MEETING

OF

DATA AND METHODS FOR EVALUATING THE IMPACT OF OPIOD FORMULATIONS WITH PROPERTIES DESIGNED TO DETER ABUSE IN THE POSTMARKET SETTING: A SCIENTIFIC DISCUSSION OF PRESENT AND FUTURE CAPABILITIES

Conducted by Judy Staffa, PhD, RPh,

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Center for Drug Evaluation and Research

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C O N T E N T S

P R O C E E D I N G S

DR. STAFFA: -- things going. My name is Judy Staffa. I'm the associate director for Public Health Initiatives in CDER's Office of Surveillance & Epidemiology. And right now that means I oversee all the post-marketing activities of our office in the area of opioids.

So on behalf of my office and the Office of Biostatistics, who has co-sponsored this meeting with us, I'd like to welcome you to this very important discussion to be talking about what more we can do to improve our data and methods to be evaluating the impact of opioid formulations that are designed to deter abuse.

Thank you all for coming. And what I'd like to do, just a couple housekeeping things, if you have not yet registered at the front desk, please do so. Please make sure to silence your cell phones and other devices. There's copies of the agenda and the slide sets, and in the slide sets are the discussion questions for each session if you'd like to be able to look those over. All the materials for this meeting

have been posted on the FDA meeting webpage.

As you speak, please make sure you use a microphone. The meeting is being transcribed as well as webcast, and the transcription will be available in about six to eight weeks.

The restrooms are located out the door and to the right.

So what I'd like to do is start off. We've assembled a very eclectic panel, and I'd like to just have everyone go around our panel and introduce themselves, both our outside experts as well as our FDA folks. So if we could start on that end with Dr. Jones.

Would you be -- thank you.

CAPT JONES: Chris Jones. I'm the acting associate deputy assistant secretary for Science and Data Policy in ASPE at HHS. I have worked on the opioid issue for a number of years.

DR. CONRAD: Fred Conrad from the University of Michigan. I'm a survey methodologist and direct our graduate program in survey methodology.

MS. CASSIDY: I'm Theresa Cassidy. I'm from

Inflexxion. And my background is in epidemiology and post-market surveillance of prescription medication abuse.

DR. CICCARONE: Good morning, everybody. My name is Dan Ciccarone. I'm from University of California, San Francisco, Department of Family and Community Medicine. I am the principal investigator of the Heroin in Transition Study funded by NIH, NIDA.

DR. BROOKS: Good morning. My name is John Brooks. I'm the senior medical officer for the Division of HIV and AIDS Prevention at the Centers for Disease Control. And I was also the incident manager for the Indiana HIV and hepatitis C outbreak in 2015.

DR. CRANE: Hi. I'm Elizabeth Crane with SAMHSA, Substance Abuse and Mental Health Services Administration. I was with the Drug Abuse Warning Network for many years until its phase-out, and now I'm leading the Ambulatory Care Services Team, which is partnering with NCHS on the National Hospital Care Survey.

DR. DEGENHARDT: Good morning. My name is Louisa Degenhardt. I'm from Australia. I conduct a

range of different studies looking at drug use, but we have been conducting a range of post-marketing studies in Australia over the past 10 years.

DR. GRAUBARD: Hi. I'm Barry Graubard. I'm from the National Cancer Institute, and I'm a biostatistician.

DR. LO RE: Hi. I'm Vin Lo Re. I'm from the Division of Infectious Diseases at the University of Pennsylvania and the Center for Pharmacoepidemiology Research and Training.

DR. DEFRANCES: Good morning. I'm Carol DeFrances. I'm chief of the Ambulatory and Hospital Care Statistics branch at the National Center for Health Statistics. We are working with FDA and SAMHSA on the National Hospital Care Survey to identify substance-involved ED-related visits.

DR. KREBS: Hi. I'm Erin Krebs. I'm a general internist and health services researcher at the Minneapolis VA and University of Minnesota. My research focuses on chronic pain management, opioid benefits and harms in the primary care setting.

DR. NOVAK: I'm Scott Novak with Battelle Memorial Institute, and I direct their program on prescription drug abuse and drug safety. And I am an epidemiologist and biostatistician.

DR. BUDNITZ: I'm Dan Budnitz. I lead the Medication Safety Program in the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention. I conduct some national adverse drug prevention and surveillance programs.

DR. SCHNOLL: Good morning. I'm Sid Schnoll, Pinney Associates. I head up the risk management programs there. And I've been working in this area of addiction and pain for close to 50 years now. I've been around a long time.

DR. SCHARMAN: Hi. I'm Elizabeth Scharman. I'm a professor of clinical pharmacy at West Virginia University and director of the West Virginia Poison Center where we manage overdose and poisonings and submit data to the National Poison Data System. I'm also representing the American Association of Poison Control Centers. For the last 25 years, I have chaired the committees that are working on quality improvement

and coding accuracy in the National Poison Data System.

DR. SHOBEN: Hi. I'm Abby Shoben. I'm an associate professor of biostatics at the Ohio State University.

DR. KREINER: Good morning. Peter Kreiner from -- senior scientist at the Institute for Behavior Health at Brandeis University in Massachusetts. I head several projects that work with state prescription monitoring programs and work with prescription monitoring program data.

DR. MIECH: Good morning. My name is Richard Miech. I'm a professor at the University of Michigan. I'm a principal investigator on a project called Monitoring the Future, which surveys about 40,000 adolescents every year about their drug use. We also follow them into adulthood.

DR. UNICK: Good morning. I'm Jay Unick from the University of Maryland School of Social Work, and I work on a number of projects related to opioid overdoses.

DR. DASGUPTA: Good morning. My name is Nabarun Dasgupta. I'm an epidemiologist based at the

University of North Carolina Chapel Hill, and I have appointments at the Injury Prevention Research Center in the School of Pharmacy. And I also work with the RADARS system.

DR. MCCLURE: Good morning. I'm Leland McClure, Forensic Toxicologist and Corporate Medical Affairs Director for our prescription drug monitoring program at Quest Diagnostics. And I've been involved with opioids and testing back to, gosh, my medical examiner days back -- starting in 1980.

DR. PARKER: Hello. I'm Jennifer Parker. I'm at the National Center for Health Statistics. I'm a biostatistician in the Division of Research Methodology.

DR. COMPTON: Good morning. I'm Wilson Compton, the deputy director at the National Institute on Drug Abuse. And it's a pleasure to be -- see so many old friends and a few name -- a few faces that I get to put with names that I've known.

DR. GREEN: Hi. I'm Jody Green, the director of research at Rocky Mountain Poison and Drug Center, which also owns and operates the RADARS system. And my

background is in applied statistics and research methods.

DR. HEDEGAARD: Hello. I'm Holly Hedegaard from the National Center for Health Statistics. I'm an injury epidemiologist in the Office of Analysis and Epidemiology. And most recently, I have been working on literal text from death certificates and also working with coroners and medical examiners to improve the quality of the information on death certificates around drugs.

DR. BOYER: My name is Ed Boyer. I'm a medical toxicologist and emergency physician and a synthetic organic chemist. I am currently at Brigham and Women's Hospital and Harvard Medical School. My research interests are all over the map, so I won't even try to describe what they are.

DR. THROCKMORTON: Good morning. I'm Doug Throckmorton. I'm the deputy director for Regulatory Programs at -- in the Center for Drugs at the FDA.

DR. MCANINCH: Hi. I'm Jana McAninch. I'm a medical officer and epidemiologist in the Office of Surveillance and Epidemiology on the Prescription Drug

Abuse Team.

DR. MEYER: Hi. I'm Tamra Meyer. I'm an epidemiologist on the Prescription Drug Abuse Team as well in the Office of Surveillance and Epidemiology.

MR. GOLDIE: Good morning. I'm Scott GOLDIE. I am Special assistant in the Office of Biostatistics in CDER.

DR. KORNEGAY: Good morning. I'm Cynthia Kornegay. I'm the team leader for the Prescription Drug Abuse Team in the Office of Surveillance and Epidemiology.

DR. LEE: Good morning. My name is Hana Lee. I'm a biostatistician from the Office of Biostatistics in CDER at FDA.

DR. LEVENSON: Hello. I'm Mark Levenson. I'm a division director of one the biometrics divisions in CDER. Division deals with drug safety and real world evidence.

DR. BY: Good morning. My name is Kunthel By. I'm a statistician at FDA.

DR. XIE: Good morning. I'm Diqiong Xie. I'm a statistician in the CDER, FDA.

DR. STAFFA: Great. Thank you everyone. We have quite the group here.

So before we get started, I'm very honored to be able to introduce our commissioner, Dr. Scott Gottlieb, who would like to provide some opening remarks.

Dr. Gottlieb?

DR. GOTTLIEB: Thanks a lot. Thanks for the opportunity to be here today.

I'll just grab my water. Sorry.

I want to thank you all for coming today to discuss how we can improve the science around evaluating the impact of opioid formulations that might be less prone to manipulation, misuse, and abuse.

We are very grateful for the chance to discuss how we've been approaching these kinds of evaluations at FDA, and this scientific discussion is going to help inform our development of an effective and efficient regulatory framework so that we can facilitate the continued development of these kinds of formulations. And it's a real honor to be with such an expert group.

I especially want to thank my FDA colleagues

who are here today. I know they've been working very hard on these issues for many years.

Opioid addiction and the resulting overdoses and deaths are an enormous national crisis. The men and women of FDA are working to help address this epidemic. At the same time, we continue to make sure that properly indicated patients who are suffering from pain conditions have appropriate access to medicines. This crisis is, in my view, the toughest public health challenge facing FDA right now.

I've asked my FDA colleagues to take a fresh look at what more we can do to confront this challenge and change the trajectory of the epidemic of addiction inflicting our nation. We need to make sure we strike a careful balance between access and safety while taking more vigorous steps to combat the epidemic.

I'm immensely grateful for the dedication of the professional staff at FDA in pursuing these goals and the efforts of our experts who work every day on these issues.

There are many elements to the work FDA is doing to confront this epidemic. Today I want to

highlight three of the clinical and policy areas that I've asked my colleagues at FDA to take a fresh look at since I've arrived at the Agency.

The first is how we combat the crisis of new addiction. This relates to people who will be exposed to opioids in a clinical setting who are prescribed treatment and then go on to become addicted to these drugs. To reduce the rates of new addiction, we need to decrease overall exposure to opioids. We need to make sure that only properly -- only appropriately indicated patients are prescribed opioids and that the prescriptions are for durations and doses that properly match the clinical reason for which the drug is being prescribed in the first place.

Given what we already know about the scope of current prescribing and the subsequent patterns of abuse, it's clear that there should be fewer prescriptions being written for opioids. When opioid prescriptions are written, they should be done so for shorter durations of use. I believe there is still too many 30-day prescriptions being written for conditions like dental procedures and minor surgery, which should

require very short-term use, if they require an opioid prescription at all.

Therefore, we are exploring whether FDA should take additional steps to make sure that general prescribing and the number of opioid doses that an individual patient can be dispensed is more closely tailored to the medical indication.

The second area I've asked my colleagues to examine is how we balance benefit and risk when it comes to scheduled drugs or controlled substances. In particular, how do we look at benefit and risk not only in the labeled indication for the opioid drugs, but also evaluate the individual and societal risks associated with illicit use.

The question is this: What more can we do; and do we have the right regulatory tools, policies, and science for assessing the overall risk associated with the illicit use of these drugs? This means carefully reevaluating not only how we make decisions to approve new opioid drugs, but also how we continually assess their safety after approval. It also means carefully evaluating the framework we use

for deciding when to revise labeling to better manage how these products are used or make a decision to request that a marketed opioid drug should be withdrawn.

FDA has a clear legal and public health mandate to consider the safety of opioid drugs in terms of the risks and benefits of the labeled uses as well as the risks associated with intentional or illicit misuse or abuse of these drugs. This regulatory principle is especially true when it comes to opioids, where intentional misuse or abuse is both too common and associated with tragic outcomes. As an integral part of our efforts to address this epidemic, we're exploring how this safety mandate can be further defined in support of our commitment to stem the tide of addiction.

The third area in which I've asked my colleagues to focus is improving prescriber training. Among the questions I've asked are these: Whether the content of existing programs is appropriate to ensure that the prescribing doctors are properly informed about appropriate prescribing recommendations; that

prescribers understand how to identify the risk of abuse in individual patients and know how to get an addicted patient into treatment; and are there circumstances under which FDA should require some form of mandatory education to healthcare professionals?

As we continue to pursue a broad range of new steps to more forcefully address this public health crisis, I want to close by highlighting three new actions that we're taking now and announcing today, starting with additional steps on training.

First, we know that most of the exposure to opioids isn't from extended release or long-acting formulations, which include most of the abuse deterrent formulations we're discussing today. Most of the exposure to opioid drugs comes from immediate-release formulations like hydrocodone and acetaminophen or oxycodone and acetaminophen combinations. America is simply awash in immediate-release opioid products. In fact, about 90 percent of all opioid prescriptions in the U.S. are written for immediate-release formulations of these drugs.

Many people who become addicted to opioids

will eventually move on to seek higher-dose formulations of these drugs or illicit street drugs, which are increasingly the low-cost alternatives. But immediate-release opioid products may serve as a gateway for patients and non-patients who may continue to use or misuse these products, which could lead to a lot of new addiction. And we all need to work to advance policies that rationalize prescribing and dispensing of these products.

As one step, we have determined that a risk evaluation and mitigation strategy plan, or REMS, is necessary for the prescribing of the immediate-release opioid products. This regulatory tool is needed to ensure that the benefits of how these drugs are prescribed continue to outweigh the risks of misuse, abuse, addiction, overdose, and death.

It's time to take direct action to address this -- the close to 200 million opioid analgesic prescriptions each year that are for the immediate-release products. To this end, FDA intends to update the existing REMS on extended-release opioid analgesics and, for the first time, extend these same regulatory

requirements to the manufacturers of the immediate-release opioid analgesic products.

To start this process, the relevant letters detailing the new requirements will be sent to the IR manufacturers in the coming weeks. The new training will be aimed at making sure providers who write prescriptions for the IR opioids are doing so for properly indicated patients and under appropriate clinical circumstances. This is part of a broader effort to take new steps to make sure providers are properly informed about suitable prescribing and the risks and benefits associated with opioid drugs.

The new REMS will include modifications to the existing blueprint for provider education, which describes the content of the education. Under the new REMS, the training will continue to be provided by accredited continuing education providers. As one part of the education for prescribers of IR and ER/LA opioids, FDA will broaden the information on pain management, including the principles of acute and chronic pain management, non-pharmacologic treatments for pain, and pharmacologic treatments for pain, both

non-opioid analgesic and opioid analgesics. The blueprint will also enhance the information about the safe use of opioid analgesics, basic elements of addiction medicine, and opioid use disorders.

In addition to training to training for physicians and prescribers, the REMS will require that training also be made available to other healthcare providers involved in the management of patients with pain. This includes nurses and pharmacists. FDA believes that all healthcare providers involved in the management of pain should be educated about the safe use of opioids.

Based on the feedback we've received from two public meetings over the past year, we're actively exploring the question of whether in the future there should be mandatory provider education and how we'd operationalize such a condition. As part of our new opioid steering committee, we'll be reviewing the data necessary to understand the most effective way to move forward.

We recognize that developing a REMS for these widely prescribed products involving numerous

application holders will present challenges. And we're sensitive to concerns about the potential burdens they may place on providers. We're taking these steps in a way that's mindful of these concerns. We've solicited a lot of public input on these issues related to these steps, and we're carefully considering the feedback and will monitor the execution of these new efforts and adjust them as needed.

A second new action we're taking is aimed at ensuring the safe use of the abuse-deterrent analgesic formulations, which mostly relate to the higher dose extended-release formulations of these medicines. We're undertaking a new study to better understand prescriber beliefs and attitude when it comes to these drugs. We want to know whether the prescriptions -- perceptions about the attributes of these drugs match the clinical realities. In particular, we want to know whether we have the right nomenclature for describing the drug features that are expected to make opioids less prone to abuse.

Among other steps, we'll be surveying doctors to better assess how they perceive these terms and

understand the clinical understanding that's been developing around ADF products. I want to make sure that the nomenclature we use to describe and label these products is accurately conveying their properties to those who prescribe and use them. In particular, we want to make sure that the labels and nomenclature enable providers to adequately distinguish between the risk of abuse and the risk of addiction.

Through the regulatory lexicon we use to describe these products and their abuse-deterrent features and drug labeling, we don't want to improperly convey a perception that a product that's resistant to manipulation and abuse is somehow also less prone to fueling addiction when that's simply not true.

The term "abuse" is defined as the intentional non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect. Different abuse-deterrent technologies target various known or expected roots of abuse. But the potential for abuse doesn't necessarily correlate with the potential for addiction. Patients can still become addicted to opioid products with

abuse-deterrent features. We need to make sure these different risks are fully understood.

Third and finally, I want to highlight for you today that we're also continuously reevaluating the safety of approved opioid products based on post-market information. We're also focused on how we can augment our post-market data collection in these areas, which is one of the reasons I have convened this meeting today.

And as we recently did with respect to a reformulated Opana ER, when we find that the risks of an opioid outweigh its benefits, including the risks associated with the illicit and deliberate manipulation, we will take action. In some cases, that action could be to request the withdrawal of certain products.

These are just a few of the steps that we're taking. Today's discussion is also a key part of these efforts. It's an important part of our work to build a scientific base to improve our oversight of opioids and make sure we have the right policies to strike a careful balance between risk and benefit in these

complex situations.

FDA is immensely grateful for your efforts and your willingness to join us today for this scientific discussion. Working together, we'll aim to stem the tide of individuals becoming addicted to opioids and misusing and abusing these products and move those who are currently addicted to opioids into safe and effective treatment, all the while, we continue to address the needs of patients suffering from pain.

Thanks a lot.

(Applause.)

DR. STAFFA: Thank you, Dr. Gottlieb.

Okay. So to get us started, I'm going to spend a little bit of time of providing an overview of how we got to this point to kind of fill you in. And then hopefully at the end of my talk, it'll be clear to you who's here and why we're here.

So I'm going to walk through what exactly is the impetus, what drove us to convene this meeting today, and why did we invite the people we invited. I'm going to walk through a little bit of logistics of how this is going to work -- this is a little bit

different than some of our other public meetings -- and then what do we see as the output; where do we want to go next.

So what's the impetus for today's meeting? Well, I'll show you the slides. You've seen this before. These are the numbers of prescriptions, and the scale here is in hundreds of millions of opioids. You can see that the ER/LA opioids, which are the green line, is rather steady. And the good news is, I guess, that the red line, the IR opioids, are beginning to come down. Of course, we don't know whether that's coming down, whether that represents a decrease of appropriate or inappropriate use, but still means that there's less opioid out there. But we still have a long way to go.

And of course, this is the CDC slide that I know you've all seen where the deaths continue. So we still have a lot of work to do.

So just a little over a year ago, our previous commissioner announced an action plan. And one of the pieces of that action plan was to encourage the development of what was called abuse-deterrent

formulations and to see if this could be not a complete solution, but clearly a piece of many different efforts to combat this.

We issued a guidance in April of 2015. Guidances are not binding, but they represent our best thinking to guide industry in how to develop these products -- what kinds of testing should be done both before and after approval.

So just to take a second, Dr. Gottlieb alluded to this, but I just want to be clear on the terminology. I think there is a little bit of confusion about what an abuse-deterrent formulation actually is. They are not abuse-proof. They can be defeated. They can be abused. The idea is to just deter that to some extent.

They are designed specifically to deter specific routes of abuse. And if you read the labeling for these products, it clearly says that, whether it's to deter snorting or to deter injecting, the idea being it's going to make it more difficult for folks who might be inclined to try to crush up tablets into a powder that's suitable for snorting or a powder that is

suitable for dissolving in a liquid and then injecting.

So these products at this point have these properties that we -- are designed to deter abuse. They're expected to deter abuse, and they have met the bar that is set by particular pre-market studies, both in vitro and human abuse potential studies.

Now, just for brevity today because, otherwise, I would have had a mutiny on my hands by all of our speakers, we're going to refer to them as ADFs. That's the short hand -- abuse-deterrent formulation. But I just want to understand. These have not been shown in the real world to form -- to defeat abuse or to deter abuse. So just to note, that is just for convenience.

So here are the products that have been labeled. There are 10 currently. Nine of them are extended-release formulations, and one is an immediate-release formulation. And again, all of these products have completed pre-market assessments, and they all have post-marketing required, or PMR, studies that they must do. The companies must complete these studies to determine how these products perform in the real world.

So just to zoom in on the -- how -- what's been the uptake of these products, this graph, the scale, is actually in the single millions. So remember the previous one was in the hundreds of millions. So this is the products that have abuse-deterrent labeling. And you can see that the blue line, this is OxyContin. This was the first one to receive such labeling, and it occupies the majority of this market. You can see that the other marketed products right along that lower X-axis. So they have not had as much uptake. And there are about six products that have not yet been marketed even though they've been approved. So they have not really had uptake, and they do not take up a majority of the opioid market.

So in our Guidance for Industry, this is the goal of the studies we've asked them to undertake post-marketing, is to actually try to determine whether their products are associated with meaningful reductions -- that's a key term -- in abuse, misuse, and the related clinical outcomes, such as addiction, overdose, and death. But this is not an easy task. We've not been able to set a particular bar or a number

because the landscape is constantly changing and we worry that setting any kind of an arbitrary bar would simply be outdated. So meaningful reduction becomes a very dynamic and changing type of phase -- phrase.

So what we have laid out in this guidance, we tried to give our best thinking to direct industry to do formal studies -- these are hypothesis-driven studies -- to look at meaningful measures of abuse in order to actually demonstrate that a particular product has changed abuse. These products -- it has to be able to differentiate the actual product that's being abused and also the route of abuse, remembering that these are not necessarily designed to deter all abuse but are specific to route. So that has to be available.

We've asked them to focus on large or national or at least large geographically diverse types of populations and to make these studies sufficiently powered to examine trends. That's just basic science. But as you saw from the earlier graph, that can be challenging if your market share is not very large.

And then we've also encouraged companies to submit what we call supportive information. The --

this is anecdotal, or qualitative, data, that can be very, very useful but may not rise to the level of hypothesis-driven study but can complement our understanding and help us to interpret the formal studies more meaningfully.

We've had to modify our approach a bit, again, because of the limited uptake. So rather than direct companies to go out and do studies that may not be large enough or powered -- statistically powered enough to be able to provide meaningful results, we've asked them to break it into two phases -- to do a Phase 1 study where you're really looking at feasibility and describing what's seen after the product is approved and marketed; and then the second part, once we both mutually agree we're at a point where a meaningful study is possible, then we move into hypothesis-driven effort, trying to save resources and do things that make sense.

So why is this important? If we've got labeling in there that says that we expect them to deter abuse based on controlled conditions pre-marketing, why is it so important to do these post-

market studies? Well, the labeling of a product and to have such a claim about post-marketing ability to deter abuse is a very big deal. It's -- the labeling is a legal document, and it carries a lot of weight. We require high-quality studies with scientific rigor to go into labeling to support a labeling claim. And oftentimes, you see that in the form of clinical trials that are done to approve use for an indication.

When these submissions come in, these folks who have introduced themselves to you lead the teams that dig into these data. These data are reviewed in depth. And when possible, we even redo the analysis, much like is seen in the clinical trial setting. And whenever we get one of these studies, these submissions for labeling claim, they come to a public discussion, typically an advisory committee meeting where we share these results with external experts and get feedback before making decisions.

So the goal of labeling is really to provide informative and scientifically accurate information to prescribers and to patients. So that's why right now none of these products have post-marketing information

in their label. And part of -- that's why -- part of why we're here to talk today.

So why is that? What are the challenges? Why isn't this something that's more straightforward to do?

Well, some of us who have been in drug safety for a very long time realize that abuse is a very, very different issue than many of the traditional drug safety issues we deal with. I've been doing drug safety for longer than I care to say. And usually, the outcomes -- the safety outcomes are -- happen in the patients who take the product.

Abuse is not like that. It can happen in the patient. It can also happen in others. It can happen in family members. It can happen in anyone. But it could be tied to the prescription for a particular patient.

The traditional data sources we often use to study drug safety outcomes -- we often use insurance, administrative claims data; we often use electronic medical records. These don't work as well because, many times, the outcomes of abuse are not captured. And these are covert behaviors that people who have

substance use disorder don't always share with their physicians. Their physicians may not be aware at all.

And then the outcomes -- the -- this may not land you in your doctor's office or in a hospital. It could also land you in a morgue. It could land you in jail.

So there's a lot of different features to this that make it very difficult to study. I have a very simple graphic to kind of show that, the complexity here. On the left side of the screen, we're trying to illustrate that there's a lot of different ways as a drug is manufactured, distributed, and prescribed how it can end up with a patient, but it can also end up being diverted and into other hands along that pathway. The result of drug diversion can end up as misuse, abuse, addiction, overdose, and death. Those are the outcomes in the center that we worry about a lot.

But also, a patient can receive this, and a patient can end up using a drug inappropriately and experience any of those outcomes. Or a patient could use a drug as prescribed and still end up within many of these outcomes. So there's many pathways to get to

these outcomes of concern.

On the right hand, we've tried to link how do we study these outcomes in the kinds of data that exist. So you can see sometimes these kinds of outcomes will end up -- we could capture them in population-based surveys or healthcare data systems or in mortality records.

And on the far right are all the different ways. There no one-on-one alignment here in terms of what we can learn about these outcomes for the kinds of data that are out there or that we're trying to build. So it becomes a very complicated picture of how to look at these outcomes and then piece them all together.

So many of these studies are using what we call an ecologic model, which is basically doing a pre-post analysis to look at what was going on with regard to the outcomes of interest, like abuse, prior to an ADF product being marketed and then after.

And as we know as scientists, these designs are fraught with challenges. The goal is to try to do those studies and end up with a result where we understand a change in abuse that we're able to

attribute to the introduction of the product. And this can be very challenging because there's a whole lot of other things going on right now around opioids, a lot of efforts to change things. So how do we zoom in on the effectiveness of one particular intervention?

Again, my colleagues will go into a lot more detail in the specific sessions today. But just to tee up, we don't have a nationally representative database that allows us to look at formulation of product and route of abuse and to understand at a national level whether a product has actually had an impact.

So we have directed industry, and we ourselves have tried what we think of as a mosaic approach, or touching the elephant in different spots, to try to see can we piece enough together from different kinds of studies, different types of data, to come up with a picture that looks at least consistent. And the currently available data sources that we're seeing being used for this work have a fair number of limitations, which can really make it difficult for us to interpret what we're seeing.

So how does that bring us to today, and why

did we all invite you here? We felt industry and FDA have been talking together for a number of years around these post-marketing required studies, trying to scratch our heads and figure out how to do this. We thought it was time to have an open scientific discussion. So this is a little bit of a different kind of meeting. This is not an advisory committee meeting. What we tried to do is to divide -- invite a very diverse group of scientific experts.

So we have folks here who have been studying abuse of prescription opioids or heroin or other types of drugs that can be abused for many years. They've used some of the data sources that we've been seeing in the submissions. They've also used other data. So we've asked you to come.

We also have folks here who have been conducting national surveillance or designing national systems for data collection for a long time to study all kinds of other public health problems. We've asked you to come.

We've got folks here who have been working with data sources that are either out there or soon to

be out there or just now out there that may be helpful in this space. But we don't know if anybody's thought about it, so we've invited you to come.

We've invited folks who are experts in survey methodology and projection science to try to understand how do we best draw samples that are meaningful and then take those samples up and project them to reflect national experience.

We've also invited some traditional -- folks who have been working in traditional drug safety and pharmacoepidemiology for a long time to try to pick their brains to see what you think.

And then we have the folks who actually have experience of trying to figure out the scientific rigor that's needed for regulatory decision-making, and that's the folks here -- that's hopefully us -- who have done this for other issues and now have to try to figure out how to get there for this issue.

So our goal is not to solve this problem today. Our goal is to start a conversation and to bring these various disciplines together in one conversation to talk about how can we do this better,

how can we do better with what we have, and how can we do better in the future to get better data and better methods.

So here's the overall plan. Today we're going to focus on the data sources. And again, we're not talking about specific names of data sources. We're talking about types of data sources. How -- we're going to talk about what can we do with the resources we have because we're all very applied, as many of you are as well. We have to determine what we can do with what we have available to us. How can we look at the data and methods we have? And what are things that we can do, ways we could think about them, analyses we could try that would help us to interpret them better?

Tomorrow is more of our brainstorming session of, okay, now that we understand what we've got now, how could we do better. Are there new data we could collect? Are there new linkages we could think about?

So today, what we've done is we set this up into four sessions. These first three sessions we'll talk -- in the first session, we're going to talk about the resources themselves and the kinds of data that are

available. The second session we'll talk about some of the sampling concerns, some of the metrics we've seen being used, and denominators. And then the third session is very challenging of how do we deal with figuring out how to make causal inferences and how to control for confounding of all the other things going. And then the last session, Session 4, Dr. Levenson and I will try to tie together what we've heard in Sessions 1, 2, and 3 and try to put forward some themes we've heard to get some consensus on pathways forward.

Tomorrow we'll switch gears and talk about, again, potential for the future. So we're going to talk about national surveys, perhaps modifying the ones we have or thinking about new ones. We'll talk about different designs to go beyond. Maybe in addition to ecologic designs, maybe we could think about the potential for following patients over time, actually collecting our exposures and outcomes in the same patients.

And then leveraging other systems -- can we link data together to fill some of the gaps we see? Are there benchmarking techniques we could use to help

further our understanding of how to interpret results out of particular resources? And again, Dr. Levenson and I will try to tie that together and feed a discussion that kind of defines pathways forward.

So the format for each session is going to work like this. Again, this is not an advisory committee, so this is a scientific workshop. Our goal is not -- we're not really asking you for advice. We're not asking you for voting on particular questions. What we're trying to foster here is a real scientific discussion for some things for us to think about.

So each of the sessions will be chaired by an FDA epidemiologist and statistician. They've partnered up. They will begin the discussion by prevent -- providing a 15-minute overview. They'll try to take some of the things you saw in the issues paper and drill them down a little bit, give you some examples, actually help you see exactly the kinds of things we really want to discuss.

Then they're going to moderate a session with the panel discussion for about an hour where we want to

hear from folks as much as we can about ideas, things you've been thinking about that would fit under that topic. Now, recognize we have artificially divided. All of these topics are connected. So we're going to try the best we can to stay on topic for each session, but we know they tend to relate to each other. So that's okay.

And then at the end of each session, we will have an opportunity for comments from our audience. And this is a little different. I know in the -- leading up to the meeting, many people weren't understanding. At an advisory committee where decisions -- recommendations are being made, stakeholders can sign up and give even formal presentations. That's not what this is about today. Today is about allowing members of our audience to be able to chime in to the scientific discussion if they would like to. So there won't be formal presentations but perhaps comments.

We have such an esteemed panel of experts here, but there's lots of experts out there that we couldn't invite to sit on our panel. So if folks

have thoughts that would be relevant that should be considered that, again, could tee up further discussion, we'd love to hear it.

In the interest of time, the way we're going to do this is, at the end of each session as we have -- and move into our 15 minutes of audience participation, we ask that people line up at the microphones. There's one on either side. And we'll go through as many folks as we can. We're going to limit your remarks to three minutes, and we'll have the familiar green, yellow, and red light just to help us stay on track.

But it doesn't mean we don't want to hear. If you have comments that won't fit in three minutes, don't worry. We have a docket open for this meeting, and it will stay open until September 11th. And we encourage you. Send us slide decks. Send us articles. Send us your thoughts. Send us books, whatever you think would be helping us. We plan to pore over that docket and look through that more detailed information.

So what do we see as the output here? Are we just -- basically just going to talk and then check the

box? No. We really want to use this information in several ways. Most immediately, as I mentioned, we continue to support and encourage the development of these products. We talk to our colleagues in industry regularly about their post-market studies, and we can take ideas we hear here and put them right back into those conversations and to help improve the studies as they are ongoing and as we try to get these studies done efficiently. And as we update and revise our guidance to industry, there's another place in the shorter term that we can put these kinds of ideas and comments to push the science forward.

In the more immediate term, we at FDA in this past year have established contracts with a number of the providers who actually have a lot of the data that industry is also working with. So there may be certain concepts or ideas that it might make sense for FDA to support through those contracts. And again, those mechanisms are in place, and we could apply funding to those and, again, actually implement some ideas if we hear things today that lend themselves to that.

We're also -- a number of our federal -- a

number of our panelists here are our federal partners in initiatives that we are working on to build new systems to look at emergency room admissions and also be looking at improving death data. So as we work with our colleagues, if there are ideas that come out of today's and tomorrow's meetings, we can feed those into those efforts to improve those as those are ongoing as we speak.

And finally, we just initiated a new project under the CERSI program. The CERSI is a grant program with FDA with different centers of excellence in regulatory science and innovation. One of our newest CERSI sites is Yale and the Mayo Clinic. It's a partnership. We just initiated a project with them where they're going to try to link together data in the State of Connecticut -- again, disparate data, medical data, law enforcement data, death data -- and try to see in that microcosm whether they could come up with meaningful linkages that might enable further look at such problems. If we come up with ideas that lend themselves, I'm sure they -- they're aware of this meeting, although they could not attend, and would be

happy to implement ideas that we may come up with.

And longer term, we have what's called a Broad Agency Announcement. It might be the best-kept secret on our website. I'm not sure. But we actually put forward, in effect, what's our research agenda, and improving our ability to study abuse-deterrent formulations is on that. And so if folks have ideas, FDA can entertain research proposals and provided we have funding. But the commissioner was here, so -- and he -- you know, he could help with that. But it's a possibility long term that, you know, if -- good ideas could get funded through FDA through that mechanism.

And also, I attended a meeting just a few weeks ago. And Dr. Jones is here from HHS. HHS has a new initiative where they're getting stakeholder input to try to improve our data infrastructure in this area. So again, some of these ideas that are good ones could end up with HHS funding long term. That's a -- it's a possibility.

So those are my remarks. And now I'm going to turn it over. We're going to start our first session right away. We'll have our break after this session.

I'm going to turn it over to Dr. Cynthia Kornegay, who is our team leader for the Epidemiology Drug Abuse Team. She and Dr. Hana Lee from Biostatistics will lead our first session on data resources.

DR. KORNEGAY: Good morning. I'm going to spend the next few minutes providing just a high-level overview of some of the current data resources that are commonly used to study ADF opioids.

But before I begin, I do need to correct a statement from the Issues Paper. The Issues Paper incorrectly states that, "The Treatment Episode Dataset, or TEDS, is a census of facilities that are licensed or certified by the state." The correct statement should read that, "The Treatment Episode Dataset is an admission-based system that includes data from facilities that receive public funds, are licensed or certified by a State Substance Abuse Agency to provide treatment, or are tracked at the state level for other reasons."

So on to my talk. Oops. There we go.

So the talk is broken up, roughly, into three sections. First, I'm going to give a very high-level

summary of the current data resources, including some of the advantages and challenges when one is considering using some of these data resources to do research on ADF opioids.

I will briefly touch on some of the general methodological considerations that we hope researchers are going to think about when they are planning these studies and, finally, talk a bit about the outcomes that are of interest to FDA and some of the issues that -- around them.

So this slide shows four broad categories of some of the most common data resources in terms of where the base population comes from and how the base population is selected. And as you can see, most of these come from convenience samples of varying sizes, with the exception of some of the federal surveys. This slide doesn't include smaller, regional, or cohort studies, and nor does it include state-based information, such as PDMP or medical examiner data.

And while we're thinking about these data resources and my -- and the characteristics that I'm going to describe, I want to emphasize that I'm viewing

this today specifically from the lens of designing and implementing ADF opioid research. Many of these data resources are used for all sorts of other things and, as such, would have a different challenge and different profile and have different uses. So this -- these characteristics shouldn't be considered a -- kind of a blanket statement about these data resources in any field.

So the first one -- oops, sorry. Okay. There we go.

The first one is Poison Control Centers. And these data are based on information collected from calls to poison control centers throughout the United States. There are over 50 such centers, so there's a very broad coverage area. And these data can often provide product-specific information and might include or capture individuals that would not otherwise interact with the healthcare system.

However, if you are planning to do analyses in these data, you might need to think about the fact that the percentage of overdose or adverse -- other adverse events that result in a call isn't really known. And

the ability to distinguish specific formulations and brand names is not always clear or constant.

And finally, severe overdoses or immediate deaths are unlikely to generate a call. And so if you're looking at those outcomes, they might be underrepresented in these data resources.

Another consideration is that how individuals interact with poison control center data, what prompts a call, and what is changing over time. And it's not really clear to us how these change -- how this change is affecting the analysis that we are doing.

The second group are Surveys of High-Risk Individuals. And these generally include folks who are being assessed for who are entering treatment for substance abuse disorders. This can, again, capture a high-risk -- high -- hard-to-reach -- sorry -- population of high-risk individuals and can also provide product- and route-specific abuse information, which can be very valuable.

However, it is difficult to define the underlying population that is captured in these surveys; and therefore, it can be difficult to

generalize analysis results to larger populations. It is also difficult or impossible to validate key pieces of information since that data can only come from the person who had been misusing or abusing a specific product.

So General Population-Based Surveys -- we define this category to include, roughly, two types of data. There is nationally representative data, such as the National Survey on Drug Use and Health or Monitoring the Future. And there are also large convenience samples, who for those -- an example of those would be internet surveys.

Now, these surveys are often not focused on those who are specifically on the severe end or the higher-risk end of the abuse continuum but can capture those who are just beginning their abuse and might be just experimental or recreational or occasional -- have occasional misuse or abuse of drug products. And some of these surveys also can capture specific populations that are seen as more vulnerable, such as adolescents or teens, such as -- in Monitoring the Future.

And the last category is Claims-Based

Information. Now, these are most useful, obviously, for clinical outcomes, such as overdose and death. They are less useful for the outcomes of misuse and abuse, although FDA is -- has requested industry do studies that assess potential algorithms for measuring misuse and abuse valid -- sorry -- assess -- create and validate potential algorithms to assess misuse and abuse in claims data. And this is part of a series of safety studies of extended-release and long-acting opioids and those -- and folks who use those long term.

Some of the things to think about, though, when you're thinking of doing studies of claims data is that almost half of the individuals with a drug overdose or other drug-related adverse event do not have a record of being dispensed an opioid. And because of that, you can't really assume that an opioid that was dispensed is the same as the opioid that was abused. And individuals, again, that come to the attention of the medical system might be anywhere. They could be experimental or recreational users, or they could be rather severe in their substance abuse disorder.

And so the next part -- oh, I'm sorry. And finally, I just wanted to mention a few additional data resources that can also provide useful information on specific topics. And these are alternative data resources, and they can include spontaneous adverse events; drug diversion data; and web-based resources, such as those that collect information on street price.

And these can provide very specific insights that can't be obtained through the more general and larger data resources, but it can be a challenge to relate these metrics to the specific outcomes and characteristics that are of interest to the Agency. And also, since some of these data resources run on anonymity, validation and verifying specific factors can be an issue.

So next, I just want to touch on a few methodological considerations that we think about a lot when we are looking at these data and trying to figure out how -- the effectiveness of ADF opioids. The first is Exposure Definition and Assessment. Now, this depends on the level of analysis. In group-based study designs, ecological studies, those are something that

we see fairly common. And in those, the exposure, we consider that to be a unit of time or some other demographic.

One of the things that has to be kept in mind in these kind of ecologic, or group-based, studies is that the individuals in the numerator may or may not also be represented in the denominator, which is generally a measure of drug utilization.

The other half of the individual studies where we would -- we might define the exposure as having possession of a drug substance and the outcome as misuse or abuse in some manner. However, it can be very, very difficult to disentangle the actual possession and the abuse, particularly if the data are gathered for other purposes beyond ADF opioid studies.

The second issue is Misclassification and Ascertainment, and this can be a very important factor in trying to determine if an ADF opioid is actually having an effect on abuse. It can have fairly large effects on pre- versus post-transition product identification. And an example of that is the "Kleenex effect" where all drug, whether or not it is a brand or

generic or counterfeit or anything else, is attributed to the brand name. It can also be affected by the data collection methodology. So the order that drugs are asked in (ph) and how drugs are identified can lead to varying levels of misclassification. So assessing the extent and non-differential nature of misclassification can be very important in understanding and interpreting ADF opioid analyses.

And just as a last consideration, I wanted to bring up this nice simple slide that Dr. Staffa showed you before. And to -- this slide is to highlight that there are many invariant routes to misusing and/or abusing ADF opioids. And in addition, there are multiple data resources that can provide information on misuse and abuse. But they capture -- each capture a different part of the phenomenon, and they also vary in their ability to reliably capture outcomes of interest to FDA.

And with that, I'm going to segue to the last part of my talk, which is actually to discuss the outcomes.

So as Dr. Staffa mentioned in her talk, the

outcomes of specific interest to FDA are misuse, abuse, addiction, overdose, and death. And since many of the technologies in ADF opioid products that we're asked to evaluate focus on non-oral routes of abuse, we are also interested in route-specific outcomes of misuse, abuse, addiction, overdose, and death.

Now, while FDA has definitions of misuse and abuse, as Dr. Gottlieb described, operationalizing those definitions in a specific data source can be a challenge. Many of the data resources have differing definitions. Some combine the concepts of misuse and abuse. And these are just not amenable to medical terminology coding, so they can be difficult to measure in claims-based data resources. And often, ascertaining a specific brand or formulation can be difficult or (sic) not impossible because it's a known or the information is just not recorded on a regular basis.

So addiction is a complex and nuanced concept. It's similar to misuse and abuse in that it is not measured well in clinical data resources. And often, even the characteristics that make up addiction are not

recorded well. So it's even difficult to create an algorithm.

And finally, overdose and mortality are someone easier to define. But few data resources can connect misuse and abuse to overdose and mortality. And also, for example, in medical examiner data, it can be impossible to attribute an event to a specific brand or formulation. And in the case of overdose, specifically, one can look at the exposure to a specific product, but overdose visits or deaths, again, cannot be product-specific kind of by definition.

And a final couple of issues is that there's a complex and changing terminology around this whole area of opioid abuse, opioid addiction, or substance abuse disorder can all mean the same thing or different things, depending on how they're used. Recent changes in the DSO (ph) from four to five and how these concepts are defined have also further complicated matters.

However, to assist -- well, somewhat to assist -- to begin to disentangle the situation, FDA has asked industry to perform a series of studies that are based

on chronic users of extended-release and long-term opioids for chronic pain. And one of these studies centers around creating an instrument that will define and validate misuse and abuse in these patients and be able to use these outcomes and definitions in different types of data resources, for example, in claims.

And lastly, I want to talk about some additional outcomes, such as doctor or pharmacy shopping measures, which again are represented in the extended release and long-acting, post-marketing studies; and proxy clinical outcomes, such as hepatitis and HIV; and finally, drug seizure levels and changes in street price. Now, these are interesting and can provide timely information, but it is not always clear how they relate to, again, the outcomes that are of interest to FDA. And also, with the proxy clinical outcomes, they can be useful if they can be validated well, but they tend to require a very specific temporal sequence or circumstance. And an example of that is loperamide abuse leading to serious arrhythmias in order to be useful for us in studying ADF opioids.

So thank you. And now I think we're going to

move into the discussion.

DR. LEE: So we have developed questions to guide panel discussion. We have big four questions that we would like to discuss over the next 60 minutes. Scott will help us, and he will be assisting us to make sure that we call on you to provide comments throughout this session.

And if you will like to comment on each question, please raise your hand.

And can we start from the first question? So this is the first question that we would like to discuss. We would like to discuss the ability of currently available abuse-related data resources to adequately characterize the underlying population of those who misuse and abuse drugs. So we would like to discuss how well do they capture -- the existing data resources capture occasion and recreational use and severe/advanced opioid use disorder. And we would also like to discuss how well these resources capture the individuals in between these two extremes.

So who would like to begin the discussion?

DR. SCHNOLL: I --

DR. LEE: Oh.

DR. SCHNOLL: I'm Sid Schnoll. I think these questions are nice, but I'm concerned that we're trying to do too much with these formulations. And early on, we were told that these formulations are designed to reduce insufflation and now injection. And now we're trying to show that they do everything else in terms of addiction, abuse, overdose.

I mean, it's nice, and I think it's important. And having worked in addiction, as I said, for close to 50 years now, I think we need to address the problem of addiction. But these products don't do that. They are designed to simply reduce insufflation and injection, and we have to look at that very carefully. And I think designing studies that will address those specific points are very important.

We have seen, unfortunately, that the introduction of these products, along with all the other measures, such as PDMPs, public information, et cetera, has, in fact, reduced the prescribing, as you've shown, but has resulted in unfortunate consequences as people have shifted over to illicit

products. Is that an outcome that's positive or negative?

Now, I think we have to look at this in a somewhat different way. And I think your questions are reasonable. But are they really the questions to address by the FDA for these specific products? And I'd like to throw that out.

DR. LEVENSON: This is Mark Levenson. Could you elaborate what questions you feel might be more relevant for FDA to address?

DR. SCHNOLL: Well, I think I did. Let's look at do these products which are designed specifically to reduce two things -- insufflation and injection. Do they do that? How effective are they in doing that? We've certainly seen in the Category 1 through 3 studies that in those controlled situations they seem to work. But are they working, really, in terms of once they're in the marketplace? If we can show that, I think that's extremely important to look at.

These other things, they're very important and problems we've been trying to deal with in addiction for as long as I've been dealing with it and going back

even further. But I'm not sure we can do that with these products, and trying to ask them to do things beyond what they are designed to do creates a distortion of what's going on. And I don't think that's what we want to do.

DR. STAFFA: So this is Judy Staffa. Could you connect that? I think that's a very reasonable proposal. Connect how do we evaluate these products and how well they deter insufflation and injecting using the kinds of populations that we have available to us. Where should we be looking at that? I think what we're trying to do is tee up -- is that something reasonable to look at in people who might answer household questionnaires, or is that something we should be looking at in people who present to treatment or people who call poison control centers, et cetera?

DR. SCHNOLL: Well, I think we've got some data on that from treatment centers. I think if we look at -- such as the Skip Program from the RADARS system and the NAVIPPRO system, we see that people have shifted away from the injection and insufflation of these products. So there are some data that are

currently available, and I think we can continue to look at that and think about potentially other sources. But again, we have to look at what these products are designed to do and study that, not ask them to do more than they can do.

DR. STAFFA: Ms. Cassidy?

MS. CASSIDY: Hi. I just -- I think Dr. Schnoll raises a very good point about the questions being broad, and I think that the questions that you've laid out here, they're important to answer and they're an important part of the discussion. But I'd like to just maybe follow on with a comment about how we can think about framing some of this as it relates to the question of ADFs versus prescription opioid abuse in general. I think that there's, really, kind of thinking about it in two tracks.

And this might be skipping ahead a little bit, not talking about data sources, specifically. But the outcomes all across the board are important, but maybe there's outcomes that are more important in sort of that broader population prescription opioid abuse, you know, track and path to think about versus outcomes

that are more, you know, specific to defining success of the ADFs themselves.

And maybe since, you know, there's a number of ADFs currently, you know, or products with ADF labeling on the market but more coming to pass, that there's sort of a larger, you know, momentum that they need to have as a group to be able to then make an impact on those overall broader trends. So if we're sort of talking about ADFs, I think we need to think about those specifically and how we term those, you know, in the outcomes and the data sources for them and, you know, and their -- what their success can be as opposed to the larger broader.

And I think that those are important, too. But I think we have to maybe sort of frame them as maybe proximal and distal types of efforts.

DR. LEE: Oh, thank you.

DR. GOLDIE: We've got several. Dr. Green, you have a comment?

DR. GREEN: Yes, thank you. I really appreciate the, I guess, illustration of the mosaic approach because there are many different outcomes and

we've listed even here many different populations. But I think that, you know, if we think of it in terms of Dr. Schnoll's comment about the route specificity and then data assistance with product specificity, focused on those as the most potentially valuable ways to evaluate the impact of ADFs on those specific routes, then, you know, a couple of the things mentioned, like the poison center utilization -- in some preliminary work we've done, we've seen that the utilization of poison centers over time is dependent upon the pharmaceutical or non-pharmaceutical aspects of products.

So when we look at pharmaceutical products specifically, calls to poison centers, the change over time has been primarily in pediatrics and not necessarily in the adults. And we've seen that utilization has stayed pretty stable in the adult population, which is what we're studying here.

So more work can probably be done to understand the impact of poison center utilization, to Dr. Kornegay's point, of one of those considerations when we're looking at trends over time.

And then also, for the treatment center data, looking more at the relationship of, you know, what do those patients represent, what do those sites represent, so looking at comparisons with the NSSATs registration data and trying to get a better feel for that representation, I think more work could be done to do that but, really, maybe focusing on those programs and how product specificity and route specificity and then working through some of those unclear questions.

We don't know if they have an impact or don't because we just don't have the information on them. So I think there's some opportunity to do some work in that area.

DR. GOLDIE: Dr. Krebs followed by Dr. Boyer.

DR. KREBS: I appreciate the comment about what these products actually can do in terms of preventing insufflation or injection as being, really, the focus. But ultimately, is that important from a patient health and a population health perspective in isolation and whether the value of the products can

really be assessed by simply focusing on their effectiveness in preventing insufflation or injection. You know, we all have seen in this area how unintended effects of a product can have a huge effect on patient health, on population health beyond the focus narrow initial indication.

And so I think for that reason it's really important to think about how, even if they are effective at their intended target, how they may or may not improve or even worsen population health, patient health more broadly, we need to evaluate the broader outcomes in addition to the specific focused outcomes that they actually are intended to address.

DR. GOLDIE: Dr. Boyer?

DR. BOYER: Yeah, thank you. I mean, I'm still focusing on the questions that are, you know, like, right here in front of us. Yeah, talking about recreational and occasional use, I don't know that there are a lot of resources that necessary will pick that because I think a lot of that learning by being occasional is by happenstance. So you're back to a poison control center model for at least acute exposure

to things. I'll come back to that in a second.

For severe and advanced opioid use, yeah, I get that a lot of people go into treatment. But in chronic pain populations that I encounter who come and demand opioids, the response then a lot of time is I don't have an opioid use disorder, I have chronic pain. And just as diabetics need their insulin to survive, I need my narcotics to survive. So they view it as an honest-to-goodness medical problem rather than a potential medical problem which has gone off into a psychiatric tangent.

Either way, if somebody in my world comes in with an overdose -- we actually did this data in our treatment sites, so this is the major, you know, referral center in Massachusetts -- we demand that the clinicians call the toxicology service with overdoses so that we can keep track of numbers. So we know that -- because we can compare actual patient presentations with number of times we get called -- and this is where we're demanding calls, so that's a surrogate for a poison control center call -- we know that fewer than 7 percent of opioid overdoses who present to the ED

actually generate a phone call for toxicological consultation. And you're correct. It's mainly in the pediatric population because there are no clinical data which predict what an opioid overdose looks like in a toddler who just has normal exploratory behavior and happens to pick up the methadone pill.

So I don't know that we can talk then substantively about what -- you know, about numbers that pop in because the calls are simply not coming in. An opioid overdose is the simplest of all overdoses for a clinician to treat. You give naloxone. If the naloxone fails, you give more. If more naloxone fails, you intubate. And at that point, you've not only done the procedure of intubating, but you've got a patient disposition. When an emergency physician has a patient disposition in place, the thinking stops.

So you know, the -- you know, like, I don't know how well you're going to be able to capture the acute and recreational. There's some problems with severe and advanced opioid use disorder. And I can tell you that the acute exposures, at least, are going to be extraordinarily problematic to pick up.

CAPT JONES: So thanks. I just wanted to echo what Dr. Krebs said, that I think you have to look at this in the broader public health context. I mean, we don't want to have industry investing a lot of money in developing products just to show that, in isolation, they can do something but, in the broader sense, they don't -- we don't get a public health gain.

I think the other potential risk in looking at just injection or insufflation is that you're not taking it -- potentially not taking it in the context of secular trends. We know from data sources from Cicero and others that people -- you know, some proportion of people went from injecting to using OxyContin orally. And so we have to account for those things and changes and trends and the fact that the vast majority of opioids on the market are not reformulated, so people can easily switch.

So is it a question of the product is really good at deterring abuse, or there's just so much else out there? So I think you really do have to take it into that context, both specifically even if you're looking at injection and insufflation, but also trying

to look at the outcomes.

And the other thing, I do appreciate that you guys put time into asking these questions and developing them, so I want to respond to the specific question. I think, you know, in the NSDUH data you can get, you know, frequency of misuse or frequency of nonmedical use, and we've done a couple of studies looking at the characteristics of people who are more infrequent users versus those who are more frequent. And we tend to see, you know, the use disorder side more in the frequent misuse side. And you can look at other sociodemographic characteristics of those individuals there.

I think the big gap is that we have household surveys -- so NSDUH or Monitoring the Future, a school-based survey. And then we have treatment, whether it be TEDS or, you know, parts of RADARS or NAVIPPRO. But we know that the vast majority of people who meet criteria for use disorder don't get treatment. So we have a gap in, like, what do those people look like compared to those who are showing up in systems where people are getting treatment.

And even if you say, well, use the NSDUH as the basis for people who did or didn't get treatment, we still have a gap of probably some very high-risk populations -- incarcerated, people who are homeless now living in shelters. So I think we have a gap in understanding that group with the NSDUH data because it operationalizes DSM-IV criteria. You could look at the specific abuse or dependence criteria that they need to look at a spectrum of people. And I think some people have done that with NESARC data as well in a recent paper.

But it is -- I think it is a gap in trying to understand, you know, who is the affected population, how do they differ. As we move towards outpatient care with buprenorphine or vivitrol, I think that will introduce another gap where ASI-MV or NAVIPPRO, other things may not be in those offices. And again, that population may be different and respond differently to different products that are marketed.

DR. GOLDIE: Dr. Scharman?

DR. SCHARMAN: Yeah, I think the other thing we need to measure that we don't currently measure is

that these ADF products, we're not going to be able to show that they work if people aren't buying them. And I think right not we have a pattern where the abuse -- the ADF formulations aren't designed until that product's about ready to go off patent and it's available generically. So from a cost perspective and insurance reimbursement perspective, they're not going to buy the ADF formulation because there's a modified-release product out there that's much cheaper.

We saw that when suboxone and subutex came on the market. And I note that the ADFs listed in the examples none of them were ones that contained naloxone. And one of them was supposedly abuse-deterrent naloxone. You can insufflate (sic) it or inject it, and that was supposed to be what was preferred after the initial trial of use. But it was never dispensed because it was too expensive.

So the one without the abuse deterrent, the naloxone, was cheap. Hospitals couldn't afford to buy it, and people couldn't afford it. So it was never used.

So I think we have to measure what inhibits

use at the beginning. And did that ADF formulation, was it so good that no one even bought the product?

So I think if we're looking at other data sources, are anybody surveying the physicians like family practices, internal medicine physicians and pharmacists to find out what are their patients asking for? So just for example, at a pharmacy, if you talk to a pharmacist, if the doctor writes for a fentanyl patch -- it's a Duragesic patch -- the patient picks. And they'll pick the gel matrix formulation every time, and they'll come up with some excuse why they don't want the non-divertible -- they can't suck the gel out of the patch -- because they say it doesn't stick.

And so -- or you'll go to the physician. What are the patients asking the physician for? I mean, I've yet to see a paper that describes anaphylaxes to naloxone, and yet they'll tell their physician, oh, I'm allergic to naloxone. It gives me a headache. I can't have it. So the physician will prescribe a form of the drug that doesn't have naloxone in it.

So I think what we have to get are what are patients asking for -- their physicians for and are

they specifically asking for a product that for some reason wouldn't be abuse-deterrent and what are they asking pharmacists for. So we have -- those two surveys, we'd find out they work by the fact that people steer away from those products and don't buy them.

DR. KORNEGAY: Thank you. That's actually a good idea and a novel concept. And also, it leads very nicely into our second question, which also parts back to what Dr. Schnoll began this discussion with, which is identifying how products specifically can reduce insufflation or injection.

And so our second question also has to do with current data resources. And it's, "Discuss the ability of current data resources to distinguish ADF opioid molecules and formulations," and, "Discuss the ability of currently available data resources for collecting information on routes of abuse."

And I understand that there are probably multiple levels of questions. The global question, that is, you know, kind of very difficult to get your head around unless you've had a lot of coffee and also

kind of some of the smaller component questions. But at FDA, we are often faced with answering these questions on individual drugs.

So despite the fact that we have to consider all of these drugs in a big picture -- and that's really what's important -- that doesn't negate our need to understand what's going on with specific drug products.

So with that in mind, is there anybody that would care to give us their thoughts on how we can identify these specific drugs and these specific routes and some of the data resources that are available to us today?

Oh, I'm sorry, Dr. Boyer.

DR. BOYER: So I'll just fire back a question at you. Do any of the newer formulations have intentionally added taggants to them?

DR. KORNEGAY: Not -- I don't understand. What was the term that you used?

DR. BOYER: Taggants. So if I'm a terrorist and I buy an explosive -- explosives have taggant molecules added to them so that you can identify the

source of manufacturer. So instead of putting an imprint on the side of a pill to figure out where it came from, you add a chemical that can be detected at a later point. Do any of the newer formulations contain a taggant?

DR. KORNEGAY: Not to my knowledge. I think that is something that we -- that our group has thought about in the past, but it would -- you know, it gets very complicated easily if you do a visible kind of identification like a different shape or a different color or a combination. After a while, you have so many different combinations. You're going to get some fatigue of I used the little purple or the round blue one. And people still don't know what they're taking.

And there's not always a toxicology or chemical testing that's associated with these events. So if it's a purely chemical signature, then you would -- this would still -- might not bring you much closer to what specific drug was involved unless it's a very severe event like a death.

DR. STAFFA: Oh, this is Judy Staffa. I just wanted to ask Dr. Throckmorton. Are you aware that

this kind of technology is used in any drug products? Because I'm imagining there would be a lot of additional pre-market testing on the safety of that for a patient ingesting something like that.

DR. THROCKMORTON: No, we have a lot of work going on around data -- around drug supply chain. We passed a law a couple of years ago we're implementing and things like, specifically tagging individual pills.

I'm not aware of -- Ed, can you say a little more how you'd see them being -- that being used? So you could think about it being used in a kind of I'm going to go after diversion and I'm going to find out who got that pill prescribed to them in a sort of law enforcement sort of approach. Or you could see it used in a way to understand better the patterns of distribution of these products from prescribed use to illicit use or something.

Did you -- what -- which direction were you coming at this from?

DR. BOYER: I mean, I was thinking about just the isolated -- you know, just -- you know, like, the point of manufacture. If I have a patient who comes in

and I collect urine and I analyze for -- and I'm just going to make up a molecule here -- oxycodone, you know, I don't know which manufacturer that oxycodone has come from. But if I've got four manufacturers of oxycodone, each of whom have a unique taggant added to it, I can distinguish if it's 1, 2, 3, or 4. And then it depends how complex you want to get with it.

If you had, you know, a different -- you know, like, supply chains, you could have other taggants added to it, which would go to different regions of the country. And I mean, you know, you're laughing because it's --

UNIDENTIFIED MALE SPEAKER: Oh, no, it gets complicated.

DR. BOYER: -- it gets complicated very, very quickly. But in terms of, you know, like -- in terms of just adding an inert molecule, it's easy to do. It can be something which is inert. There are plenty of inert chemicals that are out there that get added to medicinal formulations anyway. It just has to be something that can be identified. It can just be something identified easily from a biological matrix

and something that has to be eliminated in urine.

And truthfully, you know, there are enough of those things out there that, you know, like, from a chemical perspective it shouldn't be hard to find. I don't do regulatory science, so I'm not going -- you know, so I understand that there are complexities which are beyond my comprehension. But at the same time, from a scientific perspective, it's a really simple thing to do.

DR. DASGUPTA: Can I respond a little bit more to that? So there was -- so there's one -- there are some ADF platforms that have ion exchange shells, right, which get excreted in the feces after the ingredient has been released. And so as -- working with our -- with some medical examiners in North Carolina, we asked them to see in their autopsies whether those ghost shells were present to try to understand whether those specific ADF formulations were being ingested. And in -- there was -- it was a very low-penetration drug, so we -- there weren't -- you know, there was only a handful of cases where they could actually find those, and there's gastric motility

issues and other -- you know, other thing in chronic pain patients.

But when you started combining those autopsy physical findings with the toxicology findings on autopsy, there was a discrepancy where there were other opioids that were prescribed or used or metabolites, things like that, where it was -- it -- we kind of stopped that project because there wasn't a way to -- because there was multi-opioid exposure in almost every patient. So understanding -- you know, even with that tag, it was hard to -- it wasn't tagged, but it was actual -- a physical shell. It was hard to understand, you know, whether the mortality was attributable to this and to which opioid or whether ADF or not.

But I think it's generally a good idea, but that was one experience we had with trying to figure that out.

DR. STAFFA: Right. And this is Judy Staffa. I would also think in order to be in the feces it has to be taken orally. So it's not really getting to our point of what else is happening with it, right? So yeah, but it's intriguing.

DR. LEE: That was Dr. Dasgupta.

DR. KORNEGAY: So I would also ask Dr. Schnoll since he started it off -- how well do data resources, specifically, those can -- that can get to some of the clinical outcomes, identify the effects of insufflation and inhalation -- or insufflation and injection -- excuse me -- with specific products?

DR. SCHNOLL: Clearly, it's not an easy task to do. I think most of our current data come from sources like NAVIPPRO, like some of the programs in RADARS so -- where data are collected on how the person took the drug.

I think when you're just dealing generally -- we've got two situations that I think we need to consider. One is the prescribed drug, and the prescribed drug is in a person for whom the drug was prescribed. How are they taking the drug? Are they taking it appropriately? Are they doing something like Dr. Scharman, you know, mentioned? Are they sucking the gel out of the patch? I think it happens. I think it's a very small percent of people who are prescribed the drug who are doing those things.

And then we have, you know, general -- the leak of prescription drugs into an abuser population, and that's a harder group to get a handle on. As I said, they show up in some of the treatment centers, but they're not a group -- you know, if I asked in this group how many people have hypertension, we'd see some hands go up. If I asked how many of you abuse drugs, we're not going to see a whole bunch of hands go up. It's not a population that generally identifies themselves, and that's a real problem.

But I think, you know, we can get at that a little bit maybe with some of the surveys looking at things like the POMAQ, which is being studied as part of the PMR. But that, again, is in the treatment population where these events are very, very small.

And you know, the people who are doing these things to divert the intention of the drug, that's not the treatment population. And I think some of the comments that were made -- Dr. Krebs and Chris made about the general population, I think those are important.

But again, I get back, you know. What we have

to look at is, you know, what are these drugs intended to do. And we've got to understand there is a broader context, but there are a whole bunch of other things that have to be done to address that broader context. And I mean, we could go into that.

I just mention that many years ago there was a regular inter-agency meeting that included FDA, DEA, NIDA, SAMHSA, HRSA to discuss, generally, the prescription opioid problem. And I don't think that group has met in 15 years. And I think that getting a group like that together because it is something that has to be multi-pronged.

You mentioned the mosaic approach to collecting data, but I think we need a mosaic approach in terms of addressing the issues because not one agency -- it's a limitation of what FDA can do. And I think FDA has to do as much as they can, but FDA can't do everything in this. And so we have to address this in a different way.

This is complex. I think we all know that. And so we have to use a broader approach to deal with that.

DR. STAFFA: Thank you. This is Judy Staffa. I wanted to follow up on some of the getting back to the data source issues.

Dr. Boyer, you made a comment about -- and this is a question that's come up in our internal discussions -- about when people come into emergency departments with an opioid overdose or an apparent opioid overdose that this is something that largely is known how to treat. There's known regimens. This is not like an exotic poison that people might not know what to do about it.

So along those lines, I'm trying to understand how to interpret poison control center data, given that if I'm -- again, I'm a pharmacist from the good old days back when, you know, you had a kid ingest something that you didn't know what it was and you called because you didn't -- either the consumer called or the doctor or pharmacist called not knowing how to treat that.

Today, where we are with an opioid epidemic, are people still calling poison control centers? Or what fraction of those would be called? Or what

features of a presenting case would actually result in a call by a healthcare provider?

DR. BOYER: So regarding the numbers, I'll let, you know, the poison control center representative, you know, like, speak about that.

Regarding the quality of the data, you know, I think it's variable. You know, I -- here's an example from my past. I was interested in dextromethorphan abuse, so I pulled up some cases out of our poison control center. And 100 percent of our cases were coded as Coricidin Cough and Cold because CCC is the easiest thing to enter into the computer.

So it didn't matter what the formulation was. It was the one that was easiest to enter in a system that is underfunded, who doesn't have sufficient staffing to deal with the provincial avalanche of cases that come in. If a field needs to be filled, then the field gets filled, not necessarily correctly. Now, there's some variation around practice science, but that's what happened in our neck of the woods.

I don't know what triggers a poison control center call, at least what the medical literature says.

I know that, based on my narrow experience as being a poison control center attending for the last 15 years -- or actually 17 years now -- is that it's something that is odd, something that the doctor doesn't expect. It's something that is ill, something that the doctor generally needs help with. Or it's just something that the doctor wants to be able to say I called the poison control center, they told me to do it this way, and eliminate medical-legal responsibility for a course of action that they're trying to -- that they would like to take.

The -- you know, like, regarding, you know, like, routes of abuse, sometimes that appears. I don't know that it's a mandatory field in the poison control center data collection system. What I would say is that there is a potential data source which you haven't mentioned, and that's the Toxic Investigator's Consortium. And I don't want to oversell this because it's got enormous limitations on its own. But that is a narrowly defined set of individuals who still have a nationwide distribution who are at the bedside. But they do record not only routes of administration,

routes of abuse, but also, in some cases, depending on the study that's going on, the reasons for which the substance was abused.

DR. GOLDIE: Dr. Crane, Dr. Green, Dr. Compton, and then Dr. Hedegaard.

DR. CRANE: Jody, were you going to talk about poison control? It's -- because I -- if you are, I'll cede to you because I'm going to talk about emergency departments.

DR. GREEN: Thanks, Elizabeth.

DR. CRANE: Okay.

DR. GREEN: Sure. And the other Elizabeth, Scharman, should also probably weigh in here. But I do want to clarify. You know, most of the calls are actually from the public, not from healthcare professionals in the poison centers. So you need to keep that in mind, too, that the public, usually, their calls are because this is a newer experience for them, not necessarily --

UNIDENTIFIED MALE SPEAKER: (inaudible).

DR. GREEN: -- yeah, not necessarily just the treating physicians, which is a pretty actual small

proportion of the calls that come to poison centers. And to confirm, the routes are a required field in that database.

And I'm glad we're talking about poison center because more work can be done there. A few years ago, we actually looked at the accuracy of reporting of acetaminophen-containing products in poison centers. And acetaminophen-containing products, while they're over-the-counter, they are complex as well. There are single ingredient, combination ingredient, cough-cold ingredients, and there's hundreds of products in the database that poison centers use. So we did look at the accuracy of the recording of that data that we did some training in terms of product-specific information and looked to see if the accuracy had improved.

So two points here -- one, the initial data showed that for Substance field, it's about a 90 percent accuracy rate. So that was reassuring in terms of the data being accurately collected. And then for exposure characteristics like route is 95 percent accuracy.

So the baseline for, I think, route is

probably easier than products if you think about it to report. After we did training, two different types of training -- one more intensive, one a little bit more passive -- we found a significant increase in that product identification accuracy. So I think -- and that actually went to, like, 93 percent accuracy.

So I think some more work can be done to see -- - again, this is acetaminophen-containing products, but some of the same complexities as we have with the opioids. So we can do some more work in not only evaluating that -- what that accuracy rate is baseline, but then also knowing that some of these training programs that can be deployed throughout -- that the regional poison centers could potentially enhance that accuracy as well.

DR. GOLDIE: Dr. Compton.

DR. COMPTON: These are difficult questions. You know, discuss the ability of current data sources to distinguish molecules and formulations. Clearly, the answer is no. We don't have an adequate way to do this.

And I thought we heard a really interesting

concept from Dr. Boyer that might be amenable to research development. And certainly, if there were a commercial partner that was interested, that could be a small business innovative research program. It could be very interesting not just for this field, but for many others in terms of linking specific products to particular outcomes. There are lots of places in health where this could be a useful concept.

There was an earlier comment about inter-agency collaborations. And I would just point out that FDA has been actively leading the HHS inter-agency collaboration for many years in terms of prescription drug misuse and the opioid crisis and, as well, has been an active partner in the ongoing inter-agency collaborations that span multiple government agencies, including the Department of Justice and DEA representation.

I actually wonder if there might be room for some additional efforts in the supply side area to inform some of these questions, whether this is drug purchase on the street, value. You know, this was mentioned earlier, but that's certainly a strong

indirect indicator of how much overall misuse there is of these. And that is while we are focusing on insufflation and injection as the primary target of ADF formulations, the goal is to reduce their overall misuse in the community. So I'd be pretty happy if the price went down of all these substances on the street, irrespective of whether we could determine specifically whether it was injection or insufflation, that we're driving that.

I also wonder about internet sources. You know, it -- there has been some interesting papers on internet chats and discussions as an indirect way to get at this. You never know about the base rates (ph) or the denominator in those cases and the tendency for discussions to go in a direction just spontaneously witnessing all the viral effort -- issues lately.

The other -- I'd like to turn it over as well to Dr. Ciccarone to tell us are there local studies that might inform this question, you know, about routes of abuse and distinguishing particular formulations and what drug users are actually doing with them. We have -- we really struggle to get that level of specificity

and detail in our national surveys, and I don't think it's possible. But there are certainly local studies that can say a lot about this.

DR. CICCARONE: I guess all eyes are on me. Thanks, Wilson.

So I'll disagree with the consensus. So these are very complex issues. The questions themselves are incredibly complex. I think we all know that we start with and probably end with epidemiological data, right? Epidemiological data is going to give us the best picture nationally, the scope of the problem, the affected population, you know, the at-risk population, et cetera.

We do also need to consider qualitative data, particularly around some of these more nuanced questions like route of administration. You're just not going to get questions around mechanism of abuse easily from quantitative surveys. You can do it, but you could just imagine the amount of lag to say, okay, well, here's a new drug being misused in a new way with a new route and a new set of problems, right? To operationalize all that mechanism is going to take

quite a while. And then to get the data and to analyze the data, you're talking about years have gone by. And meanwhile, the drug has moved on. You know, the drug-using population have moved on.

So just to answer Wilson's prompt, the idea of doing hotspot studies, if there is a signal in the poison control data or in the large universe to focus down, I like the idea of repeated longitude -- sort of a longitudinal or repeated qualitative inquiry. This could be done with providers. I know over the next, you know, day and a half I can get more into some of the details.

It's been mentioned so far the idea of using -- of getting to what are providers seeing, what are the patients asking regarding. You know, there's lots of clever ways of finding out what the users -- what the patients are getting to that might be manipulative, if you will. What are providers' concerns? These could be ED providers, of course, sort of folks at the front line. What are they seeing? What concerns are being raised? And to regularly assess a sample of providers would be useful.

The work that I do goes right down to the street level. You know, I work with users on a regular basis and find out what molecules they're interested, what chemicals they're interested, and how they're using and misusing them. And that's where you get into mechanism.

So for example, when we wanted to explain the HIV outbreak in Scott County, Indiana, it was very important to know how exactly extended-release oxymorphone was being used in order to get into the mechanism of HIV transmission. The only way you're going to get that is through qualitative data.

But I'll suspend the rest of my thoughts because there'll be lots of conversations moving forward.

DR. HEDEGAARD: I actually was going to move over to mortality data. So if there are other comments that are relevant to this conversation, I'm happy to pass for a moment.

DR. BROOKS: Sure. John Brooks. I just wanted to ask a question with regard to the abuse-deterrent formulations. Are you also interested in

monitoring for the safety of the deterrent itself? Because that's a substance that's being added to these pills. And I want -- I'm glad that the segue sort of occurred here because I wanted to bring that up as something to consider in terms of data sources.

In the Indiana experience, we learned that the deterrent itself that was being added to the opioid is what really drove the rapid spread of infection. There were aspects of the deterrent that increased the number of times people had to inject each day so that, on average, it was 15 injections and, in the extreme, up to 40 per day. And that fueled this outbreak. And we were able to detect that because we have good infectious disease surveillance. So I think those kinds of -- if those were the outcomes we were looking for, I think we're pretty well positioned for that.

But there was the experience with the in-tag deterrent that was also associated with TTP -- the original formulation, not the revised formulation. And I'm not quite sure how. You know, that was classic outbreak detection. An informed consumer -- in this case, a physician in a clinic -- recognized an excess

of the number of cases that was unusual.

But being able to know -- I think what I'm getting at is being able to know in persons who have taken an opioid, whether they are using the deterrent formulation or another could be very helpful in understanding these sorts of events.

And so Dr. Boyer's point and what -- that others have raised, this idea of having some mechanism to detect was the drug -- this person taking a deterrent formulation or the standard formulation. It could be very useful.

I might just add that in formulating these deterrents, you know, those materials go through a lot of testing, I'm certain. I mean, it's not my -- that's not my area of expertise, and I presume that they're not licensed without being proved to be safe. And I wonder if, in parallel with that process, there could be a tag added to the deterrent so that it's easy to detect in a urine or blood sample.

DR. GOLDIE: Dr. Lo Re had a comment. Ms. Cassidy had a comment. And then we'll come back over.

DR. LO RE: Yeah. So I'm just going to follow

up on what was said earlier about the need for longitudinal measurements. And I think what we're hearing is that many of the existing data sources aren't really able to assess many of the important outcomes, particularly misuse and abuse. And I wonder if this might call at this point for large, multi-center, prospective cohort studies of different formulations, different opioid -- ADF opioid molecules.

I mean, we've certainly seen in the literatures, particularly in cardiology, where you had 30 to 40,000 people who were on ACE inhibitors who are followed for years or more. Why couldn't you equally create prospective cohorts of patients who are initiating ADFs, perhaps follow them longitudinally with audio-, computer-associated self-interview software to anonymously assess through a CASSI (ph) many of the questions about insufflation, abuse, diversion; evaluate the providers of those patients; evaluate for hospitalization; and perhaps even do surveillance incidence infections?

And that would allow you in the prior question, perhaps, to develop definitions for abuse and

misuse and to be able to compare characteristics of those individuals. But I don't think that's going to get at individuals who are not prescribed the drugs but who are getting them in other ways and abusing. But at least you have a denominator of all new users of those particular drugs and formulations who will be followed over time for both quantitative and qualitative assessment.

DR. MEYER: This is Tamra Meyer. I just wanted to bring up that I like the way you're thinking. And we'll have a session on that tomorrow where we'll talk more about the possibility of doing longitudinal studies and new studies in general.

MS. CASSIDY: Yeah, I just wanted to follow on the conversation about do the current available data sources adequately collect route of administration data. And I think that there are definitely some examples where we've seen that we are doing a reasonably good job at collecting route-specific data and even doing it at a product-specific level.

I think with some of the treatment center data that we have from NAVIPPRO, we've seen the

reformulation of OxyContin, and we've seen oxymorphone ER, its reformulation. The expected shifts -- some of the changes that we've seen were expected.

And you can, you know, sort of continue to think about, like, well, to what degree and what extent. You know, there may be some misclassification in the -- at the product level for, like, was that individual indicating that particular ADF product. But you can follow on from the route of administration evidence that we've seen from that treatment center data and -- that corresponds with other data for route of administration for some of these ADFs, that we are doing a reasonably good job for some populations.

Now, that's the, you know, individuals entering treatment. It doesn't necessarily capture maybe the misusers, and that might have different, you know, challenges associated with its identification. But at least we've seen those changes quickly happen in the substance abuse treatment population, and they do follow some of the expectation of what those formulations were intended to do.

So I think that there is some value. I think

we can improve that. And just to follow on what Dr. Ciccarone was saying, is from qualitative data, some of that internet conversation of, you know, the treatment center data doesn't capture the how does somebody do something to a drug. It just sort of captures whether they may have snorted it, injected, you know, crushed it, et cetera. But -- and if there was a new drug that came out with a new route, we certainly use that data to inform what we're, you know, using and improving in the treatment center collection instruments.

So I think that when we're talking about mosaic, it's not just the mosaic in sort of studied design or datasets, but also thinking about the value of different datasets to link together that can improve and enhance what we're already using and doing.

DR. GOLDIE: Dr. Scharman and then back to Dr. Hedegaard for the mortality issue.

DR. SCHARMAN: I just wanted to speak more specifically about the poison center data set. So currently, the National Poison Data System does collect route, but it's one single route, even if it's multiple substances. So one of the databases used by a poison

center is Toxentry (ph), and it has already moved to a model where at least, like, in my center and in a number of others we can collect route by drug taken. And that's a model that poison centers are likely to be moving to when it moves to a different platform that allows us to expand data fields that poison centers can export up to the National Poison Data System.

Again, that's been an expensive switch, but that should happen by January of 2019 for all centers. And that's -- that would increase our ability to add data fields to send up.

So route is required, but it's one route for all substances. But we are moving -- some centers have moved, and we are moving to be able to collect route by substance.

The other thing that, as mentioned, is about whether centers can accurately code the name of the product. As I think with any database, it's data in, data out. And one of the problems -- when you get a prescription dispenses -- so let's say the doctor wrote for suboxone. Like, in West Virginia, it's a generic-required state. So the pharmacist has to dispense

generic unless the doctor wrote "brand only." So that pharmacist is going to dispense buprenorphine naloxone. But because the prescription the doctor wrote said suboxone, what's going to happen on the label, it's going to say buprenorphine naloxone (dispensed for).

So even if the doctor wrote for -- if he writes plavix and you get generic clopidogrel, it's going to say clopidogrel (dispensed for plavix). Because brand names are catchy and easy to remember, that is what gets written in a patient record. Whether you're a triage in a hospital, that's what the nurse is going to write in the record, and that's what they're call a poison center and say.

So part of the problem of the -- what name shows up in a database can depend on state pharmacy laws and what gets put on the label. And as long as labels are allowed to contain a brand name that's not in the bottle, that's going to continue to happen.

We typically are similar to most poison centers. So most poison centers have about 30 to 35 percent of their calls now are from hospitals. So it's not the majority, but it is about a little over a third

of the cases.

One of the things that we're finding -- so we're in West Virginia, a high substance abuse state -- we've really expanded our use of lay public naloxone in our state. What we're seeing because our particular poison center is capturing this offline, so the data isn't going to the American Association Poison Control Center database. But we are using that database to collect it internally.

And what we're seeing is that about 80 percent of those patients getting naloxone are not going to a hospital and are not calling EMS. So we're now losing about 80 percent of those cases that are staying in the public and are not necessarily calling a poison center or going to an ER. So we're looking at capturing that data that is currently lost in the system.

And I'm not just saying yes or no or given. We're using our risk reduction programs at our local health departments. So when patients are coming back to refill their naloxone, we're getting to where the risk reduction pharmacist is asking so how did you use it, you know, no-harm, no-foul question. If you sold

it, fine. If you gave it away, fine. How did you use it?

And we're finding that the people are actually being pretty forthcoming in what they've done. And so we started collecting that information, which is another potential source when you have these hubs of naloxone distribution.

What we've also seen in this changing dynamic of lay public naloxone use is when people get to the hospital, they're usually revived by then. And what we did in our small study with the 25-patient opioid outbreak that we had in one of our cities was our health department had a chance to look at some hospital data. And what we found in that --

DR. KORNEGAY: Dr. Scharman.

DR. SCHARMAN: Huh?

DR. KORNEGAY: I am so sorry to interrupt you, but we are running a little --

DR. SCHARMAN: Okay.

DR. KORNEGAY: -- short on time.

DR. SCHARMAN: So just really quickly, what we found is that these patients when they go to the

hospital are no longer getting diagnosed as opioid overdose. They're getting diagnosed as withdrawal or pain syndrome.

DR. KORNEGAY: Oh.

DR. SCHARMAN: And so that pre-hospital use is changing the reliability of hospital data for accurately picking up opioid overdoses.

DR. KORNEGAY: Thank you.

So we're running a little bit short of time. And I'm going to -- I know there's several people who are queued in the line. And if you don't get a chance to speak now, again, you can also submit stuff to the docket. And we'll -- happy to listen to you over the break. But I wanted to get back to Dr. Hedegaard because she had something to say about mortality data.

DR. HEDEGAARD: So I just wanted to mention about some work that is the collaboration between FDA and the National Center for Health Statistics where we've actually been trying to look at the literal text on death certificate data to look at the drugs that are involved in drug overdose deaths. This work has been going on over the last several years, but we're in the

place now of trying to automate that and make it a more routine process.

But even though we're able to look for the names of specific drugs out of the literal text data, for about 17 to 20 percent of drug overdose deaths in the U.S., the actual drugs involved are not named on the death certificate at all. So clearly, there's a lot of work that needs to be done with regard to educating medical examiners and coroners about the importance of including the drugs that are involved in the death on the death certificate.

That percentage varies a lot by state and by type of coroner or medical examiner system in the state. So some states, the drug overdose deaths, up to 50 percent of the drug overdose deaths, the actual name of the drug is not on the death certificate, whereas other states where almost every drug overdose death it's named.

We've also used the same literal text methodology to try to look at the route of administration and just see how often is that mentioned on the death certificate on these drug overdose deaths.

And it's a very small percent where the actual route of administration is actually named. It's probably less than even 10 percent of these drug overdose cases.

So because of this need, NCHS is working with other centers at CDC to develop some guidance documents for medical examiners and coroners about what types of information would be helpful to include on death certificates so that we can try to capture these key pieces of information that I think would be useful for looking at overdose deaths.

DR. LEE: In the next five minutes, we'd like to discuss the best practices for measuring and validating misuse, abuse, and addiction. And more importantly, we'd like to hear if there's any additional important outcomes or exposure measures that could be used in the -- you know, evaluating the impact of ADF studies.

DR. UNICK: So I think one data source that we have not fully utilized are information on rates of diversion. So we have basic information on how drugs are distributed and where they're distributed. For example, the DEA collects

ARCOS data.

We also have law enforcement data on seized drugs. And looking at differential rates of diversion can provide an indirect measure of demand for substances in illicit markets. I think it's hard to do that with price because a lot of these things are ritualized in ways that are not really amenable to change with supply and demand. But demand does tell us something, and that can be determined by looking at differential rates of diversion.

The other data source are dark web websites that provide information on how users are utilizing the drugs and what demand is for those -- for different formulations. And they're quite specific about what drugs are available through those markets. So it's one of these places where we have highly informed users that describe not only how -- what the product is, but also how to use the product. And those are two sources where we can get some sense of what illicit demand for these substance is. And that provides some indication of what is potentially abusable or places where people can defeat the mechanisms.

DR. STAFFA: This is Judy Staffa. I have a question about that. We've seen diversion data, and we're not sure because, again, we're not law enforcement folks. We don't know how to interpret it because we're a little concerned. What if a community just mounts a campaign or a local police force mounts a campaign against a particular product? Is that a marker? I mean, does that mean that they would then find more of it? Or would they only do that because they perceive a problem in that community? So is it not --

DR. UNICK: No, there is definitely problems associated with it. I mean, you're not going to mount a law enforcement campaign against a specific product. You might have problems in communities like, you know, in Scott County where you then have enforce -- increase law enforcement activity, but that seems someone endogenous to the question at hand, right? So if there are more and more hotspots where particular formulations are causing particular problems and that attracts more law enforcement demand, that tells us something useful.

But you're absolutely right. There's -- law enforcement is not randomly sampling drug users. Things move up and down for reasons.

But on the other hand, we have large collections of information from DEA or more regional HIDTA kinds of information that can be aggregated above sort of these local concerns. So there is some way of detecting it. But you're absolutely right. This is going to be a very vague measure of community demand.

DR. GOLDIE: Jonaki Bose from SAMHSA, please.

MS. BOSE: I don't have any specific answer to the question, but I was wondering if it would be useful to define -- we had a slide earlier on -- what we're talking about when we talk about misuse, abuse, and addiction. When we talk about misuse, are you including even, you know, using longer or using more often, using without a prescription, using -- you know, so those type -- so kind of defining what we mean by misuse might be helpful in deciding where -- what kind of metrics we have.

And similarly, what kind of -- what is the

difference between abuse and addiction? Does addiction specifically link to having a substance use disorder and abuse maybe having a sub-threshold?

So I think maybe defining it up front might help us for the next day and a half.

DR. STAFFA: Well, this is Judy Staffa. I can kind of address that, but I encourage my colleagues to jump in.

We're kind of stuck because we can define anything we want. But if we're going with existing data systems that are used for other purposes, we're kind of stuck with what they collect.

For the purpose of this question, specifically, I think we're actually thinking misuse is -- can be used as a general term of any kind of using a product that is not the way it was prescribed to you. But here, since we're talking about, again, as Dr. Schnoll pointed out, these are -- these drugs are meant to deter specific routes. So it's really getting at abuse done through manipulation of a product in particular ways. So that's the way we have to think about it. And are there ways that we can improve the

data we have existing and the way they collect it to be able to answer these questions?

And again, tomorrow we'll talk about are there different ways we could collect data to be able to do that. But today we're really trying to be applying here. And can we twist these systems that weren't set up to do this at all to answer these questions? Does that help?

MS. BOSE: Yeah, I think the route of administration is a big thing because on the NSDUH we do have misuse and we do know how they misused it -- used it a little bit more frequently. You can cross-top that with things like sources of drugs and frequency of use. And you do find that there is a connection between all of those different things. So -- but it still doesn't exactly answer what you're looking for, and I was just trying to parse that out.

DR. GOLDIE: Captain Jones?

CAPT JONES: So just quickly on the last question, as was mentioned, the NFLIS from DEA might be an interesting partnership to pursue with the labs that they work with at the federal, state, and the local

level because they have product in hand. So they might be able to look at what particulars. They just typically report out, like, oxycodone, hydrocodone, but they have a source of that. And looking to explore with DEA whether or not that could be another source of product-specific data I think would be helpful.

I think the other challenge is that we have a proliferation of counterfeit tablets that are in -- largely impossible to distinguish with primarily fentanyl or fentanyl analog. And I think that's going to throw off all the systems. So I think there is a very tangible research project that could be done to do drug testing when people are coming in. A study was done in British Columbia where the people thought they were using cocaine, methamphetamine, and a variety of other things, and they were showing positive for fentanyl.

So you know, for the NAVIPPRO folks, some subset of those who are doing -- you know, using the ASI-MV, or whatever, when people are coming in to test them to see what are they actually showing positive for I think would be helpful. The same for, like, the

OTP's component of RADARS.

I think for validation, I mean, you know, ultimately, the work that you guys are requiring under the ER/LA I think will be very helpful here in looking at charts, particularly in trying to understand how well claims data matches up with what really happens. If you look at, like, some of the buprenorphine claims data, there are lots of people getting buprenorphine who have no abuse diagnosis probably for a variety of reasons. So if you're just looking straight at the claims, it's not going to be all that useful. And we've done, you know, claims-based studies on overdose when I was at CDC. And you tend to get a lot of not otherwise specified in your ICD-9. You know it's a poisoning, but you don't know what it was, and you obviously are very limited in ICD-9-CM codes for specific opioids.

So I think there is just the, like, unfortunate heavy lift of, like, validating through, you know, biological specimens -- what are people reporting, validating with case review and chart review what's showing up in coded systems. And you know, that

-- I think that's foundational work that has to be done. And even on some of our national surveys we often get questions back from reviewers on this is self-report; how do you know that this was reported honestly? And you -- you know, you use a CASI and other things to try to get honest reporting, but not a lot of recent work looking at, you know, using biological specimens to validate what people are self-reporting.

DR. KORNEGAY: Okay. Thank you.

I think we're going to have to move on to the audience participation section. So we are now going to -- please try to focus your comments on this session's topic. And again, there are microphones located at the end and, I think, over here.

So some ground rules. You will be given three minutes to speak. A light system will keep time and notify you when your time is complete.

UNIDENTIFIED FEMALE SPEAKER: (inaudible).

DR. KORNEGAY: Oh, I'm sorry. I'm being told you have to go to the mic at the end of the table.

UNIDENTIFIED MALE SPEAKER: That's where the

timer is.

DR. KORNEGAY: That's where the timer is. Ah, all right.

The light system works just like a traffic signal. If the light is green, continue speaking. When the light turns yellow, you have one minute left for your time, and you should begin to quickly close your presentation. The red blinking light means to stop speaking immediately and return to your seat.

(Laughter.)

DR. KORNEGAY: Okay.

UNIDENTIFIED MALE SPEAKER: (inaudible).

DR. KORNEGAY: Will the first speaker and subsequent speakers please provide your name, state your disclosures, and provide your comments? Thank you.

DR. BUTLER: Hi. I'm Stephen Butler. I'm a chief science officer at Inflexxion, so I work with the NAVIPPRO program.

And I wanted to talk real briefly about the -- how well the current systems are able to capture the molecule and the route and sort of underscore what

Theresa Cassidy said. Our data suggest that these routes of administration by molecule and by product are very consistent over time. We have a very large data set, and we're able to see these consistent patterns where snorting is high, injection is low; injection is high and oral is low within compound, within product across the years with very small confidence intervals.

And I think that while this is self-report and has those kind of limitations, this kind of consistency in itself addresses some of the validity questions. And I would -- so just as an example, the acetaminophen combination products have about 20 percent snorting and almost no injection. That occurs consistently across since 19 -- since 19 -- since 2008 in our data set. And when you go from oxycodone combination to oxycodone single entity, the injection rate pops right up.

And when there are changes within product -- I think Theresa mentioned this -- those tend to be cotemporaneous with other things happening, for instance, with the introduction of an ADF formulation.

And I've got my yellow light. So I'm just going to say one thing that I want sort of clinically

for folks to keep in mind is that, particularly, injection is a very complex behavior and that folks who inject, in my clinical experience, tend to inject. So if you take away or reduce access to something that they can't inject, they will seek something else to inject. And so changing folks' behavior who are very much into injection is going to be very difficult. And I'd be interested in other people's clinical experience on that.

Thank you very much.

DR. KORNEGAY: Thank you, Dr. Butler.

Next, please state your name, title, and any disclosures.

MR. COHEN: My name is Dan Cohen. I'm the chairman of the Abuse Deterrent Coalition, which is a coalition of ADF innovators, patient organizations, data-gathering groups, and others. I'm an officer of a biopharmaceutical company in the ADF space Kempharm and a member of the board of directors of the MedStar hospital system.

I wanted to focus my remarks where you began this morning, both with Dr. Gottlieb's charge to you,

to focus on the problem, which is IR, and more importantly, to focus where Dr. Schnoll started us this morning.

When we're looking at the questions -- and these are very good questions that you're dealing with this morning -- on the forest of prescription drug abuse, today's focus should also keep focused on the tree of what abuse-deterrent formulations are capable of doing. Many of the answers that were provided this morning talk about futuristic technologies and where we could go, what we could add on. And yet we have to come back to the core of what we can do today. If we want to get these further technologies, we have to have further deployment.

One of the slides that Judy put up earlier this morning showing the direction of prescriptions and the percentage of abuse deterrents in them bears mentioning. At the end of 2015, according to this data, there were approximately 249 million scripts of opioids issued in the United States. Of those, approximately 9 million scripts were extended-release products, and 5.6 million of those scripts had an

abuse-deterrent in them. Nearly 235 million IR scripts were issued, not a single abuse-deterrent in the technology. Approximately 4 percent of all scripts have an abuse deterrent in it.

What you're measuring is -- has the problem with small numbers. We need broader deployment to be able to answer some of the questions that you're asking about today. What we can do today is take a look at diversion. The data that's provided by RADARS, NAVIPPRO, and others, the observational data, clearly shows the products with an abuse-deterrent technology in it have a diversion benefit.

The -- whether we can actually show the answer to Dr. Schnoll's question of will abuse deterrents deter intranasal and intravenous abuse will have to be deferred to the point where we have broader deterrent deployment of the technologies themselves because, right now, with so much product available on the market that is easily abusable, abusers do not try and defeat the product as much as they try and move on to something that is easier to abuse.

We have an early stage right now of abuse-

deterrent technologies. We need broader deployment of these technologies, of these earlier methods, to be able to get the more advanced products that you are seeking and that industry would like to deliver.

Thank you.

DR. KORNEGAY: Thank you, Mr. Cohen.

DR. HENNINGFIELD: Good morning. I'm Jack Henningfield with Pinney Associates and the Johns Hopkins School of Medicine. Let me comment on the questions concerning distinguishing AD molecules and formulations.

The challenge for surveillance is much bigger than that. It's distinguishing whether the people using were prescribed patients or not and whether the molecules were illicitly manufactured prescription products or illicit street products. And when they're lumped together, as they often are even in reports by different agencies, it can lead to wrong solutions and mischaracterization of the problem.

And a couple of examples illustrate this. A lot of -- oftentimes we see reports about how many people use prescription opioids as their first opioid

in leading to opioid abuse. Probably most of those were not prescribed patients. We don't even know how many of them that were reporting a prescription opioid were actually using illicitly manufactured prescription opioid. Yet when we lumped it all together, I think we mischaracterized the problem. We don't help with the solutions. And blunt instrument approaches of telling doctors to just suppress your prescribing, that probably does hurt pain patients. It probably hurts lower-income people and minorities the worst. We already know that. And so this is really important at that level.

There are no simple solutions for this. But I think that at least federal agencies, I think if they're more consistent in how they talk about the data and the limitations of the data -- at the College on Problems of Drug Dependence meeting a few weeks ago, more than 1,000 experts, a lot of them were talking about the same data differently. And NIDA's Nora Volkow I think had a huge advance when she talked about prescription, heroin, and fentanyl and other synthetic. That's a huge advance over at least breaking it into

three buckets.

So I think we've got to recognize the limitations of the buckets that we're now collecting the data in. We don't need to wait for a lot of new measures to do a better job and be more consistent with how we're doing it, but we do need consistency across the agencies.

Two other examples are oxycodone, probably the ultimate Kleenex. We don't know how many people that actually use oxycodone were using OxyContin. But it's all lumped together. So we've got to do a much better job and focus on were they prescribed patients and was the so-called illicit or prescription drug fentanyl manufactured in China on the street, which is no more a prescription drug than heroin, or was it illicitly manufactured prescription drug. These are tough challenges.

DR. KORNEGAY: Thank you.

DR. COPLAN: Good morning. Paul Coplan from Purdue Pharma. I'm humbled to speak in front of such an illustrious panel of experts but wanted to share some insights as a sponsor. And my team and I have

submitted maybe seven reports to the FDA over the last seven years. We've been amazed at the rigor and insight with which FDA has reviewed them, but that has given us some thoughts.

There are two key points. The first one is consistency of effect, and the other one is the importance of diversion. So consistency of effect has to do with each of these surveillance systems has the limitations that was well laid out in the beginning presentations by FDA. And that's been recognized from the outset when we presented these as proposed datasets to be used in post-marketing studies of ADFs or ADPs in 2010. And the idea was to compensate for the limitations of each data source by looking at maybe 5, maybe 10 data sources and looking for consistency effect across the different data sources.

The limitation of, say, poison centers, which are all -- we all recognize if we -- and the same -- at the same time limitation of treatment centers, if we see a similar effect across 5, 6, 10 datasets, that helps to support. Also, if we see a consistency effect in Dr. Degenhardt's studies in Australia using

different kind of surveillance systems and the Canadian study at a different time period, that again goes to consistency of effect. And we think that that's an important consideration.

The second issue about the importance of diversion -- so one of the questions was what did -- what does street price or diversion events or doctor shopping tell us that's of use to the FDA? Well, we think that if you can reduce diversion of an opioid -- that's the black market for an opioid -- that's a very important goal. That -- why is that an important goal? Because that's -- that doesn't detract from the importance of measuring and understanding the risk of addiction in patients.

But the black market in and of itself, if that can be reduced, has important consequences. Firstly, it -- that black market is all going to -- for abuse and addiction. That's what's resulting primarily in the overdose and the deaths. So if we can reduce that, it improves the overall benefit-risk balance of the opioids, which is what Dr. Gottlieb was referring to earlier.

Secondly, it improves the patient-doctor relationship because the doctor doesn't -- isn't always being scammed by the patient to try to get drugs that they can divert. It also improves the situation for the patient because the patient doesn't always have a temptation to divert that opioid for -- on to the black market where they can sell it.

And lastly, diversion is very important because it helps us with causal inference because one of the ways we can differentiate between different interventions is by looking at supply and demand. Some interventions affect demand, and others affect supply.

I -- and my time is up, so I'll stop there and perhaps get back when we discuss causal inference later. Thank you.

DR. KORNEGAY: Thank you, Dr. Coplan.

DR. PASSIK: Good morning. I'm Steve Passik from Collegium. I just wanted to point out the problem of a low uptake has been mentioned a couple of times, and I just wanted to provide a little bit of additional information there because what we have here is a real catch 22, but it's also skewing the population in

interesting ways as well.

So I think one of the biggest problems we have is that you have payers who have fail-first policies so that people have to fail two non-ADFs before they can get access to an ADF. That's keeping the numbers in the marketplace down and making it difficult for these existing datasets to evaluate the impact. But in addition, it's probably also skewing the population some because if a person is going to develop a problem that involves manipulation of the dosage form, they're going to have two opportunities to do so before they ever see an ADF so that the people that you can then study on ADFs may not be representative of people who might have gotten those formulations earlier.

Additionally, I would just like to say that I think all of the -- of existing datasets also have the problem of not really reflecting the use of ADFs in -- as part of elevating the standard of care in how opioid therapy is practiced. And so all along I think we've had a problem where people are not adequately screened, their risk is not ascertained, and then a delivery of opioid therapy in a particular way that employs the

PDMP -- psychotherapy, ADFs, urine drug testing, et cetera -- may or may not get applied in a way commensurate to that person's risk level.

And so I think one of the problems you have with these data sets is you might see ADF use, but you may not see it as part of an overall plan to practice up to an elevated standard of care. And I think that's something that may be important in -- if you do some prospective trials, perhaps in a registry-type format, or whatnot, going forward where you would also record those things because I think studying the impact of ADFs in isolation for -- where clinicians who may be doing everything else wrong but written a prescription for an ADF, I think that's a tall order to expect that the ADFs will make up for all the other gaps in practice.

Thank you.

DR. KORNEGAY: Thank you, Dr. Passik.

DR. STAFFA: All right. Thank you very much for a very informative and good discussion to get us out of the gate. So now we're going to take a 15-minute break, and we'll reconvene promptly at 11:05.

Thanks.

(Break.)

DR. STAFFA: All right. Welcome back. So for Session 2, we're going to follow a similar format. The topic of Session 2 is on Sampling, Metrics, and Denominators. And I apologize. The questions are not going to get any easier as we go along. We left all the easy questions back at the ranch. We feel we can do with those. We only brought you the hard ones.

So we're going to start off. Our team for this session is going to be Dr. Kunthel By, who will begin with a presentation to tee up some of our major issues. And Dr. Tamra Meyer from Epidemiology will be partnering with him on the discussion session.

So Dr. By.

DR. BY: Thank you, Judy. Good morning. Again, my name is Kunthel By.

UNIDENTIFIED MALE SPEAKER: (inaudible) microphone.

DR. BY: Sorry. Again, my name is Kunthel By. I'm a statistician in the Office of Biostatics at FDA.

In this presentation, I am going to be

providing a brief overview about some of the issues related to sampling, metrics, and denominators. The goal is to provide some context so that we can discuss issues related to measuring abuse-related outcomes, measuring change in abuse-related outcomes over time, and for assessing the impact of biased sampling on our ability to measure population quantities.

And as you've heard from the previous discussion, some of the abuse-related outcomes that we're interested in learning about include abuse, misuse, addiction, overdose, and death.

And as ADF products target specific routes of abuse, we're also interested in route-specific outcomes, such as oral, chew, snort, inject, and smoke.

Now, in order to learn about these outcomes in the underlying population, we need to be able to quantify them somehow using some sort of metrics so that we could use them for monitoring trends in the population; for informing regulatory decision-makings affecting the population; and in the case of ADF products, for assessing whether ADF results in reduced abuse in the population.

So in this presentation, I'm going to be referring frequently to the concept of an underlying population. And I'd just like to clarify that I'm using this phrase in sort of a generic sense. I'm not referring specifically to the U.S. population, although you could make the case for it. And the reason for this has to do with what you've heard in the previous session, namely, that different data sources could be viewed as samples from different underlying populations.

So with that now, I think that's a good segue to discuss sampling. Tomorrow, the issue of sampling is going to come up again but in a more formal context in the sense that you're designing studies and actively going out and sample individuals. Here the sampling that I'm referring to is less formal in the sense that you have surveillance systems that generate information on abuse only when individuals from the underlying population interact with the surveillance system.

In general, we can learn about different aspects of the population by following these steps. You start with the research questions and a well-

defined population, and then you take a probability sample from that population. And then you ascertain outcomes or co-variates from the individuals in your sample, and then you compute some outcome metrics based on the data in your sample. And then you make statements about the underlying population.

For example, you could say something about the proportion of individuals in your population abusing product X. Or you could say something about the proportion of individuals in your population snorting X among those who abuse product X.

Now, some of the national population surveys follow these general principles. On the other hand, some of the current data sources do not adhere to these principles. For example, poison control center data or treatment center data, these data arise out of a non-probability sampling scheme. And the selection process for these data are never observable and, therefore, are not quantifiable. And the data that we get, they're often referred to as numerator-only data. And other characterizations of such data include case-only data or spontaneous data.

So when you have these data, one of the issues that come up is: What's the underlying population that generate these data? Consider, for example, treatment center data. It's been suggested that inference based on this data cannot be generalized to the U.S. population. Statistically, this is just another way of saying that the underlying population is not the U.S. You could make the case that it's some subset of the U.S. population, but then you run into the trouble of how do we characterize the subset.

Now, we find it conceptually useful to characterize this subset as consisting of individuals that are at high risk of substance use disorder. So that is helpful to some degree, but we're still left with the problem of what was the sampling scheme or the underlying selection process that gave rise to treatment center data.

And because of that, we find it very difficult to make statements about the underlying population. For example, it's not clear that the proportion snorting X in your sample estimates the proportion snorting X in your population. And one of the reasons

why this is problematic is because the unobservable, underlying selection process giving rise to the data can depend on the outcomes that you are trying to study.

For example, the underlying selection process that drives individuals to get treated for substance abuse may sample injectors of product X at a higher rate than snorters of product X. Or the -- it may sample abusers of product X at a higher rate than abusers of a different product, say Z.

And I'd just like to emphasize that the selection process is not the goal of inference. However, you really need it if we are to say something about the underlying population.

Now, with some of the current data systems that was mentioned in the previous session, they are indexed by time, and the same problem about not knowing the population and the selection process occurs at each time point. With temporal data, there is this hope that you could say something about change without fussing over the selection process.

For example, is the change in the proportion

abusing X in your sample estimating the change in the proportion abusing X in your population? And the answer to this depends on several things. It depends on the metric that you use to measure the abuse-related outcomes, it depends on the metric that you use to define change, and it depends on some assumptions about the underlying selection process.

For example, if your metric of change is the difference in proportions, then you need to assume that the underlying selection process in no way depends on the outcomes that you're trying to study. If the metric of change is the ratio of proportions, then you could relax that assumption a little bit, meaning that you could allow the selection process to depend on the outcome that you're trying to study. But you -- we're required to make sure that that dependence remains fixed over time.

And I'd like to emphasize that these assumptions, they're not verifiable, and they are unknown unless you conduct a separate study capable of learning about them.

So I mentioned metrics a little bit on my

discussion on sampling. So I'll go into a little bit more detail on the metrics and denominators that we've been considering at FDA. And the context is the data set that we have are numerator data and the selection process is unknown. So in this particular setup, how do we define abuse metrics that are capable of informing us about what's going on in the population?

So for the overall abuse outcomes, one of the metrics that we have considered is -- are the following: Abuse of product X as a proportion of the number of individuals that were surveyed, the number of individuals that were surveyed who indicate abuse of any opioid analgesics, the number of individuals who call poison centers, the number of individuals who call poison centers with exposures to opioid analgesics. And we've even considered the denominator that consists of census population within the catchment area of the surveillance system.

Now, for route-specific outcomes, we've considered route-specific abuse of X as a proportion of individuals -- all individuals surveyed, as a proportion of all individuals surveyed who indicate

abuse of X, individuals surveyed who indicate abuse of any opioid analgesics, individuals who call poison centers, individuals who call poison centers with exposures to any opioids, and individuals who call poison centers with exposures to product X.

And as noted in our issues paper, we know that the number of abuse of X depends on the availability of product X in the market. Here I'm referring to availability as utilization. And measures of utilization include prescriptions -- the number -- the total number of prescriptions of X, total number of dosage units of X, and the number of unique individuals with prescriptions to X.

And we've considered metrics -- utilization-adjusted rate metrics based on the following: The rate of overall abuse of X and abuse of X via route R per prescriptions, per dosage units, and per unique individuals with prescriptions to X. Note here that the numerator is captured by the surveillance system, but the denominator is measured within the underlying population that's defined within the catchment area of the surveillance system.

So what I've just described, there are two broad types of metrics. There are rates and proportions. The fact that you have this multitude of metrics betrays an important limitation in the sense that when you start out with data and then you're trying to say something about the underlying populations, it's actually very difficult to do so. It's not exactly clear what metrics we can use to give us a good sense of what's going on in the underlying population.

Now, this is a weird one. In the case of treatment center data, it's been suggested to us that when we're computing proportions that it's important to adjust for utilization in the population. So this leads to the following metric to capture abuse in the population where the numerator consists of the number of abuse events for product X but the denominator is a product of two quantities -- the number of individuals that were surveyed, which is a quantity captured by the surveillance system; and then the utilization of product X, which is a quantity that's measured within the population.

So it's not really clear how to interpret this quantity or this metric. Is this a proportion adjusting for utilization, or is this a rate adjusting for the number surveyed? And does adjusting really mean taking two numbers and just multiplying them and putting them in the denominator?

Okay. So what I've just described, rates and proportions, they're absolute quantities measured at each time point. Change as a metric is another important quantity that is essential when we're trying to evaluate whether ADF results in reduced abuse in the population. We measure change by first measuring -- computing a pre-period metric where the pre-period is defined as a period in which the product was marketed without ADF. And then we compute the same quantity, the same metric, in the post-period, which is a period defined where the product was marketed with ADF. And then we measure change by either taking the difference or the ratio of the metrics that you measured at each time point.

So I'd like to note that for some products, the product are never -- the products, they're never

marketed without ADF. So they come into the market with ADF. So for those products, change is an ill-defined quantity, but I'd like to note that we're still interested in the effect of ADF.

So while change is an important quantity to consider, there are some issues that we need to think about. And one of the big issues that come up in computing, change is, as I've just described, where we compute a pre-period metric and a post-period period is what's the ideal length of the pre- and the post-period? When you have a long pre-period, you sort of get more information on what's going on before the reformulation, but you run into the trouble where your pre-period underlying population structure is potentially different than the post-period underlying population structure.

When you have a long post-period, you get more information on the long-term impact of ADF, but you run into the same trouble, which is the post-period population structure might be very different than the pre-period population structure. And again, when you have both long pre- and post-periods, you also run into

trouble of the selection process that gives rise to your data. They may be changing over time, and it might be more difficult to deal with that process as well.

And that's the end of the presentation. So I would now like to begin the discussing -- discussion session for Session 2.

DR. MEYER: This is Tamra Meyer. So while Dr. By is coming back -- can you get the -- okay, and put it up?

So he and I will be monitoring the session sort of. I mean, it's kind of a free-for-all up here. We can call on you with questions.

But so we're going to put the first, and we're going to ease you in with, I think, one of the harder questions first. So we'd like to discuss the analytical approaches that enable inference about the underlying population without having to know about the selection process or without making any assumptions about it. And then sort of a second part of that question is for -- to discuss the utility of making assumptions about the selection process and the

assumptions that we might consider reasonable.

And Scott here will be writing down the names, and we'll try and keep you in order and keep you in line.

So who would like to begin the discussion on this question?

Dr. Novak?

DR. NOVAK: Yeah. I think, just sort of opening it up, it's very challenging to say, well, we're not going to make any assumptions about the selection process. I mean, that to me is sort of akin to trying to kill an elephant with a dart with a blindfold on. I mean, it just seems really impossible. So I think you need to make some preliminary assumptions about the selection process through which individuals are potentially, you know, sampled. And that sampling can be either two ways -- sort of purposefully; and you can use something like quota sampling to make sort of an adjustment where it's not sort of -- you know, you're not a priori, you know, making a list and then sort of sampling people from the list, but rather, you're organically taking people to

fit some, you know, population characteristic.

But I think one of the things that statistics, I think, needs to do a better job of or there needs to be a better communication is developing new sampling approaches that don't necessarily rely on sort of the standard, you know, a priori here's your sampling frame, here's -- you know, you're going to select every kth element because I think when we get into this notion of prescription drug abuse and you have abusers that are hidden in so many different parts of the system -- you know, you have your general population surveys, and so those are really good if you want to just pick up, you know, how many people have, you know, ever abused or misused a particular drug. I think that's okay. And then maybe you can get at some preliminary notions of dependence.

But I think where we get into challenges is that when we need to look into these patchwork systems like treatment center data -- and even then, you know, I think we treat -- we often think of treatment centers as being this one homogenous population. But if you dig further, you have the selection process of how

people get into treatment centers. Are they self-remanded, or are they remanded through drug court? Are they in, you know, general outpatient, or are they in office-based buprenorphine treatment? Are they in private inpatient services? And so -- and you know, those aren't all the same. Those aren't all the same people.

And you know, when we say, well, what's a treatment center, you know, when we look at some of these data sets like TEDS, well, you know, it's a treatment set, but it's -- you know, it collects some specific kinds of information.

So I think, you know, we need to -- you know, my point is I think we do need to be a better -- do a better job of at least trying to understand the population assumptions, trying to understand the hiddenness of the populations, and trying to understand our blind spots and then try to advance our statistical methodologies like, you know, non-proportional methods, quota sampling methods. I know that, you know, people are looking at internet sampling as sort of this, you know, new era to do a better job of hidden -- you know,

of getting hidden populations, especially getting people from the dark web, you know, sampling people from AlphaBay or (inaudible) but, you know, some of these other sort of, you know, markets where you can go on and go on chatrooms and get people into surveys and learn more about them and then track them over time so at least, you know -- that old saying where a clock is wrong, but it's wrong two -- you know, it's correct two times a day. But at least we can start to understand trends in certain proportions.

So I guess we also sort of need to think about, you know, what's our metric. Do we want to make an inference about the general population? Or in some specific populations that may or may not be generalizable, do we see changes over time in response to environmental presses, you know, like, different policies and policy shocks. So …

DR. BY: Thank you.

DR. GOLDIE: Dr. -- Ms. Bose?

MS. BOSE: Sorry. I think that there is definitely a need for a lot of different data and looking at administrative data and seeing what we can

do with it.

We also do have the issue of declining response rates, and those do adversely affect the quality of our data. But I think there has been -- and there have been other snowball samples, network samples, to get rare populations. So there are a lot of areas that I'm sure you're knowledgeable about.

But I think as federal entities making these large-scale decisions we always run the risk when we use non-probability samples of just simply not knowing what some of these differences are and not knowing if there are underlying mechanisms that are affecting who's included in the sample and who's not.

And so definitely it's an area of further growth. But in the survey methodology in the data field, there really hasn't been a lot of answers provided. And so we are almost talking about doing groundbreaking research prior to actually implementing it versus taking things that have been done and then using them.

And even within -- and I agree that sometimes you cannot get a nationally representative population,

but there are specific populations that you're interested in. And if we could look at those populations in a very meaningful way, that would make sense.

But even if we were to use the example of the dark web and go in there -- and I'm not very knowledgeable about the population, I will say -- if the nature of that population, as we define, kind of changes over time and we start making assumptions about them and how they're behaving without controlling them in any kind of way, we don't know who's coming into the sample; we don't know who's exiting the sample; and therefore, we don't know if any of the inferences that we're making about these populations hold. And so -- and that's the risk.

And that's not to say that traditional surveys are without their risks. They have coverage issues, and we have response rate issues.

And so I think that for FDA and other federal agencies, any foray into these convenience samples, we're still not at a point where we have good processes and metrics to use.

DR. GOLDIE: Dr. McClure, then Dr. Novak.

DR. MCCLURE: This may spill over into discussion tomorrow. But additional factors that need to be taken into consideration are patient behaviors. When we look at laboratory-type testing with drug testing, we find that in patient populations where we're looking at somebody prescribed a drug and they're monitoring for that, 54 percent of those results, 3 million results, that we look at we find that they're inconsistent with what's indicated as being prescribed by the ordering physician.

In those inconsistent results, we see drug substitution; we see drug supplementation that's out there. And some of these factors are going to affect any of the data that you're collecting here, assuming that you've got compliant patients. You need to understand the behavior of those populations. Maybe you can use ICD-type coding, whether it's, you know, retrospective ICD-9 from years past or ICD-10 currently on there.

And again, this may roll into discussion that we'll have tomorrow, too, for metrics.

DR. GOLDIE: Dr. Novak?

DR. NOVAK: Just quickly to respond to the -- one of the previous issues, I think we don't want to get -- fall into this trap of, like, we know what the population are because I think everything is a degree, right? We have certain expectations that we know. Like, even in, you know, some of these surveys like, you know, the National Survey on Drug Use and Health, but I mean, you still go to meetings and you still hear people talk about it as a household survey. And you know, that term has been dropped for, you know, well over a decade.

But it just shows that people either don't understand what's in that sample and they think it's -- oh, it's just a household and that's it, or the people that are running the survey think that there is just this sense of, you know, whether we know that there's an imprecision about people live at a certain address or what -- but when you make an assumption that -- it's a little bit more precise than, let's say, a quota sample.

So I think, you know, we need to sort of break

this binary thinking of, like, capital T, Truth versus this is validated and this isn't and do a better job of understanding the gradations. And I don't also -- I disagree that we need to make, like, major shifts or major groundbreaking, you know, statistical advancements to get to where we need to go. I think, like, in all places of science, there's some really innovative work that's being done in other places like, you know, computational biology and how you sample cells in different genes and gene deserts and how do they -- I mean, that's just really amazing stuff that some of our survey methodologists are learning from. And there's this cross-fertilization that happens.

So I do think that we do have some answers. I think we need to sort of break this binary thinking of, like, you know, this is we know this with a capital T and this is Truth and then start to move on and then look at degrees of acceptability, you know. And I think the challenge for groups like ours is to figure out, okay, well, where does that threshold really lie where we can say, well, you know, we sampled something from the dark web. Is that completely, you know, a

wash-in that's just as simple as a convenience sample? Or are there circumstances when you can actually move that needle a little closer to not necessarily the threshold of a probability sample, but at least move it away from it being a complete convenience sample? Because if you know some characteristics of the people, you know they're -- you know, you may not know their address, but you may not know where they live and you know some demographics. And you can start to, as Dr. By was saying, start to understand some of the selection processes that get people into these different places where we sample.

I think that's going to help us elucidate the characteristics in the population and get us where we need to go because doing these big national samples it's just not -- you know, I -- they're so expensive. I mean, not everybody has $50 million to play around with. There's only, you know, Monitoring the Future and NSDUH and some other places have that kind of cash to throw around. And you can't ask those surveys to do every single thing. I mean, they've got to -- you know, NSDUH is a congressionally mandated survey that's

supposed to help the states populate their, you know, treatment block grant and their prevention block grant. And now we're asking it to do all these other things for the FDA.

So I think we need to be very creative in terms of using the resources and the science that we have and being very creative in trying to identify these, you know, levels of truth, so to speak.

DR. SCHNOLL: Sid Schnoll. Taking maybe a more simplistic approach to this -- I'm not a statistician like some of you are -- but it seems to me that there are two big blocks that we need to look at. One, the patients for whom the drug is being prescribed -- how do they deal with it; what's going on with them -- and looking specifically at that group.

And then there is the other group, who as Dr. Henningfield said, those who are getting prescription drugs for which there was no prescription to them. And that's a different group, and I suspect there are very different behaviors in those two groups. And as Scott pointed out, particularly, that second group is a very complex group involved in a lot of different things.

So you know, when we're looking at this, I think trying to break the buckets down to some extent so that they're more meaningful can be very helpful. And you know, looking at a large survey like the National Survey on Drug Use and Health, you're covering (ph) populations. So there are a lot of different things going on. And some of those people are patients, and some are not.

And looking at that -- and we have to look at that, of course, with a specific drug of interest. And as we've learned from the data, that's a small, small group. We've got a very small denominator. And that can be a big problem. So I think if we can break it down to meaningful groups it might be a little easier to understand what's going on rather than trying to do it with one large sample.

DR. BY: Thank you. Go ahead, Dr. Graubard. Go ahead, Dr. Graubard.

DR. GRAUBARD: Barry Graubard. I feel that there are different objectives here, okay? And depending what your objective is, like you -- like the previous speaker said, required different statistical

approaches and also sampling, estimation, everything else. You have to kind of lay these out.

So national surveys clearly have an enormously important role for -- and particularly, this National Survey of Drug Use survey -- household survey provides FDA, if they were to use it along these lines -- I'm sure you are doing that -- provides some sort of a broad-brush idea of what's going on in the population in the general population that that survey can get to, okay?

But if you want to get to patient questions, then, clearly, you want to develop a target population around patients. And you should -- this gets into the next day about, you know, possibly new data sets. But there are some patient surveys are going on at the National Center for Health Statistics, the hospital health survey, whatever it's called now, and so forth. And so you could -- you can address those questions.

Also, this idea of using very nonstandard type looking at chatrooms and web scraping -- I don't know what else people are doing these days -- and provide interesting information that you can take to maybe

decide on new target populations and new types of data collection efforts. But you want something that is scientifically defensible for the FDA. You don't want something that's very ad hoc. Ad hoc is great for giving you ideas but not necessarily for making policy. It's just not going to hold much water. That's my feeling.

Okay. So I -- there are lots of interesting approaches that survey methodologists are involved with, and other people here probably can speak to that. Some of the -- someone mentioned network sampling. It's something I was involved with back in the 1970s, and I guess it's still being used.

I -- the other thing that actually -- or a general approach might be to if you can get these various data sources to do consistent collection of information, you can maybe design some multiple-frame-type methods where you get better coverage of these hard-to-get populations along with standard household survey populations and collect the information that you need to do the proper adjustments for the fact that they can be included in more than one survey at a time.

And you can combine these data sets together.

So that's about all I have to say. So …

DR. BY: Okay.

MS. BOSE: I'm sorry. Sorry. I was just going to ask a question about -- you know, a lot of times here we're talking about sampling. Where does, for FDA, the whole structure of using administrative-type data fall? Because even though they're not sample, necessarily, sometimes they are, A, not universes in their entirety, as we've been talking about; and B, sometimes they're used for different functions and there are changes in, say, local policy or local coding practices or other things that affect the ability to make decisions.

That's not exactly sampling, but it's tied to assumptions about the data. And that might be covered elsewhere in the conversations, but I just wanted to raise it.

DR. STAFFA: This is Judy Staffa. Actually, yes, we use administrative claims data and EMR data to look at traditional drug safety issues all the time, and we've actually put out a guidance. I'm trying to

remember what year. I'm getting old. We put out guidance in the last few years about good practices for how to use those data. And a lot of the way we deal with that is to do validation.

So for our drug safety outcome, we often don't trust an ICD-9 code unless folks have actually gone back to the charts and looked at those to ensure us that when that code is used, generally, it means the patient had this condition and it's not a rule-out or a lot of the other reasons why those codes are used. But we also do take into account whether they're commercially insured populations or publically insured. And so we deal with those generalizability issues all the time.

MS. BOSE: Oh, yeah, exactly. And I think it's something across the federal system. There's been a lot more and more interest. There was the Federal Committee on Statistical Methodology, FCSM, had the Administrative Records Subcommittee that then got subsumed under the, loosely put, big data committee. And so there's a number of issues like this that are being looked at at the overall federal level. And to

the extent that there are resources that the new OMB chief statistician and FCSM can provide FDA to come up with to supplement some of the work that you've done, I don't know if that's another area that might be useful.

CAPT JONES: Can I just follow up on that as well? Within HHS, the data council often talks about these issues at (ph) ASPE has (ph) co-chaired that with CDC and HRQ. So that may also be another place as you're coming out of this meeting with specific questions that, you know, other statistical agencies within HHS may be able to assist.

DR. GOLDIE: Dr. Lo Re, then Dr. Winterstein of the University of Florida, and then Dr. Green.

DR. LO RE: Yeah, so I actually think that Dr. Schnoll's suggestion about the two different populations of patients are actually very interesting. You know, much of what we've been discussing have really focused on people who are prescribed ADF opioids. But I think we need to think about the other population of people who are receiving those drugs not in a prescribed format. And I think we're going to need to think about when do those -- you know, when --

in terms of thinking about sampling those people, when do they actually come to attention and in what settings.

So for example, you know, are you going to sample people from outpatient hospital emergency department settings when they come to present at the time of overdoses? Are you going to present based on legal, you know, from -- in jails and prisons, people who are incarcerated, because of diversion? I think, you know, also, you're going to need to think about differences in geographic, differences in different regions, differences in urban versus rural settings in order to get the most generalizable results.

So I mean, I think it's going to be challenging in terms of thinking particularly for this other population of how to select these people appropriately. But I think if you come up with, you know, certainly stringent systematic standards, it could -- it certainly can be done.

DR. GOLDIE: Dr. Winterstein?

DR. WINTERSTEIN: A good part of the discussion has focused on sampling. And I'm looking at

this question again, and I say -- and I see analyses on the biased sampling. So I think the -- it looks like the majority or the focus of this question is, really, the sampling has already occurred, and we have a biased sample and what do we do with it now.

And I have been staring particularly at this first bullet. To me, that is an oxymoron. You know, if I don't think that there is -- if I don't know whether there are specific effect modifiers that's because of the sampling approach somehow skew the population that I'm analyzing, I don't think that I can make assumptions. So at the end of the thing -- at the end of the day, I think it comes down to pinpointing what specific mechanism would create a biased sample that then produces a biased answer, right?

So to make that more direct, if I am in a treatment center analysis, you have a particular drug -- it's particularly frequently abused in -- for -- in an intravenous route, or whatever -- then the question would be is that representative of that use of that drug in the underlying population of opioid users, right? And why would that not be the case if that

population is not properly represented? And the only way to get to that answer is if we have some ideas what those effect modifiers would look like.

So now there's two big buckets of prescription users versus illicit users. It may produce some help there because, with the prescription users, we may be able to link data. It goes back to the administrative data. So if we were able to characterize the population that we see in a particular survey, assuming that this is identifiable information -- and that may or may not be the particular scenario -- we might be able to start to characterize this population -- are these more older patients, younger patients, rural areas, not rural areas, what have you -- and try to see whether there are specific effect modifiers that we could pinpoint.

That's my only answer I have because I think without understanding that mechanism that would produce a biased answer, we cannot do anything with biased sampling.

DR. GOLDIE: And Dr. Green.

DR. GREEN: So if we look at the five outcomes

that we are trying to measure, they all are related to outward (ph) behaviors which, upon reporting, may also have other consequences. And so this isn't trying to, you know, find how many people generate a rash with a new hypertension medication, or something like that.

So I think, by measure, we have to rely on spontaneous reports and these convenience samplings because something has happened, an event, or something has occurred that actually bring these people to the point of revelation or revealing themselves.

And so I don't think that that makes the data invaluable or that -- we need to be careful not to throw out that -- you know, the baby out with the bath water. And I wouldn't expect calls to poison centers to represent the general population or everything that goes on. And I think we're very cautious even with treatment centers that this is, hopefully, representative of patients seeking treatment. And I think we've identified the gap, but we don't know if, you know, people with addiction or dependence that aren't seeking treatment are any better.

But then also go back to we're looking at

trends over time. So we're looking within each of these populations and the mosaic approach. There's a reason why we're getting so many -- so much data from different data sources. So while I think there are minor improvements, I think to Dr. Novak's point, that we can make in the sampling or at least understanding that's representative of that subpopulation we're studying, you know, I wouldn't expect each one of these to represent, you know, the larger population and, again, back to that mosaic approach of the value of understanding all these subpopulations and are the trends moving in the same direction.

DR. STAFFA: Actually, this is Judy Staffa. I want to follow up with a question about that. I think that's actually one of our key questions because we've seen examples where, if you look at different samples of treatment centers, you get a different answer. So that begs the question of do either of these represent the larger population. Or what is it about these different groups that are pulled together that might make them different? And so is there something we can push and begin to learn more about where these

different populations are coming from so that we could, even though we may not understand it completely, we can at least understand what it is we're looking at?

DR. GREEN: Yeah, and I think that that's where you go in and you look at the risk factors or descriptions within your data at that point, right? So I know we have a program that looks primarily at publically funded programs and one that looks primarily at privately funded programs. And those are very different patient populations.

So we know that there are some differences in there. But then you can start evaluating your data sets to say are there specific risk factors, what are the differences between these that might lend to further understanding of what happens after a certain intervention, whether it be ADFs or the REMS programs or PDMPs, whatever that looks like. But I think that we need to understand that is that really a selection bias; is that really a problem with convenience sampling; or is that an opportunity to further evaluate the differences within that population and understand different risk factors and maybe what interventions

might work more effectively in, say, you know, a lower socioeconomic group than a higher socioeconomic group.

DR. BY: Thank you. If you have additional discussion points on Question 1, take the opportunity to put it in the docket. I'd like to move on to the next question, Question 2.

Okay. So discuss methodological approaches that address changes in the studied population over time (for example, changes in individual geography, changes in demographics, et cetera).

So who would like to go first?

DR. DASGUPTA: This question confused me a little bit, to be honest, because there are, I mean, individual geography and individuals are usually kind of immutable units, right? But there are -- so there are -- in terms of time varying confounding and temporal changes to what you're observing over time, there's the temporal changes in sampling and there's the temporal changes in individual of a risk.

So I'm curious. Which are you more interested in understanding at this point?

DR. BY: So let me clarify that up. So in

terms of the geography, the example goes to the treatment center data. And the treatment center data that we worked with, they're part of a network that collects those data. And the treatment centers participate in that network.

So a treatment center in California that participates now five years down the road, they may not participate. Or the number of centers in California is declining in terms of participation. So the mix of individuals that provide information from one region is now -- while they were well represented in the initial part of the surveillance, laters on -- later on, they're no longer well represented in the surveillance.

So in a sense, the underlying statistical information is changing where there's emphasis early on from California, but now less emphasis from California. So it's sort of like meta-analysis where you have different clinical trials at different centers providing different information. But then there's the question of -- they're -- they have to come together at some point. So in that sense, the demographics may be in California and the representation in California may

be different from one period to the next as part of this surveillance system.

DR. DASGUPTA: Got it. So you're interested in the sampling -- on the sampling side. So at the same time that the sampling may be changing -- you know, the number of treatment centers in California may be going down, there's also an inherent bias in the ones that are more stable, too, right?

DR. BY: Right.

DR. DASGUPTA: So it's not -- so I don't see it as, like, a one or the other is a better approach, right? And I know in earlier treatment center and other programs, you know, the -- there was a stratified -- you know, there were stratified tables where it was here the -- you know, here are the centers that have consistently reported over the last, you know, 50 quarters, or whatever it is.

DR. BY: Yeah.

DR. DASGUPTA: And so I mean, that approach could be brought back. Do you -- would that be satisfactory? Are you looking for something a little bit more fundamental?

DR. BY: We've actually considered the approach where we restrict the sites that remain consistent over the study period. But when you do that, the amount of statistical information is reduced substantially. And we were wondering, like, you want to maximize and optimize the amount of information if you want to use every piece of information that you want. And these stuff are happening. What -- is there analytical approaches that you could do to try to address those issues?

DR. DASGUPTA: So I think what Dr. Winterstein --

DR. STAFFA: Can I just clarify?

DR. DASGUPTA: Oh, sorry.

DR. STAFFA: This is Dr. Dasgupta talking. I'm just thinking of the transcribers.

DR. DASGUPTA: Sorry about that. I'll just respond quickly.

So I think Dr. Winterstein's comments stressing -- look -- you know, what are the effect modifiers I think is -- you know, is the right direction to go for that, right, where you don't

necessarily -- I wouldn't think about restricting. I would think about stratification, right? And with stratification, you do it carefully with a priori hypotheses on these are the effect modifiers at the treatment allocation -- at the treatment center level. And maybe what's missing now is that we don't collect time-varying information from the treatment centers themselves, whereas we collect serial cross-sectional data on treatments -- on the people coming into the treatment centers.

So if we -- you know, additionally -- in addition to the people coming into the treatment centers, we can also sample the treatment center providers themselves and say, you know, do you -- for example, like, are you now providing vivitrol? You know, maybe that makes a difference. Are you -- you know, did you drop Medicaid coverage because of ACA, or whatever? You know, I think there are -- I think we could collect data one level higher on the treatment center kind of on a postured level to maybe get you at some of those stratification dimensions.

DR. STAFFA: Dr. Brooks?

DR. BROOKS: I turned myself off. John Brooks.

Yeah, you know, listening to this conversation, it reminds me of a surveillance system we use in our HIV division extensively, the Medical Monitoring Project, which might be a model you might be interested in looking at. It's a three-stage sampling survey, that serial cross-sectional surveys. And folks are sampled both at the provider level and clinical level as well as at the patient level and then interviewed serial -- in serial cross-sectional fashion generally annually right now. And you can design a system to do your sampling that, depending on the population you want to study and what you know about that underlying population, you can sample people and determine their representativeness of those folks you're looking at and weight their contribution to the ultimate score.

The way we use it is to understand how people are receiving care in who -- among persons who are enrolled in HIV care. But if you were interested in persons to -- just one of the basic questions, to

understand how are -- by what route of administration are people abusing drugs, you know, you could aim to sample, I imagine, at places where the clinical environment will encounter those people, so not only people coming in for drug treatment, but perhaps jails and prisons for people who come in and are demonstrating withdrawal -- you know they're using -- or mothers presenting with neonatal abstinence syndrome. But you could design a system to capture people experiencing the clinical consequences of abuse and then use that as the model from which to sample your group.

And if you want more information about that, our group who runs the system is very familiar with it.

DR. UNICK: Yeah, I agree with what a lot of has been said so far. I think you have to make choices about particular populations, especially when you have so many moving targets because you have to have something that's sort of fixed in order to monitor change over time. So thinking about your treatment sample, for example, a lot of people enter treatment because of law enforcement contact.

States that have legalized marijuana are going to have differential law enforcement contact post-legalization and pre-legalization. And so that's going to really affect who's in that sample.

So you really have to understand how people get into the treatment system and make choices about those populations. And so I think that gets back to that first question. You can't not make assumptions. I think you should make assumptions and then choose samples that are sort of fixed -- that can be reasonably fixed over time. And you just have to make choices and lose power.

DR. PARKER: I actually just have a question about the sample that you're talking about. Are you actually sampling these treatment centers, or is this a fixed network that you don't have control over? And I think the difference is whether you're taking a sample from a -- you know, a frame of treatment centers or whether there's external reasons why they're participating in the first place. And that I apologize for not knowing your area.

DR. BY: Right. So let me clarify that. So

the data that we get, they're from treatment centers that are part of a network that we have no control over. So a lot of the evaluations that we do in the ADF space is looking at the data that comes from this network that collects data from these treatment centers so that the treatment centers, I think they volunteer to participate as part of the network that collects the data.

MS. BOSE: I'm sorry. Could you also say what data you -- what research questions get answered by these data?

DR. BY: One of the research questions that we evaluate in FDA is does the product that's been label -- - in the pre-market setting labeled with ADF language, does it really reduce abuse in the population out there in the community in the post-market setting. And so we have access to these data, or at least through submissions, and we have to evaluate whether the product results in reduced abuse and the community are not using these data.

DR. STAFFA: This is Judy. I think if -- there's folks here at the table from RADARS and

Inflexxion, the companies that actually run these networks. And perhaps they can just briefly explain what are some of the -- you know, why do treatment centers participate in these networks, what do they gain from that, so folks can understand the incentives. They're not sampled in a probability design. They're -- they participate for a purpose. So …

MS. CASSIDY: Hi. I'm Theresa Cassidy, and I work at Inflexxion. Some of this treatment center data that we're talking about is data from the ASI-MV, NAVIPPRO data set, and it is a convenience sample. It is a heterogeneous treatment center sample where it doesn't necessarily just have, you know, only, you know, inpatient, outpatient. It has a mix.

It does, in some respects, reflect the heterogeneity in, you know, substance abuse treatment in general in that regard. But in terms of how the treatment centers participate is we have this network where individuals -- one thing to sort of keep in mind about this data set is that the addiction severity index, the ASI-MV itself, is a clinical assessment. It's -- it has clinical utility, so it's used for that

purpose.

In addition to that, we have included product-specific information for prescription medications and route -- product-specific route of administration data. So the data are being collected for -- initially for clinical purposes for substance abuse treatment centers that need to use this for their clinical evaluations to assess the need for treatment. And then we're collecting that data on the backend in aggregating that into the -- you know, to be able to try and look at some patterns and trends in prescription opioid abuse.

So you know, there is -- there are treatment centers that, you know, consolidate and close down and new ones come on board. There is a dynamic aspect to the different treatment centers over time. But there is a sense -- there is a bit of consistency in terms of the, you know, general number of -- and the types of treatment centers that we have.

I think -- just to get back to the example that was sort of raised at the beginning of this question was, you know, if we have treatment centers in California and they're somewhat -- you know, they have

decreased over time and then, you know, there's some treatment centers in Michigan and they are sort of increasing over time, I guess it goes back to what question are you trying to answer as it relates to these -- you know, the data.

And you know, if we think that, you know, the treatment centers -- you know, having a smaller group of them in California are fundamentally different from the group that existed, you know, in some previous time period in the system in California versus they are fundamentally different from individuals who are, you know, seeking -- who are seeking in being assessed for treatment in Michigan, say, as it relates to a specific product and how people would use or abuse a specific product, I think you're right, that, you know, if we're talking about trying to get -- if the question is we want a national estimate, then, you know, these data would need to have some type of enhancement and, you know, support and help to make that happen. And I think that there are probably methods and approaches that we could use to do that.

I think if we're talking about, like, you

know, what questions do these data answer, I think that, you know, we need to kind of keep that -- for the moment, we need to keep that in perspective.

So I guess, you know, going back to some of what, you know, Dr. Dasgupta said, is, like, I think stratification, talking about the different risk factors in the underlying -- the patients and the individuals in the population and looking at them rather than saying, like, well, it's just geography -- California isn't, like, as represented as X state -- you know, maybe geography is a component, but it's not maybe the focal point.

DR. GOLDIE: Dr. Graubard?

DR. GRAUBARD: So I'm also a little bit confused, exactly, you know, about the question, but I think I have a little bit of an idea now.

And so there's -- are these treatment centers that are decreasing in some states and increasing in other states? There are some -- there's -- there must be some sort of a listing of treatment centers in the United States. And if you can get information about the characteristics of these treatment centers so that

you can make adjustments either through weighting or through stratification or analytical adjustments of -- for how things are changing, this happens all the time. Any time you're dealing with any sort of a panel-type study where people -- where units are dropping in and being born and created, this happens all the time.

And so there's -- there are statistical approaches and -- that people have used -- I'm not saying they're perfect, but that you can take account of, you know. You're a statistician, and I'm sure you know of these. But so it's kind of a combination of missing data issues and also adjustment standardization-type approaches.

DR. BY: Okay. Okay. So let's move on to Question 3. You know, that's wise.

"Discuss the usefulness of these metrics for measuring and assessing the impact of ADFs on abuse-related outcomes in the population."

So Sub-bullet 1 refers to the number abusing product X as a proportion of those denominators. Sub-bullet 2 refers to number of using X through some route R based on a similar set of denominators. And then

Sub-bullet number 3 refers to the number abusing X relative to the various utilization denominators that I've listed.

And also, discuss metrics that we have not considered that you think might be potentially useful for the current data sources that we have.

And also, "Discuss interpretations when different metrics imply different conclusions."

Dr. Dasgupta?

DR. DASGUPTA: Thank you for bringing up these questions. So I'll speak to Sub-bullet 3 of Bullet 1.

So one of the distinct challenges we've heard with the newer ADFs is going to be low volume, right? We're talking about 5 percent of the opioid market. And we've also heard -- I mean, we also know from talking to people who come into syringe exchange programs, drug users, that what people use is really -- has a lot to do with what's available to an individual within a social network, within a city, within a neighborhood, whatever it is, right?

You're not going to -- so the approach that has been taken today has isolated each drug and

compared it to one comparator or maybe a handful of comparators. But we don't do much to look at the -- and I know FDA's remand (ph) is to look at specific products, right? But if we are looking at the basket of opioids that are available and any -- to any given individual, to any given -- in any given community, I think there is another conceptual piece that we are missing, right?

So if you're looking at one, like, very low-volume ADF but there -- but that area is awash in hydrocodone but also has, like, a substantial amount of oxymorphone, say, and if you go through and kind of look at the different opioid active molecules and look at kind of the mix -- the concentration and competition almost, you'll see that there's wide disparities across the U.S.

So in the economics literature, there is -- competition in markets is quantified using a handful of indices where you see kind of what market share each -- you know, the product of interest has relative to other major products in that market and kind of just standard errors (ph). And so part of the -- I think part of the

dynamic that happens in a real world I'm trying to get my drugs to get high setting is that you get -- you end up using what's available.

And right now, when we use Sub-bullet 3, we are making an assumption that there is a uniform availability of that product for every individual in that geographic unit. And I don't know that that's -- that -- when you're talking about high-volume drugs, that's kind of reasonable. But when you get to some of these very low-volume drugs, that's going to fall apart completely.

So in some ways, you know, adjusting for the number of prescriptions is something we have to do to get our mind around the comparisons we make. But at the end of the day, looking at each drug in isolation is going to kind of put you in a tunnel vision. So …

DR. GOLDIE: Captain Jones?

CAPT JONES: I think, to me, the one thing that's missing is that you're comparing X to any opioid. I mean, it's sort of getting to some of the same point. But I mean, the literature's pretty clear that people have preferences and those preferences for

specific opioids are due to a multitude of reasons. So if you have, you know, a new extended-release hydrocodone product that's, you know, reformulated to deter abuse, thinking about all opioids versus maybe thinking about other hydrocodone products or other products that are similar, I think, is an important nuance to determining impact.

I mean, we sort of dealt with this with the hydrocodone up-scheduling (ph) issue where the comparator was chosen as oxycodone-combination products. And some people would argue that that might not be the best comparator, that if you look at abuse ratios for morphine or other things, it might be different.

So I think it's important to not just lump all opioids together. That could be one measure. But I think also looking at comparators, which I think you're going to talk about later, but it's not specifically called out here, and I think that it should be a part of the metrics.

DR. STAFFA: This is Judy. I wanted to just provoke this a little bit. We've had a lot of animated

conversations with our colleagues in industry about which metric makes the most sense to answer this specific question. So if you can focus, you know, what is the right metric? Because many times, these metrics, you can look at the same data, calculate these different metrics, and you get a different answer.

And so we'd really just love some scientific insight on if you had this in front of you and you had to answer this question, which metric? And thinking about -- again, the question is about whether the abuse-deterrent formulation is deterring abuse via the route that it was formulated to do so and assuming, which we'll get to later, that it's a correct comparator, or whatever you're comparing it to. But what is the right? Should you adjust for utilization? Do you look at the proportion?

What -- I mean, really, if you can help us here, this is, you know, an -- there's no right answer here. But we need to understand. We need to get someone else's thoughts. We've been talking to ourselves about this for too long.

DR. GOLDIE: Dr. Green.

DR. GREEN: Within the drug utilization options listed, I was surprised to not see milligrams dispensed or some adjustment for tablet size because I think we all know that a 5-milligram tablet is much different than an 80-milligram tablet. So I guess I'm not sure if there was some reasoning behind that or just --

DR. STAFFA: No, no. I think it just -- we just -- there's so many ways to adjust for utilization. We just picked one. So if you think -- so does that mean, Dr. Green, that you think utilization adjusted has value for -- to answer this question in some way, whether it's --

DR. GREEN: Yes.

DR. STAFFA: -- by tablets or milligrams or prescriptions?

DR. GREEN: Yeah, I certainly do in some way. I think, again, back to the question and even the population -- and you have to look at the coverage of where your data are coming from. But in relation to all of that, I do think it's important to understand because I think the population certainly gives you that

overall public health burden aspect. But drug utilization does give you the risks associated with a specific product.

Now, looking specifically at the drug utilization options that we have, you know, we've gone through the UR, unique recipient, and prescriptions dispensed and then tablets dispensed. But if you're going to compare, you know, say, IR products to ER products or products that have very different wide range of milligram strengths, then I do think that a milligram dispensed is going to be a much more appropriate level of the drug utilization data to use.

DR. GOLDIE: Dr. DASGUPTA.

DR. STAFFA: Make it quick. I want to move on to more question before we end this session.

DR. DASGUPTA: Sorry. So when you're -- so when you use the number of dosage units instead of the number of prescriptions, there's going to be certain products that are going to jump out as being much worse than you previously thought. Fentanyl is the one, in particular, that stands out.

So I think the question is going to also be

kind of which drugs are you comparing. And it kind of goes back to the comparator issue as well.

DR. BY: Thank you. So I'd like to jump ahead to Question 5. Is it -- okay. Thank you.

So, "Pre-post comparisons have been considered extensively in the context of measuring change between a pre-ADF period and a post-ADF period. Discuss criteria that you think may be useful for determining the length of the pre- and post-period. Discuss the balance between the ability to observe trends and the changing population characteristics."

DR. GOLDIE: Dr. -- or Captain Jones.

CAPT JONES: I just have a question on this. Obviously, OxyContin is a product that has been studied the most in this space. And you had, you know, a fairly good pre-period where there was social -- capital associated with the name, and you can look at post-reformulation. You don't have that for some of the newer products that are, essentially, new formulations. Or in the case of, like, Hysingla where you had Zohydro on the market for a relatively short period of time, virtually very little pickup, so you're

pre of something similar doesn't really exist.

So I don't know if there's a question around that particular issue, but this seems to assume that you've got pre for everything, which you really don't.

DR. BY: I mentioned earlier that there are some products that we know it was never marketed without the ADF formula -- with the ADF formulation. And for those products, there's no such thing as a pre-period. And so we're still interested in the effect of the formulation for those products, and it's not entirely clear, at least not in this session, anyway, how you go about in defining a pre-period.

DR. LEVENSON: Right. This is Mark Levenson. I think your question's going to be somewhat more addressing the causality section in the afternoon.

DR. GOLDIE: Dr. Winterstein?

DR. WINTERSTEIN: I don't know exactly the structure of the survey data and how much they lend themselves to being chunked in tiny little time units, but there's always an advantage over having a time series analysis rather than a pre/post because you can appreciate trend. And considering the amount of change

that has, in parallel, happened that we all are very well aware of, I think it's extremely difficult and dangerous to just grab one particular time point, you know, assuming that this can be attributable to the marketing of ADF formulations.

So I think optimizing the time increments that can be used and still yield, you know, reasonably stable and reliable results by putting them in a time series framework would be always more advantageous than trying to identify a pre-post design.

DR. GOLDIE: Dr. Lo Re and then Ms. Cassidy.

No? Okay. Ms. Cassidy.

MS. CASSIDY: Yeah, I just wanted to comment about the time period. And you know, to some extent, this might be product -- it might be product-specific. So you know, boxing ourselves into, like, it has to be a specific time period for a specific length of years may not make sense for all products. So you know, you could have a specific product that, you know, maybe shows great promise and success in a certain period of time. And you can see that evidence is supportive, you know, conversions of data across a number of different

data sources and studies, and then that makes sense. But for another product, maybe that -- there's sort of maybe milestones or gates, that it goes forward in time and you would need to take a look at.

So I would just caution us from not boxing ourselves into, you know, there's, you know, a specific number of years or a specific period of time that needs to occur.

DR. GOLDIE: Captain Budnitz?

DR. BUDNITZ: Dan Budnitz, CDC. I was going to actually make, essentially, the same point that the time periods are going to be dependent on your expected delta, how effective you think the abuse-deterrent formulation is going to be. And you know, if it's going to be -- if you expect less effect, you're stuck with a longer post-period to try to evaluate it, and then you do have to balance all these changing population issues and other issues.

So I think that's, like, your first step, is coming up with what is your expected delta. And it may be infeasible if it's so low that you can't do it.

DR. GOLDIE: Dr. Brooks.

DR. BROOKS: Yeah. John Brooks. I just want to echo, I think, what Dr. Winterstein was getting at, which is I find pre-post comparisons in an environment where the ecology of the forces that are changing the prescription and availability of these drugs are all changing so quickly. It's going to be very difficult to tease out to what extent the change in formulation led to the observed change in the -- whatever your outcome is -- use, abuse, you know.

Pre/posts are terrific if you have a very, very stable system. But where there's a lot of other competing causes going on that could lead to the outcome you're looking at is very challenging.

DR. CICCARONE: Dr. Ciccarone. So I'll just highlight -- I'm going to repeat some of the things you just said and also go back to what Nab was saying earlier, Dr. Dasgupta. And that is there's a lot of fungibility in this opioid world. And now that there's a number of new products that have come out, ADF products, as well as competition with the heroin and fentanyl market, we just need to be aware there's -- you know, a longer period is going to be necessary to

observe what the cultural changes are going to be -- which opioids become dominant; what are the -- you know, the competing effects.

I would agree with Chris Jones that we need to compare to -- you know, the denominator needs to be compared how is this drug doing compared to the opioid pool in general.

So those are my thoughts. And cultural lag time -- it takes a while for the culture to not only figure out how to get around a weak abuse deterrent formulation, but then to pass it on in the hundredth monkey way of months to years.

DR. GOLDIE: Captain Jones before we move on to the audience participation.

CAPT JONES: Yeah. So I would just -- I agree that, you know, it's important to see what stabilization looks like over time for different products after they're introduced. I think, similarly, on the front-end side, on the pre-side, it would be good to have some historical perspective. I think if you look at OxyContin, some of the studies that have -- largely based on the data systems that have been

available and coming online 2008/2009, there was a lot of talk about the reformulated product before it was actually in the market. And you see in some of the studies the slight uptick in the pre-period, which makes the post-period comparison greater.

But if you look back in other years, like, we did a study with NSDUH where you have some more years of data, if you look at where things are, like, a couple of years after in the NSDUH data, yes, it's maybe less than the peak, but at historical levels, it's still high. And there's the question from the public health perspective of what is acceptable lowering of abuse. If it's as high as it was when people were still abusing it and dying, have we really made a public health gain? And I think that's important that you may not -- obviously, for some products, you won't have that historical perspective. But I don't think it should be just based, as best we can, on the limitations of the available data sources.

DR. MEYER: Okay. So now we're going to move on to the audience participation piece. And you'll find a microphone at the end of the table here where

I'm pointing, and it has the red light, yellow light, green light for you. So you can line up behind that.

And I have some instructions for you. Please try to focus your comments on this session topic, which is the sampling metrics and denominators. We'll give you three minutes to speak.

The light system will keep time and notify you when your time is complete. It works like a traffic signal. The light is green; continue speaking. When it turns yellow, you have one minute and you should begin to quickly close. And then the red light means that you should stop immediately and return to your seat.

And so it looks like we do have someone lined up. So please go ahead. Start with your name and affiliation and any conflicts of interest.

DR. BUTLER: Hi. I'm Steve Butler again. I'm from Inflexxion, and I work with the NAVIPPRO ASI-MV data stream. There was another topic that I would like to sort of introduce for folks to consider. And one of the things that we have been pondering is a concern about using utilization as an offset, as a denominator,

as we've been discussing here.

And essentially, what that assumes is that if you have -- in our case, we use ZIP code. So we use -- we look at abuse within a ZIP code and the prescribed availability at that ZIP code. And essentially, by using it as an offset, the assumption is that if you have a ZIP code with, say, 20,000 tablets dispensed, then your assumption is that the abuse is going to be two times a ZIP code with the -- with 10,000 tablets dispensed. So there's this proportional relationship.

And what we found is that, looking at the data, that kind of assumption does not hold up well. And if you think about it, when you have so much hydrocodone combination that's out there, in some ZIP codes, everybody in the ZIP code would have to be abusing it for this to be proportional. So obviously, there's a kind of -- you know, just logically -- I'm not a statistician, but just logically, you would think you'd get to a point where you would -- things would level off -- would have to level off.

So we've experimented with looking at models that allow the relationship between availability and

abuse and the catchment areas that we're using at this point, which is the three-digit ZIP code area, to vary and to -- for the models to reflect the actual relationship between abuse and availability. And we find -- we get very different results both pre- and post-period and also within the same period.

And so this is something we'll address in a publication and in the docket further.

Thank you.

DR. MEYER: Thank you very much.

Would the next speaker for the record please state your name, your affiliation, and any conflicts of interest?

DR. COPLAN: Thank you. Paul Coplan from Perdue Pharma. Similar to Dr. Butler, I want to address something that we didn't really discuss in this session but is really a pivotal assumption to interpretation of the data.

So it's important -- we all agree it's important to adjust for utilization. But the technique that's used for adjustment of utilization makes a huge difference. So I think it's worth spending a little

bit of time looking at that.

And there's two ways it can be fettered. One is as a denominator -- rate per 10,000 tablets. The other one is a covariate, such as how we adjust for age or sex in statistical models, which is, essentially, stratification. And the preferred metric by FDA is tablets -- is abuse cases per 10,000 tablets. That imposes two assumptions -- proportionality and linearity. Proportionality means as the per-unit increase in tablets dispensed is a unit increase in abuse. And then linearity means for the range of tablets dispensed, there's a consistent increase in the abuse cases.

Unfortunately, those assumptions don't fit the data. And I encourage FDA to do a goodness of fit of the data before making the decision to use abuse per 10,000 tablets.

Some of the ways in which it creates a distortion can be example -- for example, Dr. Jones was talking about the high -- the extended-release hydrocodone versus immediate-release hydrocodone. So you can have two patients using hydrocodone -- one

using an ER once a day, 60-milligram, the other one using 6 IRs. Each of them has an overdose within 30 days of use. The abuse rate in the one case is 1 out of 30; the abuse case in the other is 1 out of 180 merely by the number of tablets that they're using.

This also has big implications because the preferred control group that FDA likes is ER morphine. So with ER morphine, there was about -- over the last seven years, there's been about a 10 to 15 percent increase in abuse cases. But there's also been about a 70 percent increase in the number of prescription -- in the number of tablets dispensed. But within the tablets dispensed, there's been an increase in the lower-dosage tablets but a decrease in the higher-dosage tablets.

And so when adjusting for the tablets dispensed by the covariate approach, there's a -- by the denominator approach, there's a 34 percent decrease in ER morphine abuse over the last seven years. But as a covariate approach, there's a 22 percent increase because the covariate approach doesn't force any assumptions. It allows the model to best fit the data.

So that's something that we think is really important to consider. Thank you.

DR. STAFFA: Thank you, Dr. Coplan.

Just to clarify, the comments that Dr. Coplan made, we -- in individual conversations about individual questions, we may voice a preference for using tablets as a denominator or using ER morphine as a comparator.

But just to be absolutely clear, we do not recommend as a global solution to always be using tablets as a denominator or a specific drug as a comparator. We look at these as individual questions, and we tailor our advice and our thinking to that specific question.

So I just want to make sure that's clear. I don't doubt that we have said that -- those specific things, but they were in regard to specific issues and questions and studies.

Is that -- I'm looking at my team. Okay.

(Laughter.)

DR. STAFFA: All right. So it looks as if we're at the end of this session unless there's another

audience member that would like to make a comment. Again, I know we didn't get to all the questions in this session, but these are complicated questions. Please, I would encourage the panel, the audience. If you have things to contribute to us that have Greek letters and formulas in them, please, we'd love to see them. Please submit them to the docket as complicated as you like.

It is 12:30, so we will break for lunch. Lunch is on your own. I believe there's a nice map, lots of restaurants within walking distance in downtown Silver Spring. We will reconvene promptly at 1:30 to move along with Session 3.

Thank you so much.

(Lunch break.)

DR. STAFFA: Okay. If everyone could take their seats. We're ready to get started.

Okay. Good afternoon. Thanks for coming back. I think we have most of the panel back, so we're going to go ahead and get started.

So this afternoon, we're going to roll into Session 3. Session 3, we're going to be talking about

causal inference and control for confounding. And again, we understand that these are not completely separate topics. We've already touched on some of these issues.

But for this session, we have Dr. Jana McAninch, one of our lead epidemiologists, who's going to tee up some of the issues in a brief presentation. And she and Dr. Diqiong Xie, Pharma Statistician, will be leading the discussion.

So I'll turn it over to Dr. McAninch.

DR. MCANINCH: All right. Thank you.

So I know this is a postprandial session, so I will try to help everyone stay awake.

So as Judy said, we'll be discussing causal inference and control for confounding. And to get the discussion started, I will just present some of our thoughts on this topic. Here we go.

So I'll briefly discuss the concept of association versus causation and how we can think about causal inference using observational data, specifically, using the counterfactual framework and strategies to control for secular trends or confounding

by calendar time in time series studies. Then I'll briefly touch on the use of Hill's principles of causal inference and, finally, raise the question of the differences between effects seen at the aggregate level and the individual level and how this might affect our interpretation of the evidence.

So as you know, association is not the same thing as causation, and an observed association may or may not be causal. But in questions of drug safety and effectiveness, we generally are interested in understanding causal relationships, not simply associations. So when we're designing or evaluating a study, we have to consider the potential role of non-causal associations as well as causal.

So non-causal associations can occur for several reasons. One is simply chance, or random error. And we use things like confidence intervals and P values to help us determine the likelihood of an observed association being due to chance alone.

Systematic error results in bias, or findings that deviate from the truth, either due to the way study participants are selected or in the ascertainment

of the exposure or the outcome. And we have discussed today a number of issues related to these types of bias.

So in this session, we're going to focus on confounding, which refers to the influence of other factors that, if not fully controlled for, can lead to associations that do not reflect a causal relationship between the exposure or the intervention in the outcome of interest.

So one concept that can be helpful in thinking about these causal relationships is the counterfactual. And the counterfactual simply refers to the hypothetical scenario in which the exposure or intervention being evaluated did not occur but everything else is the same. So in the case of an abuse-deterrent formulation, the counterfactual can be thought of as what the abuse rates and patterns would have been for a particular drug were it not reformulated with abuse-deterrent properties.

So the effect of the abuse-deterrent properties is the difference between what would have occurred in this counterfactual scenario and what we do

observe in the real-life scenario where the drug does have properties designed to deter abuse.

So the counterfactual question that we're asking is: Is abuse of the product, or whatever outcome you're looking at, meaningfully lower than it would have been without the abuse-deterrent properties? But since the counterfactual isn't directly observable, the question is: How can we best approximate it?

So I'll walk through a hypothetical case of a product that has been reformulated with abuse-deterrent properties since that's the area that we have the most experience thus far. And different study designs might be needed for an ADF opioid without an abuse deterrent precursor or original formulation. But really, the counterfactual question is essentially the same.

So this is just a hypothetical pre-post study evaluating the impact of reformulating an opioid with properties designed to deter abuse. So here we're assuming that we've adequately addressed potential bias due to misclassification, sampling issues, things we've discussed today. So this is perhaps the simplest and most intuitive type of analysis, so comparing the mean

abuse rate for the product in the pre-reformulation period to the post-reformulation period using whichever metric you're choosing. So here you would say that the reformulation was associated with a 60 percent reduction in abuse or insufflation, or whatever outcome you're focused on.

So if you conclude that the reformulation caused this reduction, then you're using the pre-period mean abuse rate to approximate the counterfactual. So you're assuming that it would have remained unchanged during the post-period were it not for the reformulation.

But of course, as has been brought up today, the real world is not static, and there are many factors other than the abuse-deterrent formulation that are changing over time and, therefore, that can confound this type of pre-post analysis. So these include efforts like the major "pill mill" crackdowns that occurred in Florida in 2010 and 2011 and then in other places as well. We know that prescriber behavior appears to be changing, probably due to a combination of factors that are not all listed here. And of

course, we've seen dramatic increases in heroin availability and use, which is, of course, closely intertwined with prescription opioid abuse. And these trends can vary widely geographically. And in general, they're very difficult to measure, with perhaps the exception of prescription volume, which we can adjust for, although, as you've heard, the best way to do that is not always straightforward.

I just -- I wanted to note that we will also be discussing confounding in one of tomorrow's sessions on study designs that assess exposure and outcome in the same individuals over time because I think the issues are a little bit different. So here we're really focusing on these time series-type analyses.

So one approach to accounting for these secular trends, or confounders by calendar time, is to use a comparator opioid without abuse-deterrent properties to essentially approximate the counterfactual, the idea being that the comparator may reflect the effects of other factors that may be driving trends in opioid abuse more broadly.

So this figure is a fairly simplistic

depiction of this type of design. So here the index drug is on the left, and the comparator is on the right with the blue being the pre-period and the red being the post-period mean abuse rates, or rate of whichever outcome you're looking at.

So again, you see the 60 percent reduction abuse rates for the drug that was reformulated, your index drug, but you also see a 30 percent reduction for the comparator drug, which is assumed to be due to other factors that are driving down prescription opioid abuse rates more generally, so serving as an approximation of the counterfactual or what would have happened to the indexed drug if it had not been reformulated. So that leaves a 30 percent reduction in abuse rates that could be attributable to the reformulation if this counterfactual assumption is correct.

So let's talk a little bit more about means analyses and secular trends. And I know this issue was brought up a little bit earlier this morning. So this is a hypothetical example of how you could see a large reduction in mean abuse rates from the pre- to the

post-period shown here with the blue- and red-dashed horizontal lines. But this decrease appears to be simply a continuation of a preexisting trend, or a secular trend, and may have had no causal relationship to the abuse-deterrent formulation.

So similarly, there could be an abrupt reversal in abuse rate trends following a drug's reformulation but no observed change in the mean rates. And then, of course, you can have everything in between.

So we discussed a little bit about the duration of the pre- and post-period in the last session, and this figure is just to illustrate again how the duration of a selected pre- and post-period can really affect the results of a means analysis when abuse rates are changing during these time periods. So here if you compare the mean abuse rates for the shorter Pre-period A to the longer Post-period D, you see a reduction. But if you compare the longer Pre-period A to the shorter Post-period C, you see an increase in the mean abuse rate after reformulation.

So another approach that is often used to try

to account for these secular trends is the interrupted time series, or ITS, for example, a segmented linear regression analysis. And here the counterfactual approximation is a continuation of the pre-period trend following a reformulation of the drug.

And these analyses measure two things. They measure the change in level, or the intercept, which in terms of causal inference, can be interpreted as the immediate effect of a point-in-time intervention. And ITS also measures the change in slope, or a more gradual change, kind of a bending of the curve after an intervention.

So causal inferences based on this type of analysis are still based on several assumptions, or require several assumptions. And first is that without the intervention the trends observed during the pre-period would have continued unchanged. And second is that there were no effects of interventions occurring around the same time as the reformulations, so concurrent interventions.

So because these two assumptions may not be valid and they're not easily testable, a comparator

can, again, be used to try to better approximate the counterfactual scenario. And then this, again, becomes a difference-and-differences-type analysis. It does still assume that if there is an effect of a concurrent intervention, that it would be the same or similar for the index drug and the comparator.

And then this, again, raises the question that was brought up earlier: How do we select the appropriate comparators that will best approximate this counterfactual scenario? So the ideal comparator is essentially identical to the drug being evaluated except that it does not have abuse-deterrent properties. So ideally, it would have the same indications for use, similar pharmacologic properties, as well as similar baseline trends and patterns in abuse, including the routes by which it's abused.

And then in addition to the drug that we're evaluating, comparators need to have a relatively large and stable market share or prescription volume. And then again, we would want to be able to expect that concurrent interventions would have a similar impact on abuse patterns for the comparators as they would for

the index drug.

So unfortunately, typically, there is no ideal comparator, and so multiple kind of imperfect comparators are used. However, this use of multiple comparators complicates the interpretation of the analyses and our ability to try to kind of make these more clear causal inferences. For example, if you have two primary comparators and the index drug shows reductions in abuse rates or changes in trends that are significantly greater than one comparator but not significantly greater than the other comparator, what does this tell us about the effect of the abuse-deterrent formulation?

Oops. So I'm -- I am sorry. This thing is -- it seems to have advanced on its own. I apologize.

So it's important to pre-specify the comparators for hypothesis testing and analyses. But we also encourage inclusion of a broader selection of opioids to be included in analyses, including heroin, as these help us to understand what's sometimes referred to as the abuse landscape or the abuse psychology or, essentially, kind of the broader context

and the broader trends in opioid abuse patterns.

And another strategy we've seen is the use of composite comparators, for example, all extended-release, long-acting opioid analgesics. And this certainly has some intuitive strengths as an approximation of the counterfactual, but there are some challenges here as well. One of these is that the composition of these composite categories is constantly changing. And the drugs with the largest market share will tend to drive what you see for the overall category.

So there may be some stratification and weighting approaches to help address these concerns. But using this type of aggregate comparator will still mask differences, potentially important differences, in abuse patterns for the component drugs.

All right. So as we've talked about today, determining the impact of ADFs in the post-marketing setting is challenging. But ultimately, we are tasked with considering data from a variety of sources and types of analyses to try to determine whether the drug's abuse-deterrent properties have resulted in a

meaningful reduction in abuse and related outcomes in the community.

So we sometimes turn to sort of these fundamental epidemiologic principles like the Bradford Hill criteria that are shown here. And these are certainly not a checklist, and they've been widely debated over the years. But we do feel that they provide a useful framework for evaluating a large body of observational evidence to determine the likelihood of a causal association.

And then finally, before we get to the discussion questions, I just wanted to raise one more issue that's related to causal inference, and that is the difference between aggregate-level and individual-level inferences.

So the vast majority of the post-marketing abuse deterrents studies that we've seen thus far are ecologic studies. So they compare aggregate measures of abuse in groups of people across time periods. And these designs are commonly used in public health and policy arenas to assess the impact of community-level interventions. And this may certainly be useful here

to assess the community-level impact of abuse-deterrent formulations on abuse in the community. But I think it's important to note that this type of study is really quite different from a clinical trial or cohort study where you're following individuals over time to assess whether exposure to a particular drug or intervention or formulation reduces the risk of a particular outcome.

So we're interested in discussing what we can reasonably infer from changes in aggregate abuse rates over time, often in a very selected population, about the risk of an individual who's exposed to a product going on to abuse it, particularly via a more dangerous route or of transitioning from one route to another of becoming addicted or of having an overdose.

So that's all I have, and we'll go on to the discussion questions now.

DR. XIE: So we have developed questions to guide the panel discussion. Elaine will assist us to make sure that we call on you to provide comments throughout this session. If you would like to comment, please raise your hand, and then we'll acknowledge you

and write your name down on our list here.

We have four questions that we would like to discuss during the next 60 minutes, so that means 15 minutes per question.

So our first question here is, "How do we best synthesize findings from means and interrupted time series analyses in evaluating whether an ADF has resulted in a meaningful reduction in abuse?"

Anyone would like to start the discussion?

DR. SCHNOLL: I have a question related to this. A meaningful reduction in abuse --

DR. STAFFA: This is Dr. Schnoll speaking --

DR. SCHNOLL: Oh.

DR. STAFFA: -- for the record.

DR. SCHNOLL: Sorry. Yes. I have a question. Are we talking about a meaningful reduction in abuse in the patient population or a meaningful reduction in abuse in a non-patient population? Very different, as we've talked about this morning, and I'm not sure we can look at both of them simultaneously and come up with conclusions.

DR. MCANINCH: Yeah. I mean, I think we are

interested in both. And I agree that we may not be able to evaluate both of those questions or answer both of those questions in a single population or in a single study.

And so you know, what we typically see in this area, as you know, is a suite of studies to try to get at different aspects of these questions. But -- so if you have thoughts on how best to do this in one or the other of those populations or both, we'd be interested in hearing those.

DR. SCHNOLL: I would think you have -- as we discussed this morning, I think you have to separate them because they are so different. And you know, when we look at the patient population, the people to whom the drug was prescribed, I mean, I often refer back to the Adams (ph) study where they actually followed about 11,000 people who were given hydrocodone product. And about 4 percent developed some surrogates that could be related to abuse. So it's a pretty low level, and this was before a lot of this stuff that we call the secular changes were implemented.

So we're talking about very small change,

potentially, whereas in the abusing population you get a lot more. But it's harder to find those people and follow them over time. And we would need more epidemiologic approaches. With the patient population, I think you almost have to do a prospective study with random assignment to various drugs and then look at the epidemiologic data to see if it's concordant with what you're seeing in the prospective study.

DR. WINTERSTEIN: I have a clarification question, too. Synthesize findings sounds like meta-analysis. I mean, it -- well, I mean, it doesn't really seem to connect to the presented confounding issues, that question. I …

DR. MCANINCH: Yeah, maybe synthesize is not the best word. But how to interpret findings from these very different types of analyses that we typically will see, you know, means analyses, so the pre -- you know, pre-post-type analysis, and then also an interrupted time series analysis. And the -- you know, the results can be quite different. And I think in the last talk you had mentioned that for -- you know, when you have a dynamic system that the

interrupted time series may be more useful than a means analysis. But you know, the interpretation of those is somewhat less intuitive in terms of thinking about what a reduction in abuse means.

So I think we were just -- we'd just like to get thoughts from the panel on how to interpret the results of these different types of analyses that we see in this space.

Does that help at all?

In terms of making a causal inference --

DR. WINTERSTEIN: I think you --

DR. MCANINCH: -- about the impact of abuse.

DR. WINTERSTEIN: -- very well to the issues already. You know, everything that you presented summarizes the issues, and each of them -- I don't see a disadvantage in an interrupted time series analysis over a mean because the metric is the same. You just have more of it in one versus the other. And that is obviously a matter of sample size and how often -- and how many distinct measurement points you have available. And that's where the issue might lie. You know, depending on what kind of data source is used,

there may not be the opportunity to chunk it in small enough increments to really put a regression line through it.

But beyond that, the issues remain the same. I feel like I would reiterate what you just basically presented if I answered it. I think you did a wonderful job in describing the problem.

(Laughter.)

(Crosstalk.)

DR. MCANINCH: All right. We can move on.

DR. STAFFA: So you got a solution there, Almut?

(Laughter.)

MS. FERGUSON: So we have Dan Budnitz, Erin Krebs, and Jody Green.

DR. BUDNITZ: Yeah, it's Dan Budnitz. I'll simply summarize. We've used in our program means analyses when we had to, ITS when we could. I mean, it's basically the same idea that we usually don't have enough data points to do an ITS. But when we do, we prefer it.

DR. KREBS: Erin Krebs. And I don't know what

else I can add to all that. But you know, everything we've talked about today suggests that, really, what you are going to have to do is sort of qualitatively synthesize findings from multiple studies to try to understand the big picture. And there's not going to be any one method that's going to be effective for that. It'll be hard to make any real strong conclusions from any one study, I suspect, given what we know about all the assumptions that would have to be made in any design.

DR. GREEN: Jody Green. I guess maybe this adds to the list of problems. But the other issue we have is that, really -- let's be honest -- there's only one product left that actually has a pre-period of having a product on the market without an abuse-deterrent formulation. And now we have all the new products that'll be coming out that there is no pre-period. So while these methods might be appropriate for one product, they're not going to be for the rest of the products that are coming out.

So I'm not sure if that's later in the discussion or if that's tomorrow, alternative methods

of evaluating.

DR. MCANINCH: If you have -- I think that's, like, Question number 3. But if you have thoughts about different design approaches for products that don't have a non-abuse-deterrent precursor, that's something we'd be very interested in discussing.

DR. GREEN: In Question -- on Question 3?

DR. MCANINCH: You can discuss it now if it's in the forefront of your mind.

DR. GREEN: Well, I think it goes back to having a better definition to a meaningful reduction in abuse. And meaningful reduction in abuse can mean a whole lot of different things, and I think there's the meaningful reduction in abuse of the prescription products. I also have seen the introduction of adding heroin as comparators or other illicit products, which complicates, I think, things a little bit more. And I'd like to understand more about how that fits into kind of the scope of monitoring these products in the legitimate population, to Dr. Schnoll's point. But that's very different than looking at the recreational users.

But really, I mean, I think it's better definitions of meaningful reduction and then also in those comparators because you can certainly have that baseline prior to introduction of the new product if you can find that appropriate comparator and does it have an impact on that. And then we'll have to talk about confounders and how do you adjust for the other interventions, the PDMPs and all the policy -- and the changing market outside of just that new product, both the pharmaceutical and the illicit products.

So probably -- I'm not sure that's a solution. But my recommendation, anyway, would be to get at a better definition of meaningful reduction because I'm not sure that we get a good sense, as scientists, what that means and how to do it.

And also, it just says an abuse. And so does that mean abuse is the primary and we're not looking at misuse, addiction, overdose, and death? And so what -- you know, what really is that meaningful reduction's definition?

DR. MCANINCH: I think using abuse is being used generally to represent the particular outcome that

you're looking at, so maybe abuse by a specific route or other related outcomes.

MS. FERGUSON: Okay. We have Leland McClure, then Almut Winterstein.

DR. MCCLURE: When I think of hypothesis tools and I see analysis of means, the first thing that jumps to my mind is that you've got a parametric or bell-shaped population curve that's there. And that may not necessarily be the case on there. You may have something that's skewed in terms of the population in the occurrences or the frequency that's there.

Have you given thoughts to non-parametric analysis of medians tools, also? Analysis of means could skew the data if it's not bell-shaped distribution on there. And you might not get the most accurate answer that's on there. Non-parametric analysis tools for the hypothesis testing would probably give it a little bit more of a robust analysis on there. Just a comment.

DR. XIE: That's a very good point. I think the reason you mentioned, the parametric assumption, does not only apply to the mean analysis, but also the

interrupted time series as well. So do you think there is any remedy for interrupted time series?

DR. MCCLURE: I think it would depend upon the data. You really need to do normality analysis on there and then apply the appropriate tool on there, whether it's analysis of medians or means. You know, you can't transform data so that it fits a means model, but then you have to be able to back-transform that into what I would view as data that a layperson can understand into, you know, practical units of measure that are there.

DR. XIE: Thank you.

MS. FERGUSON: Dr. Winterstein?

DR. WINTERSTEIN: Yes, Dr. Staffa challenged me now. But I had a similar idea as Dr. Green. I think that, you know, there may be enough experience now for comparative safety approaches instead of time series. So essentially, thinking about the analogies of comparative effectiveness approaches of a new drug that comes on the market, you know, they are -- you could do, you know, time varying propensity score adjustment chunks of moving forward to see how abuse

starts to change with a new drug that comes on the market relative to everything else that is already on the market. And that might be a less biased approach.

Obviously, the bias is different. Now we have confounding. Before, we have time as a confounder, and now we have patient characteristics as a top confounder. Maybe they could be seen as complementary approaches. But I mean, I -- last time I started to think about this, this was my solution to this, that there is enough data now if you use more recent data sets to start to look.

DR. XIE: All right. I think it's time for us to move to the next question. "How can we overcome some of the challenges associated with using comparators to approximate the counterfactual in ecologic time series study?"

DR. DASGUPTA: I really like this question, and I'm glad you guys asked it. And I see Dr. Meyer --

DR. STAFFA: This is Dr. Dasgupta --

DR. DASGUPTA: Oh, sorry.

DR. STAFFA: -- speaking.

DR. DASGUPTA: Sorry. I'm bad at that.

And I see Dr. Meyer is going to talk about individual -- applying the counterfactual framework to an individual level tomorrow.

But you know, when we -- when you think of -- I mean, the choice of comparators has really been what's the API; was it ER or IR formulation; what's the sales volume, those three kind of dimensions are basically what has driven all the decisions.

When you put into a counterfactual framework, right, if you start at the individual level, like, why is this patient getting an ADF and what is the, you know, propensity for getting the outcome, right, so then you know what the confounders are there. And it's going to be kind of baseline characteristics of that individual, right? So when you extrapolate that to the community level, as you've articulated, it gets really confusing, right?

So what we are basically trying to say is, like, why would a community have higher rates of ADF dispensing than kind of -- you know, than other through the ZIP codes that wouldn't, right, if you have ADF exposures, the exposure, and any of your abuse outcomes

as the outcome, right?

So within that counterfactual framework then, the -- on an individual level, you would want to compare -- you would not -- you would want to compare their base -- the individual patient's baseline risk, right? So if you -- so in that sense, maybe we don't -- we shouldn't be starting with APIs but starting with individual patient risk. When -- I think that's obvious on the individual level.

So this kind of gets back to my earlier comment about -- and this is what drove that line of inquiry, was that if you have certain communities where ADFs are much more prevalent as a market share, there is something fundamental happening in those communities, which could also be driving the abuse outcomes. And I think there -- and one example I can think about off the top of my head is, in Maine and a few other states, there is financial parity and -- there's a financial parity law where ADFs have to be priced the same as non-ADFs.

And so there are places where we can start to examine what geographic-level characteristics might be

influencing ADF prescribing and outcomes, which would then give us a better idea of what the correct confounders should be -- I mean comparators should be.

I know that's a lot, but I'm happy to draw it out or talk about it more detail if you'd like.

DR. MCANINCH: Yeah, I guess I'm having a little bit of trouble understanding how that would drive our choices of comparators in a time series type -- you know, the aggregate-type analyses that we typically are seeing.

DR. DASGUPTA: Yeah, I think it's tough. You know, if -- maybe the comparator bucket isn't all ER opioids or isn't all of one API, but maybe it's some subset of those patients. So it may be there is some weighting. You know, if we know what the individual characteristics are of patients getting each different opioid and we know what the community-level exposure is to those as well, then there could be a way to weigh that exposure based on an individual-level observation at a community level where you're not just using one API or one class as a comparator but using a similar risk pool.

Does that -- I can elaborate more on that offline. But …

DR. MCANINCH: If there -- are there any other comments on comparators and choosing comparators and how useful they are to, you know, approximate the counterfactual in these kinds of time series analyses? No? Okay. All right.

DR. XIE: So the third question is, "What are some potential alternative analytic approaches to evaluate the effect of an ADF using the currently available data sources, particularly for products without a recent non-ADF precursor?"

DR. SCHNOLL: Sid Schnoll. I think I suggested it before. And looking at a patient population in a prospective way, you can do, you know, almost a double-blind kind of study offering them an ADF or non-ADF, similar API, following them over time, seeing what happens, and then looking at that in relation to more broad epidemiologic data to see what's going on. Are there similar changes? If not, why? Begin to look at it.

Again, you're looking at two separate

populations, which is of concern. But in fact, if there are general changes that are occurring because of the formulation, I think you will see it.

DR. MCANINCH: Okay. And I think tomorrow we'll have more discussion on that type of a study. But of course we aren't only interested in patients that are prescribed the medications. So you know, we are interested in, you know, reducing adverse outcomes and reducing abuse related to diverted drug and drugs that are, you know, available in the community that aren't necessarily prescribed to a patient.

And so that -- you know, assembling that type of a cohort isn't going to get you that, and it's --

DR. SCHNOLL: Well, what I'm saying is you need two parallel things going on. One is looking at people to whom the drug was prescribed. And the other is then looking at the broader epidemiologic studies that would encompass the group to which the drug was not prescribed and see what's going on.

But I'll, you know, get back to what I said very early in the meeting. I'm not sure that we should be looking at all these very general things about abuse

because these drugs were designed to do very specific things. And when you try to look at everything that may be going on, it's problematic.

And I think, you know, what we've seen to some extent now, which we really have to address in another way, is the fact that what we've been doing in terms of ADFs, PDMP, some of the education, some of the CDC guidelines, those who are abusers are now using illicit heroin, illicit fentanyl. So we have, in effect, driven those people who want to abuse drugs in a different direction, and that's a big problem. But it might, hence, generally show the ADFs are working, but we have unfortunate consequences to the fact they're working. And we need -- we can't think of the ADF as solving that. We have to look at other approaches.

MS. FERGUSON: Captain Budnitz, did you …

DR. BUDNITZ: Yeah. Dan Budnitz. I'm trying to think of approaches when you don't have a, you know, non-ADF precursor. And I mean, this is kind of simplistic but -- and challenging because the market penetration, the ADF is so low. But as it increases, you know, you can look at the rates of change of your

outcome as the rate of ADF penetration increases. Now, that's more of a hypothetical because we have such low rates of use right now, but that might be an approach if you don't have a precursor.

DR. LO RE: This is Vincent Lo Re. I like -- actually, I want to endorse Dr. Winterstein's idea of taking a comparative safety approach, which I think actually might make sense here, and focusing on only those who are prescribed the drug because I think this is going to be challenging in settings where you don't have people who are prescribed the drug.

But assuming that you had appropriate data sources, assuming that you had validated outcomes of interest, perhaps drug overdose or even death, you know, I think may -- you know, perhaps comparing ADFs to non-ADFs potentially in the same class following new initiators over time for incident, even death, and comparing relevant incidences of those over time may be of value. And it was discussed about the development of propensity scores. Certainly, people who get ADFs may be different from people who don't get ADFs in a way that may relate to outcomes of interest.

So developing propensity scores at the time of initial prescription and potentially even, you know, over each month a follow-up, for example, maybe even developing some kind of marginal structural model approach may be alternative approaches, again, assuming that you had the appropriate data sources with validated outcomes. That might be -- I recognize that doesn't address changes over time pre versus post, but it would give you some ability to compare the relative incidences and important endpoints across the different ADF versus non-ADF drugs.

DR. MCCLURE: Following up, I think, with that comment, also, where you look at comparisons of the pre and the post, you probably need to look at probably pharmacy trends, also, because of the co-presence of fentanyl and heroin that may be add-mixed with those drugs in combination on that. So you need to look at those confounding factors, also, and look at those, the pre and the post, also, as well.

DR. KREBS: And this may be entirely hypothetical. This is Erin Krebs. But another pre-post situation you could look for, if it existed, would

be a situation in which a payer or a health system or someone else substituted some sort of new product in for a previous non-ADF product or, you know, that kind of change where there -- you -- there could be a comparison between different payers or different geographic areas, or something like that. Now, I don't know if that would actually have to exist in order to analyze such a thing. But …

DR. MCANINCH: So are you referring to something like a change in the formulary or …

DR. KREBS: Exactly.

DR. MCANINCH: Yeah.

DR. KREBS: Yeah.

DR. MCANINCH: That's an interesting thought. Pardon me.

I like all of these ideas. You know, we are very limited by the fact that, typically, in, you know, electronic healthcare data and claims data, we can't get at those very outcomes that we're most interested in looking at, which is the -- as Dr. Schnoll said, the route of abuse. You know, are you changing or reducing snorting and injecting? And those things are not maybe

captured in healthcare data. And so we turn to these other kind of nonconventional or different sources, and they bring with them a host of different challenges.

DR. STAFFA: This is Judy Staffa. I wanted to just ask a question. On this patient-based approach model, I'm trying to understand. So if we start with patients prescribed these products, right, but remembering that the product is not going to stop someone from becoming addicted -- it's not going to stop someone from, perhaps, moving into an abuse mode. But the idea is we're supposed to be trying to stop them from moving into snorting or injecting, non-oral routes, say. I don't know how long that takes for a patient to get to that point. I'm not sure any of us really understands the natural history of that, but we hear lots of anecdotal information of folks at our meetings that come to the microphone and tell us tragic stories about how they started with a simple prescription that was prescribed to them and, years later, they ended up, you know, injecting heroin.

So this implies we'd be studying these patients for a very, very, very long time. But I'm not

quite sure. Are we actually going to be getting at the question -- again, the target of these products, which is this non-oral abuse, this kind of toward well advanced? That's what I'm imaging, is that it's well-advanced abuse. People who are continuing to take products orally and taking more than they should because they have developed a tolerance or have become dependent, these products we know are not going to touch that.

So I'm trying to understand that patient-based model. I understand that it's a key piece, but is it enough? Are we missing the other piece of this? I mean, I know it's the harder piece. But are we really going to get -- if we have those kind of studies, are we really going to be happy with those answers? Are we really going to get robust answers about how well these formulations work?

I'm just throwing that out there to provoke you.

DR. BUDNITZ: So this is Dan Budnitz. I -- so I think the key question that one has to ask then is what is the incidence of this type of insufflation and

injection abuse and what is the effectiveness of the abuse-deterrent formulation. And we have to start with those questions and then power our study. And we might find that it's an impossible study and an impossibly long study to make it worthwhile. I think those are the -- those kind of assumptions need to be the first step and (inaudible) in the incidence of this specific type of abuse of interest.

MS. FERGUSON: Winterstein?

DR. WINTERSTEIN: Yeah, that's a challenge. So every time we have a patient that will have an exposure, we're relying on claims data or EHR data. I get we cannot measure that type of abuse in those data unless we had a good number of resources and constructed a study where we actually pull -- follow up or pull charts.

So I think it's fair to assume that a substance use diagnosis -- that somebody who would abuse inter-nasally or IV would also have a substance use diagnosis at that point. So if the endpoint in a claims data set, assuming sensitivity -- but assuming that the endpoint in a claims data set would be

substance use diagnosis and that would then be supplemented with an additional chart review that tries to ascertain the information of how the drug is being used, that might get to this.

Another way would be to try to link the data that we have on abuse like from treatment centers to see whether that can be pulled together. But this is the general challenge, right? That's -- the exposure information that we have in claims data is not linked to abuse information that we have from surveys.

DR. CRANE: Okay. Elizabeth Crane. Based on experience with the Drug Abuse Warning Network, the route of administration was not always included, but it was in there more than you might think, not enough to produce estimates. And it was primarily there to help us identify inhalants.

But we wondered, you know, why are we -- why is it always -- it was usually things like injection and smoking of drugs. And we realized, well, probably it's because if somebody's taking an oral medication orally they don't bother to note it in the record. But if they're using it in an unusual way like injecting it

or snorting it or something, you know, it would be more likely to be documented.

Now, we never compared the route of administration, you know, by different types of drugs. It might have -- it would have been interesting to look at the opioids. But I think one of the things that were -- this is the kind of information that we're hoping to get out of the clinical notes that we hope will be submitted to the National Hospital Care Survey, which I'm guessing we'll talk about maybe tomorrow.

Again, it depends on how much people write in the notes and if we can get them. But that was where were getting the rich information from DAWN was what was being documented in the chart.

DR. LO RE: I feel like the question that we were asked here was more focused on what you had sort of clarified as the outcomes of interest -- death, addiction, overdose. But the questions that you're referring to, you know, sort of when did an ADF -- when did the patient decide that they wanted to switch to an abuse -- you know, crushing it, insufflating. I think those are the only kinds -- I don't think you're going

to get that in a retrospective. I think that's the kind of thing -- those are the kinds of specific questions that you're really only going to be able to ask patients prospectively.

I think that would be -- you know, if you're really interested in understanding more of the behaviors and the biology of what's going on, I think, you know, prospective studies where, you know, like I said -- I mentioned before about using a CASI and questioning patients over time about behaviors for the different ADFs, particularly the persons who are prescribed would be valuable.

But I think from the standpoint of if you're interested simply in what are the incidences or rates of, you know, overdoses or death, you know, harder outcomes than potentially using electronic health data, you may be able to get at some of those questions. But I think it really comes down to, you know, what are the key questions and then, obviously, designing, you know, the studies differently based on what the Agency thinks are the key questions. But I think they're different questions structurally.

DR. LEVENSON: This is Mark Levenson. We're going to have a session at the end of the day to follow up some ideas. And tomorrow we're going to have a session both on cohort studies and linking data sets. So a lot of these ideas we'll have opportunities to discuss tomorrow.

But I'd like to maybe focus this question, if we can, on this numerator-only data. Are there analytical approaches for the data sets that were introduced by Cyndy in the first talk of the day, the treatment center data or the poison center data? I mean, I find the propensity scores with the time-varying population very interesting. Do people feel those could be applied to this numerator-only data? What might be some of the complications, or how might we overcome them?

DR. NOVAK: This is Scott Novak. You know, a lot of those advanced causal inference statistical procedures like having (ph) selection models and propensity score modeling are built on really rigorous assumptions. And sometimes you run into, you know, low cell sizes with the off diagonal. And sometimes I

think that there's not enough emphasis placed on sort of testing for balance, and that's really the key thing. And there's been a lot of really interesting development on, you know, really, the misuse of propensity rather than sort of the appropriate use of them.

So you know, I mean, I think a lot of people think, like, oh, yeah, you know, it's a tool and it's great, and, you know, they use it for all situations. But it's really limited. And unfortunately, in terms of, you know, some of the questions that we have with ADF and the low uptake, you may not get the appropriate power to use those techniques and especially when you're dealing with a lot of different effect modifiers that might be of interest to you.

DR. XIE: We have the last question. "What can we reasonably infer from aggregate changes in abuse rates about an ADF's effect on the risk of abuse for an individual exposed to the product?" And the same question for the abuse via a specific route.

DR. STAFFA: This is Judy Staffa. So this is about where we are. This is what we're seeing, are

these aggregate ecologic studies.

And so I guess we need to understand if you guys have thoughts on that, on what do we do with that. Is that -- I mean, that's what we've got right now. So we'll talk tomorrow about what we can do better in the future, but this has got to be about what can we do with what we have now and what are your thoughts on that.

DR. CRANE: Could you tell us if we have -- if it's our turn to talk?

(Laughter.)

DR. CRANE: Because I'm having a little trouble --

UNIDENTIFIED FEMALE SPEAKER: Okay.

DR. CRANE: -- reading.

UNIDENTIFIED FEMALE SPEAKER: Okay.

DR. CRANE: This is going to sound a little facetious. But I would go to Dan, and I would have him talk to the folks he works with and tell them if they want any of these products because, you know, we heard a lot with OxyContin after the reformulation it's just street value. You know, people weren't that interested

in it. And it may have resurged. They may have found other ways to use it. But is it appealing to people? I mean, we -- I know that these are very small numbers and they're not out there that much, but that would be one way of getting a very superficial sense of, you know, if it's having the effect on a certain population.

DR. CICCARONE: Yeah, I'm still reserving some thoughts for the appropriate time of the meeting. But I would say for now we -- you know, one thing to -- we would like to assume that, moving forward, that the ADFs work. So what we're looking for is we're looking for the exception, right? We're looking for the one that sneaks through that is a weak ADF or there's some manipulable (sic) quality to it.

So I'll just throw that out as sort of my own provocation here. And that is I'd like to assume going forward that for this -- well, I'm sorry; I -- this is really Question number 3 -- that for the basket of meds that are coming out now that don't have any pre-data, that they work, that we actually don't see. So we're looking for blips on the radar screen. So this is sort

of a different model, and we can talk about what looking at -- picking up blips would look like moving forward.

DR. XIE: All right. Dr. Winterstein?

DR. WINTERSTEIN: I guess I have a question again. You know, when you -- when we approve a drug for hypertension, we typically don't know whether that drug will work for a given patient, right? So I mean, typically, approval decisions and regulatory decision-making is not on the patient level. It's made on the population level.

Is there something else that I --

DR. MCANINCH: Right. I think if --

DR. WINTERSTEIN: -- don't get from that question that …

DR. MCANINCH: If we -- I'll carry that hypertension example out. You know, I don't think that we would make regulatory decisions based on a study that shows that the rate of hypertension in the population before this drug was approved was, what, 25 percent and then, after the drug was approved, the rate of hypertension just in the general population was 17

percent.

And that's kind of what we have here. That's kind of what we're doing with these studies, so, you know, looking at these aggregate rates in the population before and after, you know, a drug was approved. But you don't necessarily -- you know, you don't have that -- the exposure and outcome level data in the same individual, linked to the same individual.

So I guess, you know, the purpose of the question here was just sort of to ask, you know, are we answering the question that we're trying to answer using these kinds of, you know, ecologic time series, aggregate study designs. So we'd just be interested in getting the panel's thoughts on that. But …

DR. STAFFA: Right. Or -- this is Judy Staffa. Or do we need to go to a model where we actually show that a patient who gets to a point where they were going to snort or inject this drug does not do that because of this formulation or someone who is snorting and injecting stops because of this formulation?

DR. THROCKMORTON: Well, or Judy --

DR. STAFFA: See the difference?

DR. THROCKMORTON: Or Judy, Dan's got it right that these data tell us enough that we can conclude that in -- that these products begin with an assumption of efficacy. So I mean, that's sort of Bayesian, or whatever -- tell me what the right words are -- approach.

You could conclude that. You're drawing on a broad set of background. It is not the hypertension model. I did hypertension drugs. Hypertension drugs don't always work -- don't even always work as a -- for (inaudible) populations, so we can't use that as a comparator here. But does the trend data give us enough assurance that -- you know, that you can begin with a preconception that there is plausibility that the products are going to work based on the Tiers 1 through 3 plus the available information across classes of compounds? I don't know the answer, but that does turn all of this on its head.

Then you're worried not -- you're worried about the blips, Dan. I don't know what your -- that was a good word. You're worried about the products

that have safety considerations that make them unattractive. You're worried about things that suggest they would not work because they looked fundamentally different than the other products.

DR. XIE: Dr. Lo Re?

DR. LO RE: So I'm just curious then. I mean, why doesn't the Agency then push more for randomized studies of ADF versus non-ADFs and look over some period of time for all of the five outcomes of interest?

DR. LEVENSON: Okay. Well, I'm not -- Mark Levenson. I'm not prepared to speak completely for the Agency. But I think it's probably a question of power, that, you know, for a patient population, the event rates are rather low that require very large studies to answer these questions.

There may be other complications as well if anyone wants to add to that.

DR. UNICK: So just speaking about the illicit market, users are out there -- Jay Unick. For the illicit market, users are out there figuring this stuff out all the time, and they are working very hard to

defeat these mechanisms, given available supply. And so when it shows up in large quantities in communities of injection drug users, which are -- I -- you know, you can find them in needle exchange or other locations like this.

So they know what's working and what's not working. We don't have -- we just have to find them. And they show up in various places, whether it's hospitals for overdoses or needle exchange or even treatment sites. But you have to ask the questions specifically about what they're using and how they defeat these mechanisms, and then that gives you the blips. That's what our recent experience certainly tells us.

DR. SCHNOLL: Sid Schnoll. I mean, it almost sounds like you're trying to see if the needle moves on abuse and addiction in general. And that's a hard thing to do. And you know, certainly, what I've seen now in my 50 years of doing this, that you put something that blocks one drug either as at the source or something else, and it shifts. The whole problem shifts to another drug that's more available. And it

doesn't necessarily have to be in the same class. It can be another class.

And we see these patterns. If you look over the past 50 years, there's stimulant, then there's depressant, then there's stimulant, depressant. These patterns have been persistent for a long period of time. And you know, in the overall abuse and addiction area, it's very hard to move that needle. And I agree what was said earlier, that one of the places where you might be able to get some information about the abuser population is syringe exchange programs, other programs that are dealing with harm reduction where you can ask some questions and get some data, you know, whether those data are biased in some way based on what's going on in a specific area. But at least you're getting some data on that.

And in the patient population, certainly you're aware of the development of the Prescription Opioid Misuse Abuse Questionnaire, the POMAQ. And we're looking at validation of that instrument. But that, hopefully, if it's validated, could be an instrument that's used with the patient population, and

maybe some variation could be used with the non-patient population.

But I'm just concerned about the idea of moving the needle on drug abuse in general. That's a heavy needle to move, and you need a lot of power. And I don't think you're going to move it.

DR. BUDNITZ: Dan Budnitz, CDC. I guess I was going to, I think, second that thought that -- to try to change all outcomes of overdose and death across both patients and non-patients might be a lot to ask for these products. And then to -- but to focus on the issue -- the effectiveness in preventing insufflation and injection, it might be too rare of occurrence over too long a term to really have a study that demonstrates effectiveness there.

So then we got to this point of, you know, looking for blips, essentially safety signals. But that turns this whole paradigm on its head. Now we're not looking for effectiveness. Now we're doing, you know, post-marketing safety surveillance, and a lot of folks here have a lot of experience in post-marketing safety surveillance. And that's with outbreak

detection. It's with the Medwatch reports. It's with, you know, a whole different set of tools. And it's a totally different question.

And so I think this, you know, presumption of effectiveness, you know, turns everything upside down. But I don't know if we have -- you know, I guess we have these Phase I, II, III type studies, but we don't -- I don't know the Phase IV studies. But I'm not, you know, integrally involved in this field. So I don't know.

DR. XIE: All right. I think we move on to the audience participation. So please try to focus on -- your comments on this session's topic, which is causal inference and control for confounding.

You will be given three minutes to talk. A light system will keep time and notify you when it's time to hurry up, when the yellow light is on, and when to stop, when the red light is on.

So audience, please -- before you start, please provide your name, state your disclosure, and provide your comments.

Thank you.

DR. BUTLER: Hi. It's Steve Butler again from Inflexxion. I'm like a frequent flyer at an ER room.

(Laughter.)

DR. BUTLER: Just a couple of comments here, and maybe this is -- reflects some of my misunderstanding about the -- you know, how the claims work for the different categories. But you know, to come up with a sort of permanent claim, it seems like that could be difficult, especially for new products or products that don't have a pre-version and any product that has low prescription availability because that's going to be the obvious explanation for low -- you know, low rates of abuse.

And what we've found in looking at substance abuse treatment centers is kind of what's -- people have started talking about, these blips. We start seeing the blips almost right away just here and there. It might be one for one month and one for another month. And then -- and we've seen this over and over again for drugs like Zohydro and Nycynta, even Exalgo. It's been on the market for a while.

So it's -- maybe this is ridiculous, but it

seems to me there's -- you know, to give the manufacturers something like a temporary or, you know, pending category for rating that could be removed if a drug was, you know, starting to look like it was going to be a problem.

The other thing might be to look at some of these data that we have in terms of whether there's a -- we haven't done this yet -- but in terms of whether there's a kind of pattern of abuse as the prescription availability gets larger because that's what we're really interested in, is does -- if the prescriptions start to really go up, then do we really have some kind of problem that we didn't expect. So we want to know is this ADF going to create a problem.

And the only -- the -- my last comment is about the route of administration aspect of all of this. One of the things we've found is that it's good if you have few abuse cases. But if you have few abuse cases, then you don't have sufficient power to come up with a stable sort of route of administration profile. So you can see how people are using it, but you have such wide confidence intervals that you can't be

confident that what seems to be a low injection rate, for instance, is, in fact, low.

So I think I've used my time. Thank you.

DR. COPLAN: Thank you. Paul Coplan from Purdue. I share Dr. Butler's comment about being a frequent flyer. I apologize about that.

So a couple of points, firstly about ITS versus means analysis. So Dr. Degenhardt's data from Australia shows that the -- there's an inherent difference in the abuse rate of a product that's visible relatively quickly that's inherent in the risk of abuse of that product.

With the interrupted time series analysis that may go for five years, what's being measured then is whether there's an interaction between the abuse-deterrent formulation and secular interventions, other interventions. And there's no reason to expect that an abuse-deterrent formulation would continue to have an increasing effect over time. It inherently has a different rate of abuse, and that's picked up over -- in this relatively short period of time as long it's had -- the product has had time to work through the

system.

If we start to look at trends over time for five years, it's confounded by a lot of other secular trends. And then the ability to tease out secular trends from the abuse-deterrent formulations effect gets weaker and weaker. And then it's all about this question of interaction of the abuse-deterrent formulation and the secular trends.

In terms of the Bayesian model that Dr. Throckmorton mentioned, we think that's a very -- that would be a very helpful approach to -- because if we -- we can either look at each study individually and use a frequentist approach and determine does this have a 1 in 20 chance of being explained by chance alone. But if there's been Category 1, Category 2, Category 3 studies in the label, the preclinical work, now we're going to the real-world evidence. Then we have a number of different studies. Each of them has their limitations. But if we accrue them, there's a -- but they all add to the Bayesian prior. And as -- and so the Bayesian prior holds over maybe 15, 20 different studies and different settings in different

environments in different countries and different times. So that Bayesian approach we think is maybe complex but worth looking at.

In terms of differentiating between different interventions, so one of the things that's being plaguing OxyContin is that a huge intervention occurred, which was the Florida pill mill and pill mill legislation and the PDMP. And so the question is what was OxyContin versus what was the Florida pill mill.

And one of the ways of disentangling those is by looking at supply versus demand because the Florida pill mill intervention was essentially a supply. It shut down the pill mills. That's the same thing with PDMPs. They're really shutting down supply.

From economics, we know when the supply goes down the price goes up. The diversion goes up. So for example, when there's -- in Florida when there's bad rains and the orange juice isn't made, the orange is going to rot. The price of orange juice goes up because there's less of it. And it's -- so that -- the supply side interventions increase demand, increase street price.

In contrast, abuse-deterrent formulations are a demand side. They reduce the demand. If they're effective, they would reduce the demand for that product. So a reduction in demand would decrease price of that particular product and decrease diversion. And so the diversion approach becomes a very good way to -- a useful way to disentangle those two.

We can also look at difference in timing. Florida intervention occurred one year later than the OxyContin reformulation. And the first thing we see is the reduction in prescriptions for 80 milligrams, the 80 -- the highest tablet strength of OxyContin, but we see no change for the 10 milligrams. So the high versus the low dose prescriptions becomes a useful way to disentangle these interventions.

DR. XIE: Well, thank you very much for your comments. We have --

DR. COPLAN: Thank you.

DR. XIE: -- one more audience. And then after this we'll go to a break.

DR. MAYNE: Hi. My name is Dr. Tracy Mayne. I'm the head of Medical Affairs Strategic Research at

Purdue and also a board member of the National Pharmaceutical Council.

Perhaps I'm speaking more to a future state. But once there is a single drug, a single opioid that has -- that's established as Category 4 within the label, much of this complexity then disappears. It no longer becomes needing to do more complicated time series when a simple propensity score match compared to a product that has an established rate can then be used for all future products. And I'm thinking with the COX-2s. One no longer had to have other groups involved. One could simply compare to naproxen.

So at least on a go-forward basis, once this is established within the label of a single product, many of these complexities simply go away and you can simply do a product-to-product concurrent comparison.

Thank you.

DR. STAFFA: All right. Well, thank you very much. We're going to take a 15-minute break. And then Mark and I are going to try to wrap up and have a discussion about all the ideas we heard today.

So if we could reconvene at 3:00 o'clock, that

would be great. Thanks.

(Break.)

DR. STAFFA: Okay. So we're down to the home stretch. This is Session 4, and Session 4 is the one Mark and I have gone back in trying to look and understand some of the themes that came out of some of these Sessions 1, 2, and 3. And what we'd like to do is bring up some of these themes and then turn some questions back to you guys about some of the things we've heard, perhaps get a little bit more information. And then we may go back and revisit some of the discussion questions that we didn't quite get to or we didn't quite understand the answers.

So I'm going to start looking back at Session 1. Session 1, if you'll remember, was talking about -- it seems like a long time ago, doesn't it; it was this morning -- talking about the different kinds of data that we have available and what we could do to try to learn more and understand those data better so that we could interpret the results of findings from studies using those data better.

So one of the concepts -- and Dr. Schnoll will

be very happy with me because I did hear this -- that we should be looking at patients and non-patients, and we should be looking at them separately. And I'm interpreting that. If I work that into our framework, then that means we think about formal studies in both of those groups. It seems reasonable. And we talked a fair amount about formal studies in patients, and we've talked a fair amount about formal -- we've talked a little bit about our inability to do formal studies in non-patients because it's rather hard to find them. But the risk factors are different.

And again, I know that this doesn't really relate to the data sources that are available, but I have to ask this question. As I think about this -- and I'll try to explain it again because I don't think I articulated it clearly -- when does a patient become an abuser? Or how do I differentiate these two populations? Because as we know, some patients who go on to snort and inject opioids, some of them start out in other places. They don't all start as patients, right? So those people we understand, I think.

Some people start out as patients, and they

never end up doing any of those behaviors. Some people start out as patients, and they do end up doing those behaviors. So when along that continuum do I stop being a patient and I turn into someone who abuses drugs? Because if you want to separate patients and non-patients, I think you have to understand what that distinction is. And it may just be an area that I'm ignorant of.

And again, this, to me, is teeing up our conversation for tomorrow where we're going to be talking about other kinds of designs. But is that something that folks who study abusers -- and I'm looking at Dan, but I'm looking at everyone -- of folks who study people who abuse these products who perhaps start as patients? Because I'm imagining that this could be a phenomena that would happen over a number of years. This is what we hear anecdotally from people who share their stories with us. It's not something that happens, you know, the day after you get your first prescription.

Erin -- Dr. Krebs?

DR. KREBS: I think it's not patient versus

abuser. It's really what kind of patient population are you talking about. You know, so you have a very different patient population if what you're talking about is someone -- is the patient population with chronic pain treated with long-term opioids. That's a distinct group. And you know, then there are -- if you say a patient is anyone ever treated with opioids, we could be talking about the whole U.S. population because we've so blanketed our society with at least short-term opioid therapy. You know, it would be hard to exclude anyone.

So I think it's more about where you start and how you define your patient population. Obviously, people are moving between these. We've spent some time talking about people who are addiction treatment patients today. But it is, I think, important where you start. What's the starting population? What's the outcome of interest?

If you're starting with a large population of long-term opioid users, the number that will go on to use -- to inject their prescribed opioids is probably so small, but that would have to be an enormous study

that poses its own challenges.

DR. STAFFA: Thank you.

Louisa, did you have a comment?

DR. DEGENHARDT: Sorry. Louisa Degenhardt. I just want to make things a little bit more complicated in that I think it's also --

DR. STAFFA: Thank you for that.

DR. DEGENHARDT: Sorry.

(Laughter.)

DR. DEGENHARDT: Well, I thought I'd start with a bang for my first comment for the day.

But what we've actually found, we've been doing a lot of work with people who use pharmaceutical opioids who are prescribed them and a lot of work with people who use drugs for other reasons, and many of them inject drugs. And actually, a lot of people who inject drugs actually are living with chronic pain. And even when you -- we've done a number of studies, and I might mention things along the meeting -- but looking at people who are also tampering with pharmaceutical opioids. And most of them are actually being prescribed those opioids by a doctor.

And so even this distinction between legitimate -- and I assume the opposite is illegitimate -- patients I think is a very problematic distinction to make because many people who, yes, they may be doing something other than was intended by the company and by the doctor with that pharmaceutical opioid, they nonetheless have significant health problems, including the ones for which opioids are most commonly prescribed.

DR. STAFFA: Dan?

DR. CICCARONE: Thank you, Louisa. That's spot on. I mean, that's -- the population is so -- and the problems are so intertwined that I would say there is no directionality here. There's no life course. People can fall into dependency pattern from a multiple -- multitude of ways. And there's a lot of chronic -- if not chronic pain, a lot of chronic suffering in the marginalized world of highly addicted folks who are finding -- you know, who are looking for relief in any way they can.

I do want to throw the ball to Jay -- Dr. Unick, who's a little reluctant here, just to briefly

describe a paper that's now five years old looking at the intertwining of the population -- of these two populations that we've tried to make separate or tried to have a linear trend between pill users to heroin users. And he's really problematized that quite a bit.

So are you going to pick up the ball, Jay?

DR. UNICK: Yes. Thank you for putting me on the spot.

Yeah, so these are not distinct problems. These are intertwined problems. Communities that have high levels of prescription opioid overdoses have corresponding high levels of heroin overdoses. And the vice versa is true. I've recently done a more recent analysis using death data. That was with hospitalization. We find the same thing with death data, too.

So these -- you know, despite the fact that it's difficult to pull apart, I would say you have some advantages and that you have some specific questions around the value of abuse-deterrent formulations with regard to injection or snorting. So in that case, you know, that's a pretty discreet event.

And if you can find populations that are using drugs like that, then you have some information about that versus this intertwining of where, you know, somebody that's been using opioids and escalating use, I don't know how to distinguish that from addiction after several years. It's -- there's not really a there there, I don't think.

DR. STAFFA: Dr. Kreiner?

DR. KREINER: So we've studied using prescription data patient trajectories over a three-year period for patients who hit at some point one of the risk indicator thresholds around opioids. And well, so it's -- so it complicates things, but actually, very consistent patterns where the majority of -- for the majority of patients, it's a one-time or very infrequent occurrence over a 36-month period.

There's another group that's for -- virtually all of them are hitting the indicator threshold every month over 36 months. And then there's a group that steadily increases, and there's a group that steadily decreases. Some of them, perhaps, are overdosing or dying. But it's a consistent pattern across three very

different states, even the proportion of patients that fall into these three groups.

So I mean, clearly, the -- it's a heterogeneous group, but sort of teasing out systematic patterns like that may be helpful. And I mean, these are patients, only some of whom, I imagine, are -- might be addicted, most of whom don't seem to be, based on the prescription pattern. But again, we don't have data on other sources of opioids they may be getting.

DR. STAFFA: Dan, did you have a comment?

DR. BUDNITZ: Sure. Dan Budnitz.

Maybe I'm missing something, but I think the question isn't whether someone's ever a patient. The question is whether they were a patient that were prescribed this abuse-deterrent opioid, right? And so it seems like that's a pretty definable population using, like, an insurance company data or some administrative data. You could define that group. And then you have a group of folks that were not prescribed opioid -- that particular opioid.

So it's not really are they, you know, dependent or abusers. Or -- it's just a question of

were they prescribed this opioid in this time frame, a reasonable, you know, time frame, before which they had the event of interest, whether it's an ED visit for opioids or whether a self-described abuse. Or -- I don't know exactly how to do that, but I can, you know, imagine an ED visit for an opioid overdose or a death, or something like that.

So maybe -- I guess I'm a little confused about is it that hard to identify who is a "patient," meaning a patient who was prescribed this particular long-acting deterrent …

DR. STAFFA: I guess my -- what I was trying to get at was if I am prescribed an abuse-deterrent opioid and I am a patient and I'm being treated for pain and I'm given that opioid because the premise is that these opioids -- these formulations are no different for a patient who is not trying to crush them or snort them or dissolve them and inject them. They're simply taking them for pain. There should be no difference.

So how -- my question is how long do I have to follow that patient because some of the -- what we're

trying to get at is, if I have that drug in my medicine cabinet, it may be my teenage son who's actually going to try to crush it, not me.

Do you follow me? So that's where I'm having a hard time with the linear trajectory from the patient who is prescribed this product down the road to find out how it influences the route of abuse and then the consequences of that route of abuse.

DR. BUDNITZ: This is Dan Budnitz again. So I think I was just thinking about the patient-level studies where you follow a -- what happens to that patient once they are prescribed and then they have to be continue to be prescribed until they have that outcome. But then where it's a patient's family member, then I think you're stuck with these ecologic studies.

And I don't know if I have another suggestion above that.

DR. STAFFA: Dr. Schnoll?

DR. SCHNOLL: Yeah. Sid Schnoll. I think you hit on it, Dan. I guess I've been concerned over the years that the public narrative, unfortunately, has

been Sally was a cheerleader, straight As in school, everybody loved her, she sprained her ankle in a cheerleading event, was prescribed a hydrocodone product, and six weeks later she was turning tricks in a neighborhood.

I -- you know, I think there are examples of that, but it's such a rare event. And yet that's what gets into the press. That's what people believe is the trajectory if somebody is prescribed these medications, that they are automatically going to become an addict. And that's not the case. I mean, I treated people on opioids for 15 years who never accelerated to anything else. In fact, over time, they would often cut their dose and go off.

So it's -- that narrative is not the -- not reality, but the press likes these anecdotes. And I've been in advisory committee meetings where people have gotten up and shown pictures of their children. And I've been in tears listening to the story. It's horrible. Nobody wants that to happen. But we have to let the data drive what's going on. And again, when we look at it, those are really rare events in terms of

people who are prescribed the drug.

Now, your story about somebody then going into the medicine cabinet, that has to do with a lot of things. We haven't talked -- well, it did come up. The insurance industry a little bit did come up. But I would prescribe for a patient, and I would start off with the CDC guidelines before they were even out prescribing just a week's supply of the drug. And the patients would come back, and they'd say I can get a month's supply of the drug for the same co-pay. And for a patient who's on fixed income, that's an important event. So if I'm prescribing it once a week, they're paying the same co-pay every week that they would pay for a month's supply of the medication.

These drugs are often, as has been pointed out, in Tier 2 or 3, so it's higher cost. There are lots of problems, and I think we've got to get the insurance industry involved in understanding this. That's why people have extra drug in their cabinet. You know, I paid for it. I'm not going to throw that away. I may need it someday.

But we have to talk to people about proper

storage, proper disposal. There's a lot that has to be done in a more public narrative that it's not being effectively done now.

DR. STAFFA: Okay. Oh. Dr. Compton?

DR. COMPTON: Yeah. Wilson Compton.

Judy, you brought up a really interesting concept, which was, you know, trying to distinguish patients from non-patients, or two different types of patients.

DR. STAFFA: Well, actually, you guys brought that up. I'm just --

DR. COMPTON: Okay.

(Laughter.)

DR. STAFFA: -- mirroring it back to you.

(Laughter.)

DR. COMPTON: You mirrored it back to us. But I -- it made me -- as I was sitting here, I was thinking, well, have we tried sort of taking the other approach, which is, instead of following the people, how about following the pills. And I'm not sure whether that's feasible. There are certainly studies of post-surgery of how many pills people have left

over. But have we done that with the ADF formulations? In other words, tracked what happens to the prescriptions to understand how frequently they end up being misused so that, instead of thinking from a person-oriented perspective, think from a pill-oriented perspective.

DR. STAFFA: Anybody have thoughts on that? I mean, it raises to me the comments that -- again, that was another thing on my list of what Dr. Boyer discussed this morning of this taggant technology. And it was raised, and I look at it as a method potentially for influencing misclassification because, regardless of what someone might self-report in treatment center or poison control data, if you had this technology that allowed someone to objectively determine which product it was that was used, that would get around that issue.

And I'm wondering. When we approve a product for an oral administration, all the excipients in the tablet, obviously, are tested for safety. That's routine. But it's not necessarily tested for other routes, what would happen if it was injected or snorted -- that's -- because that's not how it's

therapeutically intended.

But if we assume that we could do something like that, how do you see this working? Is this -- you had mentioned this was something that would be excreted in the urine. So would that imply that if we were able to have this kind of technology and be able to link that to people coming in for treatment or people being assessed in emergency room for overdoses or for adverse events having to do with opioids, would that be a way to avoid this misclassification issue to actually know specifically at least whether this was an abuse-deterrent formulation of a product?

So I'm asking you to take one step further and think about the idea you threw out there this morning.

DR. BOYER: Yeah, and you kept looking at me. This Ed Boyer. You kept looking at me, so I assume I was supposed to speak.

(Laughter.)

DR. BOYER: Social cues are intact.

So yeah, I mean, conceivably, it could. You know, like, the present reality -- I mean, what we're doing now is using radiofrequency emitter-tagged pills

so we know, you know, like, not only when people are taking them and where they're taking them, but also which pill they've taken, so -- and then the number of pills. So we -- you know, like, we can get pretty granular in terms of what people are taking and when, at least.

You know, the taggants, I think, for pharmaceuticals is still, you know, like, relatively -- some people -- I know a number of people have thought about it, but it's still relatively in its infancy. I mean, do you use a chiral molecule? Do you use something that cannot be metabolized, something that has minimal metabolism, how easy it is to identify and measure concentrations in the urine, and how valid those concentrations will be for duration or period of time after ingestion? You know, like, those are all things that I think probably deserve greater examination in terms of testing hypotheses.

But yeah, again, the science is not that difficult. It's the science of pharmacokinetics and, you know, like, analytical chemistry, which, you know, truthfully, has been worked out for decades, if not

generations.

DR. STAFFA: Erin, is that you raising your hand?

DR. KREBS: It is. I --

DR. STAFFA: Erin Krebs -- sorry -- for the record.

DR. KREBS: All right. So I guess, you know, so what is the mechanism by which the ERs (ph) are supposed to benefit someone, and who are they supposed to benefit? So it -- are these supposed to benefit the individual patients for whom they're prescribed by somehow interrupting a process by which they move from being an adherent user to someone with an opioid use disorder or, you know, hazardous abuse of a drug?

Or is this supposed to interrupt some sort of societal process with benefit accruing to the population because these drugs are less diverted, less popular for community misuse, for kids in the neighborhood to steal out of medicine -- you know, I -- on some level, I feel like these are kind of what -- we're going around and around. And somehow I'm lacking the clarity on what the pathway is here that we're

trying to interrupt. And therefore, what is the most important population for us to look at, and what are the most important outcomes?

DR. STAFFA: Doug, do you want to clarify -- you were around when this idea came up -- on what the intention is? My gut is telling me it's really both. It's really preventing the ability to -- or dissolve these for anyone who might want to abuse them, whether it's a patient or a non-patient. But …

DR. THROCKMORTON: Yeah, I think we've got to be broad in our goals, right? I mean, at the end of the day, the goals have to be sort of elevated. It can't -- you know, so yes, I'd like to intervene in both of those things. You know, we know less than we'd like to about so many things about what moves an individual from an appropriate use of opioids to either diversion or to a choice to make inappropriate uses of opioids to a substance use disorder, or whatever.

So choosing one of those things, we're going to focus on that thing and sort of, you know, so -- and to the -- to avoiding thinking about some of those. It seems like we don't know enough yet to do that.

So the goal here is to basically make these products as unappealing as possible for abuse, intervening in as many of those steps you think are likely to be successful, recognizing we don't have the data we'd like to. We don't know as much as we'd like to about the natural history of the progression of the disease, the substance use disorder. You guys know that a lot better than I do. There are so many things we'd like to know that we don't.

We have such an enormous public health crisis that we have to aim high, I think, recognizing that, you know, there is a chance that we're going to miss things, that there will be things that'll be -- you know, that we may be doing less than we'd like, or whatever. We may be focusing on some aspects that may not be achieved, but we really have to try to do all of those pieces together, I believe.

DR. STAFFA: Dr. Boyer?

DR. BOYER: You know, we've -- one thing that I think we've kind of left out of the conversation is, you know, the, I guess, psychosocial phenotyping of individuals who are prescribed opioids and the

potential that it can lead to problematic substance use down the road, you know, like, individuals who -- you know, like, I know they're predictors of who has problematic use. But the predictors of who's going to develop problematic use, you know, like, I think are a little bit less robust.

I mean, people who catastrophize, you know, like, minor events as contributing towards problematic use I think needs a better understanding. You know, like, before you can truly just say that, you know, like I said, has -- it's never prescribing, or at least that's not the reality. It may not be the reality, but it's, you know, people who develop a problematic opioid use after therapeutic prescriptions is not the unreality either. I don't know of a single clinician who hasn't seen -- and I'm not saying a few here and there; I'm saying lots of people in my part of the world, at least -- who have gone from a minor injury or a minor surgical event to a short-term opioid course to problematic use and then descended either into drug treatment or into rehab or chronic pain.

So you know, how those processes diverge, how

they originate and then how they diverge is something that not necessarily is in the FDA's domain but something I think we need to pay more attention to.

DR. STAFFA: Okay. Now, many of the topics that you guys brought up, there was a lot of suggestions of different kinds of qualitative data we could look at, and we wanted to get back to those probably in tomorrow's session where we're talking about leveraging data or linking data. So I'm going to kind of hold off on that as well as some of the benchmarking of the treatment centers. I wanted to probe that further tomorrow.

But I did want to ask a couple more questions to get clarity. Along the lines of misclassification, along with this taggant technology, there was also mention of better training of the folks collecting data, whether it's in poison control centers or whether it's in treatment centers, to probe further, to get beyond what just -- what's on the label, again, if there was some idea of recognizing the questions that we really would like to answer with these data.

And I was wondering if some of the folks

around the table could discuss -- does that seem feasible? Does it seem doable to actually -- do you think if we trained folks better who are collecting these data on the front lines that that would be a goal that we could get better data on the specific formulations that are being used? Or is that just a pipe dream? Is the reality of the situation just too formidable to allow that?

And I'm looking at Jody, and I'm -- all right. Who would like to go?

All right. Dr. Green.

DR. GREEN: Well, I think that -- certainly, I'll speak to poison centers first. We have, you know, the general public calling in to report their experience. It typically is an acute situation. We have, you know, the -- what we call the specialists in poison information actually collecting the caller information.

So because this is such a complex market, we actually have a couple of abstracts -- and the study I mentioned earlier that we did with acetaminophen is published -- to show that when you educate these

individuals about the market they know what kinds of questions to ask.

I also wanted to know. The NPDS data system is very different than the RADARS system. We process data differently. So the RADARS system poison center data, we collect the case notes along with the categorical data from the participating poison centers, which is -- covers over 90 percent of the U.S. population. So when we get those, we actually review them. We read every single case note to verify product information, route, medical outcomes, and whether -- the reason for the exposure, so abuse versus misuse, suicide, and other reasons.

And so we often will send memos, educational training memos, to all the participating poison centers to talk to them about what's the difference between the different fentanyl patches. And now that -- so for instance, when a product comes to market, we'll actually get the package insert, create a memo, and send that out to the poison centers to educate them on what they look like; what other products might they be mistaken with in the field; what they might also be

called, especially when generics come out, so that they know to ask. So you know, they report it's Kleenex, to the presentation earlier. I use that all the time, too. You know, is it actually Kleenex, or is it the generic of the Kleenex?

And while it's not perfect and we will always have self-report bias, by all means, I think it does at least get the caller to think about those things and not just so readily -- you know, rattle off the brand names.

In the acetaminophen training, what we do as well is actually have them go get the product, go get the product, what are the active ingredients, read the package, you know, the drug facts label. Obviously, this is different. You know, these people -- patients might have purchased the product off the street. They may not even know what it is. You know, so there are some nuances there.

But I think the more that we can train the people bringing the data in about the market and nuances of all the products, the better they can ask the right questions of the callers so that we can get

better information.

DR. STAFFA: Dr. Scharman?

DR. SCHARMAN: Yes, a couple things. I think, operationally, at -- when you get to coding training, it's always important to remember that the person being trained doesn't need just the aspects of the technical questions to ask. They need to have a true understanding of why this information is important because when they understand what it's going to be used for, they're more motivated to do those questions. So if you do the actual physical training of which questions to ask without that piece, it's not as effective.

I think the key thing we have to remember, too, is, for patients that come into an emergency department setting, for most overdoses, they don't come in with their bottle. You know, sometimes they have pills in pockets, and then those are perfect because you can do a drug ID. You know exactly which one it was. Those are great, but those are rare.

So you're stuck with what the patient calls it, which, again, goes back to what's written on their

bottle, and it goes back to what the triage nurse took the history and wrote in the record. And that becomes ex post facto what it is.

And so what you really need to drill down is training of the triage nurses in the ER who are usually getting the data because, otherwise, you're DAWN data is going to be incorrect, the poison center data is going to be incorrect, all the other databases that rely on those hospital records are going to be incorrect. So you've got to get it down to the lowest level of person who first enters the data in the medical record and train them and get to understand why that's important. Or else it just flows through the system.

DR. STAFFA: Dr. Boyer?

DR. BOYER: I will never disagree that getting the data is incorrect. I would just point out that to the implementation science surrounding getting people to change their practice for information but does not change their immediate clinical practice is going to be extraordinarily difficult to do.

You know, industry standards before we had the

wonders of the EHR were that an emergency physician had 10 minutes to see a patient, get a history, do a physical, do all the documentation, and arrange for a disposition. If I'm a practicing doctor someplace, I just want to know do I give naloxone or do I give more naloxone. I don't care if it's going to be a particular formulation in one versus with the other no matter how much training you decided to give me. If I've got a cardiac arrest coming in, I'm going to pivot my (inaudible) towards the cardiac arrest, and the information on whether or not it's -- you know, I give extended-release, immediate-release, or a deterrent form -- resistant formulation is going to be irrelevant to me.

So can you get the data? Yeah, absolutely. Is getting the correct data important? Absolutely. It's not going to happen under a current emergency department structure, particularly one that is being threatened with declining reimbursements from CMS who, as they say, well, we're not going to pay for nonemergency care. I don't know that a priori, so I'm going to turn over as many patients as I can per hour

just to protect my income because I eat what I treat.

DR. STAFFA: Thank you. Ms. Cassidy?

MS. CASSIDY: I just wanted to respond to your question about whether coder training would be -- you know, improve the identification of these products in treatment center data. At least in the treatment center data that we work with, the NAVIPPRO data, it probably wouldn't be a significant factor because those data are self-report. They're collected by the self-report of the individuals coming into treatment and identifying through the images that -- in the questions that they're asked in the assessment what specific products they take, what specific routes of abuse that they have.

But with that said, I think is the -- you know, as we're talking about the issue of misidentification of particular products and misclassification, some of that, you know, exists in all systems. And you know, we could probably work to improve what -- you know, how we're asking the questions and what questions we're asking, also maybe doing some types of studies about -- so even within the

treatment context, there is variety. Not all abusers are alike. They're -- these are, you know, folks who are coming in who, you know, are injectors and use heroin versus folks who have been sort of -- you know, come in through maybe a drug court system and they were headed DUI but, you know, maybe are less experienced.

Maybe the level of misclassification is different among these different subgroups of abusers and we could do some types of pilot studies to try and, you know, look at those individuals, you know, separately in treatment and understand better how that identification happens.

And we'd certainly be open to collaborating, partnering with folks who have ideas around that to help improve the data collection.

DR. STAFFA: Dan Budnitz.

DR. BUDNITZ: I was just going to add the comment that whether it's a patient self-report of these abuse-deterrent formulations or the poison center consultant or whether it's the ED doc, something that -- to get the right drug, just make it as easy as possible to identify that right drug.

And then there are issues, of course, with, you know, branding. But if there are standards in packaging or, like, unit dose packaging or labeling, then make it easy and obvious that this is an abuse-deterrent formulation. That can assist all those folks along the way in correct reporting. And it will take time, but then, you know, people recognize ZPack now. And maybe you're more likely to identify it as a ZPack if it is in that packaging, for example.

DR. STAFFA: And Dr. McClure.

DR. MCCLURE: I just want to add a comment. With the collection of the data for prescribed pharmaceuticals, you can get the information on that. If it's clandestine or illicit, all bets are going to be off in terms of identifying, really, what truly is on the street. There is all kinds of names for oxy, hydro, and it may not even be that.

And you know, for instance, Spice -- we've been through five generations of core-based molecules over time, and it's still coming. They're not all the same on there. So you're going to get a lot of noise with the illicits, clandestine materials.

DR. STAFFA: All right. So I'm going to turn it over to Dr. Levenson to see if he wants to get further clarification on anything that came up in Session 2.

DR. LEVENSON: Sure. Thank you, Judy.

Okay. So at lunch today, Judy and I went over some of the themes from the various sessions, and I'm going to work through some of the themes on Session 2 if you have any further things to add that would be helpful for these topics.

So Session 2 is about sampling and denominators. And it was particularly for these data sets that are case-based or numerator only. Tomorrow we're going to focus on a more rigorous sample, so I'm going to try to focus some of the ideas that came up in this session on that source of data.

So first I'd like to start with something maybe Dr. Novak brought up, the quota sampling, the network sampling, or methods that you can use that are outside of traditional sampling methods.

Do you have anything more to add to that? You -- I mean, you may not, but if you can elaborate on

some of those ideas and give us a flavor of what they're like or how they might be useful.

DR. NOVAK: Yeah, I mean, I think some of the methods that we've used in terms of web surveys have been trying to do a better job of getting at those few users that may not be well represented either in, like, web panel surveys like standing web panels that, you know, you have to opt in. And then, you know, a lot of researchers and places sort of like them because it's sort of -- it's a pre-ready sample.

And you know, I know this is sort of the difference between, you know, government research and sort of, you know, academic research. But you know, these panels are out there, and people are using them. And you know, so -- and we've investigated them pretty rigorously, and we have shown some validations in some papers that, you know, if you have benchmarks that are available, you can combine sort of a quota sample with a weighting sample called generalized exponential modeling to sample on the dependent variable with the condition that you have a dependent variable, let's say, like prescription drug abuse like opioids. And

then you understand, like, a very high degree of correlation between that dependent variable and other proxy variables like cigarette use and tobacco.

And so through the combination of those variables, you could increase your positive predictive ability to predict the outcome. And then to the extent that you can get that model area under the curve over, like, .8, which is a pretty good prediction value, you can actually sort of, you know, by indirectly weighting to those variables, sort of this rising tides raises all boats. And so you can actually kind of figure out a way to sort of weight the dependent variable indirectly through these other observables. And so you know, there's a lot of very creative ways.

And now, the challenge with that is, is that, you know, when thinking about means and medians, you know, these, really collectively, the analysis of moments, in those sort of techniques, you actually have to be sensitive to when you develop weights how they disturb the standard error structure. And so in that case, like, our studies, you know, we've shown that we've been able to actually gain some precision in the

point estimates of the means, but your standard errors are still pretty wide.

So then when you start thinking about, okay, comparative effectiveness studies, you know, what's the difference between the prevalence of this ADF and you have the -- you know, a point estimate of a mean or a prevalence and then you have a standard error around there, you know, it gives you sort of a -- you know, an acceptable range. But then you start thinking about, okay, well, how do I compare this to another product, you know, a comparator product. And you know, does an ADF confer differential risk compared to some other non-ADF product? You know, that's when you also -- the -- you start getting up against the boundaries. And so I think, you know, sort of raise, you know, the need for, like, the FDA to sort of present, you know, with the most highest, you know, standard, you know, rigorously methods available.

But I think, you know, if you can kind of think about different levels of evidence and the quality of evidence and, you know, thinking about if it all sort of points to in the same direction, you know,

that might be able to sort of supplement other sort of more standard methodologies that you might have so that, you know, recognizing that some of those standard methodologies might not get you at, you know, very difficult to reach populations like, you know, hardcore addicts that might not find themselves in your sort of standard traditional data streams.

DR. LEVENSON: Thank you. Does anyone else have anything to add on making use of non-random samples?

DR. PARKER: Sorry. Jennifer Parker, the National Center for Health Statistics.

I'll just start by saying I don't know much about this topic. But I can tell you about a research project that's going on at the National Center for Health Statistics on the web panels. We are testing whether we can augment some of our prevalence estimates from, say, the National Health Interview Survey with data from some web -- data with some web -- data from some web samples. And we're doing that by trying to calibrate the web data from one of those opt-in panels to our National Health Interview Survey.

And we have a group of highly trained math stats, and they're optimistic that it will work for some things. It doesn't work for everything. We don't really know why it works for some and why it doesn't work for others. We haven't gotten that far.

We don't have good variance estimates, so we don't know how good what we're getting is going to work. I don't know -- you know, you -- we're trying some different methods. And when we poke it a little bit further and we look at domains like, well, it might work for a total, but is it working for young people or old people or people who are black, people who are white, people who are poor, people who are wealthy? It doesn't work that well. So it depends on what you want to use it for.

I think that our work won't be ready for prime time for another while, which isn't -- but we have fairly high standards for what we put out as a prevalence estimate. And I also know that from working with colleagues and other agencies -- for example, the EPA -- sometimes you need to know something to make a decision. It might not be what we would put out from

the National Center for Health Statistics as the number of people with diabetes, but you need to know whether it's high or low or whether it's higher in one group or the other. And you need to know some information. And I know that those bars are a little different than what we put out.

DR. LEVENSON: Well, we already make use of the data. So anything that would improve it would be a step in the right direction. So thank you.

Any other comments on making use of …

DR. SCHNOLL: Sid Schnoll. And I'd sort of like to throw this over to Wilson Compton.

Quite a while ago, NIDA used to have a whole set of ethnographers who were out in the field working with people who were difficult to reach in other ways. And just wondering whether or not NIDA is still doing that and, if not, whether or not that can be done to see what's going on. It would collect some very interesting data on hard-to-reach populations.

DR. COMPTON: Yes, we still fund that type of research.

(Laughter.)

DR. COMPTON: To elaborate just a little bit, there -- I don't know anybody that has applied this directly to the problem of abuse-deterrent formulations. That's why I turned to Dan early in the day to see if he might have some insights from his sample. That's one of the ones that we've supported over the years.

Most recently, we've done a -- we're -- we've done some hotspot studies. We just funded a small project in New Hampshire to look at the -- how frequently fentanyl was an issue in the overdose population, obviously a very important topic right now.

This isn't germane to today's findings. But one of the shockings (sic) findings for us was the number of drug users in New Hampshire who were actively seeking out fentanyl. That was a surprise to me, that I thought that having a product that was killing a lot of your customers would be a deterrent. But it turned out to be a marketing technique in some ways, which was pretty shocking to me.

The largest sort of conglomeration of these would be our community epidemiology workgroup, was

disbanded in favor of a new program called the National Drug Early Warning System, NDEWS, which brings together some of the ethnographers as well as a variety of other sources. It suffers from a lack of some of the traditional data sets in that we don't have DAWN anymore and we don't have the Adams study. So two of our most robust early warning systems don't exist any longer.

To a certain extent, the internet has replaced that in terms of some availability of sort of early warning signals of something novel and new happening in -- as at least one potential source of information that we've already talked about here today.

DR. LEVENSON: Yes, please.

DR. DEGENHARDT: Sorry. Louisa Degenhardt. Just one comment about there's been reference a few times to people who might be tampering with pharmaceutical opioids or injecting or, I think, are a difficult-to-reach population. I'd just like to challenge that because we do a lot of research in Australia, but there's a lot of people in the United States who are doing a really vast amount of research.

You know, NIDA funds -- I think it's 80 percent now of the world's illicit drug research, and much of that is with people who you could classify as hard to reach, but they're actually not difficult to reach at all.

But it's the way in which you choose to engage with that group will really determine the extent -- the speed with which you can get in touch with people and the way in which they're willing to disclose information to you. But if you were doing research with people and you're guaranteeing anonymity, there's no judgment, there's confidentiality, there's absolutely no problem in accessing fairly large numbers of people who will be very honest about their life story.

DR. LEVENSON: Okay. Well, thank you.

Moving on to something slightly related, several panelists mentioned use of administrative data, particularly in the federal system. And Dr. Jones is gone now.

But Dr. Bose, do you have anything? You said there were some working groups in the federal government on the use of administrative data. Can you

say more about that?

MS. BOSE: I think just also tied into what we were listening to right now, a lot of it depends on fitness for use and what it is that you need it for and what decisional process accompanies your data. And so as Jennifer said, I mean, if they're for official statistics, then there's a certain bar we use. If we need to have some kind of a number that we need to make internal decisions, then we might use a series of data sources with -- each with their issues but -- if they're all maybe pointing in the same direction.

But I think FDA and other regulatory agencies have unique positions in where the justification is not just internal, it's also not a, hey, here's an official statistics, but there are consequences to your decisions and there are consequences that involve life and death. And they also involve a lot of money.

So I think that whether we're talking about these sources of administrative data or we're talking about what opt-in panel work or other forms of data collection, we really do have to tie it closely to the fitness for use so that it's defensible.

DR. LEVENSON: Thank you.

Any other thoughts on use of administrative data? I know Dr. Jones had something to say about it, but he's not here now.

MS. BOSE: Oh, I'm sorry. I was just going to say -- and for members of the HHS Data --

DR. LEVENSON: Right.

MS. BOSE: -- Council. And so at some point if we want to come up with ways of what -- you know, how do we use administrative records, are there specific concerns that FDA has that need to get that other HHAs -- agencies have also dealt with, then it becomes a resource to kind of talk about.

And they're -- HHS -- the HHS Data Council at this moment is going through -- I wouldn't call it a reorganization but a process through which we're kind of trying to focus our purpose and mission and what do we focus on in the long term, what do we try to do in the short term. There are staff at NCHS who are also involved in this -- Renee (ph) -- yeah.

And so I think it's a resource because we're collectively dealing with some of these issues,

especially as survey expenses go up.

DR. LEVENSON: Okay. Yes, please.

UNIDENTIFIED MALE SPEAKER: Yeah. I think that, you know, to the degree of what your questions are, administrative data may be helpful if you are interested in drug utilization. If you're interested in certain outcomes, perhaps, amongst certain subgroups -- people with preexisting chronic liver disease, chronic viral hepatitis -- looking at outcomes of death or validated overdose amongst different drugs, that may be helpful.

So it really depends on the -- you know, the use of the administrative claims data. It may depend on the questions that you -- that you're interested in.

DR. LEVENSON: Okay. Thank you.

Anyone else on that topic?

Okay. And now perhaps a more kind of epidemiological question or topic. We heard to make use of some of these convenience samples, it's important to understand the effect modifiers maybe to do standardization or stratification. Could we suggest some of the relevant effect modifiers here that might

be available in the data sets we talked about today?

DR. DASGUPTA: I can take a shot, but I think you mentioned it as well.

But I mean, for -- I mean, thinking at the -- on the treatment centers, so we know there's public versus private. There are treatment centers that have large criminal justice referral inputs. We know whether a treatment center takes Medicaid or not. I mean, these are all characteristics that could be collected on the treatment centers. And maybe it wouldn't have to be something that we burden the treatment center administrators with every month, but maybe once or twice a year we could collect that information.

And that -- you know, if we were trying -- if we're talking about trying to understand the sampling of each of the treatment centers and what's a reliable sample and what treatment centers are more like each other, those are just a few that come to mind, whether they're tied to inpatient facility, whether -- you know, which treatment modalities they use. You know, I think there's quite a few that we can come up with.

DR. LEVENSON: Thank you.

Dr. Novak?

DR. NOVAK: I have going after Nab because everything is very, you know, well laid out.

I guess one important thing we really haven't talked about is the rural-urban difference, and we did talk a little bit about some of the environmental effects. But you know, the rural areas and especially in Appalachia have just been crushed by the opioid epidemic -- no pun intended, I guess.

So anyway, just thinking about also -- and I like the way Nab did it, sort of laying out the -- you know, the micro-level issues, patient versus non-patient status and then sort of moving on up to the macro and the environment.

DR. LEVENSON: Dr. Winterstein.

DR. WINTERSTEIN: There may also really be an empirical approach to look at that, and I can imagine two. One would be -- we heard already that there are differences among different treatment centers, so which means that if there were an analysis done of differences, variation among treatment centers and just

get the information that those treatment centers have reported about their patients to see to what extent those variables can explain that variation, that might be helpful. And that could be, you know, co-existing, comorbidities. That could be age. That could be race. That could be geographic location. That could be whatever. I mean, that -- there's -- I'm sure there's a good number of data there.

There other comparison also empirical that I could think of would be to if there was some national data on utilization pattern on prescription opioids and illicit drugs, for that matter, and to look at that distribution and compare that to the distribution of what is described in treatment centers and, again, try to see whether differences in patient demographics, comorbidities, and so on can help explain those differences in both instances. That would perhaps propose a few ideas and for (ph) a few effect modifiers.

DR. LEVENSON: Thank you.

Dr. Lo Re.

DR. LO RE: I guess one of the other thoughts

we -- just thinking about things that may potentiate the effects of the drugs, so maybe polypharmacy drug-drug interactions, co-administration of certain drugs that may exacerbate effects, maybe chronic liver disease, failure of metabolism. Oftentimes, patients who are -- with chronic liver disease may not necessarily be included in these studies. So just other things to think of.

DR. LEVENSON: Okay. Well, thank you.

Let's see. The next item I have on my list is time series modeling. I -- this came out of Session 2 that time series modeling was preferred. I think a lot of this got resolved in the Session 3. But just to be clear, so by time series, do we mean anything more than these interrupted time series that Dr. McAninch spoke of? Is there something more than that, or is it just to distinguish between having means and slopes versus just means? Have some clarification, the people who were promoting time series models this morning. Okay.

DR. WINTERSTEIN: I think you need to clarify your question.

DR. LEVENSON: Okay.

DR. WINTERSTEIN: Are you specifically asking about the statistical approach to fitting regression lines for time series or …

DR. LEVENSON: Well, not necessarily the approach. What -- what's -- what do you have in mind when you suggested time series models as opposed to before-and-after models? Is it just these interrupted time series, or is there something more you were thinking about?

DR. WINTERSTEIN: Well, I mean, there is all of us who study design at some point. There's Cook and Campbell, right? So there's a limited number of causal (ph) experimental designs. And you know, in a before-and-after comparison, there is either before or after or there is time series. And there is just not more there.

(Laughter.)

DR. WINTERSTEIN: So you know, so I mean, the distinct difference is that, in a time series, I can model trends and I can incorporate trends, while in the pre-post I cannot. That is the major difference.

There certainly are approaches in time series

that try to optimize the number of time points versus the precision around each time point. And I think that's kind of the issue here, you know, right? So number one, how often do I have repeated measures at all? I don't know how that data is ascertained. And poison control centers, obviously, on a daily basis -- but I don't know how the treatment center analysis and how the data collection is done there.

So that's one part. You know, how much data do I have, how often, and how small can I make that time increment so that I have --

DR. LEVENSON: Yeah.

DR. WINTERSTEIN: -- lines that I can put data through.

DR. LEVENSON: But -- okay. But you're suggesting some sort of parametric functions before and after. I mean, there are non-parametric time series models, too, but --

DR. WINTERSTEIN: Yeah. Yeah, and I mean, that -- but that's a matter of how to fit a regression line, right? That's whatever the data tolerates --

DR. LEVENSON: Okay.

DR. WINTERSTEIN: -- best, right?

DR. LEVENSON: I think I understand what you have in mind. Okay. Thanks.

DR. WINTERSTEIN: Okay.

DR. LEVENSON: Dr. Graubard?

DR. GRAUBARD: I'll just make one point about time serial data, is that I think it's important -- just a general point, and I know FDA's in -- knows this from the clinical trials. But it's so easy to abuse that kind of data in the sense that you have so many choices you can make.

And it would be useful to have some sort of a protocol or some sort of a guideline before looking at the data what you plan to do with it because some people will say, well, if I cut the time series off here and I only go out this far on the right, I'll get this answer. I like that answer the best, you know, because it shows the most -- the big, largest effect I'm looking for. Statisticians usually like to use all the data that they have available to them unless there's a reason not to.

And so I -- just a -- you know, just a general

word of warning, the types -- you know, you go through great efforts to write protocols for randomized clinical trials. You might consider similar types of guidelines for actually doing these kinds of analyses -

DR. LEVENSON: Right.

DR. GRAUBARD: -- particularly --

DR. LEVENSON: You know, no, I -- well, I'll look to the panel members -- Louisa, please.

DR. DEGENHARDT: Yeah. I'm Louisa Degenhardt. I completely agree, particularly in the case when often -- and I'll declare it myself -- we've received untied (ph) educational grants from pharmaceutical companies to undertake post-marketing surveillance. I think it's even more crucial that you publish the protocol before you do the study than at using randomized controlled trials where you might go through, you know, an NIH or a similar process.

So I actually -- I think it's really, really important that all of these studies are registered. It's so easy. You don't have to get it published in a journal. It's very easy to get them registered online,

particularly when there is some level of involvement either direct or indirect of a pharmaceutical company who has a real interest in the study findings.

DR. LEVENSON: I'll make a few comments on both those points. You know, first, we have witnessed when you -- different models will give you different answers. So we've observed that in fact. And we do insist that the -- when we ask for these studies to be conducted that protocols and statistical analysis plans are submitted first before the study commences and we review those. So everything is pre-specified, so we're careful about that.

DR. GRAUBARD: But that's for the drug companies, right, you're talking about?

DR. LEVENSON: That's correct. Yes.

DR. GRAUBARD: Yeah, but for your own analysis, for the types of things --

DR. LEVENSON: Right.

DR. GRAUBARD: -- that you're planning to do --

(Laughter.)

DR. LEVENSON: Yeah, I mean, right. Well, I

have to say most of the analyses are done by the drug companies. For a company to get a claim of abuse-deterrent formulations it's incumbent upon them to demonstrate that and for the FDA to review the evidence and make a judgement.

Okay. So that was the time series. And the last thing I have -- I think there might be discussion around this -- is utilization. We heard some comments that simple denominators are not appropriate, that more complicated models might be a better way to handle utilization.

And on a similar topic, we heard that the sort of market picture is important, like, how much -- what the alternatives are, how much market penetration a drug has. So I'd like to discuss this a little further if there's anything else to add on utilization metrics and making use of sort of the market picture when it comes to an individual formulation.

So if anyone has any further comments to add on this, we would appreciate it.

(Pause.)

DR. LEVENSON: Okay. Well, as you've heard

previously throughout the day, we can still take comments through the docket or maybe by running into us in the hallway, or so. So if you have any further comments on that -- I think what we heard already, which are useful, but if you have anything more to add, that would also be further useful.

So that's all I have on Session 3 now -- Session 2. So -- you want to start off Session 3?

(Laughter.)

DR. LEVENSON: Okay. Session 3. Now, because this just happened, my notes are a little less organized here. I'll start with a question I did ask during the session.

You know, I agree that these propensity score modeling approaches matching on individual patients is very -- you know, potentially very useful. I'm a little concerned of how we would make use of them in the numerator-only data. Could that be done?

Is there any sort of matching -- would matching be helpful when you only have the cases and not the overall exposure? Are there any models that will make -- that could do this? I'm not sure that's

clear. But if anyone has anything to add about how we might make use of propensity score matching for numerator-only data, that would be helpful.

Dr. Winterstein?

DR. WINTERSTEIN: Well, by definition and propensity scores and exposure propensity score in the context of how we have used it -- and you wouldn't have that and -- you know, in numerator-only data unless you make inferences about the underlying population, which brings us back to the whole effect modification story, right? But otherwise, that exposure portion --

DR. LEVENSON: You still have cases that are exposed to different drugs, so there is a potential for matching, but only on the cases, not --

DR. WINTERSTEIN: Right.

DR. LEVENSON: -- not on the --

DR. WINTERSTEIN: Right.

DR. LEVENSON: Yeah.

DR. WINTERSTEIN: Yeah. Yeah, I mean --

DR. LEVENSON: So --

DR. WINTERSTEIN: -- the reason I brought the propensity score up was more -- I was thinking about

what Dan had brought up, this whole uptake and learning experience with a new abuse-deterrent agent that comes on the market, which means that its risk might change, number one. But it also means that the interest in it might change over time and who it's being channeled to.

So that was more my idea for saying, you know, ongoing propensity score matching rather than just, you know, in one single population but -- during follow-up, as there is more uptake because the distribution of the population that might get this drug might change because the interest changes and so on. That's more why I brought specifically propensity scores up. I mean, it doesn't matter how an adjustment would be done, but that's why I brought it up.

In general, you know, we are trading -- I mean, both are observational designs. A pre-post as well as a concurrent control group, they are -- we're treating one bias against the other, right? The populations are changing or there's channeling, and both has to be dealt with, with the same risk factors and adjustments. It just a different way of designing the same thing.

And you know, personally, just having observed how much this whole opioid market has changed, to me, concurrent control groups seem to be a little bit more palatable than time-based control groups because of all the issues that have happened concurrently.

And I might be completely wrong, and I'm happy to be proven wrong. We have -- we just haven't tried the other approach. Everything that we have done is pre-post or, you know, some type of time trend. But we haven't done head-to-head comparisons, even though we have now some years of use accumulated where we could start to look at them.

DR. LEVENSON: Thank you.

MS. CASSIDY: Thanks. Theresa Cassidy. I just -- and this might not be directly related to the conversation about the propensity scoring, but I think as we're thinking about numerated data and, you know, how to think about that and, you know, its representativeness, you know, I think that one thing that you -- we're circling around in some ways is that you could standardize that data to a standard population.

The problem that I think we're all sort of been discussing is what is that population, how do you enumerate it, how do you describe it, and then what would you, you know -- and how would you use that inference from what that standard population is to apply to these numerated data. And that could be an approach that's used as long as we could come to some consensus around what is that standard population. And maybe there's not one standard population. Maybe there's more than one that we can, you know, sort of infer from.

But anyways, I just thought that might be helpful.

DR. LEVENSON: Okay. Thank you.

Okay. Well, there were a lot of good ideas on that -- I'm not sure there's going to -- good ideas in this session. I'm not sure there's going to be a lot of follow-up discussion, but I'll bring up some other themes. And if anyone has any follow-up discussions, please add.

There was the idea of using a pool of comparators instead of a single comparator, a pool

that, well, sort of represents a similar risk. Does anyone have any further thoughts on that? I mean, I said it's -- I think we all recognize it's a good idea and there may not be further thoughts. But if anyone has any ideas they'd like to add to that, please jump in.

Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone. I'm just going to bring in a parallel from economics. And that is economists use pools of, you know, baskets, I guess is what they call them, of currencies or commodities in which to do comparisons on because there's things that are changing so rapidly.

And I know one of the downsides of doing this was the idea there might be a market driver. You know, there might be a dominant product. And that's -- the problem is solved with weighting for that.

DR. STAFFA: I had one question. And I don't even know who brought this point up, so I can't provoke you. But I'm going to throw it out.

Someone had suggested looking at, rather than try to separate the effects of different abuse-

deterrent formulations, to try to look at them as a group and knowing that they don't all have the same mechanism for deterring abuse and they don't all deter the same routes of abuse. Some are solely injections. Some are nasal. Some are both.

I'm wondering whether folks can expand or whoever had that thought might give a little more detail to it of what we're thinking there and what we might come away with. That's certainly -- I could see the strategy in terms of numbers -- it's certainly -- if that was our group of interest were all abuse-deterrent formulations and we were looking.

But anybody remember saying that? Or did I hallucinate it?

Dr. Green is in on my hallucination. Thank you.

(Laughter.)

DR. GREEN: Well, I wouldn't go that far. But …

(Laughter.)

DR. GREEN: I think that's certainly a group that we've had discussions about, and then it becomes

is it a non-inferiority or an equivalent study because they -- you know, you have a comparator. But then what is your anticipated comparison? Is it that it's no different than all the other ADFs?

And so I think to someone else's point on that side of the table was that, you know, is it that you -- you really don't want to be different than any other ADF in whatever group it is, knowing that it has to be route-specific because the labeling is route-specific. But I think there is some utility in looking at that based upon, as you mentioned, the low market share that we're going to struggle with for a long time.

So I think the bigger question might be what is the actual question we're trying to answer and then how are we going to establish the appropriate comparators and the sample size and the power and everything to be able to actually answer that question. So I don't know that we can say that's a good comparator group until we know what the questions are we're trying to answer. But I think it could be valuable.

DR. STAFFA: Dr. Schnoll?

DR. SCHNOLL: Sid Schnoll. And maybe Jody can answer this. But what is the feasibility of getting data on a competitor's product looking at this? I know there are some issues around that. So in selecting a comparator, how easy would it be to know what's going on with your competitor's product?

DR. GREEN: Gee, thanks, Sid.

Well, in the RADARS system, because we have many subscribers that are many different companies, we do not provide a competitors' product-specific information to a company. In the rare instance, we've had a situation where two companies can agree to share mutually back and forth the product-specific information. But otherwise, you know, it gets a little sticky and complicated. And it's -- I don't think necessarily that it's a feasible solution for all the studies coming up.

MS. CASSIDY: And I just want to add to that. I think that we've, you know, experienced some similar approaches as the RADARS system in terms of, you know, sharing data across companies. There's been -- you know, it's been a mutual agreement. That's sort of

been the past.

I do think that we're at a bit of a crossroads where, you know, there's more of these products coming on the market. And you know, we're talking about this issue of the comparator and what's the appropriate one, and it's sort of -- you know, the options start to dwindle.

So you know, at the risk of, you know, maybe poking a hornet's nest, this is sort of a pharma company -- in some respects, it's a pharma company-imposed rule on us who collect data because we collect all of the data. So we have that available. Certainly, it's something we could probably discuss and talk about how we could move forward and look at those things.

DR. GREEN: But I think that's why the drug groupings can be very valuable. I mean, you still have, you know, different -- multiple products in say, you know, an ER morphine space or a -- I'm just trying to -- ER hydrocodone space. And you can still group those as comparators. So if I have a new hydrocodone ER product, I can still compare that to all the other

ER hydrocodone products. It doesn't necessarily need to be a head-to-head to brand of product to another.

MS. CASSIDY: Right.

DR. GREEN: So I wanted to be clear that we still do the groupings, just not at the product-specific brand --

MS. CASSIDY: Right. And just to follow on that, I just -- I think you raised a good point earlier, is, like, what's the question we're trying to answer. Are we trying to answer whether this technology is better than that technology, you know, when we're stacking up different products against each other? I think that we really still need to consider what's the actual objective and what's the question we're trying to answer.

DR. STAFFA: Well, I think right now the question we're trying to answer is do these abuse-deterrent formulations work better than non-abuse-deterrent formulations. But the concept behind a meaningful reduction will change over time. And as we find products that deter abuse and then there's improvement on different products that might deter

abuse better, then you can see where meaningful reduction may end up with comparisons between products -- does this deter better than that -- because then we always run into the regulatory question of if this deters better than that, do we still need that.

DR. GREEN: And Judy, if I can -- this is Jody Green -- with all due respect, I think that's going to be a long way down the road and we should learn a lot in just trying to figure out if these ADFs, the, I guess, first generation, whatever you want to call them. If we can establish methodology now in terms of just evaluating the current ADFs and then Phase II -- we'll learn a lot, I think, once we get there. And then Phase II I think we'll definitely be deciding -- you know, looking at the different technologies and whatnot.

But honestly, until it's -- until we have an all-ADF or close to all-ADF market, I think that's going to be a real challenge. And then how can you say that one ADF might be a little bit better than the other ADF? But are they both still better than none, than no ADF?

So I think that relativeness will be interesting when we get there maybe in our lifetime. But this first phase I think should tell us a lot.

DR. STAFFA: Other comments? People want to -- yes, Louisa?

DR. DEGENHARDT: Sorry. Just a quick comment. It's a bit of a different study design. But in the cohort study that we did as part of our study, we actually go over very detailed assessment to people who were tampering with pharmaceutical opioids for every opioid type, the brand name of that, the dose they were taking, how the -- what route they were taking it by, were they prescribed that non-tampered or tampered dose of that particular opioid, or where they getting it from diverted sources. And we got that for every single pharmaceutical opioid plus all of the benzodiazepines, and then we got all of their illicit drug use.

So it is quite possible to do specific focused studies that get that level of detail, including how. So we knew what -- which dose of which opioid was being tampered with versus not for all of the opioids. You

can get that pretty readily, you know.

DR. STAFFA: Thank you.

Other comments? We'll be getting back to tomorrow when we get into our session about patient-level designs.

Okay. So I think we're ready for this session to move into the audience participation section. And folks, I think you know the drill by now. I don't think I have to explain it -- again, the green, yellow, red.

Anyone want to make a comment from the audience?

All right. Please introduce yourself and state who you are, where you're from.

DR. MAYNE: Dr. Tracy Mayne, Perdue Pharma, and Board Member of NPC.

Given that all of these are dichotomous outcomes, have you considered time-dependent survival analysis? So take a more Cox proportional hazards approach. You can allow both dose, duration, changes in dose to evolve over time towards that endpoint. But so many other techniques have been discussed, and I

hadn't heard that one.

Thanks.

DR. STAFFA: Thank you for your comment.

Any other members of the audience would like to make a comment? Going, going, gone. Okay.

Any closing comments that anyone on the panel would like to make and my FDA colleagues up here?

Oh, Dr. Dasgupta.

DR. DASGUPTA: Hi. Thanks for saying my name so I didn't have to do it.

(Laughter.)

DR. DASGUPTA: I think after listening to the discussion about limitations of a lot of these data sources, I kind of get a sense of a little cognitive dissonance in that we use -- we rely on these same data sources to say, well, the Florida pill mill legislation worked. The PDMPs have done -- have -- you know, have contributed to the reductions in prescribing or doctor shopping and that, you know -- that we know that there's a transition to heroin happening. You know, we're using the same data sources to make inferences that we feel comfortable is the truth.

But at the same time when it comes to the specific question, there's this kind of hesitation to believe the same data sources that -- and it's not just RADARS or NAVIPPRO or NSDUH or any given one, but pick the ones you believe.

So I kind of -- at the end of the day, I'm left with this -- you know, I believe these data for the big picture, but somehow, you know, the conversations picking apart each of the flaws, which I think is a very important discussion to have, doesn't kind of roll up in the same way. So I don't know. I don't know what to do with that, but I just wanted to kind of share something that's going through my head.

DR. STAFFA: Any reaction to that?

Is it Dr. Novak down there that I'm seeing raise your hand?

DR. NOVAK: Sorry. I think one of the things that the FDA needs to settle on is -- and it's been brought up a couple times -- is this word "meaningful." I think about each of the different presenters often had it. And I mean, is it a statistical significance so it's a P value of .05? Or is it some clinically

significant difference?

But I think it's something that you're going to have to keep -- that's going to keep coming back. And at some point, I think as an agency, you're just going to have to draw a line in the sand and say this is meaningful to us as we monitor the side effects. And if, you know, misuse, abuse, and diversion, overdose, these are side effects. Do they have differential levels of, you know, acceptability and evidence that supports whatever that threshold is? So …

DR. STAFFA: Thank you.

Other comments? Last thoughts? Any last advice on how we can best make use of the data we have in front of us before we move on to the loftier goals of tomorrow? No?

Well, I want to thank all of you. I would like to thank our panel members, our FDA folks, as well as our audience for a very productive day. You've certainly given us a lot to think about, some of which we understand and some of which we'll be asking you more about.

And then tomorrow we're going to be talking about how can we think about improving things and how can we thinking about doing things better. So don't lose track of some of those ideas that worked their way into the conversation today because we'll want to learn more about them tomorrow.

So thanks very much. We'll be starting at 8:30 tomorrow morning. We'll see you then.

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