects, of course, and placebo

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1 is really an active comparator for all of the
 2 endogenous analgesic systems that activates. That
 3 could always be criticized. You can never answer
 4 that aspect of it and what you kind of described on
 5 top of all the retention issues.
 6 So you can take that same hypothesis and say
 7 you could test it better in a pragmatic concept. I
 8 mean, either one. You could make your argument
 9 both ways.
 10 DR. DWORKIN: Ajay, I don't think you're
 11 right because there's no triple re-uptake inhibitor
 12 that Mike can test at Sutter, with the possible
 13 exception of a combination of Wellbutrin and an
 14 SSRI, but that's a little bit crazy. If I've got a
 15 triple re-uptake inhibitor or Ken has an anti-NGF,
 16 we just can't test that in a pragmatic trial.
 17 DR. WASAN: Right, for a new compound, yes.
 18 DR. DWORKIN: Exactly.
 19 DR. WASAN: I was thinking in the scenario
 20 of recycling some old compound, which you
 21 suggested.
 22 MALE VOICE: So again, thinking about I have

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1 a compound, let's say, hypothetically, in my
 2 pipeline for chronic pain. What you just said is
 3 probably what I'm going to need to do in order to
 4 have that entertaining adcom experience, as I would
 5 say is not necessarily entertaining, but to have
 6 that discussion about approval.
 7 Is 50 percent -- so you just threw out a
 8 number. If that's what I show with no difference
 9 in functional or those patients who were on that
 10 higher dose of opioids were functioning fine, and
 11 all I showed is I reduced it by 50 percent,
 12 function didn't change, patient said I'm not any
 13 better than it was before; my pain's not any
 14 worse, is that going to be sufficient?
 15 DR. DWORKIN: I'll stop talking, but I think
 16 the question you just asked is a great question,
 17 and my prediction is going to be the very most
 18 difficult section of what Jen is going to write.
 19 So you're right. I threw out 50 percent, but is
 20 that meaningful? Maybe we don't care whether
 21 they're on 160 of morphine equivalent versus 80, or
 22 maybe we do. In Washington, we do, but in New

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1 York, maybe not so much.
 2 DR. GEWANDTER: Deb has a question.
 3 DR. STEINER: Well, it's sort of a question,
 4 but yeah. Deb Steiner, Cambridge, still. What
 5 sponsors are going to do, we have, or Biogen has,
 6 Vixotrigine, Nav 1.7 blocker. Let's say they want
 7 to investigate whether there could potentially be
 8 opioid-sparing effects of some sort. From their
 9 vantage point -- I don't know that we're going to
 10 get to the granularity, but is it -- and it's a
 11 very similar question?
 12 What's the key? Is it that the
 13 tolerability -- you can taper the opioids. You can
 14 figure out the design exactly how you want to do
 15 it. But is it that you want to see that you're
 16 improving the things related to the opioid side
 17 effects, that discussion yesterday. Is it the pain
 18 intensity? Is it the functional outcomes? Is it
 19 everything?
 20 So I think there is really going to need to
 21 be some guidance on -- there could be primary and
 22 secondary endpoints. Maybe secondary endpoints

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1 could lead to labeling. It's a lot to undertake
 2 for people who are going into this and interested
 3 in it because I think there's a lot of commitment
 4 from sponsors working in pain to try to come up
 5 with novel analgesics, which are not opioids.
 6 So it's just the challenge of what should
 7 the key be because it can't be everything. And
 8 then, obviously, all this, well, everybody would
 9 love to do that dreaded -- the percent reduction.
 10 I just think there's so much, I'm not sure, again,
 11 whether that's the detail or whether there's a high
 12 level to start with. I'm done.
 13 DR. ROWBOTHAM: Let me just comment, and
 14 then maybe I'll just stop talking about pragmatic
 15 trials. If you're talking about things that could
 16 become standard of care or postmarketing studies,
 17 then this is the way to evaluate the impact of
 18 something in large, large, large numbers of people
 19 so that you can look at uncommon outcomes and see
 20 if there's an impact.
 21 So we heard a little bit yesterday about how
 22 cannabinoids have been legalized in some states,

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1 but not all. And so we're already in the midst of
 2 it's not a pragmatic trial because it wasn't done
 3 prospectively with thoughtfulness as to what you
 4 were -- or at least not that I know of -- what
 5 kinds of parameters they're going to be looking at.
 6 But you have this natural experiment going on where
 7 Colorado and now California and other states are
 8 legalizing marijuana, or cannabinoids, and we're
 9 going to see what the impact is.
 10 So all the pragmatic trial does is you think
 11 about it in advance, and you set up the way of
 12 measuring the outcomes that you want to look at
 13 before you impose the policy change, the practice
 14 style change, the formulary change, all those other
 15 things that you're going to impose. And the beauty
 16 of them is they're low cost per subject. And
 17 depending on what you're doing, you don't
 18 necessarily need to get individual subject consent.
 19 Nobody's really -- Congress or the state
 20 legislatures voted on the cannabinoids, and yes,
 21 we're in a democracy. But everybody who's trying
 22 marijuana now as a result of living in Colorado,

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1 they're not having to sign a consent form
 2 necessarily to enter into a study. So that's
 3 really the difference. We're talking about
 4 premarketing versus marketing or practice style
 5 issues.
 6 DR. GEWANDTER: I think Deb and then Roy
 7 have a comment.
 8 DR. STEINER: Sorry. I just thought of one
 9 more thing. What would you do in this situation
 10 where you have a new analgesic, and you may not be
 11 100 percent sure about whether there are any effect
 12 when you stop the medication or taper it, and you
 13 also don't know if there are any potential
 14 interactions with the medication?
 15 How is somebody going to weave in that type
 16 of thing to the type of study that a sponsor might
 17 consider? I just think it takes everything that
 18 we've been talking about and just makes it even
 19 that much more challenging because then you're
 20 talking about the side effects, and you're
 21 randomizing people, and giving Lomotil for
 22 potential side effects of the opioids, and what are

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1 the side effects of the drug that you're using? It
 2 just seems challenging.
 3 DR. FREEMAN: So the challenge over here is
 4 one of -- Roy Freeman, Boston. The challenge is
 5 one of endpoints. I see every endpoint as having
 6 substantial flaws. Bob's endpoint of opioid
 7 reduction, 50, 20, 90, 80 I think is really
 8 appealing to your congressmen. There are less
 9 drugs out there in the community, but what it
 10 actually really means in terms of -- your term,
 11 this meaningful prevention I think is almost
 12 impossible to ascertain.
 13 So that's the one, the opioid crisis
 14 endpoint, 50 percent less opioids out in the
 15 community. It would be a wonderful headline, but
 16 I'm not sure that it really means anything.
 17 There's the adverse event endpoint, which I
 18 think on paper sounds like a pretty reasonable
 19 endpoint. But as has come up once or twice, which
 20 do you prefer, nausea or constipation, vomiting
 21 or -- and how do you weight that endpoint? Is it
 22 going to be to use Deb's multicomponent composite

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1 endpoint? Do you get patients together to decide
 2 whether they prefer constipation, which will get 1
 3 point versus lots of vomiting, which will get
 4 3 points? It's really difficult I think to
 5 operationalize but perhaps worthwhile the effort.
 6 That to me is an appealing endpoint.
 7 Then there's function, and I think we have
 8 good measures of function, and I think we can use
 9 that. To me, that's possibly the most appealing
 10 endpoint. And then there's the hard endpoint,
 11 death. And usually death is very straightforward
 12 in a clinical trial. You're either dead or you're
 13 not.
 14 But here it's actually really tricky because
 15 one of the more interesting talks I thought was by
 16 the pulmonary guy. I'm sorry, I forget your name.
 17 And he raised the issue that there are actually
 18 several ways of dying. You can die from a
 19 voluntary overdose, suicide; you can die by a
 20 mistaken overdose, too much opioids, not enough of
 21 a 50 percent reduction; or you can die from too
 22 much pain, and pain results in respiratory

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1 depression.

2 So it becomes really complicated. You're

3 withdrawing opioids, you're causing more pain, and

4 that may result in your hard endpoint death, or

5 you're leaving patients on too much opioids, and

6 they're overdosing unintentionally, and there's

7 your hard endpoint death.

8 So this is a long way around to maybe

9 saying, well, maybe Michael, you have a point with

10 the pragmatic clinical trial. Patients will vote

11 with their feet. We don't really know how to

12 operationalize each one of these 4 endpoints, but

13 patients will know. And we'll come to a

14 conclusion, yes, with Bob's triple re-uptake

15 inhibitor or whatever we're doing, the one that's

16 available on the market. Patients prefer this or

17 that. But we won't -- and here's my problem with

18 pragmatic trials, and I really am a fan, is that

19 you come to the end of a pragmatic trial and you

20 say, well, what did we really learn over here? You

21 just lack of granularity that Bob's randomized,

22 placebo-controlled trial gives.

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1 DR. STACEY: Brett Stacey, Seattle. So I am

2 entertained by thinking about the Steve Passik

3 headline title I read, that I showed from 2007

4 about dose doesn't really matter because I've heard

5 people repeatedly tell me dose doesn't matter, yet

6 show me the study where it shows that higher doses

7 are associated with less mortality or more

8 function. They're not. Right?

9 So do you associate function, death risk,

10 adverse effects, the higher the dose, the more of

11 those who have? The data we don't have is that if

12 you reduce someone's dose, they slide down that

13 scale, and they now assume the risk at that lower

14 level. But no one can show me some big study that

15 shows higher doses are better for survivability,

16 for adverse effects, for function in general for

17 opioids.

18 So lower doses are safer. Everything we

19 could look at would say that. We don't have data

20 that says reducing is better and that's what the

21 idea of a clinical trial, is to say two things.

22 One is what interventions allow us to get to lower

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1 dose? And if we do get to a lower dose, is it

2 safer? Am I missing something with this? I know

3 we talk about, oh, it's for congressmen and other

4 people, but why is it not for people?

5 DR. ROWBOTHAM: I'm thinking through just

6 the last couple of comments. One thing that's come

7 up in some of our previous IMPACT meetings about

8 the problems in pain clinical trials, which is the

9 placebo effect and I think in a more general sense,

10 study power issues and recruitment difficulties.

11 One of the advantages of doing in-practice studies

12 is it gets you to large scale quickly, and you can

13 look at, without having to do all the work of

14 recruitment, just how malleable, just how much

15 change can be induced in certain outcomes as a way

16 of framing your studies.

17 So let's say -- and we've actually already

18 done some of this experiment. If you said 10 years

19 ago, or 12 years ago, gee, what would happen if we

20 got morphine equivalent doses down by 50 or 80

21 percent, and you proposed it as a study, well, one,

22 nobody would sign up for it. And if they did, it

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1 would just take you forever to recruit enough

2 subjects, and you'd have other issues.

3 Instead, the insurance companies and the

4 legislators did it for us. They said, "Guess what?

5 We're not going along with this anymore." And now

6 we can look at how much overdose deaths and other

7 kinds of severe outcomes have changed as a result

8 of that kind of experiment that's been imposed on

9 us.

10 So there are some framing questions that can

11 be answered by that without having the power issues

12 and the placebo effect issues in the classic

13 randomized trial. I mean, clearly, that's the

14 way -- if you really want to prove very specific

15 hypothesis, that's the only way you can do it is by

16 a properly randomized-controlled trial.

17 I'm just thinking more about the larger

18 societal issues and how to compare non-opioids with

19 opioids, behavioral interventions, all the

20 different kinds of things, is by having an agreed

21 upon set of definitions and outcome measures, and

22 then see what happens when they get rolled out in

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

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1 things -- especially the more I'm thinking about
2 what one would do as a company and trying to have
3 this beneficial to be able t study for a drug, I
4 don't see that it's going to work too easily. So
5 anyway, just a thought.
6 DR. RAUCK: It seems to me that both of
7 these have a lot of value as I sit now and think
8 about them.
9 Mike, to your point, we could take a North
10 Carolina point exactly when the legislature passed
11 some of the laws you're talking about and following
12 CDC guidelines, and in our clinic where we saw
13 48,000 patients last year, it'd be really
14 intriguing. And that's something NIH would fund, a
15 drug company doesn't care about.
16 We could come in and, look, how did it
17 change practice, and then to Brett's point, did it
18 change any pain relief? Did it really make a
19 difference or not? They might have functioned just
20 as well. How did it go, and look at that. I
21 think, Bob, yours are classic, we still have to do
22 for explanatory purposes, and the drug companies

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

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

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1 trial.

2 So Ken's going to put his anti-NGF into the

3 trial, and I'm going to put my triple re-uptake

4 inhibitor, and we'll let you know in 2 years which

5 of those drugs allows taper down to 50 percent.

6 DR. STEIN: Is that 2 years from concept

7 development?

8 (Laughter.)

9 DR. KROENKE: Just a comment on pragmatic

10 trials and clarification. There are several types

11 of pragmatic trials. Some of what you discussed in

12 its largest sense are not even trials. They're

13 using quasi-experimental, pre- and post-policy

14 changes. So whether that's a pre, post, or a

15 large cohort with a secular, it's useful. But then

16 other pragmatic trials might take clinics or

17 healthcare systems and randomize some hospitals to

18 one policy or intervention and one not. So that's

19 more aligned with large pragmatic trials.

20 Then there are effectiveness trials, which

21 takes a smaller number of people, which is usually

22 what we've done, 250 or 300, and randomizes them to

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1 a complex design, which is usually care management,

2 optimizing things versus usual care or something

3 like that. All of them are in the range of

4 pragmatic as opposed -- because they don't have

5 blinding, they have broader inclusion criteria.

6 You don't use specialized providers. You use the

7 providers that are there.

8 That being said, one limitation, the more

9 you get into the real world and saying you're not

10 going to consent, the problem is we have very few

11 of the measures we want in the electronic records.

12 If I was being a pragmatic trial in diabetes,

13 everybody gets A1cs. If I was doing it in a blood

14 pressure, everybody's got it.

15 Many electronic record systems don't

16 routinely have patient -- even measures

17 incorporated, much less function, much less adverse

18 events. About all you'll be able to get is, has

19 drug prescribing changed? Are we using less

20 opiates or more? And are we having less

21 diagnosable OUD by ICD, and are we having less

22 opioid related deaths?

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1 So I think that's a good design for looking

2 at the really bad outcomes, ranging from opioid

3 related mortality, which is the worst; opioid-use

4 disorder, which is intermediate; and persistent

5 opiate use in dose if we believe that's important.

6 I think a pragmatic design using large record

7 systems, thousands and thousands, would be good for

8 answering those more serious, less common events.

9 If we're interested in saying -- but it gives us no

10 idea about patient outcomes, or that patients have

11 better pain control, less adverse events.

12 So I think we need designs -- the large

13 thing you described would be good for those

14 uncommon, easy to diagnose events out of electronic

15 records probably before the ones that are going to

16 require measurement of pain control, adverse

17 events, have we optimized the regimen, and are

18 probably going to require patient enrollment and

19 consent probably at the level of hundreds of

20 patients, but not thousands. And that could be

21 pragmatic designs and not efficacy designs where

22 you have placebos. So I just wanted to clarify.

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1 MALE VOICE: Thank you for that.

2 DR. WASAN: I would just add one thing to

3 that. I guess number one, I think our

4 recommendations can be aspirational

5 because, for instance, Epic is actually getting

6 better at being able to capture patient-reported

7 outcomes at every visit, and some systems are

8 trying to use that enhance functionality of Epic as

9 an example for how to do that.

10 Then secondly, I think that the chronic pain

11 section is another opportunity to revisit this need

12 maybe for some different measures such as the

13 tolerability, idea of tolerability measure to

14 develop. The chronic pain session would be a good

15 place to mention that need because that can be a

16 good global summary measure that may help us answer

17 some of these questions.

18 DR. GEWANDTER: I'm sorry. Are you

19 responding to him? I'm sorry, I don't know your

20 name,, but he's been waiting.

21 DR. VERBURG: Ken Verburg from Pfizer.

22 Bob, I think you're taking the hard road on

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1 your triple re-uptake inhibitor. The first point I
2 would say is it's a very difficult. Unless you
3 already have evidence in your pocket that your
4 treatment is effective or as effective, most
5 patients -- in fact, most investigators won't take
6 a patient off something, no matter whether it's
7 appropriate or not. It's pretty hard.
8 So you need that foundational evidence, and
9 so you try to gather that in a forward manner,
10 randomized-controlled trial. The difficulty
11 nowadays, of course, is trying to randomize to an
12 active control that includes an opioid. IRBs are
13 not looking too kindly on 4 to 6 months of
14 continuous opioid therapy in patients that are
15 either naive to opioid therapy in the first place.
16 You've actually confounded the problem potentially.
17 But if your therapy is 50 percent as
18 effective as safe opioid therapy and you want to
19 test that in some fashion, I think it's a twofold
20 process, which is a randomized-controlled trial
21 with some estimate of what of what your efficacy is
22 relative to what standard of care of opioids is,

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1 and then you go into the database phenomena to see
2 how much combination therapy is used; is it lower
3 over the course of time.
4 I mean, that's the way that I would think
5 about it. So I wouldn't spend a lot of time, a lot
6 of pages of the manuscript on trying to use the
7 randomized withdrawal or lower dose effect. I just
8 think it's too doggone difficult. I'm not sure who
9 would go after that.
10 DR. DWORKIN: This is fascinating, Ken. I
11 would hypothesize and think it was worth testing
12 that -- forget about the triple re-uptake
13 inhibitor -- that tanezumab would make it possible
14 for patients with musculoskeletal low back pain,
15 who were between 100 and 200-milligram morphine
16 equivalents, to cut their dose in half. I think
17 that's reasonable.
18 Do you think we don't think that's
19 reasonable? I'd be surprised if you didn't think
20 that was a reasonable hypothesis.
21 DR. VERBURG: Well, ideally what you'd like
22 to have is an agent that's as fully effective. So

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1 the trials that go on now are actually patients
2 that have failed opioid therapy, found it to be not
3 as effective. They can't tolerate it or they don't
4 want to take it. So you're into a patient
5 population, which has gone through that process for
6 one reason or another.
7 If the drug is effective in that
8 population -- you've sort of surmised yourself -- I
9 think I have a sufficient body of evidence to say
10 that it's a pretty useful therapeutic maybe in
11 standard practice, but then you actually evaluate
12 it in terms of its effectiveness actually in the
13 practice conditions. If it's as effective as an
14 opioid or 50 percent as effective, you want to see
15 how that manifests itself in practice care.
16 I don't want to try to prove that in a
17 randomized-controlled trial. I just think it's too
18 difficult, given all the boundaries now around
19 what's appropriate opioid use or not. That's just
20 my notion on this.
21 DR. GEWANDTER: Actually, Ian had a
22 question, and Raj, and then Brett.

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1 DR. GILRON: Sorry, Bob, just to play
2 devil's advocate. We go through. This consensus
3 paper gets published in January of 2019, and it
4 inspires people to design a clinical trial of
5 tanezumab or something. So that gets funded and
6 ready to start in June of 2020. No, no, best case
7 scenario.
8 What do you think about the feasibility of
9 recruiting to a trial, I don't know, 50, 100
10 patients who are on a 100 to 200-milligram
11 equivalents morphine with low back pain? I'm being
12 devil's advocate in terms of this kind of study
13 hypothesis and trial design, and asking that in,
14 let's say, June of 2020, what's going to be the
15 number of patients, first of all, on that dose at
16 that point in time, and should we be inspiring that
17 kind of a study?
18 DR. DWORKIN: I have to defer to Brett and
19 Richard and others who see patients. My guess
20 would be that even in another year or two, they're
21 going to be plenty of patients with
22 musculoskeletal, non-specific low back pain on 100

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1 to 200 morphine equivalents. But if I'm wrong, I
2 certainly agree with you. We'd be proposing a
3 clinical trial that nobody could do because the
4 patients aren't out there.
5 DR. KATZ: I can provide a sort of answer to
6 that question, I think. Nat Katz. So people are
7 probably aware that there are 10 pharmaceutical
8 companies or so, plus or minus, that have gotten
9 together to do a large clinical trial on
10 opioid-induced hyperalgesia, where the entry
11 requirement was essentially that you're on roughly
12 that amount of opioid, and then you would get
13 tested for hyperalgesia. You get randomized to
14 either stay on your opioid or come off your opioid.
15 We did a lot of work with patients in
16 advance of that trial to try to figure out what
17 would entice you to enroll in a trial like. A lot
18 of work was done to try to figure out how to get
19 this done. And over a year and a half, the sponsor
20 spent certainly over a million dollars just in
21 patient recruitment costs, and they reached out to
22 something like 6 million individuals in a variety

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1 of different channels. And with all that
2 aggressive effort, in a year and a half, I think
3 they're randomized 19 maybe.
4 DR. DWORKIN: Nat, I want to respectfully
5 disagree. That's a very different trial. You were
6 telling patients that you were going to, on a
7 double-blind basis, bring them down to zero. My
8 trial -- actually, I think it's Ken's trial, but
9 I'll call it my trial -- is you're telling patients
10 you're going to reduce their dose by -- either keep
11 them on the same dose or reduce their dose by half
12 with a double-blinded drug that we hypothesize is
13 going to allow a 50 percent dose reduction.
14 I want to participate in my trial. I might
15 not have wanted to participate in your trial.
16 DR. KATZ: That's why I said it was kind of
17 a partial answer, so maybe you'll double the
18 recruitment rate or maybe even triple it.
19 (Laughter.)
20 MALE VOICE: [Inaudible - off mic]
21 (Laughter.)
22 DR. STACEY: I want to say one more thing

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1 about your trial. This is Brett.
2 DR. DWORKIN: And then I'll tell you about
3 another trial that you can all hate. I'm going for
4 two trial designs that everybody hates.
5 DR. STACEY: With your new analgesic drugs
6 that are coming to market, when you test them in
7 your ideal subject population, perfectly screened,
8 exactly what you want, what's the NNT? What's the
9 numbers needed to treat to get a significant
10 clinical response?
11 DR. VERBURG: Your response definition is 50
12 percent reduction. It's 1 in 15, 1 in 25.
13 DR. STACEY: Yeah. So that's going to be
14 really challenging when you get to your chronic,
15 high-dose opioid patients and start tapering them
16 down where most of them are going to fit. And
17 there's going to be a little subset that succeed.
18 So this is challenging with that when it comes to
19 actually conducting it. It's not like a regular
20 study where we're just adding something on. If you
21 don't work, oh well, it doesn't work.
22 We're adding and taking at the same time,

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1 and adding something that has a half chance of not
2 being anything. And if it is something, it may be
3 a completion, but often it's going to be a dropped
4 pass. So it's going to cause a lot of clinical
5 study disruption.
6 DR. GEWANDTER: Raj has been waiting, and
7 then back there, too.
8 DR. RAJA: I thought Ian would say this, but
9 this has been somewhat looked at in this New
10 England Journal article, which was using drug X,
11 using drug Y, which is an opioid, and the
12 combination. In that, you showed that the
13 combination reduced opioid effect -- I mean,
14 reduced the opioid dose. However, at least within
15 that sample size, you were not able to show a
16 difference in the adverse effect profile.
17 So I think this is a crossover design, a
18 kind of a trial that has been done in the past.
19 Maybe you can comment a little bit more on that.
20 DR. GILRON: Well, the thought did go
21 through my mind, and it reminds me back to what
22 Mitchell Max wrote like in the mid '90s in an ISP

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1 supplement, talking about combining opioids with
 2 other drugs. So they've been talking about this
 3 for a while.
 4 I didn't think of an opioid-plus drug X
 5 combination trial as an opioid-sparing trial. And
 6 it comes back to what I was asking about in the
 7 morning, which is, that wasn't the purpose of the
 8 trial. The purpose of the trial was can we get
 9 better analgesic efficacy without worsening side
 10 effect profile.
 11 So it ends up being a demonstration of
 12 opioid sparing, and the bonus, we can argue whether
 13 it's clinically relevant, was that we got lower
 14 pain intensity scores with the combination without
 15 the worsening side effect profile, which is -- it's
 16 kind of the -- you're proposing I guess an add-on
 17 design because they're already on the opioid, which
 18 is fine. But your endpoint, I believe, is
 19 opioid-dose reduction without making anything else
 20 worse.
 21 Is that correct? So it's a different goal,
 22 but it looks the same.

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1 DR. SCHOLZ: In light of the discussions
 2 that we have, I think the hurdles for opioid
 3 reduction as a primary outcome measure are really
 4 high. We do not have validated assumptions about
 5 what is meaningful. There's some uncertainty which
 6 adverse effects would be the target that we should
 7 seek or whether composite measures are better than
 8 single measures.
 9 So I think it's more realistic to look at
 10 trial designs that have analgesia as a primary
 11 outcome measure and then opioid reduction, and you
 12 can define that as you like, as a secondary outcome
 13 measure. It would also be easier to calculate
 14 sample size, efficacy, and so forth, simply from a
 15 design perspective.
 16 DR. DWORKIN: Mike, can I ask you a
 17 question? I know you've thought a tremendous
 18 amount about tolerance, and outside of the
 19 preclinical realm, what evidence do we have in
 20 people that opioid tolerance occurs? Now
 21 everybody, I guess, thinks it occurs because
 22 patients increase their doses over time to

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1 apparently maintain the same level of analgesia.
 2 So I'm really changing the subject here. Is
 3 another possible type of opioid sparing a drug that
 4 prevents or reduces up-titration? Jen and I were
 5 talking about this at the break. Wouldn't that be
 6 sparing if Richard takes a patient who has failed
 7 everything and decides he wants to try not very
 8 much oxycodone, let's say 40 milligrams a day, and
 9 we now put that patient on agent X -- I'm not going
 10 to use examples anymore -- and agent X versus
 11 placebo actually prevents the need to titrate up
 12 the 40 milligrams of oxycodone versus placebo?
 13 Those patients creep up over 6 months.
 14 So would that be another kind of opioid
 15 sparing that we haven't talked about, the
 16 prevention or the decrease of apparent tolerance
 17 over time?
 18 DR. ROWBOTHAM: Well, I would think so just
 19 because you end up at lower doses.
 20 DR. DWORKIN: Has anyone done --
 21 DR. ROWBOTHAM: If we're considering that as
 22 being one of the ways of measuring opioid sparing,

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1 that you'd just end up on a lower dose, assuming
 2 that the pain control is identical.
 3 DR. DWORKIN: Exactly.
 4 DR. WASAN: Well, one of the things it makes
 5 me think about is that upper titration is not
 6 necessarily the norm anymore, especially with all
 7 the ceilings and limits. Going beyond 90 is
 8 something that's unusual now. It's a strawman in a
 9 way to say that we have a natural history, is that
 10 it's going to be up-titrated when it may not
 11 necessarily because it's really so provider
 12 dependent as a standard practice.
 13 DR. DWORKIN: To go back to Brett's point,
 14 Brett would rather -- his patient is on 40, then
 15 90. So even within that below 100 realm, one could
 16 imagine that 40th day of oxycodone is preferable to
 17 the 90th day of oxycodone.
 18 DR. WASAN: You could, but the data for
 19 that, the differences between low and moderate
 20 dosing right up to 50, and then 50 to 90 for
 21 instance, is very little in terms of what are the
 22 incremental benefits, while in theory, yeah, there

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

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

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

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

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

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

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

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

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1 and there it is. But I would think if we're really
2 doing a clinical trial setting, we would want
3 measures of anxiety, depression, sleep, some
4 estimate of function. I mean, these are basic
5 things, but you can have questionnaires that are
6 pretty darn short that address those things, that
7 are done routinely.
8 MALE VOICE: [Inaudible - off mic].
9 DR. KROENKE: Just to modify what I said a
10 little bit before -- and maybe it was -- I can't
11 recall whether it was Ian who said some healthcare
12 systems are now routinely incorporating
13 patient-reported outcomes in their health records.
14 For some, it's PROMIS. For some, it's other things
15 like grief depression screens or pain screens.
16 So without stating the obvious, obviously
17 you want pain measures as an outcome. And if
18 you're going to do large studies and pragmatic
19 measures, you could decide to use it in healthcare
20 systems that have routinely recorded at least some
21 minimalistic patient-reported outcomes of which
22 pain and depression tend to be the most common.

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1 Then you could link it to prescribing. So as
2 prescribing changed, people who have reduced
3 opiates, or have less lower doses or higher doses,
4 you could then track those outcomes. So another
5 way is do that kind of trial in systems that are
6 all routinely capturing that.
7 DR. ROWBOTHAM: Right. So if I could expand
8 on that and transition into another field, now, for
9 the targeted therapy oncology trials, you really
10 need to have your patient's tumor fully
11 characterized through mutational analysis, sent to
12 Foundation Medicine or some other one. That's a
13 little bit what I'm trying to get at, even though
14 we don't have those kind of markers for pain. But
15 those are the things that, let's say a sponsor came
16 to us and said, I'm interested in doing a trial
17 with these characteristics for our new compound.
18 Tell me how many patients in your clinic or your
19 health system has all this information.
20 So that gets to what you're talking about
21 with A1c, because if you're trying to do a diabetes
22 trial and you're saying, well, you're looking at

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1 random glucoses, that's the hard way to do it,
2 whereas if you just look in the electronic chart
3 and say, well, we have a thousand patients who
4 still have A1cs over 8, then bingo, you're just
5 like ready to roll to get ready to start enrolling.
6 So that what I'm trying to get at here.
7 What are the data points? What potential outcome
8 measures would we want to have accessible to us so
9 that we could characterize our patient populations
10 quickly as preparatory to more focused studies?
11 Did that capture your comment?
12 DR. KROENKE: Well, I was thinking actually
13 outcomes in studies. Now, if you're looking at it
14 to identify potential subjects for studies, if a
15 large healthcare system like Kaiser or Cleveland
16 Clinic, as Mayo Clinic -- a number of healthcare
17 systems have started incorporation -- you could say
18 give me all of the people with ICD codes of
19 musculoskeletal pain or low back pain who have 2
20 consecutive pain scores on PROMIS or other pain
21 scores at a certain threshold. Then you'd say, we
22 got 2000 people like that.

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1 So we have a sufficient population of
2 persistent pain. That would be the A1c equivalent.
3 You could also, if you did a pragmatic trial, look
4 at the relationship of those scores in patients
5 with those conditions in relation to prescribing
6 changes.
7 DR. ROWBOTHAM: Right. That's the key point
8 that you made, really, really key point, which is
9 you get a single measure that is relatively
10 unchanging, like mutational analysis of the
11 tumor -- If there's a driver mutation, they tend
12 not to go away -- versus serial measurements, which
13 are a study in and of themselves, potentially, if
14 you're doing correlations, but are even better at
15 prep to research because you can start looking at
16 the dynamics and characterize the population even
17 much more precisely by having serial measures.
18 Is that what --
19 DR. KROENKE: And some of those systems that
20 are incorporating this also have a few other brief
21 measures, like the PROMIS 10 or some physical
22 function, which have items on sleep and fatigue and

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

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

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

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

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

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

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

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

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

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

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1 DR. SCRANTON: This is Richard. I was
2 intrigued by what you said, Richard. Some patients
3 were willing to go down to zero, and they must have
4 suffered some to get there, to then be put on
5 something that they perceived a benefit. So what
6 is that patient-reported trade-off that they are
7 willing to do? That's what I want to be able to
8 measure, because maybe it is going from 10 to 5 or
9 10 to zero or 100 to 50. It may not matter, but if
10 I could capture that motivation.

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

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

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1 right. In the other trial where all it was, was,
2 hey, here's a the trial where you either continue
3 on your opioid or you're going to be weaned off,
4 and maybe you will be better when you come off,
5 which happens. I mean, we've always seen that.
6 But try to talk them into that, you've got to have
7 something else. I think they're savvy enough.
8 These patients, like I said, somehow, body language
9 or something, we convinced to them whether we
10 really think it may be worth coming off it.
11 DR. GEWANDTER: So maybe what you're saying
12 is for research agenda, actually asking patients
13 what they're hoping for when they come off their
14 opioids or what they're expecting might be a good
15 research agenda.
16 DR. ROWBOTHAM: Question way in the back.
17 DR. SANDBRINK: Sandbrink, Washington, D.C.
18 VA. In the VA system, we've taken a lot of
19 patients down. And I think nowadays, the
20 communication and the discussion with the patient
21 has gotten much, much easier. So your experience
22 from a few years back is not necessarily what it is

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1 nowadays because patients realize that there is an
2 opioid crisis, and they perceive it more of
3 something that could potentially affect them as
4 well. They get much more input by their families
5 and caregivers who are concerned about these opioid
6 medications that this patient has.
7 So the discussions with the patients have
8 gotten, at least in our setting, somewhat more
9 easier. And maybe that's easier, in part because
10 our healthcare system in the VA, everybody talks
11 with the patients now in the same language. The
12 primary cares and the pain specialties, we do have
13 the same approach as we express caution about
14 opioids, and we ask our patients how motivated they
15 are.
16 A few years back, I think the common notion
17 was that no patient really wants to come off. And
18 often nowadays still that is the assumption that
19 providers have, "Oh, my patients don't want to come
20 off." But when you actually ask them, there's
21 actually quite a bit of motivation to reduce the
22 dosage out there. I think we have to ask all these

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1 patients now -- not a few years back and take what
2 it was a few years ago, but we have to ask them now
3 about where are you in this continuum of being
4 motivated to come off and of change.
5 DR. CRAIG: Hi. It's Kevin Craig from GW
6 Pharmaceuticals. I've been listening with interest
7 to this idea of what patients will go through to
8 get off the opioids, to get onto a new treatment.
9 And I think in clinical practice, that's
10 fascinating. My concern about that in a
11 trial -- and it's probably something that ought to
12 be studied -- is that really ramps up the
13 expectancy. And with expectancy comes placebo
14 response.
15 So getting a sense of if someone's gone
16 through 2 weeks of withdrawal to get onto a trial,
17 I wonder what that would be like in terms of the
18 placebo effects as well.
19 DR. RAUCK: So I think that's fair. That
20 probably is true for sure that you might have that.
21 But there's one big advantage to doing it that way,
22 is you can do that before you randomize so you

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1 don't have the dropouts. So if they don't make it
2 or they can't come off, while you're not supposed
3 to do that, anticipating coming into the trial, you
4 can still do it before you randomize them. So it
5 does help you in dealing with that part of it.
6 DR. ROWBOTHAM: Actually, that's another
7 good point, though, in terms of outcome measures
8 that we should be capturing
9 more routinely. For example, there's a lot of
10 anesthesiologists in this room, so I assume the sum
11 total of epidural steroid injections is probably
12 pretty high.
13 Do you guys look at whether or not the
14 patient reduces their opioid dose in the month
15 after the epidural? They don't.
16 DR. RAUCK: It's whether they pay their
17 bill.
18 (Laughter.)
19 DR. ROWBOTHAM: Yeah, exactly. That's
20 right.
21 But that's an important point because we do
22 a lot of interventions, and we don't tell the

1 patients, okay, you just had the intervention.
2 Now, I want you to cut your opioid dose in half
3 immediately. In clinical trials, I'm just curious,
4 we've talked at some of these meetings about rescue
5 medication use, especially when the rescue
6 medication is a low potency opioid, but we're
7 really not capturing that data just in routine
8 practice where we're all the time introducing
9 things, where we're really not checking to see,
10 okay, the person responded to the triple uptake
11 inhibitor or combination to effect the same. Did
12 they then start spontaneously reducing their
13 opioid? Yes or no?
14 We don't really have that information, and I
15 don't think we necessarily get it in the clinical
16 trials, especially the compounds that are in phase
17 2 because you may be excluding people on opioids or
18 they're on really low doses of opioids and not
19 necessarily likely to go off.
20 DR. GEWANDTER: So I think we've got
21 probably enough to start a draft of a paper. So
22 unless anyone has anything they really want to

1 bring up or air now, maybe we could end a little
2 early. It's getting late. And obviously, if you
3 have any other ideas that you want to send to me
4 before the first draft is drafted, you can feel
5 free to do that. You can find my email on the
6 Rochester webpage, or you can ask Valorie. She
7 knows my email.
8 So unless anyone else has any burning things
9 they'd like to bring up, maybe we should end here.
10 (No response.)
11 Adjournment
12 DR. GEWANDTER: Okay. Thank you all for
13 your participation.
14 (Applause.)
15 (Whereupon, at 3:40 p.m., the meeting was
16 adjourned.)
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