FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC)

Thursday, November 15, 2018

7:59 a.m. to 4:09 p.m.

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(7:59 a.m.)

Call to Order

Introduction of Committee

DR. BATEMAN: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, or any other devices if you've not already done so. I would also like to identify the FDA press contact, Michael Felberbaum. If you are present, please stand.

My name is Brian Bateman. I'm the acting chairperson for this meeting. I will now call the Anesthetic and Analgesic Drug Products Advisory Committee meeting to order. We'll start by going around the table and introducing ourselves. We'll start with the FDA to my left and go around the table.

DR. CAVAZZONI: Patrizia Cavazzoni, deputy center director for operations.

DR. STEIN: Peter Stein, deputy director, Office of New Drugs, CDER.

DR. HERTZ: Sharon Hertz, director of the

Division of Anesthesia, Analgesia, and Addiction Products in the Office of New Drugs.

DR. HORN: Pamela Horn, clinical team leader, same division.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the associate director for public health initiatives in the Office of Surveillance and Epidemiology.

DR. MICHNA: Ed Michna, pain physician, Brigham and Women's Hospital in Boston.

DR. LITMAN: Good morning, Ron Litman. I'm an anesthesiologist at the Children's Hospital of Philadelphia and the medical director of the Institute for Safe Medication Practice.

DR. GOUDRA: Basavana Goudra, anesthesiologist in pain medicine.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. BATEMAN: Brian Bateman. I'm an anesthesiologist at Brigham and Women's Hospital and an associate professor at Harvard Medical School.

CAPT BUDNITZ: Dan Budnitz, a medical officer and lead the medication safety program at the Division of Healthcare Quality Promotion, CDC.

DR. McCANN: Mary Ellen McCann. I'm a pediatric anesthesiologist at Boston Children's Hospital and associate professor at Harvard Medical School.

DR. SHOBEN: I'm Abby Shoben. I'm an associate professor of biostatistics at Ohio State.

DR. ROSENBERG: Jack Rosenberg at the University of Michigan and Department of Veterans Affairs. I'm an anesthesiologist, pain specialist, and addictionist.

DR. LORENZ: I'm Karl Lorenz. I'm with the Palo Alto VA at Stanford University. I'm a professor of medicine and palliative care physician, as well as a health services researcher.

DR. SUAREZ-ALMAZOR: Good morning. Maria Suarez-Almazor. I am a professor in general internal medicine, University of Texas, MD Anderson Cancer Center.

DR. FLOYD: James Floyd, general internist

and epidemiologist at the University of Washington.

DR. HIGGINS: Jennifer Higgins, acting consumer representative to AADPAC.

MR. O'BRIEN: Joe O'Brien, president and CEO of the National Scoliosis Foundation, patient representative, also a scoliosis patient recovering from my sixth final surgery.

DR. HERRING: Good morning. I'm Joe Herring, a neurologist, associate vice-president of clinical nerve science at Merck and the industry representative to the AADPAC.

DR. BATEMAN: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until after its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Moon Hee Choi, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Anesthetic and Analgesic Drug Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry

representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when

the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves the assessment of opioid analgesic sparing outcomes in clinical trials of acute pain. The committee will be asked to comment on the trial design and endpoints of these studies and how to determine the clinical relevance of the results.

This is a particular matters meeting during

which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. William Herring is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. His role at this meeting is to represent industry in general and not any particular company. Dr. Herring is employed by Merck & Company.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow

the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Chad Brummett has acknowledged he has served as a consultant to Heron Therapeutics and Recro Pharma. In addition, he has served as principal investigator, co-principal investigator, and co-investigator of several federal funded, state-funded, and institutionally-funded studies relating to opioids for pain management, opioid dependence, chronic pain self-management, and genomics initiative.

Additionally, Dr. Brummett has had involvement with a patent related to peripheral perineural dexmedetomidine and he receives no royalties.

As guest speakers, Dr. Chad Brummett and Dr. Terri Voepel-Lewis will not participate in committee deliberations, nor will they vote.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or

imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussions. Thank you.

DR. BATEMAN: So we will now proceed with the FDA's introductory remarks from Dr. Sharon Hertz.

FDA Introductory Remarks - Sharon Hertz

DR. HERTZ: Good morning, Dr. Bateman, members of the Anesthetic and Analgesic Drug Products Advisory Committee, invited guests. Thank you for coming to this meeting of the AADPAC. You're hearty souls to get here today, and we appreciate that effort.

Today, we will be discussing the assessment of opioid analgesic sparing outcomes in clinical trials of acute pain. Opioid analgesic sparing is a topic that has become an area of interest in drug

development as one more way to address the opioid crisis as well as improving patient safety and comfort in the setting of acute pain management.

Today, we hope to get some clarity on what opioid sparing actually means and how developing this area can be useful to patients and to the public health.

There are two concepts often included under the heading of opioid sparing. One is the idea of replacing opioids with alternative non-opioid analgesics. One way to reduce the risk of opioid-use disorder from opioid analgesics is to reserve the use of opioids to only those situations where alternative analgesics are not likely to adequately manage the patient's pain.

It's reasonable to consider that reducing the number of people exposed to opioids reduces the risk for developing opioid-use disorder in vulnerable patients. Not prescribing opioids when alternatives may be sufficient also can help reduce the amount of opioid analgesics in the home and in the community, which as we know is a source for

diversion and abuse.

Opioid sparing in this context can be demonstrated in a clinical trial by a reduction in the number of patients who require the use of opioids. While there are obvious advantages to avoiding the use of an opioid analgesic, as an inpatient, as discussed during a prior advisory committee meeting, which some of you attended, avoiding the use of an opioid analgesic while hospitalized, but then being prescribed an opioid for outpatient use, does not have the same opportunity for benefit from a public health perspective as not being prescribed an opioid analgesic in both inpatient and outpatient settings.

Another concept is reduction in the amount of opioid used such that patients experienced fewer opioid-related adverse events. Less sedation, a shorter period of ileus, less nausea and vomiting, and better participation in physical therapy or other activities can contribute to earlier discharge from the hospital for post-operative

patients. Less opioid analgesic use can be particularly helpful for patients who are more susceptible to respiratory depression.

However, we have to be careful that the evaluation labeling of opioid-sparing properties for novel analgesic products reflect clinically meaningful outcomes. We have preliminary data that are being followed by a study FDA is conducting indicating that some prescribers have misinterpreted some of the terms we use, in particular abuse-deterrent formulations, thinking that these mean the products are safer or non-abusable. And we want to avoid developing a situation where the concept of opioid sparing is misunderstood. So today, we're hoping to have you help us define how it can be used and how it can be meaningful.

Thank you for taking time from your busy schedules. We appreciate you being here very much and look forward to the discussion.

DR. BATEMAN: Both the Food and Drug Administration and the public believe in a

transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including BIO's non-employee presenters, to advise the committee of any financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We'll now proceed with the BIO presentations.

Industry Presentation - Richard Scranton

DR. SCRANTON: Good morning. My name is Dr. Richard Scranton. My interest in research on this topic began as a lieutenant commander in the medical corps in the United States Navy and continued that interest as I served as assistant professor at Harvard in the Division of Aging.

Today, I will be talking about the methodologies for determining opioid sparing in acute pain models, where I currently serve as the chief medical officer of Pacira Pharmaceuticals. The views I will be discussing are expressed on my own and not necessarily that of the company's.

So opioid sparing in acute pain management is multidimensional, as Dr. Hertz spoke to, and there are really two outcomes in consideration for opioid sparing. One is ascertaining the short-term benefits in determining the clinically meaningful benefit of improving or reducing opioids, but also the consideration as a long-term benefit, reducing the exposure to patients chronically.

The short term, I believe, is attainable in

our phase 3 clinical studies, as I will describe, where you can assess the outcome in as few as 100 patients, but the long-term benefit is a bit more challenging and where a larger sample size would require upwards of around 1,000 patients and would be probably more ideal for a phase 4 postmarket study.

So when we talk about opioid-sparing claims in the short term, it really does focus on the reduction in opioid-related adverse events and improvement in functional outcomes. The construct I would argue of opioid sparing is really that evaluating pain scores in opioid consumption alone is not sufficient. As we know, more opioids will reduce pain. They're effective in analgesics, but they will come at a cost of increasing opioid-related adverse events.

Reductions in opioids, however, without other mechanisms to control their pain is also not ideal. We do not want to go back to a time where patients arrive in pain after surgery because that could also lead to detrimental impacts on

improvement in functional outcomes.

It's also conceivable, based on the research of many, that avoiding opioids in the acute phase could lead to a reduction in persistent use. We know, from a single day, administration of opioids can change the neurochemistry of the brain and, and particularly for those patients who are prone or at risk, that may lead them to become persistent opioid users. But we also know from others that if we can reduce exposure from 1 day versus 7 days, that also will reduce the risk by 2X. We know that for patients who consume either high-dose opioids for greater than 7 days, they have 2 times a greater risk of consuming opioids chronically after 1 year.

So perhaps a meaningful reduction or opioid free in the first post-operative week would be meaningful as a surrogate endpoint for long-term persistent use.

The three elements necessary to demonstrate opioid sparing in the short-term would be first demonstrating equivalent or some sufficient

evidence of equal analgesia between the interventions; reductions in opioids as defined as opioid free or combination of total reduction in morphine equivalence; and then improvements in side effects and functional measures.

This is important because all of these are interrelated. Pain, the opioid use, and side effects, and the functional measures are interrelated and patient specific. But most important, assessment could be based on a responder analysis, where you could obtain adequate pain relief, minimize opioids, and then determine a clinically meaningful analgesic benefit.

What could we use for outcomes? We could look at MedDRA-preferred terms in our phase 3 clinical trials, looking at adverse events such as nausea, vomiting, pruritis, and somnolence, or look for surrogate endpoints from respiratory depression such as hypoxia or hypercapnia, or functional assessments, or using some outcome measures such as time to discharge or ambulation.

However, I would say that the adverse events

from trials alone probably are not sufficient. As we do know, they're not consistently measured across the sites. It's oftentimes the physician making the determination of the severity of the adverse event, and that may not necessarily reflect a patient's perspective on how bothersome that adverse event was. And oftentimes, these cannot be adjudicated. The solution would be perhaps to consider validated patient-reported outcome measures.

Here, I list several patient-reported outcome measures that have been validated in an acute pain setting, and they do span different domains. The Overall Benefit of Analgesia, a simple measurement tool, looks at pain and satisfaction in opioid-related adverse events. The Quality of Recovery 15and the Brief Pain Inventory look across the four different domains. And the Pain Treatment Satisfaction Scale, interestingly, not only covered all these domains, but also was trying to get at a medication preference from the patient, although I would say that was the least

correlated.

Then if we want to just look at a specific tool of a patient's reported outcome measures with regards to the distress from opioids, that could be the ODS for opioid-related adverse events.

Let's just take a theoretical look at one of the instruments or the overall benefit of analgesia. It's a 5-point Likert scale. It asks the patient about their pain at the time. And then the developers looked at the symptoms that patients reported to be most bothersome to them, such as vomiting, and itching, and sweating.

Then finally, it asks the patient about their satisfaction on their pain treatment. And we hope, from the fact that you're asking these patients these questions at the same time, the patient begins to take that into context in their response.

So this simple scoring measure, a lower score would be greater benefit or appreciation of management for their pain.

Let's look at an example here. This is the

opioid use by day in patients who are having a total shoulder or rotator cuff surgery after the intervention was with a brachial plexus nerve block versus a placebo.

In this case, the active comparator is opioids. Both groups have access to opioids. In blue is individuals who had placebo. So I would argue that a total shoulder rotator cuff is a very painful procedure in which the pain requires opioids for the majority of patients to manage their pain, and that's oftentimes the standard of care across the country.

You can see in the first 0 to 24 hours, that a significant percentage of patients -- we have the percent of total on the left and morphine equivalence on the horizontal access, and you can see the majority of patients are requiring 30, 40, 50 morphine equivalence to manage their pain. And that does persist, but it does decrease from 24 to 48, to 48 to 72 hours.

Compare that with the intervention arm. What we're seeing is an observation where the

percentage of patients who require little to no opioids are being shifted to the left. A higher proportion of patients were requiring maybe 10 morphine equivalence to manage their pain for the first 24 hours, and that persists through 24-72 hours.

But in this trial, the outcome was differences in analgesia. So in this exploratory analysis I'm sharing with you today, it's to look at the subset of patients who actually received the intervention but now have similar pain scores. And we divide this in two groups, so that now we're looking at equal analgesia, but now the only difference being the opioid consumption. So again, all these groups did receive the intervention.

So here we can see the pain is VAS for the first 24 hours, about 134, so equal in both groups. That equates to about a pain score of about a 5 on an 11-point Likert scale.

Now, you can see the difference is just the amount of opioids consumed, a pretty marked difference in opioid consumption, and that

correlates with an improvement or difference in the OBAS. Typically, a change in 2 would be clinically meaningful in the OBAS. This is a much larger improvement in the OBAS, and that also suggested a greater analgesic satisfaction; so just an example in which you could demonstrate this is a phase 3 clinical study.

Another way to consider this is yet another painful model, a total knee arthroplasty, and looking at functional outcomes, which is what we all hope to obtain after having a knee surgery, is high functional recovery.

In this case, this was an intervention of a long-acting local anesthetic as a periarticular infiltration compared to an immediate-release bupivacaine periarticular infiltration.

What we're observing here in the first 0 to 48, 0 to 72 hours, 10 percent of the patients who received the intervention were opioid free compared to the bupivacaine. Again, here, the active comparator is opioids. And also that demonstrated total opioid consumption was markedly reduced for

the first 0 to 48, to 0 to 72 hours.

Looking at two different outcomes are functional measures, one using a discharge readiness score. It was a standardized score using a multitude of studies that links the ability of patients to ambulate, whether they're having nausea or vomiting. A greater percentage of patients met discharge readiness criteria, 42 percent versus 27 percent. This also equated to greater patient satisfaction with their overall analgesia care.

Here's the hypothetical example of an ideal opioid-sparing design. We have the treatment arms to evaluate opioid sparing. We have the test product, whatever the new entity is. The standard of care here would be the opioid comparison because that is what we're trying to reduce. And also, I'm suggesting we use placebo because we know that in pain trials, there is a significant placebo effect.

The surgical model, then, would be procedures that are associated with moderate to severe pain, where high-dose opioids are a necessary component of contemporary pain

management.

The placebo group, therefore, would need opioid rescue, and depending upon the intervention, the biological plausibility of how long that duration of effect of the intervention will be, you would expect the pain duration to match that, so in this case, 24 to 72 hours.

The hypothetical trial outcome would be this, one, that we know in all clinical trials in pain that a proportion of patients will not have adequate pain relief, so that will drop out in both arms.

The second would be there will be a proportion of patients that will require none or minimum opioid use. You would expect that to be a greater group of people to meet that in the test product if it's having good analgesic. And the standard of care arm would have to take more opioids to obtain that same adequate pain relief.

Then we would take an agreed-upon favorable score in a global assessment of analgesia, some of the measurements we talked about, and there again,

we would see a greater proportion of patients being able to obtain that ideal outcome compared to the standard of care, which would then result in a successful composite endpoint of a difference of 50 percent to 25 percent. And that was an adequately powered study of around 100 patients per arm and would allow us to obtain that outcome.

The conclusions on the methodologies of short-term benefits of opioid sparing, demonstrating short-term benefit of opioid sparing is feasible in phase 3 studies. Keys to design the trials is having an appropriate acute pain model where opioid control is needed, accounting for pain, opioid use, and global patient outcome in the opioid-sparing definition.

The remaining challenges would be, however, we couldn't expect in all trials that opioid free is the goal because that is not always possible for a multitude of reasons. And the definition of minimal opioid use that constitutes a clinically meaningful reduction; we could still argue what that is, but from literature that's been published

already, a 10- to 20-morphine-equivalent reduction does seem to correlate with meaningful changes in patient-reported outcomes.

So now let's switch to opioid-sparing claims for long-term benefits and reducing the number of patients who use opioids chronically. Many factors, however, influence this. Short-term consequence of opioid use, we know. We know they are true. They happen in a majority of our patients when they take opioids, even at the prescribed recommended dosages. But there are many factors that influence the likelihood of chronic opioid use after surgery.

One could be inadequate pain management. Also, the excess use of opioid in the acute phase may lead to hyperalgesia. It may put those patients who are particularly prone for genetic or physiologic reasons or other environmental factors; those patients will go on to become persistent opioid users.

But perhaps one of the biggest problems here -- and this has been published by Dr. Bateman

and others -- is that prescribing practices vary greatly among providers. And those differences in opioid prescribing, even after minor surgical procedures, doesn't necessarily correlate with better patient outcomes, and yet, this is one of the chief challenges we would have in changing persistent opioid use.

Let's take a hypothetical example, based on the literature to date, that if patients who are naive to opioids undergo surgery, that 1 in 16 of them, or 6 percent of those, will go on to become chronic users. We could look at longer initial exposure, as we said, that those individuals who do take opioids initially for greater than 8 days, their risk is greater. Their risk increases to about 13.5 percent.

We could also look at high-risk vulnerable patient populations like our military, or VA, or those who have a history of addiction; the risk for persistent use in them is much higher. But nonetheless, if we go with the general arm of 6 percent of surgical patients use opioids 1 year

after surgery, and assuming our test product could reduce that risk by 50 percent, then we would require about a sample size of about 1,000 patients per arm for a 1-year study.

So again, doable, possible, but most likely more applicable in a phase 4 study where we could demonstrate the long-term benefits.

Phase 3 studies could inform the acute opioid-sparing effects and would help us to require the estimate size for a long-term impact on chronic use, but as I said, the study design challenges are many. Again, I will go back to Dr. Bateman's study looking at shared decision making, where you would need a commitment from both providers and patients that the goal is to minimize unnecessary opioid use; that you have to establish an opioid protocol that IRBs and physicians would generally accept that we are going to reduce greatly the amount of opioids; and we would have to confirm in some mechanism, opioid-free status over the observation of the study.

In conclusion, opioid sparing in the acute

pain model, the impact of reduced opioids can be done in the use of the context of adequate analgesia. And it's multifactorial, so if the center goal of today is to reduce opioid use, we can do so by a model in which we obtain adequate pain control, demonstrating reduction in opioid-related adverse events, and improved physical function.

This I think in the acute setting would lead to a patient's perception and general well-being being improved, knowing that they just had a very painful surgical procedure in which they were able to recover and to avoid the use of opioids. That could then be carried over to a 7-day reduction in opioids, which would serve as a good surrogate that we would avoid likely the persistent opioid use.

With that, I'll turn it over to my other colleague.

Industry Presentation - Randall Stevens

DR. STEVENS: Good day. I'm Randall Stevens, chief medical officer for Centrexion Therapeutics Corporation, clinical professor of

medicine at Rutgers Medical School, and I'm talking about chronic pains of acute pain, and just trying to put together a different approach to looking at the treatment of patients with chronic pain and opioids, to come to an outcome measure which is going to balance the analgesic effects of drugs, quality of life, function of patients, as well as potentially reducing opioid use.

My main focus for analgesia is to improve patient pain and reduce that, but the effect of pain is on multiple different domains as outlined on the left-hand side. With the reduction in pain, one should be looking at each of these types of measures, or at least a composite of them, so that you balance the analgesic effects with the benefits in function, quality of life, sleep, et cetera, that may be impacted by this specific pain in the patient.

There are general outcome measures which we look at categorically: numeric pain scales, use of rescue analgesics, and I won't read down the list of general outcome measures for pain.

When you're looking at pain, and then specifically areas that you want to assess, whether that's in analgesic effects overall or in reducing opioid use, the use of specific outcome measures in the condition you are treating is most appropriate and can be supplemented by other outcome measures which are more general.

One of the key issues in looking at any pain analgesic or trying to reduce opioids is what are the patients you're trying to study. What is their opioid use? What is the amount of their opioids and how they're using them? If you're looking to not initiate opioid therapy, then RCTs, randomized clinical trials, are good. Patients on PRN opioids need less or no opioids, and this can be done, again, in an RCT.

I think with patients on long-term opioids, that gets to be more complex. Patients who are strongly motivated to reduce or stop opioids can probably be done in randomized clinical trials. Though the number of clinical trials are very good, quality is sparse.

Patients' concerns of dependence, withdrawals, et cetera, and needing multimodal therapy, which are individualized to each patient, is probably best real-world practice evidence. Then of course, one has to ask the question, is there really a utility of, quote, "opioid-sparing language" in analgesics versus the products that directly address the dependence and other issues with opioids.

Opioid-sparing utility; we do want to reduce opioids, but with an associated improvement in pain control and function, because if we do not do that, there is no utility in trying to get the patients treated.

How to define opioid sparing in chronic pain? Instead of absolute numbers of opioids, the amount, let's start looking at a benefit-risk ratio in patients. Decreased opioid use along with increased pain relief in patients and benefit in physical function, mental function, quality of life are what we're looking for. And specific percent or absolute reduction of stopping opioids can be

but need not be the final determination of benefit.

What we're looking for is reduced harm, and that can be associated with the adverse events of opioid use, and that can be done by reduction of severity or the incidence of opioid-related adverse events or outcomes.

Opioid sparing; what is a clinically meaningful effect and reduction? This we can link to what's a clinically important difference, and just noted here, as I said before, there are many studies, but many of them are not of high-quality evidence.

What we've seen from a couple of studies is that long-term and chronic-pain opioids are not particularly effective. They're no better than standard analgesics, but they do come with additional harm. And with chronic analgesics, you see studies where the pain of patients who are non-opioid analgesics tends to be less, but the adverse events and harms for patients on opioids tend to be greater.

Opioids and chronic pain; can we look at

harms to assess? I've simply listed the adverse events, which you see here, and withdrawal symptoms also. So we need to look at both aspects for patients.

Opiate harms and dose; here's a CDC guideline review. And again, you have to choose patients properly, the study properly, conditions of the patients, and what you're trying to achieve. You know that history of substance abuse disorders associated with younger age, major depression, psychotropic medications, the CDC has defined harms as opioid harms, opioid-use disorder, et cetera.

One large fair-quality retrospective cohort study found that there is an increased risk with regard to overdose events which are nonfatal and overdose events that are fatal. The MMEs per day, you can see above.

When asking yourself how can we manage the harm versus benefit and you're trying to figure out what could be a good outcome measure, one way is to identify subjects. And for clinical trials that actually have the upper range of these MMEs because

by reducing one category or two categories, you effectively reduce the hazard ratio or odds ratio of a nonfatal or fatal overdose.

Try to build a profile of pain management, opioid adverse events versus withdrawal symptoms, and how can we combine what we know from the standpoint of combined measures. We have absolute change, percent change, time frame over one month for trial duration and an analysis of AUC or landmark.

Changes in opioid adverse events and withdrawal symptoms, you can have overall score, you can have the most bothersome adverse event and withdrawal symptom. And there is precedent for that because of opioid-induced constipation. Naldemedine has been approved for the reducing of opioid-induced constipation, and that was looking at the number of spontaneous bowel movements.

The difference between that outcome measure, response measure, between the drug and placebo was between 13 and 19 percent, which was statistically significant and considered to be clinically

meaningful. Therefore, if one wanted to have a relatively simple measure, we'd enroll patients who had opioid-induced constipation and use that as the outcome measure of improvement.

Change in pain and pain-related events, again, having specific and general outcome measures to ensure that what you're doing for patients as you provide the analgesia is to improve their state and function, pain, and other outcome measures.

So what does this mean? In the literature, there are a number of combined outcome measures. This is the American College of Rheumatology 20 score, which includes tender and painful joints, swollen joints, and then there's 5 other criteria, 3 out of 5 you have to meet, which includes patient outcomes, a laboratory assessment, and a decision investment. That has been used very effectively to combine the patient outcomes and the objective measures.

OMERACT and OARSI have done the same for response with osteoarthritis, and in that case, there's a 50 percent improvement in pain or

function with an absolute increase in improvement by at least 2 or more; or there is picking 2 out of 3 outcome measures in pain, function, patient global impression of pain, or other measure.

What that does, then, is that encompasses both the patient outcome, a specific outcome that is measured and combine many of these outcomes and assessments.

So if we're defining success, this is not a recipe, but if you're looking at change in pain, function, change in associated measures, change in opioid AE withdrawal symptoms, and change in opioid dose, one can look across the chart and see where the benefit is and at what point and the clinically important difference in which areas would be considered to be a meaningful benefit for both the analgesic, but also in the opioid-sparing aspects.

Looking at this combined outcome is a way of having both patient benefits on function, pain reduction, and reduction in adverse events and issues with opioids.

So overall, then, what we're looking at is a

combination of a drug for analgesia, which provides improvement in function, quality of life, and other outcomes that are impacted by the pain, as well as a reduction in opioid harm and dose. And this combination can actually be useful in defining benefits and powering trials.

There are a number of precedents for this in other areas where combinations of positive measures are used. Thank you.

Industry Presentation - Scott Kelley

DR. KELLEY: Good morning. My name is Scott Kelley. I'm the chief medical officer at Flexion Therapeutics. My background is also in anesthesiology and pain management. I'd like to review with you this morning some opioid-sparing considerations specific to chronic pain trials and actually using osteoarthritis as a model indication. These are my disclaimers, that these represent my opinion and not an official position of Flexion, and that I'm an employee and compensated by Flexion.

So again, some starting assumptions; as

Dr. Hertz mentioned, one of the goals here is to facilitate both the development and demonstration of therapies that could have an opioid-sparing benefit. If I put that as a category in intervention -- and in this presentation, I'll refer to intervention X -- being studied to achieve opioid sparing, as we heard from Dr. Stevens, the minimum expectation is it will maintain or improve pain control in a chronic pain setting or indication.

It's our hypothesis that intervention X could demonstrate meaningful opioid-sparing effects by preventing the initiation of opioid use, a meaningful reduction in total dose of opioid, or reducing the frequency of opioid use in a setting of a chronic indication.

To bring some context to this, I do believe a problem analysis for a chronic pain indication is helpful, and I'd like to review with you the opioid use in osteoarthritis as a background.

The key questions we look at in assessing this situation is what is the current utilization

of opioids in a specific chronic pain indication of osteoarthritis; and then secondarily, is that utilization problematic?

Opioid use in osteoarthritis has actually been recommended to be almost an end-stage treatment for these patients with continuing escalating pain as their disease progresses. And because of the prevalence and the availability of joint replacement, surgery as an optimal end treatment of failed disease management or continued disease progression could perhaps be the final stage prior to joint replacement.

Opioids ideally are based upon a foundation of other non-opioid analgesic strategies, both pharmacologic and non-pharmacologic.

Guidelines are prevalent in this disease space and include professional societies as well as general guidance from CDC and the American Pain Society. And they generally recommend opioids, consistent with that triangle I just showed you, as a last resort in osteoarthritis. Of note, some of these guidelines do consider tramadol separately

and perhaps earlier in the OA treatment paradigm.

Despite this, the data from the literature suggests that there's been a more prevalent utilization of opioids in the chronic pain indication of osteoarthritis. In 2012, one evaluation of patients that received any degree of prescription pain medications in a two-year period found that 72 percent of those patients received an opioid prescription.

More recently, in a review of 2014 Medicare data patients, 40 percent had received at least one opioid prescription and notably, a substantial increase in the time period from 2003 to 2009, with some correlations to gender, functional limitations, COPD, and other statuses of general overall health.

More recently, in 2017, using a very precise linkage of the diagnosis of knee osteoarthritis with an opioid prescription, an estimate of the prevalence of opioid use was at 16 percent.

An abstract published this year at the American Academy of Pain Medicine found a

description of utilization of different types of opioids within osteoarthritis. In general -- and I think this will be a clear situation for designing a trial -- intermittent use, almost PRN use, occurring less than or equal to 4 days per week of opioid analgesics is common in osteoarthritis.

In addition to the utilization of opioids, there are clear consequences that require attention. There's been some focus already, particularly from the CDC, about particular hazards of use in the elderly patient population. These patients in general have a higher number of comorbidities and are likely more vulnerable and at higher risk for complications. That may be secondary to polypharmacy. The CDC did identify the challenges related to delirium, falls, fractures, and injuries in addition to motor vehicle accidents.

We're also now seeing a specific focus on the prevalence of opioid-use disorders in those patients receiving opioids as part of their management for arthritis. In this cluster

analysis, grouping patients with opioid-use disorders, it was demonstrated that 10 percent of patients with opioid-use disorders are actually coming from older patients in the disease category of arthritis. And interestingly, these patients have a different pattern of care for their treatment for opioid-use disorders.

We're also learning about the types of opioids in addition to their prescribing patterns will also seem to trigger some of the risk factors for opioid-use disorders.

In this recent analysis, a retrospective observational study data, it was demonstrated that the utilization of long-acting opioids, or a combination of long-acting opioids and short-acting opioids were more likely to lead to a greater diagnosis of opioid-use disorders within the 3-month time period.

In a similar manner, that use or that pattern of opioid utilization in terms of intensity of opioid treatment is also correlated with both all-cause hospitalizations as well as

hospitalizations directly related to the diagnosis of osteoarthritis.

As I mentioned earlier, because of the final linkage of joint replacement surgery in the care of patients with osteoarthritis, an interesting perspective has been developing that opioid use in osteoarthritis also drives greater use of healthcare utilization at the time of arthroplasty. In particular, long-acting opioid use prior to arthroplasty predicts perioperative complications in joint replacement surgery.

This can also have functional consequences in reduced walking distance, the requirement for discharge to skilled nursing facilities, increased length of stay, and the overall 90-day complication rate.

With a focus on patients undergoing total hip arthroplasty, prior opioid use is linked to continued opioid use after discharge, longer hospital stays, and significantly worse clinical outcomes when assessed by a Harris hip score following hip replacement.

This slide also shows that prior opioid use in osteoarthritis will also drive increasing duration and frequency of utilization of opioid prescriptions after arthroplasty. So as we heard earlier that the onset of acute pain in surgical procedures is a clear landmark, prior opioid use can oftentimes accelerate the potential implications of acute pain.

This landscape analysis of the problem of opioid use within osteoarthritis gives some key takeaways. The treatment guidelines generally recommends opioids as a last resort, yet it's not clear that that's the way current physicians are utilizing it.

Opioid use in managing osteoarthritis pain is well documented, but there are widely disparate rates of use anywhere from 16 to 72 percent, which makes it challenging to fully quantify the magnitude of the problem.

Recent characterization that intermittent use of short-acting opioids appears to be the most prevalent regimen, and the specific agents

hydrocodone, oxycodone, and tramadol appear to be the most widely prescribed.

This landscape analysis also reviewed some of the consequences of opioid use in osteoarthritis patients and identified consequences that are of significance. Taken together, this analysis suggests that opioid use in osteoarthritis does appear problematic and therefore represents an unmet need worthy of opioid-sparing interventions.

So with that as a backdrop, we've thought about potential trial design considerations that can evaluate the opioid-sparing effect within that chronic pain indication.

As I said earlier, there are three potential objectives and perhaps different patient populations where this could be demonstrated in a specific disease indication. The first is preventing opioid use, the second is reducing the total opioid dose, and finally, reducing opioid utilization.

For preventing opioid use in osteoarthritis pain, a simple randomized-controlled trial would

seem reasonable to achieve here, that we could imagine taking patients with baseline osteoarthritis pain that is escalating or challenging and is no longer able to be appropriately managed by non-opioid pharmacologic and non-pharmacologic strategies.

These patients could then be randomized to either a placebo or this intervention X, and at some point to assess for both continued management of osteoarthritis pain control; that is pain management persists or is improving in that time frame, as well as the time to initiation of first opioid dose.

This will also present some both opportunities and challenges. It is randomized, blinded, and placebo controlled. It may be particularly challenging to find patients and actually providers who are willing to identify patients who are right at the cusp of opioid initiation.

Likely, it will require screening tools to identify those patients with other motivating

tendencies towards opioid initiation. The CDC has also provided guidance on helping us identify some of those patients. Importantly, this actually removes opioid administration as a fundamental element as part of the trial because it's the endpoint of a need to progress to opioid analgesia.

Reducing opioid use in the current patient population taking opioids for osteoarthritis pain is another approach. We believe there is a population of patients, and I think the recent data suggesting that three-quarters of patients are in some ways utilizing intermittent short-acting opioids less than or equal to 4 times per week represents that population.

If they have achieved a stable pain control with this intermittent opioid use, they could then again be randomized to an intervention versus placebo, and then we could assess their outcomes for both pain control and total opioid use over some time period, and we're proposing here 4 weeks, with additional follow-up for at least 3 months.

This does provide the strength of a

randomized blinded placebo-controlled study. There's a strong preference to study patients who are already on opioids as opposed to either withdrawing or initiating opioids as part of a rescue medication regimen.

Ideally, a 30-day run-in period would allow the assessment and confirmation that patients are achieving adequate pain control with stable intermittent opioid dosing. Again, it's important to include screening tools and other tests to minimize the inclusion of patients who are misusing opioids.

The idea that the patients could maintain their own 30-day opioid prescription is ideal, but these patients would have to agree and participate with pill count measures as an outcome measurement.

The 4-week time frame for a final read-out to minimize the influence of seeking the next opioid prescription seems reasonable, but importantly, to follow patients for 3 months after the intervention to assess the durability of opioid-sparing effects. We expect this trial will

be difficult to execute in a pre-approval setting.

Finally, most challenging is trying to look at the larger population -- and, again, that number could be up to 70-75 percent of patients currently taking opioids -- in reducing their overall opioid utilization. We believe the right approach here is a real-world evidence strategy.

There are new tools available, patient registry or a variety of electronic health records and individual healthcare systems or integrated delivery networks. This could identify a cohort population of osteoarthritis patients that are currently taking opioids, and then either using a different approach to randomization with propensity matching over time or pragmatic randomization in a delivery care model.

The care with approved intervention X as opposed to care without approved intervention X could then be assessed and the number of opioid prescriptions provided to those patients and filled over 1 year.

This is clearly a different trial design,

but it does allow the potential for assessing opioid sparing with the currently available non-opioid therapies. There are always challenges with the quality and completeness with electronic health records as a data source, and there's particularly an evolving regulatory landscape regarding expectations for the quality and detail of real-world evidence studies to support approval of new indications and labeling.

In terms of defining proposed endpoints for these three different types of trial designs, for prevention of initiation of opioids, I suggest that preventing at least 20 percent of patients, 1 in 5, from initiating opioids would be a meaningful reduction in that utilization of opioids.

For reducing the current total opioid dose, there seems to be a general acceptance now of a 50 percent reduction as a meaningful amount of opioid reduction in the chronic pain setting.

At the IMMPACT meeting this July, there was general acceptance, particularly if the patients are currently receiving greater than or equal to

100 milligrams morphine equivalents. We held a recent advisory board with a variety of opioid stakeholders -- patients, orthopedic surgeons, rheumatologists, pain management physicians -- that also agree that a 50 percent reduction in current opioid dose is clinically meaningful.

Our hypothesis is that a 50 percent reduction -- and I think we heard some linkages from Dr. Stevens that, that degree of reduction, particularly with the risk reduction for opioid-use disorders, both fatal and nonfatal -- is sufficient that it doesn't require additional reduction in opioid adverse events.

How long is feasible? Again, a proposal of 4 weeks is a reasonable and feasible time frame as long as it's coupled with a follow-up phase to gather durability data.

In terms of reduction in opioid utilization and in terms of reducing the total pill counts that are entering into the home and the public system and the potential for diversion and misuse, suggesting that a 20 percent reduction in opioid

prescriptions written over a 1-year time period would be a meaningful improvement.

I hope our interactions today may explore some of these regulatory considerations. Demonstration of opioid sparing in the chronic pain setting is particularly challenging, especially in support of an approved label claim, and will take innovative thinking and collaboration between sponsors and the FDA.

In the pre-approval setting, FDA should prioritize review of clinical trial protocols aiming to study opioid sparing as a robust secondary outcome measure. FDA should characterize within product labeling any opioid-sparing experience from pre-approval trials that assess that endpoint in a valid, high-quality manner.

Ideally, the FDA should encourage sponsors to collect post-approval opioid-sparing experience through real-world evidence studies and be open to including those data regarding opioid-sparing results within labeling.

In conclusion, characterizing opioid use in

a specific chronic painful condition is critical to understanding the unmet need and identifying a target patient population for study. We reviewed that chronic disease of osteoarthritis this morning.

Any product enabling opioid sparing, at a minimum, must maintain or improve pain control for these patients. This morning, we reviewed three separate clinical trial objectives that could represent meaningful opioid sparing: a greater than 20 percent prevention rate in initiation of opioids for these patients; a greater than 50 percent reduction in opioid dose over 4 weeks; and a greater than 20 percent reduction in opioid prescriptions written over 12 months.

Innovation and collaboration between sponsors and FDA are critical to initiating meaningful progress on opioid sparing for chronic pain patients. Pathways for describing opioid-sparing effects in product labeling is critical to enable proactive sponsor communications. Thank you.

Clarifying Questions

DR. BATEMAN: Are there any clarifying questions for BIO? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. This is a question for Dr. Kelley. I'm trying to get a sense of your recommendation that we reduce the 20 percent opioid use over a 1-year prescription period. I didn't see a background for that number. Was that just your best guess or do you have data to support that?

DR. KELLEY: There is no specific data to suggest that, but again, it's that idea of reducing 20 percent in terms -- and particularly with the recent Medicare evaluation showing there's been an increase in opioid prescriptions over time, to somehow bend that curve. And again, a 1 in 5 reduction I think passes that initial test of what could be meaningful.

DR. BATEMAN: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Thank you for your presentations. This is a general question that applies to all three presenters. Other than the last example using real-world data, I'm a little unclear how in these other trials, it would be proposed to measure the opioid use.

There are two approaches to this. One would be a more pragmatic clinical trial aspect where, basically, the participants would be allowed to take opioids on demand. The other one would be an approach where the opioid prescriptions are driven by the level of analgesia. And it wasn't clear to me what the proposals were from that respect, more of an efficacy versus effectiveness approach.

DR. STEVENS: I'll be short. So it depends on what you are trying to achieve in the patient population within which you're studying. So if you're looking, as I say, at high users that are using large numbers of MMEs, then you may want to have them go down to a lower level to reduce risk of overdose and overdose death.

It depends on the indication for what you're

looking at. Overall, the idea is to look at the harm of opioids, and each individual patient tends to have a different response to that dose and that harm.

So that's why I didn't give a specific amount, per se, of opioid reduction, but actually looking at a more general approach of maintaining analgesia or improving analgesia while at the same time improving function, quality of life, and the opioid reduction is based on reducing the adverse events associated with that opioid. That would be then a composite measure that I've talked about.

DR. SUAREZ-ALMAZOR: Yes. I guess my question is more around that composite measure because if whether they take opioids or not is related to the actual degree of analgesia, then the composite measure is already -- I mean, they are not independent, so I was a little unclear how that would be operationalized.

DR. STEVENS: Sure. So if you look at the American College of Rheumatology, ACR 20 for rheumatoid arthritis, you have two requirements, a

reduction of 20 percent in painful and swollen joints, and then you have 5 other measures, which include patient and physician assessment of pain, an NSAID rate or CRP, and other outcome measure.

What that does is it gives you objective measures and it gives you subjective measures. In that, you can also include a composite to look at the adverse event profile of patients on opioids. And you could choose, as the other presenter said, a list that always has the adverse events and their severity, collected that way. You can look at a specific outcome measure, which would be the constipation induced by opioids. And then you would have to enroll patients who actually had that specific adverse event to look at a reduction.

So it really depends on the type of patient indication for which they're receiving analgesia and what you're trying to achieve from the standpoint of benefit versus harm.

DR. BATEMAN: Dr. Lorenz?

DR. LORENZ: Sure. I wonder if each of the presenters could comment on the issue of durability

of opioid reduction. I was surprised to hear a 4-week recommendation. I think of opioid reduction as an extremely difficult undertaking.

Four weeks for smoking cessation would be problematic for most patients, so I'm kind of surprised by the brevity of the claim, and I wondered if you could comment on the evidence or lack of evidence supporting a duration.

DR. KELLEY: That specific trial design mentioned 4 weeks as a feasible endpoint for a clinical study, particularly in the backdrop of the patient who already has an opioid prescription, ideally for a 30-day window. In addition, it then led into a 3-month follow-up period. So that total management experience would be over 3 months.

As we've approached this, the real challenge is with how the sponsor may have to enable opioid administration in the trial design, and this is one way of looking at that without withholding the access of the patient to those prescriptions.

DR. BATEMAN: Dr. Michna?

DR. MICHNA: My question is for everybody

again. It's the issue of the role of patient education prior to acute surgery pain patients and what role that plays in terms of opioid utilization, and the variability of that in the real world compared to your clinical trials. So in other words, how transferable is that to the real world when you have a study where patients supposedly have a higher level of education and expectation setting as opposed to what happens in the real world.

DR. SCRANTON: That's an excellent point, and I do agree that in our trials that we've run today, we don't actually do as much patient education. I think for a follow-on study, if you're trying to offset the continuing use of opioids, there's going to have to be a lot of shared decision-making in setting the right kind of ideal outcome with regard to the patient's perspective; how much pain are they able to tolerate and how much are they willing not to use opioids to treat that pain?

That is a different trial. It requires a

lot of education and training, and it's some of the work that other groups have been doing, American College of Surgeons, to provide that patient education, setting expectations, and the right appropriate outcomes after surgery, but is very variable.

I'd also say there are also other factors, such as catastrophizing and other patient factors, too, that significantly impact our ability to avoid opioids in the acute setting as well.

DR. STEVENS: Also to that point and the other point, if you have a patient who's using PRN opioids sporadically, the likelihood of being able to get them off opioids in a shorter period of time is better than someone who's on a chronic daily high dose. That's going to take a long time, and those patients actually have to agree that they want to reduce their opioid dose; otherwise, you're going to go nowhere.

The other thing, although we talked about patient training, is also physician training. I think, if you're going to set up for reducing

opioids, then you actually have to have a proscribed way of reducing opioids and also a proscribed way of when to initiate or continue opioids for the physician because you have to reduce the number of variables in order to actually get an outcome measure in a reasonable amount of time with a reasonable number of subjects.

DR. KELLEY: In addition to that, I think the patient motivation is probably increasing to a very fast extent. At our recent advisory board, we had a representative from a patient advocacy group, and they were challenging us. They said that reduction should be to zero percent.

So that belief that they're looking for pure non-opioid analgesic substitutions is pretty strong. It's very challenging. But they believe, yes, educating their network of patients, and for osteoarthritis, it's a very large network. So I think that patient motivation and education will be critical to these trials.

DR. BATEMAN: Dr. Rosenberg?

DR. ROSENBERG: I was wondering about

whether or not there's been some exploration to better describe opioid sparing because opioid sparing, as a term, is being used to describe a wide variety of conditions from opioid avoidance, opioid dose reduction; whether or not we want to precisely describe what opioid sparing is in a different language rather than try and fit opioid sparing for acute pain, a chronic pain; whether or not we need precise language that would better inform the prescribers in how we're labeling our medicine; and whether or not opioid sparing should be what we're trying to loop all these benefits under.

DR. BATEMAN: Dr. Hertz?

DR. HERTZ: And that's why we're having this advisory committee. So let's hold that discussion for when we're done with all the presentations.

DR. BATEMAN: Dr. Litman?

DR. LITMAN: Thank you. So the challenge here, which is obvious, is that there are so many different pain models, and all these considerations are different.

Dr. Scranton, I will push back a little bit on what you defined as short-term benefit. You had said it's 1 to 4 weeks. Now, traditionally, this committee, when we evaluate an NDA and we would potentially in the future give opioid-sparing language on the label, the studies we evaluate are for short-term painful procedures, like bunionectomy is a popular one or some kind of abdominoplasty.

In my career as an anesthesiologist, I can't think of many acute procedures where the pain requires opioids for even up to a week. I mean, for the vast majority, there's got to be exceptions of course. Most patients don't need opioids after 48 and possibly 72 hours, and obviously that's just a guess. And the ones that do are outliers. I would think that, also, it would be very difficult for a company, a sponsor to both financially and logistically carry out those kinds of evaluations past that time period.

So I just wanted to ask you about the short-term follow-up of 1 to 4 weeks. It seems kind of

long to me for a procedure that we would normally be evaluating here.

DR. SCRANTON: I agree with you. Unfortunately, the literature will support that there is a lot of excess opioid use that is prescribed even after minor surgeries. And there is a 50-fold variation even within a single institution. So that's one challenge.

But I do agree that in the short term, while I was using 1 week, even in any trials that we run, we have safety follow-up to do that expands beyond even the duration of the drug, so that's a reasonable time period. We typically in all of our trials will have at least a 30-day follow-up for safety. So adding a question with regards to overall benefit or analgesic consumption during that time would be still doable even in an acute trial setting because of the required safety follow-up.

But that's why I did limit that -- we could agree on what an appropriate surrogate would be, and maybe 7 days, based on the literature, if you

could avoid opioid consumption within 7 days, that should then theoretically lead to a reduction in persistent use in general.

DR. BATEMAN: I have a question for Dr. Scranton. You mentioned in your presentation that a 10- to 20-milligram morphine-equivalent reduction in opioids was correlated with an improvement in patient-reported outcome measures. I just wondered if you could elaborate on that a little bit, the clinical context where those data were generated.

DR. SCRANTON: So that's part from Zhao's work, when they looked at the incremental differences in opioid use and linked that to side effects and burdensome side effects with patients. But to your point, there hasn't been a lot of studies that really demonstrate that, and there's high variability from a person's perspective. We know that a single dose of 5 milligrams of oxycodone can cause nausea and vomiting in patients, so it does need to be better defined.

DR. BATEMAN: But the Zhao study; was that

an inpatient setting, and was a reduction in 20 milligrams in a given day?

DR. SCRANTON: It was for every incremental increase in opioids, and they demonstrated an impact on patient-reported, quality-of-life outcomes in the acute setting.

DR. BATEMAN: In the acute setting.

Dr. Goudra?

DR. GOUDRA: Hi. Basavana Goudra from Penn Medicine. This question is for Dr. Scranton. On slide 5, you mentioned that patients who use 1 day of opioids, at least 7 days, had twice the risk of using opioids chronically 1 year after surgery. Further on, you also stated that 1 in 16 opioid-naïve surgical patients become chronic user.

Can you elaborate on the kind of evidence you have to support that? I mean, you have a CDC study, which is presented as a --

DR. SCRANTON: There are scores of studies. The first one that reported that goes back to 2012 was Heinbel [ph] reported the incidence of persistent opioid use after minor surgery, even

laparoscopic procedures, and that rate was somewhere in the range of about 1 in 15. Carroll out of Stanford repeated that study.

Since that time, there have been scores of studies not always showing the same percent prevalence rate, some showing greater; for example, patients undergoing bariatric surgery, who may be particularly prone if they've already demonstrated an addiction to food, which is a dopamine reward system. You remove that, and then you give them another reward, which is opioids. Their persistent rate is much higher. A persistent rate after total knee also may be higher. A persistent rate of patients who have a prior history of addiction or a prior substance abuse such as smoking; those rates may be higher.

What I did, it's an aggregate or conservative estimate. If you look at all of that across the general patient population, it's somewhere between 1 and 15, which is that 6 percent rate.

The CDC is had looked at -- there was a

determination, is it a duration of exposure or is it the amount of exposure, and do those correlate with a greater likelihood for persistent use. I think the jury may still be out on that, but it does tend to seem a longer duration of exposure, even at the recommended dosages. If you're on 7 days, the risk goes up. If you're on 2 weeks or if you're on 30 days, your likelihood of having persistent use continues to increase.

DR. GOUDRA: Are there any factors other than, say, genetically? Do these patients handle drugs any differently? Is there any evidence in that direction?

DR. SCRANTON: There is a lot of work in the genetic, particularly with regards to metabolism of opioids, and some subset of patients may indeed be at greater risk. Some of the work of the DoD for pain catastrophizing and all that also may be a strong predictor, as well as depression and other factors.

There's a lot more we should know, and that information I do think is part of the education to

patients. Giving out opioids, even at the recommended doses, are associated with potential harms.

DR. GOUDRA: Thank you.

DR. BATEMAN: Dr. Budnitz?

CAPT BUDNITZ: Thank you. This is a related question for Dr. Kelley. I think it's slide 20 on trial design, preventing opioid use in OA pain. You talked about including screening tools to identify patients with other motivating tendencies towards opioid initiation.

Are you suggesting to exclude such patients with such tendencies or what was the point of that bullet? Could you explain that?

DR. KELLEY: I think it's a real challenge and likely to exclude those patients. If there are other motivations for pursuing current or access to opioids, there are real confounders. So to really measure the efficacy of the drug, I would want to remove those patients from the trial.

CAPT BUDNITZ: So you do have a randomized design, though, so those patients should be

randomized to each arm. Right? So is the point to try to look at other factors that might be in the post hoc analysis? That's what I'm trying to understand.

DR. KELLEY: Yes. And again, in the pain study, these types of patients are really truly confounders, both for pain reporting and achieving their goals. So I think specifically to assess the overall efficacy in a cleaner patient population is worthwhile.

CAPT BUDNITZ: I'm sorry, so just one point. So you would exclude patients who have some kind of tendencies in the trial?

DR. KELLEY: Yes

CAPT BUDNITZ: Is that what you're saying? Okay.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: I also have questions about study design. In all the presentations I've seen, placebo-controlled study designs are proposed for the trials that have been done or for the future. I have two questions. One, why the preference for

placebo-controlled designs instead of active comparators?

Second, in all these placebo-controlled studies, is the background other effective analgesia? So my question is, are people getting an intervention or placebo on the background of no other therapy or are they all getting standard of care, other therapies? For all the presenters.

DR. SCRANTON: That's a great question, and it's one that we've had much discussion about. Theoretically, I would say, since there isn't a comparator that I can go against that has established an opioid-sparing claim, we are in novel territory. There's no drug, Tylenol, non-steroidals, that have a claim that they have opioid sparing.

So if we look at McQuay's work as far as an opioid consumption or analgesic consumption model, that's really what we're talking about. In this case, we're using opioid as the analgesic consumption that we're trying to avoid. So in that case, it makes sense that my drug is being compared

against the opioid as a way to reduce the opioids.

If I was to go against another active comparator, then my claim would be that I am more opioid sparing than that active comparator; different study, different goal. But you're absolutely correct, and as we've heard from the patient preference and pushback from physicians, there's the presumption that the majority of providers out there want to give some type of multimodal opioid sparing, particularly in acute pain.

The reality is, however, when we do real-world studies, there is no standard of what that multimodal regimen would be for any given pain model, and there's wide variation and acceptance of those adjunctive therapies.

In the one trial I did show there, they did have a background. Both groups did get acetaminophen, for example, because an IRB would not allow us to allow that at least to be part of the regimen. But I think, from a purer standpoint, no, the comparator would be against what we're

trying to reduce, which is the opioids. The placebo is there for the placebo effect.

DR. BATEMAN: Dr. Rosenberg?

DR. ROSENBERG: This is for any of the responders.

DR. FLOYD: Can I follow up?

DR. BATEMAN: Dr. Rosenberg, Dr. Floyd had a follow-up question, and we'll come back to you.

DR. FLOYD: Just a very brief comment on the response, and I can save this for the afternoon, too. It sounds like what's being proposed are placebo-controlled trials in the background of little or no other analgesia, and I have serious concerns about that.

I think that any drug that has analgesic properties, you will see some reduction in opiate use in a health system where opiates are prescribed. It's simply another dimension or element of that effect of analgesia, that you don't see the downstream effects.

So I would like to have some discussion later today about the various study designs and

whether this opioid-sparing kind of language is a reliable outcome.

DR. KELLEY: I do have to make a comment that, in particular for a chronic pain indication, particularly for osteoarthritis, where you assume that treatment paradigm includes a variety of both pharmacologic and non-pharmacologic analgesic strategies, so the core layers include both non-steroidal anti-inflammatories, acetaminophen, and other analgesics, there's no withdrawal of that.

I think we are specifically trying to measure the incremental efficacy of an intervention in order to prevent opioid utilization or path to opioids. Finally, in the real-world evidence, it was not randomized to placebo but a comparison of care with intervention X versus current standard of care or other interventions, to really look at that overall net effect. So there's no withdrawal of other analgesics that are supporting these patients.

DR. BATEMAN: Dr. Rosenberg?

DR. ROSENBERG: The guidelines for both

acute, chronic, and end-of-life care for pain all involve multimodal analgesia, and it's talking about not just medications, but also physical treatments as well as psychological treatment.

Is that accounted for in your study design, that multimodal is being applied? And is it fair to just focus on the opiates when, for example, non-steroidals, which have a known side effect profile -- shouldn't they be also part of the mix of side effects that we're trying to reduce while looking at multimodal treatment?

DR. SCRANTON: So yes, this has particularly been complex in the acute pain trials. There are a lot of medications that are, I would say, the kitchen sink, gabapentin used with limited evidence. Non-steroidals, however, in some cases, in spine surgery, they want to avoid non-steroidals because of concern of impact on fusion.

So again, we have to pick what we think is the appropriate pain model. And then yes, in some cases, we will have a background of some acceptable other non-opioid analgesic medication. As I said,

acetaminophen perhaps will be there as an added therapy. But there's such a variety of different interventions, oftentimes we're going to have to limit what the number of those interventions are in the trial as we're trying to determine equal analgesia, and then reducing opioids, and then measuring the impact of that difference in the opioid consumption.

These will be the challenges of how we design those acute pain trials because of that complexity. And there are other things, cooling packs, ice packs, psychotherapy. There are a lot of other things we could actually add on. Those become very large phase 4 studies of comparative effectiveness, of each one of those interventions.

DR. KELLEY: That's a great question about the utilization of the multimodal strategies. Recently, at the American College of Rheumatology, a large dataset looked at guideline compliant care, which included those fundamental pharmacologic and non-pharmacologic strategies beneath opioid utilization.

Those patients that did not have guideline concordant care were more likely to receive an opioid prescription than those patients that did. Distressingly, some of those utilization of guideline-compliant care were associated with lower socioeconomic status, BMI, and other factors that are difficult to control. But fundamentally, I think adherence to that concerted and pretty rational use of multimodal strategies to control osteoarthritis-related pain is something we would have to factor into our trial design.

DR. STEVENS: One other aspect to get to your point is that in the chronic pain trials, you can use rescue medication in both arms and then sequence the use of those medications, such as acetaminophens, NSAIDs, opioid, so that you have the same sequence in each group and you can see how many patients go from acetaminophen to NSAID to opioid or back again, depending on the effectiveness of the analgesia over time.

DR. BATEMAN: Are there any other clarifying questions for BIOS?

(No response.)

DR. BATEMAN: If not, we're a little ahead of schedule, but we'll move on to the first guest speaker presentation.

Our first guest speaker is Dr. Chad Brummett from the University of Michigan.

Guest Presentation - Chad Brummett

DR. BRUMMETT: Good morning. I'm Chad Brummett. I'm an anesthesiologist and a pain physician at the University of Michigan, and today, I'll be talking about the Opioid Prescribing Engagement Network, an effort here at the University of Michigan that is actually a statewide effort, together with the Department of Health and Human Services, with funding from NIH and BlueCross BlueShield of Michigan.

I do have disclosures. I have funding from the NIH as well as Michigan Department of Health and Human Services, SAMHSA, CDC, as well as Department of Anesthesiology funding. I have a patent that I won't discuss today, and it has no current royalties. And I consult for both Recro

Pharmaceuticals and Heron, and I won't discuss any of their products today.

I was asked to maybe put this into context of why surgical prescribing matters, and we've talked a lot about data today. I started giving this talk a couple years ago, and I would say 78 Americans die every day from opioid-related mortality, and then 91, and then 115, and now today, 134 deaths per day.

Again, we put it in numbers, and those are striking numbers, but I'm moved by stories. And as we think about surgery, I think it's important to remember these stories are real, and I hear them every week. I go back to the story of the mother whose husband became addicted to opioids after his spine surgery, and whose daughter found him in the bathroom with a heroin syringe in his arm, dead.

Or if you flip it around and don't think about the patient who's actually having that care that day; in other words, we've talked a lot about the individual, but the spillover effect in the community, I'm moved by the stories of the Savage

Foundation in South Bend, Indiana, where I was introduced by a surgeon.

My colleague, Mark Thompson, introduced me and said, "We lost two boys in our community, high-school boys. They took a couple pills, they drank a couple beers, and they went to bed, and they didn't wake up." And while I knew I never cared for those boys, I wondered if it was my excess surgical prescribing that led to their experimentation that night and directly led to their death.

I think putting this in context is important because I'm not against opioids. I believe they have a role in acute pain. I manage patients in my pain clinic with opioids, but I think we've gone way too far with surgery.

Our group took a bend a couple years ago that I think was important. It really felt like most of the country was focused on all these downstream effects; the chronic user, what to do with medication-assisted treatment. These are really important topics that merit more funding,

more attention. But at that time, there weren't very many people talking about this. If we're going to have a healthy narrative around opioids, shouldn't we be doing what we're talking about today, which is to think about a preventative narrative?

In other words, can we take these predictable exposures like surgery and shepherd people through a path where they don't go down a path of morbidity and where they don't pose a risk to their friends or family members?

We published a study earlier this year showing that the relative contribution of new prescriptions when you think about surgery and dentistry is increasing. As the CDC guidelines have kicked in and the preamble to the CDC guidelines, that bottom category there, the yellow, which is primarily primary care and family practice physicians, is decreasing over that 7-year period while, by comparison, surgery and dentistry have increased.

Moreover, surgeons prescribe by far the most

opioid in that first exposure, and that went up pretty significantly between that 2010 through 2016 range. However, if you really even look at the last couple years, the 2014 to 2016 range, we see that surgery remains high and remains flat, and at the bottom there, primary care physicians have started to reduce the amount that they prescribe.

Now, as an anesthesiologist, it's maybe not fair for me to come in and tell surgeons what they think, but I actually think the same things as a pain physician. I worry about time. I worry about phone calls. I worry about patient satisfaction. And we put perverse incentives between patient satisfaction and pain med. And even as we've removed that HCAP incentive, people still care.

We've published a couple papers, and I know Dr. Bateman has similar data to show that there is no association between the number of pills prescribed after surgery and patient satisfaction with their care, nor is there an association between the number of pills prescribed after surgery and the likelihood of refill.

Refill happens. If you take abdominal surgery, it happens about 7 percent of the time. But whether you prescribe the equivalent of less than 6 pills of hydrocodone or more than 60, the refill rate is about 7 percent, and it doesn't vary whether you look at it in an adjusted way or an unadjusted way.

Dr. Bateman did a similar study in women undergoing C-section, obstetrics patients undergoing C-section, showing that the more you gave patients, the more they took with no changes in pain satisfaction or refill rate.

We talked a little bit about this in the last couple lectures, and just to sort of complement, what is that morbidity, what are we talking about today, and why is this important, this is probably the paper for which we got the biggest splash.

We showed that about 6 percent of people not using opioids in the year prior to their surgery continued to fill long past what would be deemed normal surgical recovery. These are claims data,

nationally represented claims data.

What was interesting is there's no difference between major surgery and minor surgery, so this is not just post-surgical pain. I studied post-surgical pain. This cannot be explained by post-surgical pain.

I wasn't particularly surprised because we had published this paper the year prior, showing that 4 percent of hip patients and 8 percent of the knee replacement patients became new chronic users. These were prospectively collected data as part of an NIH-funded study. What was very interesting here was that we used the gold-standard measure for change in knee or hip pain, stiffness, and function, and there's absolutely no association between the change in that person's knee pain over that 6-month period from pre-operatively to post-operatively and that likelihood of continued use. In other words, this is not surgical pain.

So I think that these things are important. So what do we think is happening here? We think that patients are taking these medications for

other chronic pain conditions for which their primary care physician might appropriately not be prescribing currently.

We think that some take it for sleep. Sleep is a major unmet need after surgery right now. And then we certainly also appreciate that there is misuse and abuse. And misuse and abuse doesn't simply mean getting high. We certainly think about those anxious patients. We talked about what risk factors are there, anxious patients sometimes describing a leveling, that opioids level them, they make them feel right, not necessarily making them high.

Thirteen percent are hand surgeries; 13 percent is spine surgery; 4.8 percent of teens and adolescents undergoing elective pediatric surgery, and these data bother me. Ten percent of curative cancer surgery. I think we have a different prescribing pattern for cancer patients, and then probably our most challenging population, breast cancer patients, where there's reconstruction and care after surgery, and we see

about a 19 percent rate.

I think, though, if you compared that 10 percent rate in that second-to-last line to the first line, the surgical incisions are very similar, but the rate is much higher likely because patients are prescribed more because they have cancer. Even though these are curative cancer surgeries, the cancer is removed as a part of that surgery. I also think people feel enabled to take opioids because they have cancer.

The last is, we talk about morbidity associated with post-surgical prescribing. We looked at a national dataset of 70,000 kids and young adults undergoing a third molar extraction, wisdom tooth extraction, something that's done 3.5 million times per year in the U.S.

Eighty percent of kids in 2015 got an opioid as a part of that care even though we have randomized-controlled trial data to show that there's no additional benefit of an opioid in lieu of acetaminophen and ibuprofen in combination. And just getting that prescription was associated with

a 2.7 times increased risk of becoming a new chronic user after adjusting for demographics, patient comorbidities, psychiatric diagnoses, pain diagnoses, and the impaction status of the tooth.

So the actual exposure matters, and I think that's an important part of today. What are we talking about? Why does this matter? Just getting the medication mattered, and we didn't see overwhelming effect sizes or real strong associations between the kind of medication or the amount that they received. It was just the exposure itself that was associated.

So I think the good part about being in this space is that we really are in a place where we can improve prescribing. And I'll take you back to where we started, which was, a couple years ago when we were trying to figure out what was happening, we thought we needed to know what was happening in our own house before we could go around the state and the country talking about this problem.

So we took a very common procedure,

laparoscopic gallbladder removal, and we looked at prescribing. What we found is at the University of Michigan, we prescribed on average about 50 pills. Now, that's a shocking number, but I will tell you, in the Truven data from 2017 all the way through the first half of 2017, the national average is still probably about 40 to 45 pills. So if you think that this is historic data, this is still the average after a lap chole probably today.

What we found is that when we looked at how much people actually used, the median use was about 6 pills. So early in our effort, we knew that 75 percent of people were being satisfied with 15 pills, and going from 50 to 15 seemed like a good start.

So we had a resident who did a voiceover PowerPoint and everybody watched it. And sure enough, in the next 370 patients, we dropped from 50 pills to 15 with a really tight standard deviation.

We saw no differences in refill rate. We saw no differences in self-reported pain. And at

the top there, you can see that the median use dropped from 6 pills to 4 pills. Now, that may not seem very big. That is only 2 pills. But let's project that out now to a bigger surgical condition like knee arthroplasty or spine surgery, the amount we prescribe matters.

We've known this for a long time in the food literature. This is a phenomenon called anchoring and adjustment. And again, Dr. Bateman showed this in women undergoing Cesarean section. The more pills we give people, the more they're going to take. We are conditioning people to take more pills by giving them enough so they, quote, "won't run out" and taught people that. I'm part of the problem. If we think about the context of that, 35 pills less per patient over that 370 patients, that's 13,000 pills not in the community, not subject to abuse.

We're uniquely structured in the state of Michigan. We have almost a single private payer in the BlueCross BlueShield of Michigan. So between Medicaid, Medicare, and BlueCross BlueShield, you

pretty much have the majority of insured patients in our state.

They have, for more than a decade, been funding a network of collaborative, and these are just two of the collaboratives. There are mainly surgical and acute care collaboratives, both a general surgery collaborative and anesthesiology collaborative, coming together 3 to 4 times a year to talk about quality.

We went to Michigan Department of Health and Human Services about 2 years ago, almost 3 years ago now, and said let us take this unparalleled platform to superimpose an opportunity to get real-world patient consumption data and for dissemination.

True to our goals, we have actually populated -- we've created the first evidence-based prescribing recommendations based on real-world patient-reported outcome data from 33 hospitals in our state, representing all the way from small hospitals, to urban hospitals, to teaching hospitals. And I've received some not-positive

feedback on social media, saying these numbers are still too high. And I agree, but these represent major reductions in prescribing as compared to what's actually happening today.

Now, our model, however, is to make these regs and then re-assess; are we reducing prescribing. And I can say, in the state of Michigan, we've just gotten a recent data dump we've had pretty major reductions in prescribing in our state, and we're also seeing reductions in consumption.

So true to our goals, while monitoring patient satisfaction and patient-reported outcomes, we've actually updated these recommendations and will soon be adding recommendations for knee arthroplasty, hip arthroplasty, cardiac surgery, and a couple other orthopedic surgery conditions, as well as soon some pediatric surgery conditions. he goal is to get about the 100 most common surgical conditions to help guide care.

Now, how does that relate to today? Well, that's great. Going from a lot to less is an

important outcome. That's going to be important. But I really think one of the areas where we really need to move is elimination of that exposure when it's not necessary.

In the last session, you heard that there are many people that after 48 to 72 hours, don't need opioids, and that's true. We've actually seen that in our own data, both through some quality improvement work as well as some prospectively collected data. Really honestly, with a little bit of education, most patients don't need pills after 48 to 72 hours.

So I do believe that there are opportunities, and it would be a clinically important outcome to eliminate prescribing or eliminate exposure where possible, because time after time, we have seen a weak effect associated with the amount prescribed, but really honestly, the exposure is probably the most important piece.

When opioids are necessary, we believe we can reduce them. We do believe that new persistent use is an outcome that can be virtually eliminated.

We think that this is an opportunity with education both for patients, and for surgeons, and for primary care physicians, we can eliminate this. But we can do this in a patient-centered way. I certainly hear from the patient advocacy groups that I'm not interested in pain, or I don't care about pain, or I don't care about functional recovery.

I care a lot, but what we see consistently is as we reduce and as we change our prescribing, we can still manage pain appropriately and enable functional recovery.

For those times where we do have to prescribe, I do believe education is key. This idea that I'm going to make you pain free is not really the best goal. We want people to functionally restore. Giving somebody the expectation that they're going to be pain free is probably setting up the wrong expectation and probably leading to increased opiate consumption.

I think education also is required for our surgical population. Primary care physicians have

received a lot of education in the last few years because of the CDC guidelines. We need to do the same for our acute care providers.

We need to encourage simple things. Acetaminophens and non-steroidals have a powerful role and very low morbidity in most cases. I believe that there are important opportunities with local anesthetics, and I think there are other - non-opioid, non-medication things like behavioral care that could be very important.

We need to avoid prescribing benzodiazepines together with opioids, and we really encourage prescription drug monitoring programs. For the cases where opioids are prescribed -- and I think this to be true for the trials as well -- we think one short-acting pill is the right way. We see many times where surgeons prescribe multiple. We don't believe in long-acting opioids in people who are otherwise opioid naïve.

We don't believe that pre-operative prescribing is appropriate, giving a prescription to a person before their surgery. We see this as

independently associated with poorer outcomes, probably because people are starting those opioids before surgery and becoming tolerant. And we believe naloxone has a role.

So again, I am moved by the stories from STAT news, and these are the stories that I hear every day when I travel around from parents, from family members, and maybe from people on the panel today.

So how do we stop this from happening? I believe if we get data, and we share data, and we get different types of data, I think this is an opportunity for the public and private sector to partner.

I think we need to reward change. One of the areas where I do believe our program is novel is that BlueCross BlueShield of Michigan has been very thoughtful in creating payment incentives around changes in prescribing, both pay-for-performance measures for hospital systems but ProFee modifiers for surgeons, for protocols that we've come up with. We have a new modifier 22

program that's been rolled out in our state that allows surgeons to increase their professional fee if they follow guidelines that are not just about opioid reduction. They're also about education and good opioid stewardship.

We've got to collaborate. I really do think that this is great to see forums like this come together. I really become concerned when anyone tries to own or say that they fixed this problem because this is a very complex and very messy problem, and it requires all hands on decks.

These are my collaborators. Mike Engelsbe is a transplant surgeon. Jen Waljee is a hand surgeon, two of the most effective people I know. We're a couple years old, but we've been cranking hard, and they are an incredible team. With that, I would encourage you, if you want to learn any more work, find our prescribing recommendations, you can go to Michigan-Open.org.

I did not discuss it today just because of time, but we do have a Precision Health initiative. We have 60,000 patients that have been enrolled in

an opt-in bio repository that have all been genotyped, and we are looking at the genetic associations between that exposure around the time of surgery and new persistent use. Thank you.

Clarifying Questions

DR. BATEMAN: Are there clarifying questions for Dr. Brummett? Please remember to state your name for the record before you speak. If you can, please direct your questions to Dr. Brummett.

Dr. Rosenberg?

DR. ROSENBERG: Dr. Brummett, do you ascribe much of the effect on the state of Michigan to the change, which is pretty drastic opiate laws versus the initiative?

DR. BRUMMETT: Yes. So the question about whether the opioid laws are driving this, we have data that are not published yet, but we haven't seen any effect in the 7 states that we have looked at between these 5- and 7-day limits and any change in prescribing.

So actually, no. All of our data right now are pre-legislation, because I would look at it

this way. What is 7 days' prescribing? If you have 2 pills every 4 hours as needed for pain, that could be 84 pills over 7 days. If you go back to our prescribing recommendations, we have nothing that comes close or even bumps up on 84 pills. I think our biggest recommendation to date that will come out soon is probably 50 pills for a knee arthroplasty, which I believe is still too high, but the current standard in the community right now is probably more like 100.

So I appreciate that everybody's convinced that policy of just 5- and 7-day limits, or 3-day limits, or 1-day limits, I don't believe this is a patient-centered approach. I believe that there are ways to get people to decrease their prescribing through education and evidence. And I know that that's maybe slower, and I wish we had done what we're doing now 10 years ago.

But no, we don't believe that this is because of policy, and I've been intimately involved in that policy both change at the local University of Michigan level but also working with

our licensing board as they tried to roll out and understand that policy.

I think that there is a healthy mix of practice and policy, but I don't think the 5- or 7-day limits are going to change surgical prescribing at all, not in the same way that prescribing recommendations will.

DR. BATEMAN: Dr. Michna?

DR. MICHNA: I was wondering if we had any data on the persistent use on the incidence of clinically significant psychiatric comorbidities and what role that has, and other risk factors. And to that point, what you think about the role of pre-screening before surgery of all patients for risk and applying an education both to the patient at that point and to the physician in getting patients off opioids as soon as possible.

DR. BRUMMETT: Thank you. It's a complex question because there are actually a lot of things packed in there, so I'll unpack them if you don't mind.

With respect to psychiatric comorbidities, I

think probably the most commonly described are anxiety and depression. And I would say we talked a lot about catastrophizing. Catastrophizing has overwhelming overlap with depression. We're talking about a similar phenomenon. It is popularized because it's got a better name. But I think these factors are associated.

We haven't seen overwhelming associations in claims data. I think claims data unfortunately aren't the right way to do this because you have to see the right doctor, you have to have seen them recently, get the diagnosis.

We do see anxiety in prospectively collected data as being independently associated with increased opioid consumption. Now, what I don't want that message to be is, oh, anxious patients use more opioids; I should give more opioids. What it suggests is that we're not giving them the right medications. This is an opportunity for behavioral care, or there are multimodal medications that address anxiety.

The question of risk tools today, while

we're doing work in genetics now and I'm excited about that work, I think there are some simple things we can do today that surgeons don't do, which is to ask about previous substance use disorder. We don't ask. Do you personally have a history of opioid-use disorder or heroin use? If you ask that question -- or does a family member; have you ever had another substance use disorder?

Those are important questions. Certainly, untreated severe anxiety and depression are ways forward. And then I think the other places where we don't measure well and we have to measure better is in social support. It's a hard construct, and physicians and researchers are not very good at this, but I believe they're important pieces. Thank you.

DR. BATEMAN: Dr. Goudra?

DR. GOUDRA: Hi. Dr. Goudra from Penn Medicine. It's good to know that patient satisfaction isn't affected by decreased prescribing, but I also see that it's a national trend that opioid prescription is going down, but

we also know that the number of deaths are also going up.

Do you have any explanation for that?

DR. BRUMMETT: Yes. It's a great question. Thank you. We do see an increase, a spike in mortality, that's largely driven by fentanyl and heroin. And I would say that if we look at that, the average person who's on fentanyl or heroin is on the far-right end of the curve, and I think we can expect that severe mortality to continue.

However, I will come back and show the data that was published in the New England Journal of Medicine, showing that 75 percent of people who move down the path of heroin start with a prescription pill.

So they're starting with medications, opioids that are prescribed, maybe not directly to them, but to friends or family members. We know that among kids 12 and older who admitted to misusing or abusing an opioid medication the year prior, 55 percent of them got them from a friend or family member; 17 percent of them had been left

over from their own care; and only 4 percent mentioned a drug dealer as part of that problem.

These are easy to access. I asked juniors and seniors from a local high school, how many of you could go home and within an hour access an opioid? 75 percent of the kids, of these 100 kids, immediately raised their hand. I don't believe that means 75 percent of the kids are abusing their medications, but I think that they processed it.

So we need a parallel narrative that is about getting rid of our 30 years of overprescribing because they're sitting in medicine cabinets. In our opioid drives we see -- we do statewide opioid drives. We see medications that date back to the '70s.

So I think prescribing still matters, and I think it's part of the healthy narrative. It is not the full narrative today, and certainly there are many important things going on at SAMHSA, NIH, FDA, CDC around naloxone and medication-assisted treatment, and I think those should continue.

DR. BATEMAN: Dr. McCann?

DR. McCANN: Thank you. That was a great presentation. Mary Ellen McCann from Boston. You mentioned that there's evidence for a single exposure post-operatively, sort of sensitizing patients.

What about interoperatively? Is there any evidence? As an anesthesiologist, that would be really, really hard to change that practice, although in pediatrics, we do a lot of regional blocks.

DR. BRUMMETT: I think there is a hashtag on social media, #opioidfreeanesthesia. It is a hashtag without evidence. So I would say that it's interesting. When I talk to anesthesiologists, I encourage good opioid stewardship. However, I don't believe that there is any strong evidence to suggest that that sensitization goes beyond maybe the PACU.

So there are data to suggest that patients exposed to remifentanil or high doses of fentanyl, interoperatively when compared to saline, are maybe hyperalgesic. But that hyperalgesia appears to be

very short lived, and we don't know yet is that sensitizing or putting people down the pathway.

I could get deeper and sort of say if we think about reward pathways, if you give people fentanyl under general anesthesia, are we actually activating reward pathways? We don't know that. Ketamine's effect on the brain depends on your state of consciousness, and so we don't know this yet with opioids. It's certainly an area that our group is interested in studying. It is a complex question, and the data sources are not simple to get because intraoperative data aren't readily available in claims data, so we are trying with the multicentered perioperative outcomes group to answer this question.

DR. McCANN: A different question is we're working very hard in our pre-operative clinic to manage expectations, and we actively tell parents your child is not going to be pain free, but we don't want him to be miserable.

Have you come up with any guidelines to guide us to help our patients, or is that something

you're working on?

DR. BRUMMETT: On the michigan-open.org website, we actually have patient materials. I don't know that we've done a great job of tailoring them to pediatrics, but we've got patient materials for surgery, dentistry, and oral surgery, emergency medicine, and there's a primary care one coming out.

They're about acute care exposure, and they're there to educate patients about safe use, safe storage, and safe disposal with a box there for them to take some notes as they have that conversation, and we hope that these prompt education.

We've just done this through word of mouth. We have about 100 health systems in 20 states using these materials. They're colorful and engaging and hopefully are better than 8-and-a-half-by-11 printed paper that ends up in printouts, because you are right; setting expectations and educating patients is critical.

DR. McCANN: Finally -- sorry I'm sort of

hogging it here -- it struck me during your presentation that if you could send patients out the door with 6 pills or 4 pills because you figure they need 18 to 24 hours' worth of opioid pain management, that that would be patient centered as well as would eliminate a lot of patients ever hitting a Walmart or CVS and getting their 30 pills or whatever the surgeon is prescribing. And it would be kind to the surgeons, too.

DR. BRUMMETT: We are doing that now as part of our care pathway. We have done this now with about 75 patients who got 5 pills for things like laparoscopic gall bladder removal, thyroid surgery, sort of minor surgeries, but still that require opioids. And when you give people 5 pills, they use about 1.3. When you give them 30 pills, they use about 13.

DR. BATEMAN: Dr. Litman?

DR. LITMAN: Thanks. So many really interesting things to talk about, but I wanted to get your take on another influence of this that I didn't hear you speak about.

We just completed an analysis of opioid prescribing after surgery in children over the last 5 years, and even though it decreased, there were some other external factors that influenced it so much.

For example, in Philadelphia, we're on the cusp of New Jersey and Pennsylvania, and state laws differ as far as opioid prescribing, and insurance companies' policies differ. And the surgeons would go by that.

Not only that, but when I talk to my surgeons about what influences them, there are two main things. One is the hassle factor. They don't want to get called for more prescriptions after a certain number of days because they can't just easily call it in over the phone. That means the parent obviously has to bring the child to the closest emergency room if they're still in pain or the doctor's office. They have to go pick up the physical prescription.

The calls come in, and, of course, at least in an academic practice, the calls come to the

residents first. My ENT service would probably be the most active. There's a limited amount of resources. So a lot of it is practical.

The second thing is just simple computers, Epic. Our surgical attendings don't write the prescriptions. They say to the resident, "Give this kid the discharge instructions. Here's what you're going to write for afterwards" whatever, oxycodone or Vicodin. And when the Epic screen comes up to print the prescription, it's got suggested doses and suggested durations. And if you're a surgical resident, you're not going to really think about it; you're just going to click.

So those kinds of things really are, at least in our experience, really the main drivers, so much more than actual pain.

DR. BRUMMETT: Thank you, and you're right, and thanks for your work. We've done some work in pediatrics. Actually, Terri Voepel-Lewis, who will be talking later, has probably done more work in the pediatric space, but I'll say this. Again, I'll reiterate the fact that there's no association

between the number of pills prescribed and the likelihood of refill, and we know that that's driving it.

I will remind people that Atul Gawande wrote a really thoughtful piece in the Annals of Surgery suggesting that ePrescribe should be a national standard. We really have to leverage. Many people who have Epic don't ePrescribe because they haven't learned how. Let's just be blunt. They haven't learned how. They could ePrescribe those medications, the patients don't have to come back, but they have to learn how to do that. And that's an education piece. That's an unmet opportunity.

With respect to the suggestion, we are working on decision-support tools in Epic that I think need to be more thoughtful than just an order set. If you have to have just an order set, and if everybody has to know where that order set is, I don't know that that's the right way forward. But I do think at least an easy start is pulling together the order sets. And we've done that at Michigan, and it's been positive.

If you pre-populate 15 pills or 5 pills for a surgery resident, it'll go better. We have data that are coming out showing that academic medical centers prescribe about 20 percent more than non-academic centers, probably because residents drive the prescribing, and advanced practice practitioners, PAs and NPs, prescribe about 15 percent more than their physician peers.

Why? Who's handling the phone calls? So we know that there is a disconnection. Many surgeons and many practices don't actually know how many pills they prescribe, not because they don't care, not because they're bad people, but because it's just not part of the current care pathway. Yet, I believe that every surgeon needs to feel a responsibility for how much or what they prescribe going forward.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Yes. Joe O'Brien. Thank you very much, and very interesting. Does your data include adult spinal deformity patients? I'd be very interested in that because as you gave your

story, in real-life world, there's the rest of the story.

There is the rest of the story where you have a large patient population who is in pain, real pain for them, both in terms of the acute post-operative pain and in chronic pain for a longer period of time, with 30 percent complication rates, comorbidities, et cetera or they're playing it, that have very often explained that they feel tortured in certain states and certain areas; that they did not receive the amount of medication to manage their pain within the post-operative environment; that they felt abandoned when they left the hospital in terms of getting the amount of medication that was necessary.

They felt hassled in terms of now being the demon for something that they didn't ask for. They weren't going in asking for it. This is a result of something that they needed. So they feel hassled in terms of that. They feel demonized in terms of that.

So in essence, you have a large

part -- you'll not start everybody for sure, but you have a story where you have many patients that feel that they have become the problem, where they didn't ask for the problem to begin with. So they're looking out and saying, "Hey. Stop blaming me. Get a better medication."

So in the end, the sense is that you're very concerned about mistreating the medication that I'm given when the bottom line is they're being mistreated. That's the bottom line.

Do you get that?

DR. BRUMMETT: Thank you, and thanks for the opportunity to clarify because I love the opportunity to say a few things. Number one, I care about patients, and I am a pain physician. I came into pain medicine because I care about people. And I believe in patient-centered approaches to post-operative pain management, thinking about the full gamut.

I also believe opioids have a role. I manage patients with opioids, both in the acute world and the chronic world. It is probably not as

much as you would see in many practices. I'm very tight with how I manage my opioids in a way that's patient centered.

What I would say with respect to what I've shown today; I primarily am talking about people not using opioids before surgery because this has really not been a part of our conversation to date. We focused a lot on the chronic opioid user, and right now, the management of the chronic opioid user after surgery is best opinion medicine. That's the level of evidence we're working with in terms of how to best manage that person using opioids beforehand. It's an important category, and it's a category that needs to be filled, desperately needs to be filled.

I am in complete agreement that we need better medications for chronic pain, and I do know that there are people out there where physicians are misinterpreting the CDC guidelines, mismanaging patients after surgery, and I think this is the point of evidence-based regs, and these are recommendations.

I think the point is we're trying to give people a sense of where to be because we know we've vastly overprescribed for a long time, and we can prescribe a lot less. And that doesn't mean they can't get a refill. In fact, they will get a refill in many cases.

So while we hear those stories, and I agree there are two ends of a story, our group certainly isn't against opioid management after surgery, especially in complex cases, nor did we start with your complex cases. Why? Because there are millions, tens of millions of easier cases where we're grossly mismanaging patients in the country, and there's a lot of opportunity.

We are now doing work with spine surgeons. We are now doing work in knee and hip replacement. These are the more complex cases; shoulder surgery, painful surgeries where I think opioids have a role. But I'll push back a little and say that I don't know that after 7 days, being on an opioid because you have chronic post-surgical pain is the best choice in most cases. I would actually argue

it's not the best choice in most cases, and that's where I'll push back. And I think it's probably an area where we just won't agree.

MR. O'BRIEN: It's not agree. Now I can speak from a personal experience that, clearly, all the education in the world -- I'm very well educated on the situation, and I've gone through it 6 times, so it's not my first rodeo. So I've gone through it, and fine.

But pain is pain, and that's real, and we have to get around that. So in certain cases -- and this is patient specific -- you can have all the education in the world, but when you're in pain, you need something for that pain. And if you don't get it, that creates a problem. We knew that from before. We were undermedicating in previous lifetimes. So that is a real thing.

The concern I have now is also -- and we touched upon it a little bit and we discuss it with every panel meeting here -- there are always unintended consequences. So from an academic standpoint, you do something, it looks good, it's a

guideline. But there is a lot of misunderstanding.

I'm afraid that we're going to be back here for overdosing on gabapentin. I think there's overutilization of gabapentin as sort of a way. There's a misunderstanding with that. There's a shifting to long-acting. Why? Because of the number of pills. It gets under the radar, and you shift. You can get more MMEs if you shift a pill, so it's creating an unintended consequence that's going to create a problem. And we're going to be back here discussing in a different panel for a different problem.

So I get very worried in terms of the discussion only at an academic level. I think it's very important, and I praise you for looking at a real-world situation and making sure that in complex and simple procedures, that we do really have the opportunity for education at the prescriber level and allow that to be very patient centered.

We've gone through the last decade of talking a lot about patient centered, patient

centered, patient centered. We seem to have gone away with it on this topic. We're now more topic centered and not so much patient centered, so I don't want to lose sight of that. I think you have a lot of group of patients that are not feeling well served. Thank you very much.

DR. BRUMMETT: Thank you for the comment. And I appreciate you noting that ours is a patient-centered approach because that is what we believe in. Thanks.

DR. BATEMAN: Okay. Any other clarifying questions?

(No response.)

DR. BATEMAN: Well, in that case, we will now take a 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. We will resume at 10:25.

(Whereupon, at 10:04, a recess was taken.)

DR. BATEMAN: We will now continue with guest speaker presentations. Our next speaker is

Dr. Voepel-Lewis, also from the University of Michigan.

Guest Presentation - Terri Voepel-Lewis

DR. VOEPEL-LEWIS: I'm Terri Voepel-Lewis, and I'm a nurse researcher, and I'm here to represent the pediatric data, particularly related to the transition from legitimate or medical opioid use to adverse outcomes, including persistent use, misuse, and abuse.

I want to thank the committee for having me. I've spent the last 25 years of my career studying and trying to help others better manage pain in a way that's safe and more effective, so I'm really honored to be here to represent my team in this data.

I have no conflicts of interest, but I would like to acknowledge the funding that I have from the National Institute on Drug Abuse that funds my work related to educating parents, adolescents, and young adults on the risks of opioid pain management.

I also want to acknowledge my colleagues at

the University of Michigan, my teams at both the School of Nursing and the Department of Anesthesiology. I will be representing a lot of their work today on prescription opioid misuse and pain management, as well as risk understanding. The work of my colleagues has largely informed my understanding of this topic and also the work that I'll present today.

Lastly, I want to thank the earlier speakers for allowing me a little extra time because I may go a little rogue at the end of my talk today because I want to talk a little bit about measurement that I did not include here in my slides.

My goal today is to walk you through the trajectory after a prescription pain medicine use in childhood to the negative trajectories of, in particular, opioid misuse and abuse. As the earlier panelists talked about, there are other short-term adverse events that I have also been interested in my work, but today I'm going to spend my time talking about these adverse trajectories.

The other thing that I'll do is summarize for you the risk factors or the known risk factors that may heighten the risk for the adverse experience of misuse and abuse. And then lastly, I'm going to end with talking about at least my perspective on some of the targets that we could have to reduce the risk of prescription opioid use in children.

Some of the panelists have already talked about some of the trajectories. It sounds like what most of us would agree on is the expected or the hoped-for trajectory after prescription use is adherent short-term use, particularly after an acute pain insult such as surgery or trauma. That would be our goal for patients, is to use an opioid effectively and use it for the short term.

I would argue that sometimes persistent or recurrent use may be acceptable, particularly in cases of larger procedures or trauma, and I'll talk about some of those risk factors later. But in general, it sounds like what we're agreeing on is that persistent opioid use is also perceived to be

a negative trajectory after prescription opioids.

Finally, the topic that I'm here to talk about is misuse. There are several operational definitions of opioid misuse in the literature. There's what I would call non-adherent use or the misuse of one's own prescription where a patient, an adolescent, or a young adult takes a drug in a way that's unintended.

There's also misuse of others' prescriptions. And I think Dr. Brummett talked a little bit about this, the diversion that's in our communities, an adolescent or young adult taking someone else's medication. That has been referred to in the literature as non-medical use.

Lastly, there's abuse, which has been described or defined, at least by NIDA, or the National Institution of Drug Addiction, as the use of a prescribed medication for a psychotropic effect. It is really hard from the literature that we have to disentangle some of these operational definitions, so for this talk, I'm going to be talking about misuse in general, and then I'll be

more specific wherever the data allow me to be more specific.

The final adverse trajectory after opioid use are these adverse events, and there are adverse events that have been talked about earlier, constipation, nausea, those things that we know about, but in particular, the adverse event that we're most disturbed about is overdose, dependence, and addiction.

The path from prescribed use to these adverse outcomes remains a little bit unclear. We have some data in adults to suggest that persistent opioid use may lead to dependence and addiction. It probably does in adolescents. We don't have a lot of that data for adolescents and young adults.

We also know -- and I'll talk about these data -- how misuse of opioid analgesics can lead to dependence and addiction. Those data are really sparse, they're very limited, and I'm going to talk about those as well.

This very busy slide is meant to just give you a gist of where we get the data on misuse. All

of the data on opioid misuse comes from self-report and the main surveys that have been used to elicit misuse in adolescents and young adults.

In general, like the Monitoring the Future data, which has been asking this question since the 1970s, Add Health, which is the Adolescent to Adult Health Longitudinal Survey, and the Secondary Student Life Survey; these kinds of surveys had asked broad questions to try to get at prescription opioid misuse in kids. You can see, like the Monitoring the Future question is broad: take narcotics on one's own without a doctor telling you to do so.

A couple of these surveys have tried to get more specific to break down whether or not an adolescent or a person is using their own drug in a way that wasn't intended versus using someone else's, and that breakdown in question was really meant to try to differentiate what is perceived to be a riskier misuse of a medication, using someone else's versus one's own.

Again, as I walk through the data, I'm going

to refer to these surveys, and I'll talk about the limitations in our understanding based on these questions.

The other data that I'm going to talk about is this move to persistent opioid use and also persistent pain. As Dr. Brummett mentioned, the persistent opioid-use data has been derived not from self-report, but from large administrative databases most primarily, and these are private insurer database.

The definition "persistent opioid use" has been used differently by different researchers, and I would argue that it may be a misnomer because people have used it to indicate someone got a refill for an opioid between a period when you wouldn't expect someone to get a refill, usually generally more than 90 days after a procedure that you would expect pain to be resolved.

Persistent pain in much the same way, that data that we have has been derived from self-report, and again, it's self-reported pain that is outside a period that we would expect the pain to

have been resolved. And that could be 3 months, 6 months, 12 months after a surgical procedure or after a traumatic insult.

So these definitions of persistent, I'll use that term "persistent" but we need to take it within context. It could be recurrent, could be new pain, could be new use, and that. So that limits our understanding of what "persistent" means.

What do we know about prescribing in adolescents? The best, most recent data that we have tell us that more than 2 million prescriptions are dispensed to kids under the age of 18 years annually. These rates are going down to some degree, but still leave a lot of kids exposed to opioid analgesics. And you can see from this slide, the second line down is the prescription rate to adolescents, which we consider to be a slightly higher risk group, and adolescents far and away receive the majority of these opioid prescriptions.

This slide summarizes some of the Monitoring

the Future data on self-reported medical use or prescribed use and misuse. And as you can see from this slide, medical use self-reported has been going down over the last few years. But what's interesting to me about this is that it looks like, from these data, that misuse sort of parallels or aligns very closely with prescribed use. So the more prescriptions we have dispensed or that kids receive, the more likely they are to misuse or at least there's an association there.

There's a lot of variability in the prevalence rates of misuse across misuse, and I've just given just a little indication here that from Monitoring the Future, to the National Substance Use Database, to Secondary Student Life, there's variability. And this is based on the time of reporting, the way the questions are asked. But in general, about 1 in 10 kids by the age of 12th grade will admit to misusing a prescribed opioid. And when you get to the young adult population, it goes up in some surveys to about 1 in 20, or goes down based on the time frame asked.

Our colleagues at the University of Michigan have tried to dissect patterns of misuse in adolescents. What this slide, this again very busy slide, shows from the Monitoring the Future data, since 1976 until it ends at the far right in 2015, is that the majority of people who are exposed to prescription opioids do not admit to any misuse. But the data that tries to break down misuse has shown that the majority of kids who say that they've misused an opioid, and that's take it in a way that wasn't intended, take too much, take it more frequently, use it in a way that it wasn't intended, they did so after medical use. So they were prescribed a drug and then later misused the drug. Far fewer kids will report having tried the drug before they got a prescription for it.

The data from the Secondary Student Life Survey, which is a longitudinal survey of kids from junior high through 12th grade, my colleagues used this data to try to get at the trajectory from one year to the next in the pattern of misuse.

What this slide shows is that about 1 in 5

kids admitted to getting a medical prescription for an opioid by 12th grade. Once the prescription was given in year 1 of the survey, which was prior to 12th grade, about 81 percent of kids reported that they never misused an opioid. 1 in 5 kids who got an opioid prescription claimed to have misused their own medication, and a much smaller percentage, about 5 percent, reported misusing someone else's opioid prescription.

Then by year 2, that adherent group, the kids who got the prescription, used it in its appropriate way the first year and about a third of them reported getting a prescription the second year. We don't know if that's persistent use, recurrent use, new use. We have no idea, but they reported getting a new prescription.

Then about 15 percent of those adherent kids from the first year went on to misuse an opioid the second year. And you can see that the 19 percent who misused their own prescription the first year, about 15 percent of those kids went on to misuse others' prescriptions the second year. Then

finally, the kids who misused others, about a quarter of those continued to misuse others by year 2.

There have been a couple of different studies that have looked at the trajectory or the pattern of misuse in young adults, and these kids are mostly college-aged kids up to the age of about 23.

The top study used cross-sectional data from a large college life sample. and the bottom data used the Monitoring the Future longitudinal data. Both of these studies suggested that about 12 percent of college students claimed to have misused an opioid on more than 1 occasion, or more than or equal to one occasion.

You can see that the majority, a small majority, misused only on 1 or 2 occasions on the top data, whereas 1 in 5 misused on more than 1 occasion. And I think we would all agree that the more frequent the misuse, the more risky.

The bottom data suggests that about two-thirds reported misuse during one wave of a

survey only, that is a 1-year time frame, whereas about 11 percent reported misuse more frequently and chronically over several years. Again, we would I think agree that this 11 percent represents a high-risk group.

Dr. Miech from the University of Michigan did probably the most elaborate study to try to get at how does a prescription drug itself, when controlled for a lot of other risk factors, lead to the risk of misuse. What Dr. Miech did is he took the Monitoring the Future question, which again was that broad question, have you ever misused or the use of a prescription opiate on your own without a doctor's permission, but he tied it to a motive, to get high, to relax, or for some other reason. The reason that he did that was to try to get at abuse.

So these data apply to a small subset of kids who misuse their prescription for the purpose of getting high. We cannot extrapolate from these data to kids who misused for self-management, self-medication, and the treatment or self-treatment of symptoms.

What Dr. Miech did was he risk-stratified his group of students from 12th grade to 23 years of age, and he took out and tried to control for confounding of substance use the child's grades, the parents' education, and all the factors that create high-risk situations for misuse and abuse.

When he did that, he was able to identify that the prescription itself was a risk factor for misuse during young adulthood. It increased the risk by 2 to 3 times in these lower-risk groups of kids.

Dr. Miech also in that study was able to show a dose response from how frequently a kid misused an opioid, or in his definition abused the opioid, by 12th grade, and then later misuse or abuse during young adulthood. And as you can see here, the higher the number of occasions of misuse, the higher the number of occasions of misuse later in young adulthood.

Another cross-sectional sample of college students suggested -- and again this is self-reported data from a smaller study -- that self-

reported lifetime medical use, that is, prescribed use, was associated with twice the risk of misuse. And this study didn't control for as many factors, but did adjust for personal factors, the year of the survey, and for some reason, diversion as well.

The Monitoring the Future data has also been evaluated over time to examine how medical use by 12th grade or misuse by 12th grade led to misuse and abuse later in life at age 35. Monitoring the Future does these surveys every 5 years, so one of the things that I would note about this data is there is a 46 percent loss to follow-up. And I'll talk about limitations of the data later.

This study showed that medical use increased the odds of later misuse almost double that rate, whereas kids who misused by 12th grade had triple times the risk or 3 times the risk of later misuse during mid-adulthood.

So again, it's hard to unentangle the data on opioid misuse to abuse and dependence. But these same researchers have used the Monitoring the Future data to examine how does the pattern of

misuse relate to abuse of other drugs, other prescribed drugs as well as illicit drugs.

What our team found was that the kids who used medically before they misused had higher risks -- these are cross-sectional data, so higher odds of reporting other illicit drug use at the same time they reported misuse and also misusing other prescribed medications. The group who misused or tried an opioid before they were medically prescribed were at higher, much, much higher risk of reporting those same negative associations.

The other data -- and Dr. Brummett alluded to these a little bit -- that we have try to help us understand how prescription opioids themselves relate to abuse or addiction and dependence come from mostly retrospective data. These are data that have taken samples that report, or meet the diagnosis, or are in treatment for dependence and addiction, and then they recall what their first exposures were.

So they give us some sense that, yes, being

exposed to prescription opioids earlier and misusing those did happen before they moved to a dependent state or an addicted state. And this applies to both patients or people who are addicted to any schedule III drug or any prescription drug as well as those who are heroin users.

Of note, this top study, what they identified is that the lower the age of first misuse -- that people who recalled earlier onset of first misuse, that those kids were at much higher risk for abuse and dependence.

The data that I've sort of summarized to date talk about those trajectories. What's really more interesting to me is why do kids why do young adults misuse these drugs. And by far and away, the data that we have on prescription opioid misuse suggest that kids do it to manage symptoms. The highest motive is for pain relief or pain management, and then a lot of kids misuse these drugs to manage sleep or to help them sleep, to relieve anxiety. And about 1 in 10 kids who have misused this drug do so to get a psychotropic

effect, to get high or to experiment.

I'm going to talk about pain and misuse because I also think that's why we're here, is to talk about how we manage pain, and how we measure pain, and how we measure these outcomes so that we can reduce these negative trajectories.

The data that we have, again, self-reported, suggest that there is a strong association between pain and misuse. Dr. Groenewald from the University of Washington looked at the Adolescent to Adult Health Data, the Add Health data, and this was a longitudinal study from 1995 through 2008 that followed kids from adolescence through adulthood. And they found that kids who had reported chronic pain during adolescence had a much higher risk of later misuse when adjusted for other known risk factors, and this risk carried on into later adulthood as well. The sample was about 28 years of age when they followed them up at their latest time point.

The other risk factors that were also identified in this study included recent legitimate

use suggesting that these kids or that this sample also went on to continue to get opioids during adulthood. So this may indicate a persistent pain, persistent chronic opioid-use population, but again, we don't have all the details on that.

Substance use in childhood, adverse experiences, including neglect and abuse, were also related, and then another study that used that same database found that pain was a mediator between those childhood adverse experiences and later misuse.

One of the areas of my research has been to find out why people make the decisions that they do. And we surveyed about 1,000 community adolescents to emerging adults, and what we looked at, we wanted to know why these kids made deliberative intentions to misuse an opioid, and specifically for the purpose of managing pain because that's what I'm interested in.

What we found was that the group that indicated past opioid misuse were at higher risk. The people that had a higher preference for pain

relief or a higher need for pain relief indicated they were at higher risk for intentionally making decisions that would indicate intentional misuse, and then those with recent substance use also were at higher risk.

Probably most notable from my data was that we found that when people had higher perceptions of opioid risks and the risks of misuse, that that group was much less likely to misuse or to intentionally misuse an opioid. And what these data told us was that if we could boost people's risk perceptions, that we may be able to eliminate some of the misuse in this population.

The other data that we have related to pain gives us a little bit better understanding of persistent opioid use. What we know from community samples is that about 1 in 5 kids reports chronic pain. The students that I talked to in my studies have shown that these kids have ongoing or recurrent musculoskeletal pain, headaches, abdominal pain. It's very common in our communities.

When you look at after surgery, after spine fusion, after major procedures, we also have data that suggests about 1 in 5 go on to have persistent pain after surgery or an initial trauma. And then the data that Dr. Brummett talked about was that we know that from selected procedures, that about 5 percent of kids will go on to have what has been termed "persistent opioid use after surgery." And that is, again, use outside of a time frame that we would expect them to use it.

The risk factors for persistent pain and opioid use are not too surprising, at least to me, and I would imagine that they wouldn't be too surprising to most of you.

Major surgery, major abdominal surgery, in particular for kids, is associated with chronic pain after surgery and chronic opioid use. A gastrointestinal comorbidity, irritable bowel syndrome, which as we know is also a chronic pain condition.

Pre- and perioperative pain and opioid consumption, people have talked about that before,

but those are risk factors for ongoing and persistent pain. And then kids who need ongoing procedures. We have a lot of children who come in for procedures for chronic conditions and if they need a repeated procedure 6 months from now -- spine fusion is one of those -- those kids are going to have a higher risk for persistent opioid use.

The other thing that we have -- and someone asked a question about this earlier -- is what do know about mental health conditions. These are really important data that just came out, again using the large administrative database from private insurers, that these data found, this study found, that the diagnosis of any mental health condition during adolescence was associated with both opioid use and long-term use. And if a child had more than one mental health condition, it quadrupled the risk for opioid use and persistent use. And again, not surprisingly, substance use disorders and particularly opioid-use disorder quadrupled and increased the risk even greater.

So mental health diagnoses, mental health issues seem to be related, and I think Dr. Brummett also talked about that, depression and anxiety.

That finding isn't just from the large administrative databases. My colleagues have found that through Monitoring the Future data, through the Secondary Student Life surveys, that substance use -- and it's been measured in many different ways. But in general, substance use is associated with both medical use and misuse.

The other thing that I think I need to hound on is the relationship of substance use and abuse and misuse a little bit because all of these databases suggest that kids who need these drugs medically, who misuse them, misuse their own, and misuse others are all at risk for having either concurrent or future substance use disorders.

As you can see from this slide, misusing one's own opioid is associated with a much higher risk than just medical use alone, and then misusing others' prescriptions again increases that risk even more for substance use disorder or meeting

criteria for substance use.

I don't want to misrepresent these data because we know that there are limitations to all of our research, no matter what it is, whether they're well-constructed, randomized trials. But the limitations for these data are pretty great. We know that the operational definition of misuse has differed across the studies, which makes it really difficult to disentangle misuse based on why these drugs are misused.

There have been variability in the time frame of assessments. There are selection biases, obviously. Most of these studies are very well representative of our communities of kids, but kids do select to be in them. And then, of course, there's report bias, recall bias, and then loss to follow-up when you start looking at the longitudinal data. Then I would just mention that there have been imputation techniques for missing data that I believe personally also introduce a bias.

So I want to leave you with a few takeaways

that I think that these data tell us. Number one, we need to improve pain and symptom management in kids, and we need to do better longitudinal follow-up. And I know there was some discussion here about do you follow someone up for 4 weeks, that that's good enough?

I don't believe it is. I think that we need to follow up kids longer. And I know that those studies are difficult to do, but particularly after major procedures, I think we are remiss if we do not follow up patients longer, both clinically and in research.

I think we need to do better mental health substance use assessments, and when we note problems, that we need to intervene. I do know that for clinical trials, we tend to exclude kids with some of these disorders, and then we miss out on the opportunity to find out what happens and how we address pain in kids with mental health disorders. We know that at least in our setting, at the University of Michigan, we have a lot of kids that come in with mental health issues.

We need to improve the type of risk information that we give to adolescents at the time of prescribing, and this doesn't mean just rattling off a list of possible adverse effects, but helping kids understand what are the riskiest problems and how to avoid those problems. And I would also suggest that that's something we need to do for all patients, not just adolescents.

Then for future research, I think we need to adapt consistent definitions of what these adverse outcomes are. There's a really good article here that I'm going to leave you with here, Smith, that really defines what misuse and abuse is. And I think that those definitions, at least for me as a clinician and researcher, seem to be good enough operational definitions. So thank you very much.

Clarifying Questions

DR. BATEMAN: Thank you.

Are there clarifying questions for Dr. Voepel-Lewis? Please remember to state your name into the record before you speak.

Dr. Rosenberg?

DR. ROSENBERG: Dr. Rosenberg. There is evidence that 6 to 7 percent of middle-schoolers inject some illicit substance. Do you have any evidence for opiates and injection behavior?

DR. VOEPEL-LEWIS: I don't have any of the data here on injection. Some of my colleagues have gathered data on that particular method of misuse, and I didn't represent it here, so I can't tell you what those numbers are.

Six or 7 percent seems really high for me. I don't know where those data would come from because most of the data that my colleagues have when they ask about what route was used to use, most of them would inhale. Most kids who abuse for psychotropic effects, inhale.

DR. ROSENBERG: For our county, Washtenaw County, that's the number, but obviously it may be illicit steroids.

DR. VOEPEL-LEWIS: Maybe it's other prescription.

DR. ROSENBERG: It's just illicit substances, not specifically opiates.

DR. VOEPEL-LEWIS: Yes.

DR. ROSENBERG: But I agree with you. I found that incredibly shocking, but I'm told that number is middling for counties in general.

DR. VOEPEL-LEWIS: Yes. I guess we shouldn't be shocked too much, although I'm not sure -- so there's one other limitation to data that I have to mentioned when you're talking about high-schoolers and junior-high-schoolers. There's this thing called mischievous reporting, this little term called mischievous reporting. Researchers have tried to get at what is mischievous reporting and how does it affect the outcomes, and that kids will over-report behaviors.

But in general, when you start looking -- the data that I've presented, and I always think about that when I'm asking kids to self-report, is are they telling me the truth. And these data. because they're pretty consistent across most of the studies, suggest that kids are fairly honest, but we can't assume that they're honest. And I'm wondering if some of that 6 and

7 percent comes from mischievous reporting. I don't know. Maybe it's accurate. I'm not sure.

DR. BATEMAN: Are there data that you are aware of regarding the indications for opioid prescribing in children and adolescents, the proportion that are attributable to surgery or dental procedures?

DR. VOEPEL-LEWIS: I have some colleagues from -- well, now at the University of Denver, or at University of Colorado and also from Johns Hopkins that are trying to get around that, evidence-based guidelines. I've worked with some of my pediatric anesthesiologists from the Society of Pediatric Anesthesia to try to get at that, and there are people that are working on that.

The one thing that I would caution -- and this sort of addresses the gentleman here that was talking about surgery, or his own surgery experiences -- is that evidence-based guidelines apply to an average patient.

One of the things that I really believe is that guidelines can help us look at what the

average patient would use or need after surgery, but we know from these data that some patients need more. And they may need more because they come in with chronic pain or they come in with chronic conditions and those kinds of things, but we don't know. But the guidelines, I have not seen any specific guidelines yet, but I know they're coming out because I know my colleagues are working on it.

DR. BATEMAN: So I wasn't so much asking about the amounts that children are prescribed, but what are they getting opioids for? Do you have data regarding --

DR. VOEPEL-LEWIS: Oh, just in general.

DR. BATEMAN: -- due to injury, surgery, dental work, things like that.

DR. VOEPEL-LEWIS: Yes. The data that we have for kids suggests that most adolescents who get prescribed are getting them from either sports injuries, which is very common, surgery, and also dental procedures. So those are driving the highest opioid prescribing rates in kids.

DR. BATEMAN: Have there been any efforts to

link the indication for medical exposure with misuse?

DR. VOEPEL-LEWIS: The only data we have come from that study by Dr. Miech, that tried to dissect out -- well, he dissected out prescription use to his definition of abuse, which was misuse for the purpose of getting high. And it's about 2- to 3-fold increase, but the rate is really low.

DR. BATEMAN: Does it vary by the indication for the initial --

DR. VOEPEL-LEWIS: I don't think there's any data to suggest that.

DR. BATEMAN: Dr. Higgins?

DR. HIGGINS: I have two quick questions. Jennifer Higgins. We know that there inherently are problems with self-report data. Are you working on any standardized or more objective measures to get at this?

The second question is, what if any effects does exposure to treatment have with respect to trajectories for future misuse among adolescents?

DR. VOEPEL-LEWIS: Self-report for

misuse -- well, it's actually for all of these. I can't -- I've tried to come up with better measures, and if you know any of my work, we've tried to look at how we measure pain, for instance, after surgery. And self-report is the gold standard for how we do that, is we ask the patient.

For misuse, I would imagine that trying to get at asking kids how they've used these drugs in an adherent way or not in adherent way is the best way to get at that, unless you could get somehow to their parents or peers to find out whether they're misusing. But most of these kids and the kids that I've talked to actually just go into the cupboard and self-medicate, so self-report is the best thing that we have.

For pain and for persistent use, I would say, again, asking patients is probably the best measure that we have, but I would say that we probably shouldn't use overly simplistic measures, that we should use more broad measures about functioning and how pain interferes with regular activities because, to me, those are better outcome

measures.

So I'm not sure if I answered your question because you're talking about self-report in general, and these are outcomes that are pretty hard to get at if we don't go to the patient themselves.

One thing that I would say is, though, my colleagues, when they've tried to ask the self-report misuse question, is they've couched it in a way to indicate to the child that it's okay to report misuse, that we know that a lot of people use their medications in a way that aren't intended. So it gives people sort of this okay, this you can be honest with me because we know people do this.

So if we tell people that we're trying to find out how people use their medications, that we might get more honest answers, but that's the only thing I could say might get better self-reported data.

DR. HIGGINS: Then the second question with respect to treatment interventions affecting the

trajectory of future misuse.

DR. VOEPEL-LEWIS: We have no data right now that suggest that we can reduce the misuse rates except the data that I showed you that aligns with prescribed use. So decreasing prescription use might decrease exposures, and then it will remove the ability to misuse medications because the prescription won't be there. There won't be as many leftovers.

So that data, we do have. We do have some data on that, that suggest that alignment. So decreasing opioid prescribing from the start will decrease exposure.

The one thing that I would say is better pain management. If we can better pain manage -- and the data, I guess, given the associations between the pain outcomes and misuse, kids and patients need to manage their symptoms, and they're going to do it on their own if we don't do it for them.

So that's one target. If we can get kids to better manage pain in non-opioid ways, non-drug

ways, then maybe we can get kids to not misuse.

The other thing that I would say is managing other symptoms. It's fascinating to me how many people misuse their medications for sleep, and we know that opioids disrupt sleep. So they think they're getting sleep after opioids, but they're using it to manage sleep.

I've had parents during my surveys tell me they keep their opioids because they want to sleep on the plane when they're flying overseas. And I'm thinking to myself, it's just going to disrupt your sleep and make you feel worse later, but that's what they do.

So I think, if we don't help people understand how to better manage symptoms without these medications and address their mental health needs to decrease their anxiety, then we're going to have misuse because people will need to manage symptoms.

DR. BATEMAN: Dr. McCann?

DR. McCANN: Hi. Mary Ellen McCann from Boston. This may be getting to what Dr. Bateman

was getting at, but I think what you talked about is that early exposure is associated with an increased risk of later dependency and problems. And the implication is that that's causal, but maybe it's not. Maybe it's just impulsive, risky kids managed to fall off the jungle gym at an earlier age and are exposed because they're the personality type that's going to take risks with narcotics and are going to take risks with their body in terms of trauma.

So one way of possibly looking at that would be to divide out the indications that these kids were prescribed their opiates. Kids with appendectomies, you wouldn't think that that would be associated with risky behavior, but kids needing shoulder surgery, I mean, if you play football, you're not too worried about risk.

But you don't have any data?

DR. VOEPEL-LEWIS: No, but that's a really interesting point. And one thing I want to mention is that data that talked about earlier misuse, those are recall data. So we can't make any causal

assumptions at all about that. And you're right that the kids who misuse an opioid, or at least recall misusing an opioid before the age of 13, may be an entirely different group. They may be exposed in an environment -- they may have all kinds of those risk factors that go together.

So I do agree with you that studies that would differentiate, like underlying diagnoses, physical diagnoses, the reason that they were originally treated for pain are really important; though, all those surveys that we base the misuse data on don't really get at a lot of health data. The Add Health data is probably the best that we have, but a lot of those databases that people are evaluating now to look at this don't really have a lot of definitive -- they're all self-reported data. They don't have their diagnoses.

Then the administrative databases with the prescriptions things, they have diagnostic codes that can help us understand if they've been diagnosed with a mental disorder, but they can't help dissect other things.

So it's kind of really hard with the data that we have right now to get at that. But I would say that, going forward, we need to assess -- we would know going forward why we're prescribing a drug, but what we don't know unless we do it in a methodical way is assess for substance use in kids.

We haven't done it very well ourselves at the University of Michigan. We don't assess that very well. We don't assess mental health issues prior to surgery. We don't assess those things. They might have a diagnosis in an electronic chart, but we don't do that very well. And I think we need to be more methodical about how we do that.

DR. McCANN: Thank you.

DR. BATEMAN: Dr. Goudra?

DR. GOUDRA: Hi. Dr. Goudra from Penn Medicine; a couple of things. I know it's all self-reported data. Do you have any information on either race, or ethnic differences, or regional differences?

DR. VOEPEL-LEWIS: The data that we have on race, again, I didn't put all those data up here,

but we do know that the kids who are mostly prescribed are usually white kids. Minorities are prescribed less often. And in our samples, race was also associated with misuse.

I think the data on abuse and addiction is also panning out that way, that we've prescribed mostly to white, probably people with insurance, and those kids, at least in these data, seem to show up as having more medical exposure to opioids and more misuse.

DR. GOUDRA: The second question is what would happen if these kids who are either abusing or misusing are denied access to these drugs? What's your opinion?

DR. VOEPEL-LEWIS: Can you repeat that question, the first one?

DR. GOUDRA: What would happen if they don't have access to these drugs?

DR. VOEPEL-LEWIS: This is the caveat, because in my mind, the laws and the practices are changing to prescribe less. I guess my thought is that we can prescribe less for the majority of

people, but there are going to be people, kids and adults, that have ongoing persistent pain.

I just participated in a panel at the University of Michigan a couple weeks ago, and we had a panel of patients, and many of them had chronic pain. We have those patients with those issues.

So if we do not replace the opioid with other better pain management strategies, non-opioids and I would say, non-medical, non-medicinal approaches, and help people manage their pain and their mental health problems, that we're going to have ongoing misuse of other people's drugs or of street drugs.

DR. BATEMAN: We have time for one more short clarifying question. Mr. O'Brien?

MR. O'BRIEN: Thank you. Joe O'Brien. Thank you very much for your presentation. I enjoyed it. My question relates to following up on Dr. McCann and others on the slide, the second slide on misuse to abuse, and on timing.

Two decades ago, I was on a school

committee, and every year, we would get our surveys of the students, which were always alarming because you saw our trend. And it was always on both their drug and sexual behavior. And it was interesting to see because they seemed to be correlated.

So to Dr. McCann's point, there may be some indication there of the risky behaviors that go hand in hand that may affect later on rather than just exposure to the particular drug.

But my question was, with regard to the 4 or 5 adolescent heroin users, and again indicating that their first exposure memory was with prescription opioids, it always was in the past; alcohol was the first exposure.

So was this a directed question or was this a pure open question to say that opioids were in fact -- or was alcohol actually their first exposure to a substance?

DR. VOEPEL-LEWIS: Those data were based on qualitative surveys or interviews of patients that were in treatment for heroin or heroin and other addictions. So they're very minimal data, and the

recollection was the first opioid that they were exposed to.

So it could very well be that they were using other substances like alcohol, marijuana, and other things, and in fact, most heroin users use a lot of different substances. So the heroin users are really that far extreme of the opioid-dependent addicted people, aren't they? The opioid addicts that I have heard speak and have talked to said they were never going to go to heroin, but then it became the cheapest drug that they were going to use. But in the meantime, they were using all kinds of other substances to manage their symptoms, and to manage their addictions, and to avoid the withdrawal.

I just want to mention one more thing about risky behavior in kids. I do a lot of work on risky decisions, and we do tend to think that there are these impulsive kids, and that is true, but we also know that when kids have an exposure to a substance or they have an exposure to a behavior, like they drink or they take a drug, and they have

a good outcome and they don't have any bad outcomes with it, that decreases their risk perception dramatically.

So if a kid misuses their opioid that we prescribed them, they take a little more of it, they take it more frequently, and it relieved their pain, and by the way, it helped them sleep and helped them be less anxious, their risk perception plummets.

That's why in my data, you see that previous opioid misuse was associated with an intention to misuse, and I'm finding this in parents right now. I'm interviewing parents who take their kids home, and we're surveying them, And we're finding a link that the people that want to keep their opioids, the parents misused their opioids in the past. They either used someone else's, they shared their drug, they gave it to one of their kids, and it was okay. Nothing bad happened.

So they're willing to keep opioids in their house because nothing bad happens when they do this. If you have higher risk perceptions -- so

it's not just about impulsive behavior; it's also about perception.

MR. O'BRIEN: Thank you.

DR. BATEMAN: Thank you very much.

We will now proceed with the FDA presentations. Our first presenter from the FDA is Dr. Mallika Mundkur.

FDA Presentation - Mallika Mundkur

DR. MUNDKUR: Hi, everyone. My name is Mallika Mundkur. I'm a medical officer in the Office of Surveillance and Epidemiology, and in this talk, I'll be providing yet another public health perspective for the rationale on the development of opioid-sparing, opioid replacement drugs.

The main objective for this talk is to provide you with a framework for understanding some of the potential public health benefits of opioid-sparing drugs. We'll describe a number of existing public health issues relating to prescription opioids, where the introduction of opioid-sparing alternatives could have a positive impact.

First, we'll review recent data on prescription opioids and overdose deaths. We'll then highlight recent guidelines and policies that have created a pressing need for more alternatives to opioids and pain management. We'll describe changes in the levels of opioid prescribing in recent years and discuss the opportunity to further improve prescribing in certain settings such as following surgery, which we've heard quite a bit about now.

Finally, using the post-surgical setting as an example, we'll discuss the problem of leftover opioid analgesics, again which we've heard about nicely in the previous talks, and their contribution to the problem of opioid misuse in the general population.

In 2016, the most recent complete year of data that we have available from the CDC, over 60,000 deaths in the U.S. were due to drug overdose of which two-thirds involved an opioid and one-third involved prescription opioid specifically. Many of us are familiar with this

data, trending opioid-involved deaths over time in the U.S., with projections in this case for the year 2017.

In this graph, each line represents a different opioid type, and the blue line of course is most eye catching. These are deaths involving fentanyl, mostly illicit. However, you can also see that deaths involving prescription opioids, included in the group represented by the green line, also appeared to be on a steady rise and are predicted to continue rising through 2017 to a count of nearly 15,000.

This picture alone provides rationale for why safer and effective alternatives to prescription opioids are needed. Perhaps we could prevent some of these deaths.

To help clinicians with the very complex decision making surrounding opioid prescribing, a number of guidelines have been issued in recent years, and of these, we've listed some of the better known ones: the interagency guideline on prescribing opioids for pain, issued in 2015,

covering a broad range of pain conditions and scenarios; the CDC guideline on prescribing for chronic pain, this one targeting primary care clinicians and again prescribing for chronic pain specifically; the Michigan Opioid Prescribing Engagement Network we've heard about earlier from Dr. Brummett; and the Johns Hopkins Post-Surgical Pain Management guidelines, the last two being more heavily surgery focused.

In addition to these guidelines, multiple policies have been implemented or proposed in recent years to reduce the amount of opioids prescribed. Many of these, including the ones highlighted on this slide, have taken a sort of uniform one-size-fits-all approach with the occasional exception for specific conditions.

A number of states have passed laws limiting initial prescription durations or amounts. The DEA has proposed decreasing manufacturing quotas for several prescription opioids. And very recently, Oregon Medicaid has proposed tapering chronic pain patients on opioids to doses of zero, and these are

just a few of the policies that have been rolled out in the past few years.

While likely well intentioned, such policies do not account for variation and variation in patients, conditions, or reasons for use. They may lead to inadequate treatment of pain or other negative unintended consequences and create a need more than ever to expand options for the treatment of both acute and chronic pain.

Given the growing awareness of problems resulting from prescribed opioids together with some of the more recent policies, it's not really surprising to see that the amount of opioids prescribed has finally begun to decline.

In this graph, summarizing data from IQVIA National Prescription Audit over the period 1997 to 2018, we see units of opioid analgesic products dispensed, corresponding to the Y-axis on the left in the blue bars, and oral morphine equivalents in metric tons corresponding to the Y-axis on the right in the green bars.

In this graph, we see a peak in prescribing

around 2012 with a subsequent decline, in this case with projected data for the year 2018. Focusing in on more recent years, this graph also showing data from IQVIA, but for the period 2006 to 2017, we have on the Y-axis prescriptions in millions and on the X-axis the year.

The solid gold bars represent the total number of opioid analgesic prescriptions dispensed per year, while the blue and red lines represent data for immediate-release and extended-release formulations, respectively. These data also suggest a peak in dispensed prescription in 2012 with a subsequent decline to 196 million prescriptions dispensed in the year 2017.

You'll also note that the changes that are occurring are most prominent for immediate-release formulations, which are often prescribed for acute pain, though may also in certain cases be prescribed in the context of chronic pain.

Despite these changes in prescribing, which do appear promising at a high level, many of the policies, which likely have contributed to some of

these changes, have been strongly criticized by patients and clinicians for being blunt instruments, that on the one hand may decrease access for patients with a legitimate need for opioid analgesics, while on the other hand, not reassuring us that overprescribing in all scenarios has been fully addressed.

Taking these factors into consideration, Commissioner Gottlieb has said that one of the agency's goals is to reduce overall exposure to opioids while preserving access for those patients who will benefit.

As part of FDA's strategy in identifying opportunities to further improve opioid prescribing in the population at large, the Office of Surveillance and Epidemiology has conducted an extensive review of opioid use in the post-surgical setting.

One study that we've done using the Sentinel Distributed Database attempted to identify post-surgical populations where opioid exposure might be safely reduced while simultaneously identifying

patients where aggressive opioid reduction strategies may be more difficult.

In this study, we used administrative claims data from the period 2009 to '15, prior to the widespread implementation of limits on opioid prescribing, and identified opioid-naïve patients undergoing 1 of 12 common surgeries. We assessed how much patients were prescribed in initial prescriptions, graphed here with these box plots, and estimated use based upon patterns of refill.

We identified two groups of surgeries, which we'll refer to as higher opioid need surgeries and lower opioid need surgeries. In the former group, higher need refers to patients who, on average, received larger initial prescriptions and were more likely to receive additional opioid fills.

Our data suggest that for these procedures, spinal fusion, hip replacement, knee arthroplasty, and hip fracture repair, any widespread restrictions on opioid prescribing to these populations needs to be accompanied by much closer monitoring of patients for pain management needs

and opioid refills when appropriate.

For surgeries we identified to be lower need, we refer to patients who on average received smaller initial prescriptions and were also less likely to receive additional fills. For these procedures, laparoscopic cholecystectomy, hysterectomy, Caesarean, appendectomy, and tooth extraction, our results suggest that further reductions in opioid use may be appropriate despite the already lower levels of prescribing.

Dr. Brummett referred to this study I think earlier in his presentation, but to dive a bit more into detail here, this study is one example of a study that we've reviewed that extends our findings and gives us some similar insight on what patients actually need.

This study was based upon 33 health systems in Michigan during the year 2017. These are adults 18 and above. Patients in the study were included if they were prescribed an opioid after surgery and responded to a patient-reported outcomes survey.

Only surgeries with at least 25 patients

were included for analysis, explaining the distributions of surgeries we have represented here, which are predominantly general surgeries and gynecologic surgeries.

In this figure, the dark blue represents the median number of pills prescribed and the light blue represents the median number of pills consumed. Across the surgeries, it's very evident that rates of consumption vary, ranging from 3 percent for thyroidectomy to 67 percent for ileostomy colostomy, indicated by the red boxes. Of note, 24 percent of patients in this study took no opioids after surgery despite receiving a prescription.

In addition to looking at these rates of consumption, reflecting the problem of overprescribing and possible overexposure, this study also assessed leftover tablets, which we've heard pose a separate problem for patients and their families.

Here, we've highlighted a few of the surgeries that we identified to be lower opioid

need based upon our analyses that were also examined in this study. Moving from left to right, we see surgery type, the number of surgeries evaluated, the median number of pills prescribed, and the estimated number of leftover pills. Finally, we have the total number of leftover pills for that surgical category.

We can see that, with existing prescribing practices for these surgeries, leftover tablets across populations of patients can accumulate to a very large number.

We won't go over this table in detail, but this summarizes data from other studies that we've reviewed, underscoring the same points. The amount of opioids consumed varies extensively by surgery, though cross-surgical types, leftover opioids are a consistent problem.

In summary, our assessment of the post-surgical population through our own analysis in Sentinel as well as our evaluation of the literature suggests there are likely substantial opportunities for targeted improvement of opioid

prescribing practices, particularly in certain post-surgical subgroups. Opioid-sparing alternatives may play a key role in addressing some of these issues for the post-surgical population.

Although this may be self-evident, we just want to take a moment to really spell out the risks of leftover opioids in the post-surgical setting or any other setting, where more opioid analgesics are provided than used.

Leftover opioids are potentially problematic in that excess supplies combined with non-secure storage and lack of disposal, which we know is happening, can feed into other problems like third-party access, misuse, and related outcomes like abuse and addiction in patients themselves as well as family members. Leftover opioids can also lead to accidental exposures in children or adolescents, resulting in fairly serious outcomes.

Why do we know leftover opioids are a problem? Here, we have data from the 2017 National Survey on Drug Use and Health, a federally funded household survey of individuals 12 and older from

the general population.

Out of the estimated 11.1 million individuals who reported misuse of prescription pain relievers in the past year, the top sources where pain relievers were obtained were either from a friend or relative or the patient's own doctor, reported by 53 percent and 34 percent of individuals, respectively. In other words, when patients receive more than they need, those leftovers can be and often are misused by patients themselves in the future or by their friends and relatives.

Of note, NSDUH defines misuse fairly broadly, and this definition encompasses use of a drug in any mode other than as medically directed, including but not limited to abuse. According to NSDUH, the main reason reported for misuse of opioid analgesics was actually taking these medications to relieve pain, indicated by the red section of the chart.

While this reason may seem benign, this is self-treatment. It was not medically supervised,

and such self-treatment could lead to problematic patterns of use down the line.

A number of other reasons for misuse were reported, including to feel good or get high, to relax or relieve tension, to help with sleep, to regulate emotions, being hooked on the drug, or simply having the desire to experiment. With these reported reasons for misuse, it may seem a bit more obvious that they're potentially problematic.

By attempting to reduce the amount of leftover opioid analgesics available for non-medically-directed use, we may be able to prevent these behaviors before they begin in patients as well as their contacts. Replacement of prescribed opioids with opioid-sparing alternatives could have a large impact on levels of opioid misuse in the general population.

In summary, with this overview, we've attempted to provide you with a framework to appreciate the potential public health benefits of opioid-sparing drugs. We've described guidelines and policies that have led to potential issues with

access to pain medications that are expected to become more pronounced, highlighting the urgent need for new non-opioid alternatives to fill a rapidly growing void in pain management.

We've pointed out that opioid prescribing has decreased, though these changes might be more dramatic if effective alternatives to opioids were readily available and if overprescribing of opioids was targeted in a systematic evidence-based manner.

We've described our analysis on some of the literature relating to post-surgical populations, highlighting the problem of excess prescribing and leftover opioids following several common procedures, which are likely to contribute to the problems of misuse, abuse, addiction, and accidental exposure.

Opioid-sparing drugs, if used to replace opioid analgesics, could decrease leftover opioid analgesics and may in turn have a positive impact on the problem of opioid misuse in the general population.

Finally, to return to where we began with

opioid-involved deaths, we've discussed the large number of deaths that continue to involve prescription opioids, underscoring the fact that prescription opioids continue to be a major problem in the U.S. With the development and use of opioid-sparing alternatives, we could have an impact on some of these deaths.

In conclusion, opioids are associated with serious risks of misuse, abuse, addiction, and overdose, and opioid-sparing alternatives could be a great public health benefit by expanding safe and effective options in pain management while simultaneously helping to reduce the public health burden from adverse outcomes related to prescribed opioids.

I want to acknowledge the review team and end there.

DR. BATEMAN: Thank you.

The next FDA presenter is Dr. Pamela Horn.

FDA Presentation - Pamela Horn

DR. HORN: Good morning. My name's Pamela Horn. I'm a clinical team leader in the Division

of Anesthesia, Analgesic, and Addiction Products. Before I begin the content of my talk, I'd just like to thank Dr. Robert Shibuya as well as my other fellow team leaders and my division management for their assistance in preparing for this presentation.

Opioid sparing is a broad topic, and I'm going to try to focus my talk on information that can help the committee think about and discuss the questions that we have for them today.

As we saw in Dr. Mundkur's presentation, there's a huge public health burden associated with opioids currently. Sparing opioids has a potential role in meaningfully reducing this burden.

The types of effects that could be considered to be opioid sparing are fairly broad, and as Dr. Hertz mentioned this morning, they include decreasing the amount of opioid taken for analgesia while achieving comparable analgesic benefit, all the way to replacing opioids completely or replacing them in a certain setting, such as the inpatient setting, an outpatient

setting, or for a certain period of time.

Now I'm going to briefly go over the sections of my talk. I'll give an overview of relevant recent publications that we identified in a search for articles that included the term "opioid sparing" and then I will talk about relevant approved products for acute pain and briefly touch on precedence in defining a clinically meaningful treatment effect for opioid-related adverse reactions.

Then I'm going to shift to discussing options for study designs for future studies and what information they could provide about opioid-sparing outcomes and other effects that they could have.

In this section, I'm going to talk briefly about the study designs of the articles that we identified in the published literature. This is not meant to be comprehensive, but rather to give an idea of what is being studied and published in recent years.

The first point I'll make is that all of the

publications we identified were in surgery patients. In the studies described in these publications, all treatment groups had opioid available for rescue analgesia, and thus they weren't designed to manage pain without an opioid. All of these studies that were reported used quantitative measures of opioids as an outcome and most had no planned safety-related outcome.

Here, I've listed the different classes of interventions that were studied, and you can see that there's a broad range. Here, I've got a table of some of the other characteristics of these studies. In the left column is the first author and the publication year. The next column is the specific intervention. And as you can see, all of these studies were placebo controlled except for the first two.

Of the two that did not include a placebo control, one was a multimodal pain regimen which consisted of celecoxib, gabapentin, dexamethasone, acetaminophen, and ondansetron given at various times during the study, and that was compared to

usual care. And the other that was not placebo controlled, the control was paracetamol and oxycodone patient-controlled analgesia, and the intervention groups were different doses of levobupivacaine.

The studies all had opioid available as a rescue analgesic, as I mentioned, and a few studies specified opioid-related adverse events as an outcome of interest.

In summary, most of these articles report studies where an effect of an intervention on how much opioid was used for analgesia was compared to how much opioid was used in a placebo control group to see whether the intervention resulted in less opioid being used.

Now, as you'll see in the next section, this parallels the study designs for studies where opioid analgesic rescue use was described in an approved product label.

Now, I'll move on to summarizing the study designs and the labeling language in relevant approved products. There are four products that

describe opioid use in the clinical studies section of the label that are indicated for use in acute pain.

In the background document, we included two other products, and I will cover those separately because they are for different indications and not for acute pain. You can see that all of the studies enrolled a post-surgical study population. The study populations selected cover a fairly broad range, but they're pretty typical for these types of studies.

The products are two NSAIDs, an injectable ibuprofen for intravenous use and a ketorolac nasal spray, and there's an injectable acetaminophen for intravenous use and bupivacaine used for infiltration or nerve block.

All of these studies were randomized and double blinded. They were placebo controlled and the comparison to placebo established the treatment effect for the intervention being studied. As with most pain studies, all these studies allowed rescue analgesic medication, and in these studies, an

opioid medication was allowed as rescue in all cases.

Another possible way to study efficacy would be to use an add-on to standard of care, but these studies did not employ that design.

There were different opioid rescue medications used in these studies. All but the bupivacaine studies used morphine patient-controlled analgesia as the opioid, and patients in the bupivacaine studies had either intramuscular morphine or oral oxycodone available as needed as part of the rescue use available. These studies all measured pain based on patient-reported pain intensity on a rating scale, and opioid use was recorded by study staff during the treatment period.

The primary efficacy outcome in all but one of these studies was either the sum pain intensity difference over either 24 or 48 hours or the area under the curve for the pain intensity scores over 72 hours. In one study described in the ibuprofen product label, the primary planned efficacy outcome

was the difference in morphine consumption, and this was supported by the results on a pain intensity endpoint.

For the opioid-use endpoints, there were several ways that opioid use was summarized as an endpoint. The most common way was to calculate the mean milligrams of opioid use for the treatment group during the time period of interest, which did not go beyond 24 to 72 hours.

For the ketorolac product, the use in the ketorolac group was expressed as the percent reduction in use compared to the placebo group. And for the bupivacaine product, the endpoint was the proportion of subjects that used no opioid.

In the product labels, which were included in the background documents, all the labels described less opioid consumption in the active group compared to placebo. The mean milligrams of morphine or morphine-equivalent opioid were described in three labels, and the percent less opioid compared to placebo was described in the ketorolac label.

In the bupivacaine label, the percent of subjects that were opioid free at 48 and 72 hours were also described. Two out of the four product labels included a caveat that the clinical benefit of these findings was not demonstrated or established.

Here, I've summarized the information on opioid use in the labels of products where morphine PCA was used. Some of this information comes directly from the label and some of it is in publicly available reviews. You can see that the differences in morphine PCA use in the first 24 hours were similar.

A few things that may be of interest to describe in a label but aren't described in these labels are a difference in opioid-related adverse reactions and the number of patients who didn't require opioids at later time points.

As I've already noted, one of the products describes the proportion of patients that didn't use opioids in the first 3 days after surgery, but there may be other outcomes of interest such as

measuring how many patients didn't use opioids over a longer period than 3 days or after leaving the hospital, for example.

Now, I will briefly also cover two products that have different indications. These products aren't for acute pain, but they do describe opioid analgesic use in their labels.

In the first row, the product is indicated for endometriosis pain, and the opioid use in the studies was measured for a longer period of time. In this label, the proportion of subjects that discontinued opioids for their pain at 3 months and at 6 months is described.

In the second row, this is a product indicated for prostate cancer. And in one of the studies that's described in the label, as you can see in the last column, subjects were not taking opioids when they enrolled, and they were followed over a long period of time. And then the time to taking opioids for pain was assessed and reported for the treatment groups.

I've covered products with labeling related

to a decrease in opioid use. No products have labeling related to a reduction in opioid-related side effects. However, there are products approved in this area, and I'll briefly cover those.

The reason I'm mentioning these products is that we are asking the committee to think about a variety of possible outcomes related to opioid sparing, and I want to give examples of how a clinically meaningful difference in a couple of opioid-related adverse reactions has been defined.

One of the other previous speakers mentioned opioid-induced constipation, and that's the first one I have listed here. There are four products approved for this indication, and I've listed them here.

The efficacy studies that supported the approvals for these products were placebo controlled, and the primary efficacy outcome was a responder endpoint, where the response to the treatment was based on a measure of spontaneous bowel movements.

This next set of products is for

post-operative nausea and vomiting, and I've listed the five products approved for this indication in the table below. These studies were mainly placebo controlled with a superiority comparison, but there was one product that used an active controlled design and did a noninferiority comparison. The primary endpoint was also a responder outcome, and this one was based on vomiting and no antiemetic use over a relevant time period.

I've given an overview of what's been done in this area to date, and now I want to shift to some of the issues that we need to consider to guide future studies and development.

First, a quick reminder of what we stand to gain by investigating and describing opioid sparing; the first set of potential benefits are for individual patients, and they could include typical opioid-related adverse reactions. Then there are the substantial and far-reaching potential benefits in the realm of misuse, abuse, and addiction, both for individuals prescribed opioids for analgesia, as well as for people who

are exposed to opioids who are not prescribed the medication.

Having noted the potential for doing a lot of good, it's prudent to also think about what the possible unintended consequences could be. None of these are meant to suggest that we would not want to pursue opioid sparing but rather to point out some things that we should consider as we decide how to pursue studying opioid sparing.

First, let's consider if clinical practice in prescribing opioids changes as a result of advances in opioid sparing. If the analgesic benefit of the alternative approaches is not comparable to those of the opioids they are taking the place of, there could be a reduction in the effectiveness of pain management practices.

If approaches employ multiple analgesics given concomitantly or consecutively, the risks of each of these analgesics and possible interactions between them will need to be considered. And with the introduction of a novel analgesic, there may also be a new abuse liability introduced.

If less opioid is needed to manage a given clinical situation, prescribing will need to be adjusted accordingly to avoid increasing leftover opioids in the outpatient setting.

Finally, depending on how we approach describing an opioid-sparing effect, an effect that's measured in studies and described in product labels may not confer the benefit that prescribers and other stakeholders expect or hope to get for patients and for society in a real-world setting.

Now, I'll move into some other study design considerations that concern the questions we have for the committee. First, we want to ask the committee to consider possible study designs that could help determine whether a product could serve as a replacement for an opioid in a certain clinical setting.

The first piece would be to find and select the study population where opioid-level analgesia is clearly needed. Next, we should consider the control. For a placebo-controlled trial, the comparison will be superiority to placebo on

efficacy. We want the committee to discuss whether when studying a population requiring opioid-level analgesia, a comparison to placebo could be adequate to conclude that the intervention could replace an opioid or whether we would also need to see a direct comparison of the intervention to an opioid comparator.

If the primary comparison is to be the active comparator, then it would likely be a noninferiority comparison on efficacy. And another possible comparison to make would be to compare the proportion of patients that are not using rescue analgesic medication.

Now, I want to briefly say a few things about noninferiority studies since I brought them up. First, a noninferiority margin is needed. In this case, it would be the amount of difference in the treatment effect between the new treatment and the opioid that could be observed and still conclude that the new treatment is noninferior to the opioid.

The noninferiority margin chosen affects the

sample size needed, and the smaller the margin chosen or the less difference we are willing to accept between the treatments, the larger the sample size that will be needed. And finally, a potential problem with having only an active control and no placebo control is establishing assay sensitivity.

Even with opioids, the observed treatment effect in some types of pain studies has not been consistent. In a noninferiority study, if a difference is not observed between the active control and the new treatment, it could be because both treatments are successful in managing pain or it could be that neither treatment has been successful in managing pain in the study.

I'm going to say a few more things about the type of study that we've been more familiar with and that I've discussed today, first in the literature and then in the relevant approved products.

The ones that we've already looked at were by and large placebo-controlled trials with opioid

available as analgesic rescue, a primary prespecified superiority comparison on pain, and a secondary comparison on an opioid rescue outcome.

For completeness, I'd like to point out that another possibility would be to do an active-controlled trial with an opioid to demonstrate noninferiority on pain and superiority on an opioid rescue outcome.

Finally, the study can be designed to measure or compare clinically relevant differences in opioid-related adverse reactions. We'd like the committee to discuss where this should fit into the objectives of these studies and how such study results should be described.

The study design, particularly whether there is an active comparator, will directly affect the analgesic rescue and potentially the blinding and feasibility of the study. I'd like to make a few points about opioid rescue use for consideration.

First, rescue analgesic use can reduce assay sensitivity. One of the ways we address that in a study of acute pain is to take pain intensity

measurements prior to the patient receiving a dose of rescue medication. Another possibility is to use an integrated assessment of pain and rescue analgesic use.

The next point is that opioid patient-controlled analgesia is often used, and it can overshoot a patient's pain symptoms and not always be well correlated with pain scores.

Finally, I'll note that in a study where the goal is to show that an intervention can replace an opioid, designing the study with adequate rescue analgesic medication could be challenging.

On this slide, I've just listed a few of the non-opioid drugs or drug classes that could be considered for use as analgesic rescue in studies, and then lastly, I'll touch on possible approaches to defining outcomes that could be used to characterize an effect on opioid consumption.

One possibility is to only describe differences in consumption that have been associated with a clinically important outcome. In this scenario, a small difference in mean

milligrams of opioid used, for example, would not be described if it hasn't been shown to be correlated with lowering a risk associated with opioids.

Another possibility would be to use a dichotomous outcome of opioid use, which we've seen in some of the product labels that I have discussed. There is a broad range of possibilities such as whether a patient used an opioid for analgesia at all, or in a certain time period, or a certain clinical setting.

Then finally, we'd like the committee to consider a scenario where any difference in opioid consumption can be described in a product label, and prescribers can interpret how clinically important it is in their own patients and practice.

One potential benefit of not defining a threshold for when an effect can be described is that they all can be described, and if larger and more beneficial effects continue to come through innovation over time, the effects would be available for comparison in improved products.

Another possibility is to measure opioid-related adverse reactions. As I've shown you, there's precedent for defining a clinically meaningful effect on nausea, vomiting, and on constipation. And here, I've listed a few other adverse reactions, though not exhaustive, that may be able to be measured in a clinical trial.

In summary, there may be substantial benefits for individual patients and for public health and society in general to studying and describing opioid-sparing outcomes. To date, there is the most experience with studies that measure differences in opioid consumption between an intervention group and a placebo control group, and there is precedent for describing study results for these types of studies in product labeling.

There's also precedent for defining a clinically meaningful effect on an opioid-related adverse reaction, and then there are the other potential study designs that we'd like the committee to consider and discuss today.

Having said that, it's also important to

consider what other impacts describing these effects could have. Thank you.

Clarifying Questions

DR. BATEMAN: Thank you.

Are there any clarifying questions for the FDA speakers? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. We only have about 25 minutes, so if people could limit to just one question on the initial round, and then we'll come back to you if you have additional questions.

Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. This was a question for Dr. Horn. In your review of literature, did you come across any studies of specific procedure types that maximally benefit from certain modalities?

I'm thinking about feature studies, and I think that would be an area where there would be need, but I'm just wondering if you had come across anything.

DR. HORN: Could you be more specific with what modalities you're referring to?

DR. HIGGINS: So different therapeutic modalities.

DR. HORN: I think there was a pretty broad range of interventions, and it included things like multimodal therapies. So I do think that there's a pretty broad range out there of interventions that are being studied.

DR. BATEMAN: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Yes, Maria Suarez-Almazor. Most of the whole review has been on reducing aspects of opioid use, but you're also mentioning potential trials and replacement for opioids.

There were no trials that actually looked at replacement for opioids in this setting or they just have not been covered in this presentation?

DR. HORN: No. As far as approved products that have that as a claim, there are none. And in terms of the literature review, really, all of the study designs were such that there was opioid

available for rescue. So there was not a design that was intended to have a patient get no opioid and just have an intervention with that opioid.

DR. SUAREZ-ALMAZOR: Okay. But there was no parallel design that allowed for opioid rescue even in patients who are taking a fixed dose of opioids, compared to another comparator?. That hasn't been looked at?

DR. HERTZ: That would effectively be more of a standard-of-care comparator. For instance, the studies for the parenteral ibuprofen and acetaminophen, the studies were more of an add-on design, where we looked at -- let me take a step back for a moment.

Demonstrating efficacy for certain products is always a challenge, so if you want to look at the efficacy of parenteral acetaminophen, for instance, it's hard to find a situation where someone would use acetaminophen, alone perhaps, in a parenteral form where it would make sense.

So if you look at it in a perioperative setting where it might be useful for providing

additional analgesic benefit, it can be hard to show a difference in pain scores, so in some studies, it's hard to know how to actually demonstrate the effect.

In the study that Dr. Horn described, we did look at the amount of opioid that was not being used, or the difference in the amount of opioid being used. In that study, there was opioid use in the comparator, but it wasn't a fixed dose. But there was enough opioid use in both treatment groups that they could look at the amount of difference.

DR. SUAREZ-ALMAZOR: Okay. But for example, you have tooth extraction as a big area of use of opioids. There's no comparative study comparing opioids to a non-opioid analgesic at all? That does not exist.

DR. HERTZ: The problem with comparative studies is when we have a novel analgesic being developed, we always ask for comparative study. We want to know how the product compares to known analgesics. We think it would be very informative

for prescribers to have a sense of where a product fits in, aside from opioid sparing as a concept; just how does the drug work relative to known entities.

It's very hard to convince anyone to do that type of study. So we don't typically get comparisons to that type of active comparator in registration studies. A lot of times, it is against placebo with opioid rescue, but it's not getting to exactly what you're looking for.

DR. HORN: Were you also asking about the literature? The literature, we just looked at recent publications just to give an idea of what was being studied. So I can't really speak to things that were published 10 years ago.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: These are related questions on study design for Dr. Horn and Dr. Hertz. I understand these are placebo-controlled trials. I'm trying to understand if other background therapies were in the protocols.

For example, in a trial of an NSAID where

all participants are given acetaminophen or topical anesthetics, for a trial of a topical anesthetic or a local anesthetic, did everyone receive NSAIDs? Or did the patients in the placebo arm truly receive nothing except for an opioid rescue?

DR. HORN: For the approved products that I went over, the norm was not to have any background therapy. It was to have some type of opioid rescue in the placebo group, but it was substantial. So for the morphine patient-controlled analgesia, if you want to see my slide where I put the quantities, the average -- let me just check. I can ask them to put it up.

Slide 35. You can see that the consumption was fairly significant, so the mean morphine consumption on the PCA was 57 milligrams, 56 milligrams.

DR. FLOYD: Related to that, I'm trying to think if the reduction in opioid use captures anything other than the analgesic properties of the drug. Does the FDA think that that measurement captures anything other than the analgesic

properties, or is there something that I'm missing?

DR. HERTZ: For these studies, it was just used as another way to assess the analgesic effect of the study drug, and that's why, in the labels as described, the clinical relevance of those differences is reported as unclear or unknown.

DR. BATEMAN: Dr. Rosenberg?

DR. ROSENBERG: One of the problems in pain management post-surgery is that we have patients who are comfortable at rest, but then when you try and get them up for PT or they get up for the bathroom, they have extreme pain. And some of the methods for treating pain might be effective for at-rest pain, and that you gave them more so that they would have less pain for movement, that they would be sedated inappropriately for when they're not moving. But some of these agents may have the ability to work and not cause the side effects.

How would you describe that, if I'm not getting into the language issue? And is there any labeling that could be advantageous to the practitioner to cover this situation?

For example, in orthopedic surgery, a lot of times the nurses will give the patients pain medicine before they go off to physical therapy. So that use is something that, if we could provide practitioners, might make a difference.

DR. HORN: I mean, that's a very interesting idea. What is the question; whether we're interested in something like that? I think we would be.

DR. ROSENBERG: There is static versus mobile pain control. So you could argue that some of the non-steroidals, acetaminophen, regional anesthesia, have the potential to provide good pain control with movement while the opiates are good at rest, but not so good at movement.

DR. HERTZ: This is Sharon Hertz. We actually have studies in a different setting where we look at weight-bearing pain on movement; for instance, if somebody wants to study an ankle sprain.

So if somebody felt there was a drug that could address that particular aspect of pain with

or without others, there is a mechanism to study that, and we could describe it in labeling.

DR. BATEMAN: Dr. Lorenz?

DR. LORENZ: I think what you are asking, Jack, is also whether there's a corresponding measure of function for the inpatient setting. This applies, in a general sense, not just to patients undergoing surgery, but patients undergoing medical treatment who are elderly and whose discharge can be delayed because of delirium.

So it's striking that the studies don't look at those kinds of outcomes, but surrogates can be days to discharge or where a patient is discharged. There are a lot of ways of thinking about that. As a person who cares for elderly patients, it's a common complication of opioids.

DR. HERTZ: When we talk about opioid sparing with respect to adverse event profile, that could be something that would be very useful to know. If you can reduce the need for centrally-acting analgesics or for opioids in the elderly, that's exactly one example that I think

could be very useful to understand.

In terms of functional measures in the post-operative period, we struggle with that because we do think it's important. We see a lot of patients who have a variety of orthopedic surgeries used as models for studies. And if you have thoughts on what could be a good functional outcome, time to discharge is interesting, but what about falls?

So overall, they may be discharged early, but maybe there's more falls in that group as well so that you get an outlier group. What we need is a way to look at it in a clinically relevant setting for each, I think, clinical situation.

DR. BATEMAN: Dr. Rosenberg?

DR. ROSENBERG: Dr. Rosenberg. You have to look at that, though, dynamically because immediately post-op, you have different functions that are really important. For example, respiratory function starts to take predominance, or if there's a circulatory problem, those issues take predominance. But later on in the recovery, there are other functions that may be predominant,

urinary function, constipation, that they don't have confusion, which can develop in delirium.

So the recovery process is dynamic and it's by operation, that the orthopedic procedures tend to leave the GI system alone. They leave the respiratory system alone, while the intra-abdominal or transthoracic procedures impact those functions quite a bit.

So what you're asking, yes, we can monitor it, but it would have to be in huge population studies. And there's not a reasonable size population that we could ask a developer to come forth with that, that's going to be able to monitor to the extent that we would really like to see, to look for all these function returns.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. I have just a clarifying question for Dr. Mundkur on slide 9. I'm not familiar with the Sentinel Distributed Database. I was just interested in the classification of spinal fusion by levels primarily in terms of its utilization for opioids. There's a

vast difference by age.

Does that database break out by adolescents versus adults, or even primary versus revision surgery?

DR. MUNDKUR: Yes. We do have an age-stratified analysis as well. We haven't presented those data. We didn't look at the pediatric population in this round of analyses, but we agree that age is a critical factor as is the number of levels in the case of spinal fusion.

MR. O'BRIEN: Thank you.

DR. BATEMAN: Dr. Budnitz?

CAPT BUDNITZ: Dan Budnitz. In some previous presentations, we heard about screening tools to identify motivating tendencies toward opioid initiation. Is that something that's done in these other studies of other analgesics or other opioid trials, or was that done in some of these opioid-sparing studies?

DR. HORN: We have been seeing some of that in the submissions that we've been receiving, but the things that I put up there were approved

several years ago, those products. I don't know for sure, but I doubt it. I think it's becoming more frequent that we're seeing it and more recently.

DR. HERTZ: We do have a lot of studies that really exclude patients who have a history or propensity for substance use because that could cloud the assessment of analgesic efficacy if they're using opioids for other purposes, which is a problem in other settings in terms of understanding the overall risk of the product. It's multilayered, as you can imagine.

DR. HORN: One other thing, I will say that when we review study protocols, if we see that people are being excluded for psychiatric conditions, we always think about whether it's really appropriate to exclude them because we want to generalize as much as we can.

DR. BATEMAN: I have a question. Have you generated guidance regarding the use of patient-reported outcome measures, or have you seen patient-reported outcome measures in the

submissions you've been receiving, and which ones are people using?

DR. HORN: I just want to clarify. Are you asking about adverse reactions that are opioid related?

DR. BATEMAN: Yes, or some of the scales like the overall benefits of analgesia, quality of recovery, things like that.

DR. HORN: Yes, we do see them, but we have not seen them -- generally, they're not primary or key secondary outcomes. So they generally aren't included in the analysis plan as something that's a key outcome.

DR. BATEMAN: Dr. Lorenz?

DR. LORENZ: I was just going to follow up on the question about what other inpatient outcomes might be important to consider. I would just say, somewhat speculatively, that I would wonder about the appropriateness of something like delirium, especially in older adults. Of course, it's multifactorial, but because medications play such an important role, and it's so common in older

adults, I would think of it as an outcome with a great potential importance. And although it's not the same as function, it definitely significantly impacts patients' ability to participate in things like rehabilitation, so there are many reasons it would be important.

DR. BATEMAN: Are there any other clarifying questions? Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. It seems to me that we need a validated composite scale of opioid-related adverse events. Did you come across anything like that in the literature review? It seems to me, before we move to opioid-free treatment, that would be something that we'd want to start with.

DR. HERTZ: This is a challenging question that's been something we've been discussing with companies, how to look at opioid-associated adverse events. I think the scale that's been proposed most often is the Opioid Distress Symptoms Scale.

We've been somewhat reluctant to look at multi-domain scales here because it's hard to know

what's driving the outcome, and we think that's important. But as we move forward, we'd like to hear thoughts about that. If anyone's familiar with a particular tool, I think it would be useful and maybe adequately validated.

DR. BATEMAN: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Very quickly, just a question that I asked from industry before and that I was wondering. In these studies and in the way that you foresee these clinical trials to be performed, how was the rescue dose of opioids established? Is this a pragmatic approach where it is on demand, or is it, if pain is more than 5 over 10 on a scale, then a rescue doses are administered?

DR. HORN: For the patient-controlled analgesia, it's on demand, and that was most of the acute pain trials. For the as-needed ones, often there is a criterion for administering it in the acute pain trials. Then the other two products that were in chronic conditions, that is much more a patient decision because it's being taken on an

outpatient basis and chronically.

DR. BATEMAN: Any other questions?

(No response.)

DR. BATEMAN: In that case, we'll break for lunch. We'll reconvene again in this room one hour from now at 1:25. Please take any personal belongings you may want with you at this time. Committee members, please remember there should be no discussion of the meeting during the lunch amongst yourselves, with the press, or with any other members of the audience. Thank you.

(Whereupon, at 12:21 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:26 p.m.)

Open Public Hearing

DR. BATEMAN: I guess we'll get started. We're now going to have the open public hearing session.

Because the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making, to ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with industry. For example, this financial information may include industry's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the

beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and

any organization you are representing for the record.

DR. SINGLA: I'm not sure of the order, frankly. I'm Neil Singla. I am a speaker today.

DR. BATEMAN: No. You're speaker 3.

Will speaker 2 step up to the podium and introduce yourself?

(No response.)

DR. BATEMAN: Will speaker 3 step up to the podium and introduce yourself?

(Laughter.)

DR. SINGLA: I told you. I told you I was speaker 1. No. Thank you.

Yes, I'm pleased to be here today. My name is Neil Singla, as I said. And what I would like to do today is just kind of go over some background on opioid-sparing outcomes and share some information with the committee to help with its deliberations later today. This is a topic that has been of academic and scientific interest to me for my whole career, so I'd like to provide some information that will hopefully be helpful.

First, I'd just like to go over my biography really quick. I am the founder and CEO of Lotus Clinical Research, which is an analgesic research site and CRO in California. I'm an anesthesiologist by training. My main academic interest has been to understand and analyze how variability in analgesic clinical trials can be reduced, so I'm basically a clinical trialist. I design clinical trials.

In my role as a CEO for Lotus Clinical Research, I work with multiple drug companies, many of whom have applications in front of the FDA currently. My travel was not supported by any company today. Here, posted in the public docket, are the companies that I've worked with recently.

So that being said, starting here with the first slide, I wanted to talk about the value to drug developers of an opioid-sparing label claim and why what you're doing today is so important.

Historically, the information about opioid sparing has been buried in the clinical sections of the label for very good reasons. But because there

haven't been clear label claims around opioid sparing, what has happened is that developers have stopped pursuing in their clinical trial designs the very things that are being talked about today because there's been a really nebulous path forward for them as far as achieving a label claim.

So I guess the point is that the work that the committee is doing and will do in the afternoon is very important, and hopefully the outcome from that discussion will be some concrete recommendations so that developers can follow those recommendations and get label claims.

It's kind of a chicken-or-egg phenomenon. If the expectations aren't laid out, a lot of times people won't even try in their clinical trial designs to achieve those outcomes. And of course, the purpose of the label claims is to inform prescribers of what will happen with their patients, so for both of those reasons, this committee's work is very important.

I'll say that for the last 20 years, I've done probably 500 studies as an investigator on

analgesic drugs, and we've been looking to understand how to get label claims, so we've had a long history of failures. I'm going to go through about 4 or 5 slides describing what we've tried, and what hasn't worked, and what has worked, and hopefully that will help the committee to some degree.

Why do we have this long history of failures? First of all, as the first bullet point, as was discussed earlier today, there are only probably about 4 drugs that have any kind of label claim information in them in acute pain, and most of that information is incomplete and has lots of caveats.

The agency has rightly required robust evidence, and what has been required so far -- and again, I'm saying correctly required -- has been replicate evidence in multiple trials with prespecified endpoints that achieve significance, measured with a validated scale. That has been the benchmark so far from the FDA, which again is appropriate, but very difficult to achieve.

Why is it difficult to achieve? There are two main problems. A typical acute pain study is 100 patients per arm, and if you look at any one opioid-related symptom, only about 30 percent of patients will have it in a normal perioperative environment.

So studies are currently designed with a regulatory endpoint in mind, which is efficacy, so you can achieve efficacy endpoints with 100 patients per arm in an analgesic clinical trial. However, if only 30 percent of those patients are going to experience an opioid-related adverse event, then you only have 30 patients in each arm that you really have to compare to one another.

Therefore, getting a statistically significant result with those 30 patients is hard, regardless of which efficacy endpoint you choose or ORAE, let's say, nausea, vomiting, constipation, whatever. It's just hard to power it properly. So it's a powering problem, number one.

The second major problem, which I'll go through, is that there are not validated scales for

most adverse events of interest to opioids, and that argues potentially for a composite endpoint, which we can talk about also.

I'm going to go through 5 adverse events and our experience with them. First, nausea, nausea is a good one because it's problematic for patients, so they care about it a lot. It's frequent in the post-operative course. We know how to predict it with the APTHAL [ph] rating scale, so we know who's going to probably get it. As I said, it's clinically relevant and commercially important because of its clinical relevance.

The reason that you haven't seen label claims for nausea -- I think out of all of the label claims, this is the one that you could actually interrogate -- is because studies are underpowered. Like I said, it's a 30-patient-per-arm problem, and they haven't been prespecified, et cetera. So that's the problem with nausea.

I will say, based on one of the presentations earlier that listed 4 or 5 drugs, including Emend, et cetera, that had appropriately

interrogated the question of nausea, that is true, but those agents were primarily for the treatment of nausea. And therefore, those clinical trials were designed and powered with those endpoints in mind.

This is a different situation when you look at opioid sparing because these studies are powered for efficacy at the primary agent versus placebo. So you just have to try to win on this secondary endpoint, which most people don't experience, and that's really what the genesis of this whole problem is.

The other thing I'll say about nausea, the one good thing about it is, the patient-reported outcome in nausea, the NNRS, the Nausea Numeric Rating Scale, has been validated because other people had that primary endpoint like Emend, et cetera. They had to go through the process of scale validation because that was an important endpoint for them, and that hasn't happened with other opioid-related adverse events.

Vomiting is another good one, and just

quickly, it has the same problems as nausea. The only difference is that vomiting is easily quantifiable. It's not a patient-reported outcome. It's an observable outcome, measurable outcome; did you vomit? Yes/No.

Respiratory depression, this is a tough one. There was recently an advisory committee on this issue for a drug that was trying to demonstrate a respiratory depression endpoint. The one thing I'll just say to the committee, so that you can consider it, is if you're doing an efficacy study for a novel analgesic agent, which is what all of these agents are -- they're not agents to prevent respiratory depression like naloxone. That's a clinical trial you can do, and it's very easy to do. This is a clinical trial on an analgesic agent to show that that agent itself is better than placebo.

So then you have a 30 percent reduction in a morphine arm that's appropriately used between two different arms of patients that are getting hip replacements. It's very difficult to show the most

clinically relevant endpoint for respiratory depression, which is apnea, severe hypoxia, et cetera, because the incidence of those problems is so low.

So this is the problem with the respiratory depression endpoint, but it is the most clinically relevant and most important in our perioperative environment, I would argue as an anesthesiologist, because it's the most dangerous.

Constipation. The drugs also that were mentioned in the presentation for constipation did in fact show differences, but those were, again, primary agents for the treatment of opioid-induced constipation, number one; and number two, they were in chronic pain populations.

In acute pain populations, it's really difficult to show a difference in constipation just because patients who are in an inpatient environment, whether they get opioids or not, tend to have some degree of ileus. There's been years and years of development and attempts to demonstrate differences in these outcomes, and it's

been difficult in acute pain.

The last adverse event I'm going to speak about is somnolence. Again, it's really important because we want our patients to be awake, and somnolence leads to lots of downstream problems. But again, it's very difficult to measure because of the measurement error problems. It's really difficult to know how somnolent people are. Sometimes it's the nighttime. Sometimes it's daytime. You walk into the room. You wake the patient up just by the very nature of you being there. This has been our difficulty with somnolence.

This is the last adverse event, so at this point I'll talk about what have we turned to. Because of the powering problem, because of the lack of PROs, we've turned to composite scales. I think that composite scales, if the committee agrees that they are clinically relevant -- which I know there's been some discussion of whether they are or not, and I think that's a really good discussion. But if one agrees that composite

scales give you a good clinical relevance, then it would be an important, I think, step forward for us to be able to know what the agency thinks of them and which ones we can use.

I think the problem with the current composite endpoints is that they're not validated appropriately through the validation portion of the FDA's division, which I don't understand much about. But I think a first step here would be to understand the committee's feeling on whether composite endpoints are clinically relevant and important. Then if they do believe that they are, then I think that this process of scale validation can move forward. And if they believe that they're not relevant, then that process won't move forward. So that's kind of one of my wish-list requests to the committee.

I want to spend two slides just speaking on this topic, which is the difficulty of clinical trial design when it comes to these opioid-sparing outcomes, and I think this will help the committee in their future deliberations.

Let's use a hypothetical study here, where you're just doing the common pain model, which is bunionectomy, and the endpoint is a summary of pain intensity differences over 48 hours, or really what's relevant about that is that the endpoint is pain. It's about pain. It's not about opioid consumption.

You have to show a difference with your potent NSAID, which is your test drug, so you have some kind of new NSAID, let's say, versus placebo. And the difference you're trying to show is the difference in pain. Half the patients will get your drug and half the patients will get placebo. They'll have a bunionectomy, and then that's how the outcome will be determined.

Now, because half the patients get placebo, you have to use some type of drug for rescue. And if you're interested in demonstrating an opioid-related adverse event outcome as a secondary endpoint, that drug has to be an opioid. The rescue drug has to be an opioid; otherwise, of course, you won't have any opioid-related adverse

events, and the whole thing is nonsensical.

Here's the problem and the question that we face as study designers. If in fact your goal is to -- well, before we go there, if you allow the patients to have as much rescue as is possible, as much opioid rescue -- so you give them an opioid PCA and they take a lot of opioid in both arms, then it equilibrates their pain scores so that patients in both arms will equilibrate somewhat to the middle.

Now, we've seen that they don't equilibrate all the way, so patients that get an effective drug, even if they have a PCA, still have better pain scores than other patients, but it does reduce the assay sensitivity of the study if your primary endpoint is pain, which it is for regulatory purposes mostly.

If, on the other hand -- so if you use very minimal rescue and you say the patients can only have oxycodone once every 6 hours for pain, 5 milligrams -- that's in contrast to the PCA example I just gave -- then your pain scores are

going to be way different, but your opioid consumption is not going to be that different.

This is the problem when designing these clinical trials, is that the regulatory endpoint of pain is in opposition, to some degree, to the secondary endpoint of opioid consumption and then demonstrating differences in opioid consumption between the two arms.

This is just an add-on, another thought, which is, again, to the committee's discussions earlier today, that opioid-free patients is a very important endpoint that can be considered. Why? Because it's easily quantifiable from a clinical trial design standpoint. It doesn't interfere with our analgesic endpoint, either, of better pain control. It's not like the opioid-related adverse event problem. You don't need a measurement scale. It's easy to count. Did the patient get opioids after their surgery or did they not?

A couple of things I would bring up regarding this opioid-free patient and the things that we need are we need to know what the committee

thinks about what is relevant as far as a difference between opioid-free patients in the two arms; so how much opioid free. It's not going to be 100 percent, obviously. And in order to get a label claim, what does the committee think? And these are the guideposts that we as developers need and really help us design our studies and power our studies.

Someone mentioned earlier today 20 percent. A difference of 20 percent between the two arms of opioid-free patients is relevant. I think in acute pain, even just looking at the amount of opioid prescriptions, I would say between 10 and 20 percent, but that's for the committee to deliberate.

The other thing I would say is that in acute pain studies, you cannot achieve opioid-free patients in certain surgical models. There are certain surgeries that are so large that no matter how potent your drug is, you're still probably going to need perioperative opioids.

I think there was a slide with the high-use

opioid and the low-use opioid surgeries. When I say 20 percent difference, my feeling, of course, is that that 20 percent difference should be in the low-use opioid. Those are the people you can make opioid free. They're mostly outpatient surgeries. And in fact, it's the outpatient portion of the patient's course that's most important when it comes to being opioid free because that's what leads to dispersion of opioids in the community, not the inpatient portion.

If the patient gets Vicodin on their post-op day 1 of their knee replacement in the hospital, then that's still happening in the hospital, and those opiates are not getting out in the community.

Now, I'm not saying that that exposure to Vicodin while the patient is awake doesn't affect the patient's neurochemistry and is not a problem. I don't know that. But I do know that the prescription doesn't go out there. There's no pill bottle. So again, it's a very complex situation, and I'm just here to provide my thoughts, my personal thoughts.

This has been discussed, so I only have two slides left, and I don't think it's really worth going over again. I will say that, just anecdotally, I had a friend who had a bunionectomy. I do a lot of bunionectomy in clinical trials, and she wasn't in a clinical trial. She called me and she said -- it was with a well-respected orthopedic surgeon in our community, and she got 30 Vicodin and 30 Percocet to go home with, which I thought was extremely excessive, as has been discussed earlier today.

She called me. We kind of laughed about it, and I said, "Don't take it" only take opioids as you absolutely have to. And 3 days later, she got a car wash, and the pills got stolen out of her car. So they got dispersed into the community, which I think is what happens.

This slide also has been discussed. I will say here that we run a summer internship program for kids at our CRO, and one of the things we talk about opioids and what are opioids. One of the problems that I found to be really interesting is

we put up on a screen, marijuana, alcohol, Vicodin, Percocet, oxycodone, Tylenol, Motrin. Which of these are opioids? And the kids don't know which ones are opioids and which ones aren't. They know opioids are a problem. They started to hear that, but they don't know what are opioids.

When you give an 18-year-old that had a wisdom tooth extraction 20 Vicodin and their parents are telling them to take it because the doctor told them to take it if they have pain, that's really where the problem starts. So there's a lot of public education that needs to be done.

In any case, in conclusion, those weren't non-sequiturs, but those are just my feelings about this really serious problem. The problem is really serious and real. We as developers are trying to help solve the problem, and I really appreciate the fact that the committee came together today to contemplate this important subject, because giving us guideposts and goalposts really helps us move the ball along. Thank you.

DR. BATEMAN: Thank you.

Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. WALTON: Good afternoon. I'm Ashley Walton. I'm here representing the American Society of Anesthesiologists. No conflicts to report, but I will say I'm sure a few members of this committee are members of ours.

The ASA has about 53,000 members, and as a staff member, I work predominantly with our committee on pain medicine, which advises on a lot of the issues that you're discussing here today. In order to be more brief and not repeat a lot of what's been said, I'll just reiterate a few of the points that we think that clinical trials for acute surgical pain should include.

Really, our membership thought that the focus should be on patients undergoing elective surgeries and that those trials should focus on utilization of non-opioids and multimodal approaches for post-operative pain management;

focus on preventing the transition of acute to chronic pain after surgery; address adverse events related to opioid use in the perioperative period; and study opioid-induced hyperalgesia or OIH.

I think a few background points that really bear mentioning is that in the conversations I've heard here today, it's refreshing to hear that FDA has taken up this issue because in explaining I guess the relationship of anesthesiologist to other stakeholders who are part of this broader effort to address the opioid epidemic, I don't think it's always been the most obvious relationship.

So as a staffer that's worked with our membership, I feel I've frequently been out in the public, really explaining that the surgical period is an opportunity to address this issue early on and really provide prevention.

So again, to get back to these key points about the clinical trials, the multimodal analgesia is really, I think, the bread and butter of what our membership does. We think that trials on acute pain should aim to not only decrease opioid

utilization during surgery, but also examine utilization after discharge; so really trying to follow these patients' long-term outcomes down the road and not just short term.

Over the last decade, there's been a greater recognition of the problem of transition from acute to chronic pain following surgery, but it's still a pretty big phenomenon. So really, this is an opportunity to get more information and study the specific issue through these trials.

I know decreasing adverse drug events have kind of been a sticky topic today, but it's really, I think, an important thing to address in really deciding trial design and what product is effective.

Then lastly, opioid-induced hyperalgesia can occur with patient exposure to opioids during surgery and really result in those patients becoming more sensitive to pain. So there are multiple issues that contribute to this problem, but again, clinical trials can shed more light and new information on identifying risk factors for

preventing, reversing, and managing OIH.

So lastly, just to touch on outcomes, successful clinical trial on acute pain will measure the functional improvement of patients and their quality of life. So to repeat some of the points that were mentioned earlier by others in this room, quality of life is really based on psychological well-being post-surgery, so going beyond whether or not the patient returns to work, but overall mobility and if their life has returned for a large part as normal.

So again, thank you for your time today, and we did submit our comments to the docket, so you can take a greater look at those there. Thanks.

DR. BATEMAN: Thank you.

The open public hearing portion of this meeting has now concluded, and we'll no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We'll now have the charge to the committee

from Dr. Sharon Hertz.

Charge to the Committee - Sharon Hertz

DR. HERTZ: I think today we've heard a lot about the importance of reducing the use of opioid analgesics when possible. We've heard about consequences of early exposure. We've heard about the importance of reducing the amount in the community.

There are many reasons why this topic is important, and you've also heard that there are many challenges in determining how to best study this. But I think what we'd really like to hear in addition to how to study the problem is what should we be using the term for, because I think if we're going to use the term without understanding a definition, it's going to be very hard to convey useful information both to companies developing products, as well as to physicians and patients once products are approved potentially with this type of claim.

So we're going to go through this series of questions, and they're going to be read into the

record, so I'm not going to go over them right now. But we very much want to hear your thoughts, and we hope that at the end of the day, we'll have a lot of suggestions to work with as we move forward on developing what opioid sparing means with regard to drug development. Thank you.

Questions to the Committee and Discussion

DR. BATEMAN: So we will now proceed with questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

So we'll start with question 1. Question 1 has 7 parts, and I thought we would break it into 4 sections. The question is, discuss how to define a clinically meaningful decrease in opioid use to support an opioid-sparing claim considering the following options.

Maybe we could start with parts A and B. A is a statistically significant difference in average opioid use, considering that minor

differences in opioid use could reach statistical significance but may not be clinically relevant, and, conversely, that there could be a clinically relevant decrease in opioid exposure for many patients that's not reflected by a substantial difference in mean opioid use between groups. And then of a somewhat related point, reduction by an absolute amount in milligrams of morphine equivalents, for example, or percentage decrease in opioid use.

Are there any questions regarding the discussion question posed? Dr. Floyd?

DR. FLOYD: Are we just going to go around and give our answers to the questions or are you intending to have discussion beforehand?

DR. BATEMAN: So this is not a voting question. This is for open discussion. I thought we would take up A and B, and then we'll do C, D and E together, F and G, for question 1, and then there are two voting questions at the end. But initially, this is just discussion.

So if people want to weigh in with what

their answer to these questions are or make related points, please do so. So back to Dr. Floyd?

DR. FLOYD: Thanks. Before we get into a lot of these pretty technical questions, I wanted to step back a little bit and raise some issues about whether the use of this term "opioid sparing" on a label is appropriate to start out with.

I think there are two questions that sometimes get conflated. One is, is there a public health benefit to reducing opioid usage? Clearly, I don't think that's up for discussion.

The question we're being asked is, is there a public health benefit to labeling a drug as opioid sparing? And I think that's different issue, and I think the answer may be no. And I wanted to list three reasons why I think that.

One is that, in terms of looking at opioid use in a clinical trial after randomization, the determinants are the analgesic effect of the drug, which we care about, is biologically important. There's the use of background therapies, which as we've learned, typically there isn't much

background therapy. These are placebo-controlled trials, where the placebo arm is getting no effective analgesic.

Then most importantly, there are contextual factors that are completely external to the study design and the biologic effect of the drug. These are the local prescribing practices, the local opioid stewardship, the calendar year the trial is done based on trends, and even things like clinical decision support tools in Epic.

Dr. Litman mentioned his experience locally. I've experienced the same thing in my practice in a county hospital, where the house staff practice differently from one year to the next based on what the template orders are.

So these contextual factors are really strong determinants of this outcome that make me think that this is not a reliable outcome for which you can make a general statement that generalized to other settings. So that's one concern I have.

Another is that it may create incentives to use trial designs that don't really reflect

treatment decisions. So I think there are these competing pressures to try to show a reduction in opiate use, which may motivate trial designs that use no background therapy, which in my mind doesn't reflect how we practice.

If I have someone who had a tooth extraction or a minor laceration repair, I'm not thinking, do I give them no analgesia or do I give them an NSAID? I give them an NSAID or Tylenol. So I'm not really interested in the analgesic effect compared to placebo in that setting, and I think those are the trials that we're getting because of these perverse incentives.

Lastly, I am very worried about unintended consequences, and our patient representative highlighted some. I think that there is potential for inappropriate marketing and prescribing when we label drugs arbitrarily as opiate sparing when that really is just capturing their analgesic effect.

We have the recent experience with gabapentinoids, which is a different issue. These aren't drugs that have opioid-sparing labels, but

we've seen an explosion in use when the long-term effects of these drugs weren't known at the time of registrational approval, and now we're starting to learn them. So there are real risks from some of the labeling issues that are hard to predict.

I do think there is a role for studying these outcomes, however. Dr. Horn raised hypothetical study designs, and I think we like to see active comparator trials. Noninferiority trials are a possibility. They are a weak study design, but you can make a proper inference, especially when you have an ancillary benefit.

So you're making an inference that a drug is effective based on information totally external from the study you're doing. That is the weakness. And the reason you do that is because of some ancillary benefit, a reduction in side effects, maybe a reduction in opiate usage. So I could see a setting where it's important to measure that, and that could provide ancillary evidence that a drug has a beneficial risk-benefit profile.

Thanks for letting me get my comments out.

DR. BATEMAN: Dr. Lorenz?

DR. LORENZ: Thanks. I might take a slightly different tact. I'm thinking out loud a little bit, which is always a bit dangerous here. I agree with many of the comments Dr. Floyd made but might think about it a little differently.

When I think of unmeasured confounders and contextual factors that affect the outcomes of studies, for me that's an issue of both the stage of science -- in other words implementation versus effectiveness versus efficacy, et cetera -- and also trial design, randomization essentially, too often account for unmeasured factors. I think the hardest issue that you raise is that of how we think about controls.

So I think that the studies are important to do, but one of the challenges -- and maybe this partly gets at what you're saying, James, in a different way. I'm not sure we want just opioid-sparing trials. We want opioid-sparing trials and we also want opioid risk reduction trials. And this was discussed in one of our maybe

earliest presentations this morning.

If I were going to design a labeling strategy, I would not want us to use entirely surrogate endpoints related to some of these important clinical outcomes because of issues like unintended consequences. I think the bar for demonstrating societal benefit is high, especially when the costs of the drugs themselves are very high, which they might well be.

I also thought that in the discussion we had today in the preliminary evidence, the context of the trial is also very important in thinking about labels. It's not just opioid sparing or opioid sparing and risk reduction. It's also acute and chronic.

So I don't know exactly how many flavors I guess there are around opioid sparing, but it seems to me that the issue of whether it was the drug or the risk/outcome, and whether it was a short-term and/or chronic context in which to understand that were important as maybe dimensions of labeling.

DR. BATEMAN: Do other people want to

comment on the question that Dr. Floyd raises around the general utility of this opioid-sparing claim concept?

DR. ROSENBERG: I'm glad that we're finally getting to the language issue and completely agree with my colleagues here that acute and chronic are separate worlds and really should be discussed in separate entities because they're very different. But I think also, we need to be clear that we have to be precise in our language, that opioid side-effect reduction, opioid risk reduction, opioid adjuncts, opioid replacement, opioid alternatives need to be talked about and not just lumped into opioid sparing.

The label may be different depending on the application. Perhaps we could use acute versus minor surgery as a category because some medications may be effective opioid replacements for minor surgery, but they would not be for major surgery.

So I would like us to develop a language to describe what opioid sparing really is and to

appropriately label the benefits thereof.

DR. BATEMAN: Dr. Budnitz?

CAPT BUDNITZ: Dan Budnitz. So I'd like to add just a little bit to what Dr. Floyd was talking about. I agree with folks, that everyone has talked about, that there's a difference between acute and chronic indications. There's probably a difference between acute adverse effects, the effect on cumulative dose or time to discontinuation, and we'll talk about that.

But I do want to talk about this term "opioid sparing" and follow up with Dr. Floyd saying it should not necessarily be identified in an efficacy trial for the reasons he indicated, but rather maybe in like a phase 4 trial.

I think about analogy to the other AC I typically sit on, the EMDAC, and discussion about cardiovascular outcomes trials for indication of diabetes drugs for affecting cardiac outcomes, not just its ability to lower A1c. And those are done with a background of clinical practice.

So maybe that could be a way that an opioid-

sparing effect or indication could be identified and labeled, but only in comparison with opioids in actual clinical use, with a background of NSAIDs or acetaminophen and this active comparator.

DR. BATEMAN: Anyone else want to weigh in on this question? There are clinical contexts where opioids are routinely used. So if an analgesic could demonstrate that's non-opioid in nature to reduce the need for opioids in that clinical context, wouldn't there be utility of alerting clinicians to that potential use of the medication? I guess maybe we can comment on that thought.

Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Yes. This is more of a question to the FDA around labeling, and whether we are talking about referring to opioid sparing as a class of drugs or to a line in the description of the drug that says it has been shown that this drug was able to reduce opioid dosage in whatever setting. I think that's different, and I think part of your concern was creating a class of drugs

that's considered to be opioid sparing as a definition as opposed to just mentioning the actual results of what the trial shows.

For instance, I'm a rheumatologist, so some of the things we look for is quality of life, so you could find a drug that says it improved quality of life. So in the same way, it was able to reduce the dosage of opioids versus creating some sort of label around it. So I wasn't sure exactly what you were thinking of as far as labeling. I mean, the examples that we had, had all different language.

That was one comment. Another general comment that someone already made, I'm having some difficulty trying to think about a trial design that would encompass all the different conditions that we're talking about because it's very different, a tooth extraction from major surgery or a knee replacement, where you want someone without pain within 24 hours, to get them out of bed. So I'm having some difficulty as well with that.

DR. HERTZ: We have difficulty with that, too, and that's why we're here. This may be more

of the beginning of a conversation as opposed to the complete conversation, I'm predicting, based on my AC experience and your comments, where this may be going.

So I'm going to turn this back around to you, my committee. Should there be a class of opioid-sparing drugs -- I'm sort of hearing some concern with that -- versus describing what the difference in opioid use was, perhaps in section 14 of the package insert, which is the clinical trials section; and I'll throw out there more specifically, or would it be part of the indication?

Part of our thinking on this is how do we define all of this. We also worry a lot about unintended consequences. I mean, that's one of my primary jobs, is worrying about unintended consequences. But we also want to provide an environment in which development of products that could lessen, replace, and spare opioids is there for industry. So there must be something -- or must there be something to include in labeling?

So I'll turn that back to you. But I think it's all on the table for discussion. And I'm sort of hearing that our discussion might start to inch away from our specific questions, and I'd like to encourage Dr. Bateman to give some leeway to the conversation if it looks like it's productive, but not necessarily quite -- if our questions didn't quite capture it in a way the committee can express.

DR. BATEMAN: Okay.

Are there other comments around this issue that we're talking about?

DR. LITMAN: Thank you. Thank you, Dr. Hertz, for giving us that leeway because I had a bunch of comments here that I'm not quite sure where they fit in the framework. But they do build and in some instances say the same thing as some of my colleagues here have already said.

One of the things that has always bothered me about this subject, and some of the other studies that we evaluate here on the committee, is the prospective randomized-controlled study is, of

course, the gold standard. We all kind of agree to that. But the problem with that is it involves such a circumscribed set of patients because the most important aspect is to maintain internal validity, but that's not the real world. The real world is external validity. And getting to what Dr. Budnitz, that can only come from phase 4 trials.

What I fear is that if we're looking at this specific parts A and B here, where you can only approach that -- well, not only, but mainly approach that with a prospective study, we'd be missing many important aspects that might not be valid for different people and different conditions.

So I don't think those kinds of studies that we traditionally ask sponsors to submit to FDA for approval -- I think that would be a really tough task to ask our committee, or anybody for that matter, to decide whether or not they truly are opioid sparing.

What's better than opioid sparing, though,

is better than opioids. There are many different conditions or procedures where the drug in question, if you compared it against an opioid, would work better. There are two that appeared in the FDA's briefing material. One was for endometriosis and one was for prostate cancer. I don't know the literature comparing to opioids, but they don't address pain per se. They address the cause, the mechanism of the pain.

The other thing that comes to mind in my clinical practice is children who have urologic surgery will often respond to non-steroidals because of bladder spasms -- what's the other drug for bladder spasms; bethanechol? I'm trying to remember -- whereas an opioid wouldn't help.

So getting back to, Dr. Bateman, what you said before, it would be important to the public to let them know that an opioid would not be as effective as one of these other drugs that's specific for the mechanism of pain. I completely agree with that, and I would encourage trials of specific mechanistic drugs against the reason for

the pain as opposed to just treating the pain itself.

Those of us who have gotten opioids, we know that opioids aren't really good at treating the pain itself. They're really good at making you not mind it as much. Those are my comments. Thank you.

DR. BATEMAN: Dr. Michna?

DR. MICHNA: I think the term "opioid sparing" is too broad of a brush, and it's similar to my dislike for the whole abuse-deterrent labeling, too. It's the same thing. It really didn't describe the benefit the product brought to it. It was too broad of a thing. I think the same thing exists here with this opioid sparing. It's just too complicated and too broad to provide that kind of labeling.

You can see what's happening in other areas. People are taking this public health crisis of opioid abuse, prescription opioid abuse, and taking advantage of it from a commercial standpoint.

That's part of my fear here, too, is that

giving such a broad labeling claim will put pressure to utilize these agents maybe not always in the best interest of the individual that's going to receive the drug or in the interest of treating the problem in the first place. Those are my concerns.

DR. BATEMAN: Dr. Goudra?

DR. GOUDRA: Dr. Goudra from Penn Medicine. Just to echo some of the comments that were already made, in order for the term "opioid sparing" to be used on an uniform basis, I think you need to eliminate too many confounding factors when you're designing the trial. For example, it has to be pretty much patients undergoing similar surgery, similar pain intensity, similar background, because that's the only way you can compare is if, say, manufacturers want to use the label "opioid sparing."

The second thing is maybe they should also use the sparing in a 20 percent reduction or a 30 percent reduction instead of just giving one blanket statement that they are opioid sparing.

The next question, if there are two with a different mechanisms of action, is combining two drugs, one at 20 percent, another is 20 percent, are they going to have 40 percent pain reduction? So there's a rule that clinicians might start thinking along those lines, and as a result, yes, there could be unintended consequences, and the patient might suffer.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. I don't have any expertise in clinical design, study design, but to me, a clinically meaningful decrease is not necessarily in the opioid; it's in the negative effects of opioid.

Last month, we had a potential novel drug that was able to have two different pathways. One would activate the positive aspects of analgesia without having the negative aspects. So I could see that being there, so we may have something that, in fact, has the opioid receptor, but it provides a very important process.

But for me, if you're going to have -- I do

not like the term "sparing" -- a reduction, or elimination, or something, from a practical perspective, I would say that what's proposed here, B, to me from a practical level is important because what I see is the prescribers are being monitored by the MMEs. The patients are being educated and advised that they have to reduce down their MMEs.

So it reflects a very practical real-world pathway, what's happening out there, so to me, it is nice to connect whatever the design is to that real-world impact that's going to go all the way back down to the patient and in between. So I particularly like that measure that's there.

DR. BATEMAN: Dr. Budnitz?

CAPT BUDNITZ: Dan Budnitz. I would just like to give a response to Dr. Hertz's question about where would information on, quote, "opioid sparing" effects that we talk about appear. I do think the label in part 14 is an appropriate place. That's where, like, for example, I mentioned cardiovascular outcomes trials are described in

labeling for diabetes drugs.

So the trial that's used to justify this indication is described in section 14, and then one could have an indication that explicitly describes -- for these particular drugs, looking at the label is to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease.

So it could be something similar where it said that spared opioid -- the amount of opioid prescribed or the duration of opioid for patients after this procedure, in this setting. We can talk about -- or maybe a chronic patient in this setting, depending on how the trial was done.

So one could use such a term like "opioid sparing" but really would have to define what is meant by that.

DR. BATEMAN: So really giving some specificity in terms of clinical context to where the reduction of opioids were demonstrated.

Dr. McCann?

DR. McCANN: Mary Ellen McCann, Boston. I

don't think the term "opioid sparing" helps prescribers at all. I don't think any information is conveyed with those terms. It may help the drug companies market their drugs, and I guess that's important, but as a prescriber, a drug is a painkiller or not a painkiller, an opioid or not an opioid. And every clinical context is a little bit different, and you make your judgments as to what is the best pain management for the patient within the context of the patient's disease and pain state.

So I don't think the term "opioid sparing" regardless of how you define it, whether you say it's a 10 percent decrease in the total opioids the patient uses, or 10 percent patients need less opioid, whatever, I don't think it really helps the clinician or prescriber.

DR. BATEMAN: Dr. Lorenz?

DR. LORENZ: In testing the utility of the definition of "opioid sparing" I was actually pondering whether an antidepressant that addressed depression and pain complaints, for example, would

thereby be opioid sparing. Maybe it sounds like a strange question, but actually I think there is some clinical evidence there.

One of the other thoughts I had in terms of unintended consequences is this is an area where the pragmatism of the control is actually important because a lot of our opioid sparing -- NSAIDs or gabapentin was mentioned, and in certain clinical situations, they're appropriate and safe.

I guess this question, again, isn't just about the analgesic efficacy relative to a placebo, but two drugs in the current armamentarium that we might consider sparing but that are likely not to ever get a label. So I just wanted to throw that out there.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: I wanted to follow up on a comment that Dr. Bateman made. I've tried to raise the issue that the prescribing of opioids is so heterogeneous, that the term "opioid sparing" is inherently misleading. And it's also because it's a downstream effect of its analgesic property.

It's not an inherent unique property of any drug, so that's fundamentally problematic.

But you also I think responded with, well, there are some surgeries or situations where opiate use is uniform. I can imagine for some complex spine surgeries, that may be the case. And I think those would be the settings where, even if you restricted to section 14 in a very precise, descriptive way, you still have to restrict it to those populations where there isn't heterogeneity. So I think that's critical.

DR. BATEMAN: So you would see some utility in those clinical circumstances, potentially in those clinical circumstances where opioids are the mainstay of the approach to analgesia.

DR. FLOYD: Yes, but it's somewhat arbitrary. I tend to think that older patients undergoing a total hip are all going to get opiates. I just took care of someone in the last few months who needed none, and I was shocked. So there is heterogeneity I think that we can't predict. It's dependent on patient factors,

prescriber factors.

So I think even identifying those clinical scenarios where opiate prescribing is uniform in the standard may not even be as easy as we think, but even to make those claims in a very specific precise way, we have to restrict the patient populations.

DR. BATEMAN: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I will say straight up that I have real concerns about the lack of efficacy demonstrated via the current research and the movement away from standard of care. If I were thinking about designing trials, I would look toward standard of care being offered in different doses, different dose amounts versus a comparator as an add-on only. I have real qualms as a consumer rep about the thought of offering surgeries or post-surgical care without opioids. That's my bias.

With respect to part B of this question, we bantered around a couple of different percentages, 10 to 20 percent might be advisable regarding a

reduction of opioid use, but I don't think we have hard data on that, and I would be hesitant to come up with an absolute number.

Michigan was an encouraging bit of information, but I think more data are needed to answer that specific question.

DR. BATEMAN: So several people on the committee raised the idea of unintended consequences if a drug was labeled as opioid sparing. I don't think we've defined what we're envisioning in that regard and with much specificity.

Can people comment on potential unintended consequences that could accompany labeling a non-opioid analgesic as opioid sparing? Dr. Goudra?

DR. GOUDRA: It could be, for example, if I am talking about, say, combining two drugs, acetaminophen and ibuprofen, you're going to have side effects because of those two drugs to start with, and you might also have a situation that patients and prescribers might be drawn into this

false sense of comfort that our patient is not going to have too much pain, and they might suffer in pain because they're not getting sufficient pain relief.

DR. BATEMAN: So a neglect of using the drug in place of an opioid leading to inadequate analgesia potentially. Dr. Michna?

DR. MICHNA: Yes. There's such zealotry in abandoning opioids I mean, we see it all the time. I had a patient who had rheumatoid arthritis, and he was admitted to the hospital. He's not on chronic opioids and he has 5 flares a year. And he comes in, and he gets his opioids.

On the last visit, he did get a shot of an opioid in the ER, but when he went to the floor, it was a new paradigm. There was a team that was sent. We're the non-opioid alternative team, and we're going to talk you through this flare of RA without using opioids. And he was like, "Oh, my God, what are you talking about?"

But that's what's going on out there. There's a lack of individualization of care,

particularly when it comes to these opioids and the clinical situation. And that's the fear that I see out there, that there's more push to use these alternatives, which is great, but there are situations when they might not be appropriate. And there's the possibility out there that everybody gets so wrapped up in this, they're not looking at the patient, and what that patient needs, and what that patient's telling them. It's kind of a denial of what they're seeing in the rush to use these alternative agents.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: So I think I mentioned two classes of unintended effects, and I can elaborate a bit. One is simply widespread use of a drug with unknown long-term effects.

Take, for example, NSAIDs. I think we know the side effect profile of most NSAIDs, the common effects, but there are some that have idiosyncratic effects such as liver failure and things like that, things that we really don't know until thousands and thousands of patients are exposed. So we're

moving from the use of drugs that are very well studied to drugs that are unstudied, that are typically studied in a few hundred, maybe a thousand people if you're lucky.

The other is I think harder to quantify, but it's the incentive for trial designs that are less informative. So as I mentioned, I'm kind of puzzled at the trial design where you're not using some background therapies that are common in use. So while you have some internal validity in evidence of efficacy, there's little translation to effectiveness, I think. So there are some incentives that are hard to quantify, but are real.

DR. BATEMAN: Although presumably the latter concern could affect a trial that was just intended to demonstrate its analgesic efficacy. I don't see how it's tied closely to the opioid-sparing claim.

DR. FLOYD: You're right. They're together. And again, I think the reduction in opiate dose is simply a downstream effect of the analgesic effect. But if that is a main motivator, trying to get an opioid-sparing indication, you're going for that

number, that reduction in dose, so you're going to try to use as few background therapies as you can to maximize the use of opioid rescue. That's simply how you get the maximum effect in your trial. So I think that is an incentive.

DR. BATEMAN: Dr. Suarez?

DR. SUAREZ-ALMAZOR: I think there is a little bit of difficulty in wrapping around what we are really discussing now. Some of the unintended consequences, they really relate to chronic use, and chronic disease, and chronic pain. But I think, today, our focus is more on acute pain in the post-op setting and how to try to reduce the number of days because we know that more days may lead to chronic use.

But I think we need to narrow the discussion to that particular setting because, otherwise, we are going too broad and we're discussing use of antidepressants or gabapentin in the chronic setting. And I don't think that's our purpose today. Correct me if I'm wrong.

DR. HERTZ: No, that's right. We're really

more focused on the acute setting right now. We're tackling that first.

DR. SUAREZ-ALMAZOR: It will be more difficult later on, I guess.

DR. BATEMAN: Dr. Budnitz?

CAPT BUDNITZ: Dan Budnitz. I think the main unintended consequence is just overuse of this. The good consequence is to encourage development of alternatives. The unintended consequence would be, as mentioned earlier, misunderstanding of what this term means.

That's why I think these follow-up next questions about what exactly do we mean by opioid sparing in terms of duration of use, amount of use, opioid free is the real key issue that can hopefully avoid misunderstanding, if we can define.

DR. BATEMAN: So maybe we will go back to the question. We're going to discuss how to define a clinically meaningful decrease in opioid use to support an opioid-sparing claim, all of the concerns around opioid-sparing claims aside.

So the first two components are a

statistically significant difference in average opioid use, and you can read all of the components of that point, and then B, a reduction by an absolute amount or percentage decrease in opioid use.

Maybe people can comment on those endpoints. Mr. O'Brien?

MR. O'BRIEN: I don't know about those endpoints, but just the last thought, the sparing, I have such a difficulty because, in an acute setting, post-operative, whatever, as we've seen over and over again, there's such variability at the moment. What's standard of care? What are you sparing from? There are a million patients and there are a million different prescriptions that are out there, so I don't know what the base is to say you're sparing from. You could have two doctors that are going to have a 50 percent difference in what they prescribe, so it's very hard to define.

DR. BATEMAN: Dr. Suarez?

DR. SUAREZ-ALMAZOR: I don't think A is

really very useful because a statistically significant difference does not speak at all about a clinically meaningful decrease, so I'm not even sure why it's considered there because that's so dependent on sample size, so it doesn't really give information on what's clinically meaningful.

B, I think it's useful because it's quantitative. The problem is that we don't know how that translates into the outcomes that we're interested in, the clinical outcomes, or at least I don't know what's the difference in milligrams or the percentage decrease in opioid use, and whether it depends on how high you start with, whether in that case a percentage is more appropriate than an absolute amount, or whether it's just reaching a threshold where the adverse events at that dosage can be a little bit more limited.

So I think it's a good outcome, but I don't know that I for one have the information to really come up with what would be appropriate. And I don't know if there is any data around that, either, from the trials that were presented.

DR. BATEMAN: Dr. Shoben?

DR. SHOBEN: So I just want to make a quick statistical point, which is to say that this average difference in opioid use, if you're talking about pills going home, could very well be a meaningful question in terms of total number of pills that are going out into the community and reducing that by even a small amount might have important public health consequences

DR. BATEMAN: Dr. Lorenz?

DR. LORENZ: I have a question because I don't work in acute pain as much as I do chronic pain, or at least my work is more distributed across both settings. But my framework for answering this question is what do we know about thresholds of risk. In the chronic pain literature, there actually are risks across various levels, even though the guidelines pick certain ones that are closer to 1 or 2, where we talk about goals for prescribing, but I don't know if that's true in the inpatient setting.

So I'm kind of asking, I think what we heard

in terms of evidence and what would make me think is important on the basis of what was presented is the ability to forego opioids in opioid-naïve patients would be a crucial outcome here because it's actually exposure to the drug that I believe I heard was crucial unless someone can correct that impression.

DR. BATEMAN: Does anyone want to comment on that point?

(No response.)

DR. BATEMAN: So the question being raised; is there an evidence base for a meaningful reduction in daily use in milligrams morphine equivalent or a percentage decrease in opioid use that would translate into clinical benefit, or reduction in side effects, or other opioid-related adverse effects? Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. I guess the only thing I would say is that everything that we said just seems to define that less is best. So it's just a matter of less. You know what I mean? That's fairly what it seems to be. There's no real

definition that I'm aware of.

DR. BATEMAN: Dr. Goudra?

DR. GOUDRA: Since the topic for discussion is in the larger context of opioid epidemic, for a second ignoring the utility of using an opioid-sparing definition, I think both parts of A would be relevant. Both would indicate decreased opiate use anyway in some form. And again, B, absolute amount was a percentage decrease.

It's kind of a bizarre question. I'm still trying to get my head around it, and I'll just leave it at that.

DR. BATEMAN: I am personally not aware of any literature that's clearly demonstrated what are the meaningful differences.

DR. LORENZ: I'm just imagining in a critical care setting, where patients are supported in an intensive care unit, that risk means something very different than in an unmonitored setting.

Again, when we think about risk, are we thinking about the risk during the hospitalization

or the risk down the road? Clearly for the latter, it seemed like exposure alone was significant for some small percentage of patients. But the risk of respiratory failure when you're already ventilated, we're talking about something different.

DR. BATEMAN: Other comments on this point? Dr. Floyd?

DR. FLOYD: I just wanted to second what Dr. Lorenz said about absence of use, especially in settings where use is uniform and there's not much variability, it's probably a higher priority than differences in dose, so I support that.

DR. BATEMAN: Maybe I'll just push back on that a little bit, though. You could imagine scenarios after major surgeries where patients typically require very large amounts of opioids and have pretty significant side effects associated with those, a 50 percent reduction could be extremely meaningful.

Other comments? So maybe moving on to C, so a decrease in the duration of opioid analgesic therapy that's required in the inpatient setting;

for example, opioid analgesics only being required in the immediate post-operative period.

So I guess here the idea is if there was an analgesic that allowed opioids to be given for just a very short time and then were adequate to control post-operative pain, for example, beyond the first day or so after the procedure. Would that be a meaningful endpoint? Dr. Suarez?

DR. SUAREZ-ALMAZOR: Yes. I think that's an appropriate outcome. Yes.

DR. BATEMAN: Dr. Litman?

DR. LITMAN: I agree, especially in light of the evidence that people who tend to stay on the opioids past the acute period are more likely to stay on them for a longer period of time, so I agree.

DR. BATEMAN: From the presentations we had, clearly opioids dispensed to patients after discharge have public health consequences in terms of the potential for diversion down the line. And so if there was an analgesic that allowed the patients to just have a very short course of

opioids and not require opioids after leaving the hospital, that would be potentially meaningful from a public health perspective.

Dr. Lorenz?

DR. LORENZ: I was just going to offer that it's hard to comment on this apart from other outcomes that one might envision. So again, part of it is setting, like a dose reduction means something very different potentially in an ICU than in a ward setting, but also, it is particular as well to the goal of the opioid reduction.

There's the patient with comorbid ESRD and then there's the patient who's recovering from hip surgery, and those are very different risk situations. We talked a little bit, for example, about function or proxies for function or other kinds of outcomes that might be important.

Again, you're balancing analgesia, other goals for the patient, and pain relief is very important in achieving mobility right at the same time that opioids can provide it and take away the capacity for mobility.

So it's very hard to think about it in isolation because the reduction in dose by itself could imply a tradeoff in some of those. So you couldn't just measure reduction in dose and be confident that you were achieving it, although I agree with your statement that it's very important in some settings.

DR. BATEMAN: Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I agree with it in principle, but I'm just wondering, in practice, how this would be discerned. Again, to sound circular perhaps in my comments, I don't know how we would ever assess this without offering someone nothing in the post-operative period. If an agent did not have the positive effect that we expected, would they have placebo or nothing? And that to me seems scary.

DR. BATEMAN: Other comments on these three points?

(No response.)

DR. BATEMAN: So maybe I'll just try to summarize where I think we are in terms of the

discussion so far, which will not be easy. I think everyone acknowledges the need to reduce opioid use, inappropriate opioid use. Many members of the committee were concerned about labeling of medication as having opioid-sparing effects because it's really difficult to define what exactly that means. It's going to be highly context specific depending on the particular surgery that the patient underwent and specific patient characteristics.

It's a very broad category, and there's concern that by labeling a medication in this very broad way, it could lead to unintended consequences, including overuse of that medication, using that medication, and decreasing the amount of opioids that the patient's prescribed inappropriately, leading to inadequate analgesia.

Some people question whether it would be clinically useful, that it's more important for the clinician to know that the medication has analgesic effects and then they can incorporate it into their analgesic plan for a patient, which may

include many different types of therapies.

There was some concern around the perverse incentives that going after an opioid-sparing label might introduce into trial design whereby standard approaches to analgesia might be withheld, like NSAIDs or Tylenol, in a way that might not reflect real-world practice and may overestimate the impact of the medication in terms of its opioid-sparing effects.

In terms of the specific points raised in the question posed by the FDA, I think many people voiced the opinion that a statistically significant difference alone is not necessarily important. The reduction in absolute amounts, either in milligrams of morphine equivalent or percentage decrease in opioid use, is really hard to define what would be clinically meaningful based on where the evidence is and, again, will be something that's highly context specific.

I think people voice the opinion that if there are medications that can decrease the duration of opioid analgesic therapy, that could be

impactful. But again, it's going to be very dependent on the clinical circumstance for the patients being treated.

Is that a fair enough summary? Any points to clarify?

(No response.)

DR. BATEMAN: Maybe we'll move on to part D. So I guess these are other potential endpoints, so a decrease in the number of patients who used no opioids in the hospital, even if they're prescribed opioids and discharged for use at home.

So I guess the question is, is it meaningful that we can get patients through their inpatient stay without opioids with a particular medication, but if they're prescribed a lot of opioid analgesics at the time of discharge, is that going to be impactful? Anyone want to comment on that? Dr. Suarez?

DR. SUAREZ-ALMAZOR: I think for the majority of situations, this probably wouldn't be a primary outcome, and I'm forgetting about the discharge for use at home. Most of these patients

are going to need narcotics at some point early on, so that would only be appropriate for a minority of the conditions that we might be interested in.

So I think it would be interesting to collect the data, but I would never put that as a primary outcome because it would be very difficult to achieve.

The other component -- I don't know. That's a separate outcome, what happens when they are discharged. I don't know why it's joined with that. You have that later on? Yes, the next one.

DR. BATEMAN: I'll just offer a comment on part D. So there are several papers in the anesthesia literature where people have looked at the impact of opioid-sparing approaches in the hospital on the outcome of persistent opioid use or time to opioid discontinuation. We did some work looking at open abdominal surgeries, comparing patients who had an epidural, which would be an opioid-sparing approach, to those who didn't. And there have subsequently been papers done in orthopedic surgery, looking at patients who

received regional blocks versus not.

In all of these papers, the opioid-sparing approaches, the use of those in the hospital, did not impact on how long the patients stayed on opioids after they were discharged, the time to discontinuation, the total amount of opioids they received in the months following surgeries.

So I think one explanation for that potentially is that there doesn't seem to be a coupling of opioid prescribing at the time of discharge to what the patient's using in the hospital. And absent that coupling, it's probably not surprising that opioid-sparing approaches in the hospital don't translate into a sustained benefit.

Dr. Lorenz?

(No response.)

DR. BATEMAN: How about part E, the number of patients who did not require opioid analgesics after discharge regardless of analgesic regimen used while hospitalized? Dr. Suarez?

DR. SUAREZ-ALMAZOR: I think it's important,

but as you say, these will have to be part of a comprehensive care algorithm because if it's dependent on practice patterns or the discharge orders, then it doesn't really reflect the need. It just reflects practice patterns.

DR. BATEMAN: Dr. Budnitz?

CAPT BUDNITZ: I think I would say that this would be a clinically meaningful outcome. Certainly, it could be dependent on practice patterns. Someone could remain in the hospital post-hip for 4 weeks or something.

It seems unlikely, but I think in a phase 4 trial, if you had a new therapy and after something like major hip surgery, the elderly population, again, using an active comparator with usual care and one group required on average, whatever, how many doses of opioids and the novel agent had zero, I don't know how you could not justify a claim that that's opioid sparing as defined by at-discharge use of opioids by patients, and narrowly made the indication that it was based on that trial for that indication.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. Yes. It seems to me, again, if someone comes forward and has evidence to show a claim, whether that be a new potential drug, or ketamine, or acetaminophen, or others that have been studied in pediatric spine fusions, if that shows that it can reduce it, and particularly if they can go home without an opioid, that's important. So if there's clear evidence for that, I think we should consider that.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: Dr. Budnitz, in that situation, would you then describe the effect on the label, though, as limited to that population, so total hip arthroplasty, specifics, things like that?

CAPT BUDNITZ: Yes. That's the way it's done, for example, in cardiac outcomes trials, patients with diabetes and these risk factors, use of this drug will prevent these specific cardiac outcomes in these time period.

It is different because a cardiac outcome is different than opioid sparing, which one is a

physiologic outcome and one is based on basically standards of care, essentially. But I think it is important to encourage alternative therapies, and this might be one way to do so.

DR. BATEMAN: Any other comments on part D or part E?

(No response.)

DR. BATEMAN: So let's take part F. Reduction in opioid-related adverse reactions; for example, nausea, vomiting, constipation, respiratory depression, sedation, and urinary tension, and perhaps at this point, we can discuss some of the composite measures that people have proposed and we've heard about in some of the presentations and whether they may have utility.

Dr. Litman?

DR. LITMAN: Thank you. I would say absolutely, yes, that this would be an important component. But it leads me down that whole discussion of what we talked about last month, when a drug had potentially less reactions, yet the studies showed that it wasn't quite as potent as

the comparator.

So I do remember it. We had some discussions back then; well, is that meaningful?

I've got to defer to Mr. O'Brien here. If you're going to titrate -- let's take a major surgery like a spine, or hip, or knee -- and you titrate the meds, the opioid, to patient comfort, well, then, the exact dosages may not matter. What matters then are the side effects only if you're titrating to comfort.

That's a really difficult concept, and there would have to be some parameters for this committee. And I would imagine the FDA in their approval process, what are those parameters in judging those less side effects? Do you have to prove equipotency, or do you have to just show not necessarily potency on a milligram-per-milligram basis, but patient comfort? And that's sometimes difficult to do.

DR. BATEMAN: Dr. Goudra?

DR. GOUDRA: Dr. Goudra, Penn Medicine. While at least in the acute post-op setting,

there's a problem. In most hospitals, I think almost everybody who undergoes surgery gets some kind of anti-nausea medication. Almost everybody gets Zofran. So that's one. Even in view of constipation, quite a few patients in the general population who might have some form of IBS, or constipation, or whatever.

The problem of designing any of these studies is, one, are we going to select the patients who were not prone to post-op nausea and vomiting and to selectively go for those surgeries, and second, in order to do this, are we not going to give any prophylactic, nausea, vomiting medications? And third, once we introduce these opioid-sparing medications, are we going to stop giving these anti-nausea medications?

So as a result, I think at least the first three are pretty much out of the window, but the last three -- respiratory depression, sedation, and urinary tension, especially the respiratory depression and sedation -- are very relevant if the opioid-sparing drug can raise the opioid

consumption as a way of assessing it.

DR. BATEMAN: Dr. Suarez?

DR. SUAREZ-ALMAZOR: Yes. I have some difficulty trying to conceptualize a way this is presented as opioid-related adverse reactions, almost like a reduction in the adverse reactions is a benefit or it's a measure of efficacy.

To me, adverse events are adverse events. It doesn't matter what drug is causing them, and to me belongs in the section where all adverse events are considered together because you could give an NSAID and, yes, you have less nausea, but you end up having a GI bleed.

Again, I don't know if that's the intent or not, but it almost seems like a reduction in opioid-related adverse reactions is considered a beneficial outcome when, to me, it belongs where toxicity belongs in comparison to the other agents that might be used in the other arm.

DR. BATEMAN: Yes. I think the notion is that if you did a trial where you were comparing either a new medication in comparison to opioids or

looking at the new medication in combination with opioids compared to an opioid-alone arm, if you saw a reduction in opioid-related adverse effects as a consequence of the patients using less opioids, is that a meaningful endpoint?

DR. SUAREZ-ALMAZOR: Yes. But any reduction in toxicity is a meaningful endpoint, but it shouldn't be considered a beneficial outcome, the reduction in adverse events. To me, it belongs with the adverse events component on that because you could have a reduction in that, but an increase in other adverse events.

I have a problem putting adverse events on the side of benefits. To me, those are risks and they belong in the comparison of risks across all arms of the study.

DR. BATEMAN: Dr. Shoben?

DR. SHOBEN: Sure. So I just want to agree basically and say that I think -- we had a long conversation in the beginning about language, but I think this is actually even more related to that, and it's even more challenging for me to see a

reduction in opioid-related adverse events as an opioid-sparing-type label claim.

I think you'd just be arguing that you would have fewer side effects from your new medication rather than this opioid sparing leading to fewer side effects from opioids. That seems even particularly problematic.

DR. BATEMAN: Dr. McCann?

DR. McCANN: As usual -- Mary Ellen McCann -- I'm thinking concretely, but I'm thinking of ketamine. It's not an opioid, yet it's got a really bad profile in terms of patient comfort in terms of side effects. It does cause some nausea, maybe some vomiting, but the rest of it, it doesn't have.

Would that be in contention for an opioid-sparing drug? Is that what the committee thinks?

DR. BATEMAN: Dr. Rosenberg?

DR. ROSENBERG: I would agree that these are important things, especially if you added confusion to that list. But to me, the ketamine would be,

but it would not be opioid sparing. It would be a medication to reduce opioid side effects. It's not opioid sparing.

DR. McCANN: It has analgesic properties.

DR. ROSENBERG: It does have --

DR. McCANN: So wouldn't it spare the use of some narcotics?

DR. ROSENBERG: But for testing the analgesia, certainly you can do anything with ketamine. But the particular effects, if they looked for these effects and they were vastly reduced, you could have the verbiage in there that this drug reduced X, Y, and Z. And it's very specific, people know it, and it would be part of a multimodal regimen, which is where it sits in the guidelines.

DR. McCANN: I'm still confused.

DR. BATEMAN: Dr. Suarez? Any other comments on this section? Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. Yes, I'm always confused. As we saw last month, I think clearly, patient comfort is a very important part. Now, is

it a primary endpoint to say it's sparing? No, I would not say that. But I think Dr. McCann's point is very valid. If someone came before us and said, "Listen, we've got this. I can cut it by 20 percent, your usage, but your patient's going to be vomiting like crazy and retching out the door" well, that's an important part. You have to consider that.

Last month, when we had a particularly new novel pathway that appeared, if it was robust enough, it wasn't, but if it was robust enough to say that it had the capacity to deliver the same analgesia, and it was nontoxic, and it had none of those effects, then I think that's a very important drug to put out there, and the patients would very much appreciate it. It has to be labeled appropriately to what it is and what it's not, but I think those are important factors.

To some patients, that's extremely important for a segment of the population. Then for the others that have a particular surgery, those elements are also extremely important to them as

they lay on that bed, even if you have a drug that can overcome it in 15 or 20 minutes. But in that 15 or 20 minutes, those are important issues for them.

DR. BATEMAN: Does anyone else want to speak in favor of the idea that reduction in these adverse reactions could support an opioid-sparing claim?

Dr. Hertz, did you want to?

DR. HORN: I'll just say one thing about one of the products that I discussed in my talk. In one of those products in the review that is posted online, the reviewer looked at adverse reactions, and these are adverse events measured the way we usually do in clinical trials. It wasn't a prespecified outcome. And in the label, it describes a reduction in milligrams of morphine-equivalent use in the PCA, but then in the review, there were small numbers of patients enrolled, and there was no difference in the adverse events in the typical opioid-related adverse events.

So I think that's sort of what we were

trying to get to with some of these questions, is what do we do with that kind of information if that's what we get from the trial?

DR. BATEMAN: So the notion is that there is a demonstrated reduction in opioid use based on the trial, the way the trial was designed, but perhaps underpowered to detect a difference in opioid-related adverse events or perhaps there was no real difference, and then what does FDA do with that.

Anyone want to comment on that? Dr. Litman?

DR. LITMAN: Yes. If it's not a primary outcome, and it's not powered to detect it, you can't do anything with it. It's just not right.

DR. HORN: Right, but what do we do with the milligrams of morphine difference? We have it in the label as part of section 14.

DR. HERTZ: Another way of thinking about it is, if you're trying to determine the clinical relevance of a reduction in the amount of opioid used, could F be a way of defining the relevance? I think that's what we're -- is that a reasonable way to try and define the difference in opioid

amounts was clinically relevant?

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: So I think there's a difference between what to do post hoc from a small trial when you have this finding of a reduction in opiate usage and a non-significant difference in the downstream adverse effects versus giving sponsors guidance on how to power and design their studies to get this broad claim of opioid sparing.

Please correct me if I'm summarizing incorrectly, but a lot of the advice has been that it's hard to identify any lines of evidence that support a very broad base, kind of blanket claim of opioid sparing. As far as what to do with these kind of post hoc findings, I don't think there's much you can do than be specific. I think if a sponsor wants to say something about the reduction in dosage, they also have to say that there was no difference in related adverse effects, too.

DR. BATEMAN: Does anyone want to comment on the composite measures we heard about, so like the opioid distress scale, or anyone have experience

using that in their research and want to comment? Dr. Goudra?

DR. GOUDRA: Going back to what I stated earlier, I think respiratory depression and sedation are more easily quantifiable in the post-operative setting, and if any opioid-sparing drug can reduce the incidence of respiratory depression and sedation, I think that would be something quite useful.

DR. BATEMAN: Maybe we will go on to G. Are there other criteria for defining a clinically meaningful decrease in opioid use? Dr. Suarez?

DR. SUAREZ-ALMAZOR: I think that one of the worries that we have is the persistent use of opioids after discharge. I think measuring whether patients are using PRN or persistent use of opioids, let's say 30 days after it, would be appropriate.

DR. BATEMAN: Dr. Lorenz?

DR. LORENZ: Sure. To play my broken record, I would just say time to mobilization. I'm not aware of a specific measure that looks at

global satisfaction with pain management, but it does seem like some kind of integrated -- actually, better than trying to pre-weight the side effects as the idea of obtaining the data from a patient or maybe their caregiver, challenges with that, but trying to get a global impression of pain management and care.

DR. BATEMAN: Dr. Rosenberg?

DR. ROSENBERG: Dr. Rosenberg. One criterion might be how fast they get through the ERAS. For each surgery, they have these accelerated recovery protocols, which are surgery specific. So time through these defined protocols could be used as a criterion for effective recovery.

DR. BATEMAN: So meeting certain functional targets and --

DR. ROSENBERG: Correct, and like I say, it's surgery specific, which makes sense.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Yes. I was switching back to my chronic thoughts again, but I do think if there

was a drug that came forward that had the same analgesic effect without the addiction, to me that's important, and that's very meaningful if they can show that it does not have an addictive -- and I was thinking more of the chronic in terms of withdrawal symptoms, if there was a drug that came out that said, listen, we can eliminate the withdrawal symptoms so that it's very easy for these patients that are addicted to these to come off of it, the ease of use of transition away from it to me would be important.

DR. BATEMAN: Other comments?

(No response.)

DR. BATEMAN: So maybe I'll just try to briefly summarize our discussion from this section. I think there's general skepticism by members of the committee about the idea of a broad, opioid-sparing claim. That said, when we consider these individual components and whether they might be clinically meaningful, part D, the number of patients who used no opioids in the hospital but were discharged with opioids for use at home, I

think people voiced the feeling that that was not a particularly meaningful endpoint, particularly from a public health perspective because it still results in the introduction of opioid medications into communities.

For part E, that was potentially a more meaningful metric, the proportion of patients who don't require opioid analgesics after discharge. Then for part F, I think there was mixed opinion on the committee, with some people feeling that a reduction in opioid-related adverse effects could be used in support of a context-specific opioid-sparing claim, while others felt the broad range of side effects and medications, both are attributable to the opioid-sparing analgesic that was being trialed as well as the opioids needed to be described, and if there may be a tradeoff between having opioid-related adverse effects for adverse reactions that are attributable to the non-opioid analgesic, that might not be captured if there was a focus on just opioid-related adverse reactions.

Then finally, in terms of other criteria that might be clinically meaningful, persistent use, so use of opioids beyond a defined time point where you'd expect the acute pain that's being treated to have resolved, time to mobilization, time to meeting certain functional goals, and then finally validated integrated global measurements of quality of analgesia or quality of recovery can be developed, that could also be a meaningful endpoint.

Any points to clarify on that summary?

(No response.)

DR. BATEMAN: Time for a break. We will break for 15 minutes. As a reminder to the panel, please don't discuss the issues at hand amongst yourselves during the break. We'll resume in 15 minutes at 3:25.

(Whereupon, at 3:10 p.m., a recess was taken.)

DR. BATEMAN: We will get started again here. We're going to move on to question 2, discussion question 2. We've touched on some of

this in our previous discussion, but discuss the pros and cons of the following study designs to assess opioid sparing, or alternatively, a novel design to assess opioid sparing.

Design A is study drug versus placebo with opioids restricted to rescue, and B, standard of care with add-on of study drug or placebo.

Any questions about the structure of the question or clarifying?

DR. HERTZ: I'm wondering if some of the lack of vertical cards might just reflect that there was a fair amount of discussion of this.

DR. BATEMAN: Yes.

DR. HERTZ: Does anybody have anything more to add?

DR. BATEMAN: We get a pass. Question 3.

(Laughter.)

DR. BATEMAN: Discuss how much difference in analgesia, if any, would be permissible in a study of an opioid-sparing drug relative to the standard of care with an opioid?

Any clarifying questions? Is the idea here,

if there was a noninferiority study, what the noninferiority margin might look like?

DR. HERTZ: Yes. But even on a more descriptive or less quantitative way to look at it, if there was a hypothetical drug that was able to offset the use of opioid in one of the ways we consider meaningful, but there was a little bit of a decrement in analgesic effect, is there some way to describe how much would be okay to give up on analgesia if you could really have a drug that was -- again, assuming it was clean and it wasn't going to wipe out livers and all that other kind of stuff, how would we approach that?

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: This would be an active comparator design. Is that correct?

(Dr. Hertz nods yes.)

DR. HERTZ: It could be or it could be the add-on design where we're taking standard of care, adding on the active drug, or adding on placebo, and then looking at the amount of opioid difference. Presumably, a highly effective drug

would reduce the opioid use quite a bit, and then the question about how much pain.

DR. FLOYD: I see. So even in a placebo-controlled design, the intervention arm could have worse pain than the placebo arm if the placebo arm had a lot more opiate use.

Is that the scenario? I didn't have a comment. I was just trying to understand the question better.

DR. SUAREZ-ALMAZOR: But that would not be possible, let's say, if there was PCA or on demand opioid use. That would only be possible with pre-established --

DR. BATEMAN: But if the study was designed in a way where they could only receive rescue every 4 hours or something, then you could end up in a situation where --

DR. SUAREZ-ALMAZOR: Yes.

DR. HERTZ: Let me make it more theoretical because you're clearly very practical thinkers. Would it be reasonable to create a situation in which there would be some degree of loss of

analgesic effect if it meant a meaningful reduction in some way of describing opioid risk, and how would we go about looking at that?

DR. SUAREZ-ALMAZOR: I think it's all condition specific. I think it depends on the overall level of pain that one can expect for that condition. So again, if we are talking about pulling a tooth, it would be very different from a major surgery, abdominal surgery, or knee replacement, or spinal surgery. So I don't know that we can answer this in a blanket statement.

DR. BATEMAN: So does anyone take the position that it would not be permissible to have any difference, that when you integrate the risks of opioids and the importance of analgesia, that no difference could be tolerated?

DR. SUAREZ-ALMAZOR: For any condition, even just a tooth extraction?

DR. BATEMAN: Right.

DR. SUAREZ-ALMAZOR: I would not agree with that.

DR. BATEMAN: So no one is going to take the

position that you wouldn't tolerate any difference, so then it becomes a question of degrees. So are there ways to measure analgesia where we could define a difference that would be acceptable or not? Dr. Floyd?

DR. FLOYD: This is a very interesting question. I'm thinking this is an example where the context could be very important. So you could have a minimally effective analgesic that results in a lot lower use of the PCA. So the pain is worse, but the pain is better in the placebo arm. And it's simply an artifact of PCA being in the study design and perhaps prescribers being very willing to go to the rescue therapy.

So it almost is very dependent on the study design and the contextual factors than the analgesic properties of the drug. So I think it's dangerous to allow for a loss of efficacy when you're not really capturing benefits of the drug but kind of features of the healthcare delivery system.

DR. BATEMAN: So what about a noninferiority

study? Maybe we could talk about that. What would the noninferiority margin be?

DR. FLOYD: That's what I was thinking about at first before they posed this kind of strange study design. I think that a loss of efficacy is tolerable compared to substantial gains in ancillary benefits, especially safety, but to a lesser degree, cost or convenience.

I think it's very hard to design this prospectively, for example, for a guidance because the ancillary benefits are very hard to define. I don't think they're well defined in terms of opiate dosage reductions. I think the health benefits are not well defined when that's the outcome quantity. I think if you look at things like PROs for opiate-related symptoms, you can begin to do that, but it's very difficult. It depends on the magnitude of reduction of the symptoms as far as how much loss of efficacy you might tolerate.

DR. BATEMAN: Maybe just to clarify and other people can weigh in, but if you're designing a noninferiority trial, you may not know what the

ancillary benefits are going into it, so you'd have to design the study with a prespecified, noninferiority margin.

So anyone want to comment on what that might look like? What would be a tolerable or permissible difference? Dr. Lorenz?

DR. LORENZ: I just wanted to comment on the fact that in a number of these studies, I think I saw pain intensity as the measure of analgesia. And I would take issue with it only being a measure of pain intensity because it doesn't capture the individualized treatment goals, which I have seen very widely for patients, to the point where some patients actually want to experience pain that I definitely would have judged intolerable. So I think it can't be pain intensity alone.

DR. BATEMAN: So you would favor something more like a global measure of satisfaction?

DR. LORENZ: I don't think it's exactly satisfaction that you're getting at, but yes. I don't know. I have been unsuccessful in measuring some of these things in our own work, where you're

getting beyond pain function, especially in the acute setting where, again, we struggle with what the right functional indicator is. But I think you're getting more at the person's experience and goals.

DR. BATEMAN: Dr. Rosenberg?

DR. ROSENBERG: I think that function is the key. For example, for bowel surgery, you'll often accept decreases in analgesia in order to get their ileus resolved. So the improvements in function or that they're meeting their recovery guidepost would be acceptable, but not necessarily as good as the opiate protocol might be a reasonable alternative.

DR. BATEMAN: Dr. Suarez?

DR. SUAREZ-ALMAZOR: Yes. I also think that it's not so much a difference. It's more the concept. And I think it's related to what you said of whether the pain is tolerable or not. So it's almost a threshold that's individual, and that's per patient.

So I don't know how you would operationalize that from a statistical perspective, to come up

with a noninferiority margin other than using -- there are some scales out there. I don't know how reliable they are, but they try to target more whether the pain is tolerable or not or whether it interferes with function or not as opposed to the pain intensity. That's a way I would go.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: So sorry for the repeated comments, but I'm just thinking on the fly about this question. I'm thinking about the examples we have for successful noninferiority trials. We have antithrombotic therapies replacing warfarin, and in that example, we had a clear ancillary benefit, which was, you don't have to have your INR monitor. That was very well defined, so you kind of know what the ancillary benefit you're getting is.

In addition, there seems to have been some safety benefits as well, which maybe weren't anticipated. And from that, they also justified a reduction in efficacy based on the reproducible substantial treatment effect of warfarin. So I think that was an example of well-conceived,

well-designed and conducted noninferiority trials.

Another area is anti-infectives. For a number of bacterial infections, there's guidance where you can conduct noninferiority trials based on reductions in symptoms and sometimes mortality. There, the ancillary benefit is less clear. The purported one is that we need more antibiotics and resistant infections. I think that's questionable when the trials study patients with typical pathogens.

In some cases, there are comparator drugs that have clear toxicity; for example like linezolid, which causes cytopenias. And there are other anti-infectives that have very clear, well-defined toxicities. And the idea is that the investigational drug has none of that and no unanticipated side effects.

So I think in most of these examples that I know of, the ancillary benefit is well defined. For this noninferiority opiate trial that we're thinking of, this hypothetical trial, I think it's important for us to establish the treatment effect

of the active comparator, whether from a previous trial or from a 3R noninferiority trial. I think that has to be well measured.

But the ancillary benefit is very hard to define. Unlike warfarin, where you don't have to measure INRs, or anti-infectives where you have this new drug that can treat resistant pathogens or you don't cause cytopenias or things like that, it's harder to justify the noninferiority design without knowing what the ancillary benefits are.

DR. BATEMAN: So maybe in response to what you raised, you talked about the example where there's a clear, well-defined toxicity associated with the comparator. I guess you could make the argument, based on all the presentations I heard this morning, that opioids are a class of medications where there is clear toxicity; there's all the risks and side effects.

DR. FLOYD: I think the magnitude has to be well defined, which you could do from a phase 2 trial. In a similar patient population, you could estimate the treatment effect by looking at the

real opiate-related adverse effects, and quantify them, and power your phase 3 trial appropriately. So it probably is possible, but it does require well-conceived phase 2 studies.

DR. BATEMAN: Dr. Goudra?

DR. GOUDRA: Yes, Dr. Goudra from Penn Medicine. Another major problem I can see, if the idea of the FDA is to give this label, opioid sparing for new drugs, the problem of putting any number in terms of a percentage of difference or dose reduction, a percentage reduction, one, if the drug is not good, it will rate it off [indiscernible] because it's not going to meet the criteria. But if the drug is somewhere in between, manufacturers might find ways of trying to meet those numbers in order to get the label.

DR. BATEMAN: Any other comments on this question? Dr. Higgins?

DR. HIGGINS: I keep going back to this idea -- and it was a question I raised to Dr. Horn about the idea that you have certain types of surgeries or procedures, and then you analyze

certain types of modalities and their effectiveness for different types of procedures. So in a certain sense, you're categorizing the kinds of procedures, and therefore can anticipate a certain outcome.

I don't know if that's possible to examine in a trial, but it gives me sort of a benchmark, what we could expect from a certain intervention, procedural intervention, and what the outcome would likely be for someone. Maybe that's not an ethical way of studying this, but that's kind of where I would go.

DR. BATEMAN: Any other comments?

(No response.)

DR. BATEMAN: Just to briefly summarize, I think no one on the committee took the stand that they wouldn't accept any difference in analgesia, that no difference in analgesia is permissible in comparing an opioid-sparing drug to the standard of care.

We talked about how the difference in analgesia would probably best be measured not just on a pain intensity level, but also looking at more

global measures, including functional measures, although exactly what those are is not well defined.

We talked about the idea of noninferiority studies and how the noninferiority margin would need to be defined, considering the anticipated ancillary benefits of the opioid-sparing drug relative to opioids and what might be expected in terms of risk reduction.

Any other clarifying comments?

(No response.)

DR. BATEMAN: Let's move on to number 4. Discuss the study design for a study of a novel non-opioid analgesic intended to be used in place of an opioid analgesic, taking the following points into consideration. A, discuss whether any evidence of efficacy is enough when evaluating a novel analgesic intended to replace an opioid, whether adequate analgesia is an acceptable outcome; B, discuss when the use of an active comparator is necessary to make a determination that a novel analgesic provides opioid-level

analgesia in a setting usually managed with an opioid analgesic; and then C, discuss how the use of rescue medications should be taken into account in the evaluation of efficacy in this setting.

Does anyone have any clarifying questions?

DR. SUAREZ-ALMAZOR: So this is replacing. This is not to reduce opioid use.

DR. HERTZ: This is the novel non-opioid analgesic.

DR. SUAREZ-ALMAZOR: But you say replacing in a couple of places.

DR. HERTZ: Right. So this is an analgesic intended to be used in the same setting as an opioid, but in place of an opioid.

DR. BATEMAN: So a clinical context where opioids are routinely used, and the intention is that this drug would be substituted for an opioid in that clinical context.

DR. HERTZ: Yes.

DR. BATEMAN: How do we establish that? Dr. Litman?

DR. LITMAN: Thanks. So in contrast to my

comments before, I do think that this would be appropriate use of a phase 3 prospective trial with the caveats that the two important pieces or the components besides efficacy, per se, would be rescue. And typical rescue is an opioid. I can't think of anything else because, in the real world, we would be giving Toradol -- sorry, an NSAID -- and possibly acetaminophen at the same time because their therapeutic margins are usually pretty good.

So if you can't use them as part of your standard of care, I can't imagine that they're going to be useful as rescue. So the only other rescue I could think of is the opioid.

But then there's the other part, which we discussed before, and that's to make sure that the side effects of whatever the non-opioid novel modification is not the same or greater than the opioid side effects. The first step would be taking a specific procedure where there's a feasible mechanism that the non-opioid would work just as well, like bladder surgery or something

where traditionally, opioids, you don't respond well.

When you think about the kinds of operations or surgeries that traditionally require a lot of opioids, like bony spines, hips, knees, tissue trauma is not amenable to anything I know about except local anesthesia of course. So if there's something else that's novel, that would be great, but all those other things have to be taken into consideration.

DR. BATEMAN: Dr. Budnitz?

CAPT BUDNITZ: Dan Budnitz. In answering this question, I imagined two phases. One is the phase 3 efficacy study, which could be against placebo to get a drug approved for an analgesia indication. And then, for the opioid-sparing claim, it would be a second study that would be a phase 4, that would be against usual care, would be against an active comparator, where the medication for breakthrough would be an opioid.

So you determine if it's opioid sparing or not because that would be the breakthrough

medication used to treat as a rescue medication.

DR. BATEMAN: Dr. Floyd?

DR. FLOYD: So are you inquiring about an active comparator design, where your investigational drug is, for example, like an NSAID and the active comparator is an opiate? Is that a potential study design?

DR. HERTZ: I'm not going to answer that directly. What we are trying to understand is when a novel analgesic, non-opioid analgesic, is coming to market, a lot of times, we see placebo-controlled with all the usual study design elements and that shows it's an analgesic. But if they want to be considered opioid replacing, what should that study look like? Is placebo enough? Do they have to have an active comparator? How should that be defined? How should we look at that?

A lot of times we know that a product works, but we just don't know how it compares to others.

DR. FLOYD: So separating the issue of labeling and calling things opioid sparing, I do think that type of study design would be very

informative, studying an investigational drug compared with an opiate. And the rescue therapy can be an opiate.

I think of an analogy of diabetes, where the rescue therapy for type 2 diabetes is insulin. You can titrate that to any effect. And sometimes you compare a new oral drug to insulin, especially in the previous era when there were fewer oral options.

So I do think that is an acceptable study design, and as long as there is enough separation in opiate use across the two treatment arms, you can get information that is useful both in terms of efficacy and safety. And I think if you have a big separation, you have a very good chance of demonstrating a reduction in opiate-related adverse effects.

So I'd be curious what other panel members may think, but I think that could be an informative study design.

DR. BATEMAN: Although I'm not sure that this label of opioid-level analgesia is all that

meaningful. The amount of analgesia that an opioid provides is dependent on the dose that you give. I guess it would be looking for novel analgesics that are affected in the treatment of moderate to severe pain and would be perhaps a more meaningful way of conceptualizing it.

DR. FLOYD: Would you agree that study design would be informative? If you could handle the labeling and kind of reward for developing that drug in some way that represents its actual benefit, that study design --

DR. BATEMAN: Yes, compared with opioids, which would be the most commonly used treatment for analgesia for moderate to severe pain would make a lot of sense to me. Dr. Budnitz?

CAPT BUDNITZ: Dan Budnitz. In these phase 3 trials for analgesics -- again, I'm not typically involved in them, but doesn't one control out usual care for approval typically to demonstrate efficacy or do you allow usual care in both arms, plus placebo in one and the investigational drug in the other? I thought my impression was that that

didn't happen, but I could be wrong.

DR. BATEMAN: If you imagine a novel analgesic that was going to be used in a perioperative setting, I think you would need an active comparator. I can't imagine really doing the trial with a placebo in the setting of patients who have severe pain.

CAPT BUDNITZ: So I'm thinking about not so much in the inpatient setting, but like on discharge. I'm thinking about patients on discharge and how does one control for usual acre of over-the-counters, of cold compresses, or whatever else is used, and can you truly call something opioid sparing from a control trial setting that's used to demonstrate efficacy.

I guess I'm not familiar enough with how constrained those trials are and how much they really would reflect the usual care among the spectrum of patients that are not highly selected. I think we heard about screening out patients that might be susceptible for opioid use in these trials, and I think that's important not to do in a

phase 4 trial if you're making a claim of opioid sparing.

So I guess my concern is how much do phase 3 trials designed for efficacy will really be able to reflect usual care in order to make a claim of opioid sparing in the real world, in real-world settings?

DR. BATEMAN: Dr. McCann?

DR. McCANN: Mary Ellen McCann. Although it's not really asked in the question, since you're conceptualizing a drug that would be a non-opioid replacement, you're thinking about a drug that could possibly be used over many, many millions of patients. And I think that it's really important, before you approve a drug like that, that you really have a lot of toxicity data.

That's not part of the question, but that's what I would be worried about. We've seen it in a prior meeting, where there was a faint signal, and we don't know if the signal was meaningful or not, but it was enough to give the committee pause. And if you're looking to replace morphine, then you

really should make sure the replacement is as safe as morphine.

DR. BATEMAN: Dr. Suarez?

DR. SUAREZ-ALMAZOR: My view is that if the claim would be to replace an opioid, then there has to be an opioid as an active comparator. That's the only way you can get to it. But I think it goes back to the issue of noninferiority, and if we factor other things as just toxicity, what's the level of efficacy that we are willing to give up in terms of the toxicity? So to me, it relates a little bit to the discussion that we had before.

DR. BATEMAN: Other comments on this question?

(No response.)

DR. BATEMAN: Dr. Hertz, are we capturing what you're looking for in this?

DR. HERTZ: Yes.

DR. BATEMAN: Any other comments?

(No response.)

DR. BATEMAN: So just to briefly summarize, I think the feeling of the committee was that a

trial that was going to attempt to show the efficacy of a non-opioid analgesic that was intended to address the same clinical needs that opioids address would perhaps be best studied in the context of an active comparator design and that opioids could be used as rescue medications in the context of that type of trial.

There's also several on the committee who voiced the concern that toxicity of any novel non-opioid analgesic be fully evaluated prior to approval because, as opioids are widely used, any replacement for opioids would also likely be widely used in practice.

Any clarifications?

DR. HERTZ: Dr. Bateman?

DR. BATEMAN: Yes.

DR. HERTZ: Would anyone care to comment just on what that adequate assessment of toxicity might look like, just as a little side note?

DR. SUAREZ-ALMAZOR: I would say what's usual for trials of this nature. I'm not sure what you're trying to get at. Maybe if you can be a

little more specific.

DR. HERTZ: If the answer wasn't really clear, I don't want to get us sidetracked, so we'll go back to the questions.

DR. BATEMAN: Any other comments on this question before we move on?

(No response.)

DR. BATEMAN: The next question is a voting question. The question is, is any reduction in opioid use sufficient to warrant labeling as opioid sparing? And if not, describe the criteria that would support such labeling.

Any clarifying questions?

DR. SHOBEN: So given all the question about opioid sparing as problematic wording, do you want to leave it as is or make any sort of --

DR. BATEMAN: I would say that we vote on the question as worded, and then people can clarify the way they want their votes to be interpreted as we go around the room.

So we will be using the electronic voting system for this meeting. Once we begin the vote,

the buttons will begin flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote on the screen into the record. Next, we will go around the room and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

So everyone can go ahead and vote on question 5.

Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection,

the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. BATEMAN: Everyone has voted. The vote is now complete.

DR. CHOI: For the record, we have 1 yes, 11 no, and 1 abstention.

DR. BATEMAN: So why don't we start to the right with Mr. O'Brien?

MR. O'BRIEN: I think that there has to be something meaningful. We already showed in certain cases. I think 80 percent was the criterion that existed already that I've seen, and I think just for a 5 percent change, that's not enough to make a change. In the risk-benefit analysis, we have to have something meaningful that's there.

DR. BATEMAN: Just as a reminder, please state your name and the way you voted.

MR. O'BRIEN: Joe O'Brien. No.

DR. HIGGINS: Jennifer Higgins. I voted no.

I would feel more comfortable with language somewhere on the label that says something to the effect of this product has been shown to be used as a partial replacement for opioids in certain clinical situations such as blah, blah, blah. That would be something I'd feel more comfortable with, given what we've reviewed today and the lack of data we have.

DR. FLOYD: James Floyd. I voted no for reasons I've already stated today. I don't think any line of evidence would support a broad labeling of a drug as opioid sparing. But as other committee members have said, based on specific populations and findings from studies, I think some information could be incorporated in a label that's precise.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted no for the reasons stated.

DR. LORENZ: Right. I think many issues have been covered here, but I would say, in general, the issue is what harms are avoided or what benefits are achieved through avoidance. Some

of those, we might accept as proxies, given current levels of evidence, for example, avoidance of opioids, but others, like milligram reductions, I think are much less established and maybe much more contextual.

So those would be my considerations, but I would certainly vote no in general, only accepting opioid reduction.

DR. BATEMAN: Just remember to state your name and the way you voted.

DR. ROSENBERG: Jack Rosenberg. I voted no for the reasons that have already been stated.

DR. BATEMAN: We have to go back to Dr. Lorenz.

DR. LORENZ: Sorry. This is Karl Lorenz. I voted no.

DR. SHOBEN: Abby Shoben. I voted no primarily based on the concerns about the wording of what does it mean to be opioid sparing. And then just to reiterate some other points that were made about picking a meaningful outcome, so we discussed that a lot in question 1, reducing the

percentage of patients going home with an opioid prescription or potentially reducing the number of total pills dispensed, like that are going out in the community, would be more meaningful to me.

DR. McCANN: Mary Ellen McCann. I voted no.

CAPT BUDNITZ: Dan Budnitz. I voted no. The criteria that might be most supportive of such labeling for me is the percent of patients who are no longer on opioids for a certain day for a certain procedure, relative to a treatment arm that was treated with opioids.

DR. BATEMAN: Brian Bateman. I voted no for reasons other panelists have stated.

DR. GOUDRA: Dr. Goudra. I decided to abstain because I think the whole notion of giving this option of opioid sparing itself is incorrect. In fact, I do remember many, many years ago, when I was in England, when intravenous acetaminophen just came in, the manufacturers were trying to claim that 1 gram intravenous acetaminophen given during the procedure is equipotent with 10 milligrams of morphine sulfate, and we all knew what happened

afterwards.

DR. LITMAN: Ron Litman. I voted yes, but I could have voted no or abstained. To me, it's all the same. I agree with all the panelists and their explanations for their no vote, but I could foresee a situation where a certain drug showed that it was just as efficacious, yet had less side effects than opioids under certain clinical circumstances. I think that could be achieved either by a phase 3 prospective study, although that would be really circumscribed circumstances and I don't in general favor that.

But I could foresee it in a large phase 4 study, which has a robust external validity. During the discussions today, we all have talked about these kind of conditions and certain situations where other drugs are better than opioids for certain periods of time like a local anesthetic or for certain conditions like bladder spasms. So I do think it's feasible in certain conditions that it could meet those criteria.

DR. MICHNA: Ed Michna. I voted no because

I think opioid sparing is just too broad and lacks definition.

DR. BATEMAN: We will move on to the next voting question, question 6. The question here is, is it sufficient to claim opioid-level analgesia for a novel analgesic compound based on the clinical trial population and without an opioid active comparator. If not, describe the type of comparison that would provide support for a finding of opioid-level analgesia.

Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you are unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

Any clarifying questions on this?

(No response.)

DR BATEMAN: We'll move forward with the vote.

(Voting.)

DR. BATEMAN: Everyone has voted. The voting is now complete.

DR. CHOI: For the record, we have 1 yes, 12 no, zero abstentions.

DR. BATEMAN: Now that the vote is complete, we'll go around the table and everyone who voted should state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We'll start with Mr. O'Brien again.

MR. O'BRIEN: Joe O'Brien. I voted no. I would want to see a comparator to what's out there in the market before I would agree with it.

DR. HIGGINS: Jennifer Higgins. I voted no. As I stated previously, I would recommend a study design that had standard of care in different doses versus the test comparator as an add-on only.

DR. FLOYD: James Floyd. I voted no. I think the label "opioid level" might be problematic. And also, I think that, for anything like that, you would need an active comparator

that's an opiate, but still be very attentive to good principles of noninferiority trial design, in particular, assay sensitivity.

I could conceive of a trial where you study patients where opiates are minimally effective, your new drug has no analgesic properties, but you still demonstrate noninferiority. So you have to be careful to either strongly justify or demonstrate explicitly in a three-arm trial the assay sensitivity.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted no for the reasons stated, and I think that a trial design would vary according to the condition and context where the new agent would be employed. So it would be very hard just to use a design that fits every single situation.

DR. LORENZ: Karl Lorenz. I voted no for the reasons already described.

DR. ROSENBERG: Jack Rosenberg. I voted no for the reasons already spoken.

DR. SHOBEN: Abby Shoben. I voted no also for the reasons already described.

DR. McCANN: Mary Ellen McCann. I have to explain myself since I voted the only yes. I took the question -- I think you probably could define what opioid-level analgesia is if you used a particular patient population like bunionectomies.

I don't know that I would design a trial without an active comparator, but I could see it being done, and that you would get useful information from it. So that's why I said yes.

CAPT BUDNITZ: Dan Budnitz. I voted no.

DR. BATEMAN: Brian Bateman. I voted no. I think the term "opioid-level analgesia" is a bit problematic, but if we're thinking of trials for a novel analgesic that's intended to be used in the same clinical context, where opioids are routinely used, it's hard for me to envision a trial that would be done that didn't have opioids as an active comparator.

DR. GOUDRA: Dr. Goudra. I voted no for reasons everybody's stated. In fact, even if you want to claim equivalency after comparison, the study has to be pretty robust.

DR. LITMAN: Ron Litman. I voted no for all the reasons, of course, that have been stated. But also, despite all the bad things, opioids are an incredibly great godsend to people in pain, and it would be a high bar for me to attempt to replace them with something else without comparing against them.

DR. MICHNA: Ed Michna. I voted no. Opioids can be used in so many different situations, it's hard to imagine any valid comparison without using an opioid as a comparator.

DR. BATEMAN: Any further comments from the committee? Anyone have anything that they want to say before we wrap up?

DR. ROSENBERG: Just that, to describe it as an opioid level, I could see the day, not too far away, where we have potent analgesics that are equal in efficacy that no longer will we be seeing opioids as the king of the hill. So I would say potent analgesics might be a better label rather than opioid level.

DR. BATEMAN: Thank you. Any other

comments?

(No response.)

DR. BATEMAN: Any last comments from the FDA?

DR. HERTZ: Just my thanks for your time taking away from very busy schedules and for all the helpful discussion. Clearly, this is going to be a difficult topic to continue to tackle, and we will keep working on it.

Adjournment

DR. BATEMAN: Thank you.

Panel members, please take all personal belongings with you, as the room is cleaned at the end of the day. All materials left on the table will be disposed of. Please also remember to drop off your name badge on the registration table on your way out so they may be recycled. We will now adjourn the meeting. Thank you.

(Whereupon, at 4:09 p.m., the meeting was adjourned.